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Influence of plasma matrix metalloproteinase levels on longitudinal changes in Alzheimer's disease (AD) biomarkers and cognitive function in patients with mild cognitive impairment due to AD registered in the Alzheimer's Disease Neuroimaging Initiative database

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ABSTRACT

Objective: The present study investigated the effects of plasma matrix metalloproteinases (MMPs) on longitudinal changes in Alzheimer's disease (AD)-related biomarkers in cerebrospinal fluid (CSF), brain atrophy, and cognitive function in patients with mild cognitive impairment due to AD (MCI-AD).

Methods: We used data from the Alzheimer's Disease Neuroimaging Initiative database. We included 95 ApoE4-positive patients with MCI-AD who were confirmed to have low $A\beta_{42}$ and/or high phosphorylated-tau (p-tau) in CSF. We obtained baseline demographic data, plasma MMP levels, including MMP-1, −2, −7, −9, −10, and tissue inhibitor of MMP-1 (TIMP-1), longitudinal annual data on $A\beta_{42}$, total tau, and p-tau in CSF, MRI-measured hippocampal volumes, and cognitive function evaluated by the Mini-Mental State Examination (MMSE) and AD Assessment Scale-11 (ADAS-11) over 4 years. We examined the effects of baseline MMP levels on longitudinal changes in CSF AD biomarkers, hippocampal volumes, and cognitive function using a linear mixed regression analysis.

Results: No significant differences were observed in baseline plasma MMP levels between MCI-AD patients and control subjects, except for MMP-10, which was significantly lower in MCI-AD than in controls. The baseline levels of MMPs did not correlate with longitudinal changes in CSF biomarkers. Declines in hippocampal volumes and cognitive function evaluated by MMSE and ADAS-11 were significantly faster in MCI-AD patients with high-MMP-9 levels at baseline than in those with middle and low MMP-9 levels at baseline.

Conclusion: High plasma MMP-9 levels in MCI-AD patients might enhance neurodegeneration and cognitive decline.

1. Introduction

Alzheimer's disease (AD) is the most predominant cause of neurodegenerative dementia and one of the leading sources of morbidity and mortality in the aging population [1]. The pathological hallmark of AD is the deposition of amyloid-β (Aβ), neurofibrillary tangles induced by phosphorylated tau (p-tau), and neuronal loss [2]. These pathological changes develop many years before patients manifest subtle cognitive changes.

Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia, is caused by various neurological conditions, including AD, and is clinically defined by a measurable deficit in cognition in at least one domain in the absence of dementia or impaired activities of daily living [3]. Patients with MCI convert to dementia at a rate of 10 to 15% per year, which is approximately ten-fold higher than the conversion rate in healthy controls [4].

There is currently no practical approach to treat AD or halt its progression after patients reach the dementia stage. Thus, there is an urgent need for biomarkers that identify patients at a higher risk of developing dementia at the prodromal stage [5]. To target this issue,

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[1] Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). Therefore, investigators within ADNI contributed to the design and implementation of ADNI and/or provided data, but did not participate in the analysis or writing of this manuscript. A complete list of ADNI investigators may be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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the Alzheimer's Disease Neuroimaging Initiative (ADNI), a longitudinal and worldwide multisite observational study, was launched in 2003. ADNI data is open to the public to validate AD-related biomarkers in MCI [6].

Matrix metalloproteinases (MMPs) are attracting attention as novel AD-related biomarkers. There is increasing evidence to indicate that MMPs play important, but complex, roles in the regulation of diverse biological processes under normal and pathological conditions, including embryonic development, inflammatory diseases, cancer, and neurodegenerative diseases, including AD [7,8]. MMPs are calcium-dependent zinc-containing endopeptidases, several of which are expressed in neurons and glial cells. MMPs constitute a family of at least 28 MMPs, which may be divided into six subgroups: gelatinases (such as MMP-2 and -9), stromelysins (such as MMP-3 and -10), collagenases (such as MMP-1), membrane-type MMPs (such as MT-MMP-1), matrilysines (such as MMP-7), and other uncategorized MMPs (such as MMP-12 and -19). They cleave and remodel the extracellular matrix to regulate many signaling and homeostatic systems that range from tissue morphogenesis to wound healing. Many molecules, including proteinases, growth factors, cytokines, and cell surface receptors, function as substrates for MMPs, and their activities are influenced by the induction of transcription by inflammatory mediators and through posttranslational modifications by free radicals or cytokines. Some MMPs are also suppressed by inhibitory proteins, such as tissue inhibitors of metalloproteinases (TIMPs). For example, TIMP-1, a well-known TIMP, has been shown to inhibit MMP-9 activity [9].

MMP-2, -3, and -9 have been examined in detail in the field of AD. The levels of these MMPs were shown to be elevated in the plasma and postmortem brain tissue of AD patients [10,11]. Previous studies demonstrated that MMP-2 and -9 were induced by Aβ [12,13], and tau is a common substrate of MMP-3 and -9 [14]. These findings suggest a close relationship between MMPs and the pathogenesis of AD. A limited number of cross-sectional studies have reported correlations between MMPs, AD-related biomarkers, and cognitive function [14,15]. However, the effects of MMPs on the long-term course of AD remain unclear.

Therefore, we herein investigated the relationship between the levels of all MMPs and TIMPs available on the ADNI database (5 subtypes of MMPs and 1 subtype of TIMPs) and longitudinal changes in validated biomarkers of AD (Aβ, tau, and brain atrophy) and cognitive function annually over a 4-year period in patients with MCI due to AD (MCI-AD).

2. Methods

2.1. Data source

Data used in the preparation of the present study were obtained from the ADNI database (adni.loni.usc.edu). 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 investigate whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments may be combined to measure the progression of MCI and early AD. Each participant in the ADNI study provided written informed consent, and each ADNI site obtained local Institutional Review Board approval.

2.2. Patients and samples

Patient inclusion criteria have already been described [16] and are available on the ADNI website. In brief, the diagnosis of MCI was based on subjective or objective memory decline evaluated by education-adjusted scores on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale-Revised. The Mini-Mental State Exam (MMSE) score was between 24 and 30, and the Clinical Dementia Rating (CDR) was 0.5. In the present study, we included ApoE4-positive MCI subjects with baseline plasma MMP and TIMP data and 4-year annual follow-up data on cerebrospinal fluid (CSF) biomarkers, such as $A\beta_{42}$, total tau (t-tau), and p-tau, brain MRI data, and cognitive function. The diagnosis of MCI-AD was confirmed with AD biomarkers, namely, a decrease in CSF $A\beta_{42}$ and/or increase in CSF p-tau. Based on previously reported data by ADNI, the cut-off values for CSF $A\beta_{42}$ and CSF p-tau were 192 and 23 pg/ml, respectively [17].

We included 95 MCI-AD and 58 controls with normal cognition who had baseline data on plasma MMP and TIMP. All data used in the present study were downloaded from the ADNI website on 22 November 2019.

2.3. MMPs and TIMP-1

We obtained the following MMP family data, which were publicly accessible on the ADNI website: MMP-1, MMP-2, MMP-7, MMP-9, MMP-10, and TIMP-1. These data were obtained from the file "Biomarkers Consortium Plasma Proteomics Project RBM Multiplex Data and Primer (Zip file)", which was downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=11&subCategoryId=33). These biomarkers were measured using Luminex xMAP technology (Luminex Corporation, Austin, Texas, United States), the details of which were attached to the Zip file described above. Briefly, Luminex xMAP technology uses fluorescent polystyrene microspheres called beads, which are coated with a ligand or capture antibodies, and each bead contains a unique color-coded signature that is read by the flow-based laser apparatus.

We calculated the mean values and standard deviations (SD) of each MMP level in control subjects. We then defined baseline MMP biomarker levels more than the mean + 1SD as high, less than the mean -1SD as low, and the range in between as middle.

2.4. Evaluation of CSF $A\beta_{42}$, t-tau, and p-tau

CSF levels of $A\beta_{42}$ and p-tau were obtained from the file "UPENN CSF Biomarker Master [ADNI1,GO,2]", which was downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=11&subCategoryId=33). CSF $A\beta_{42}$, t-tau, and p-tau were evaluated using a microbead-based multiplex immunoassay, the INNO-BIA AlzBio3 RUO test (Fujirebio, Belgium), on the Luminex platform. Detailed methods are available in the file "UPENN CSF Biomarker Master Methods (PDF)" on the website described above.

2.5. MRI data

Data on bilateral hippocampal and intracranial volumes (ICV) were obtained from the file "UCSF - SNT Hippocampal Volumes [ADNI1]", which was downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=14&subCategoryId=30).

Hippocampal volumes were evaluated on MRI using a commercially available high dimensional brain mapping tool (Medtronic Surgical Navigation Technologies, Louisville, Colorado, United States). The position of the hippocampus on individual brain MRI data was manually identified using 22 local landmark points. Fluid image transformation was used to match individual brains to a template brain. Pixels corresponding to the hippocampus were then labeled and counted to obtain volumes. Details are available in the file "UCSF - SNT Hippocampal Volumes Methods (PDF)" on the website described above.

ICV was calculated as follows: to generate the mask, the baseline image was automatically segmented; all thus-defined brain and ventricular voxels were given the value 1 with all other voxels 0. This binary mask was then repeatedly smoothed with a Gaussian kernel to produce a simply connected uniform mask, covering all sulci, the boundary of which tapered smoothly from 1 to 0 over the length of a few voxels. The mask ideally ended on the skull and included the brain stem down to where it starts to bend with the neck. Smoothing may be controlled to begin tapering at the skull such that voxels with a mask value of less than 1 may be considered to be outside of the ICV and,

Table 1
Summary of demographic and clinical data from baseline up to the 4th year.

	Baseline	1Y	2Y	3Y	4Y
n	95	80	24	21	19
Age	73.65 ± 6.63	73.80 ± 6.41	73.80 ± 6.02	72.62 ± 6.84	70.44 ± 5.83
Sex (male)	58 (61.1%)	50 (62.5%)	15 (62.5%)	15 (71.4%)	14 (73.7%)
Race (Caucasian)	92 (96.8%)	78 (97.5%)	24 (100%)	21 (100%)	18 (94.7%)
Education (years)	15.69 ± 2.81	15.91 ± 2.72	16.38 ± 2.32	16.38 ± 2.71	16.11 ± 3.04
$A\beta_{42}$ (pg/ml)	134.96 ± 32.25	134.70 ± 29.03	135.08 ± 15.49	126.67 ± 14.23	127.63 ± 21.52
t-tau (pg/ml)	123.23 ± 67.31	122.60 ± 55.74	125.04 ± 67.13	109.75 ± 54.31	124.38 ± 69.44
p-tau (pg/ml)	42.36 ± 17.64	50.10 ± 31.61	41.21 ± 16.76	43.29 ± 19.16	50.09 ± 20.72
n	87	75	22	10	0
H/ICV ratio, (natural log)	−5.46 ± 0.14	−5.50 ± 0.15	−5.54 ± 0.13	−5.57 ± 0.16	N/A
n	95	80	24	21	15
MMSE	26.99 ± 1.75	25.63 ± 3.14	24.83 ± 2.90	23.76 ± 4.58	20.67 ± 13.25
n	95	79	24	20	9
ADAS-11	12.81 ± 4.47	13.27 ± 5.87	14.14 ± 6.97	15.77 ± 7.37	20.67 ± 13.25

Demographic and clinical data from baseline up to the 4th year are summarized.
Age, education, Aβ42, t-tau, p-tau, the H/ICV ratio (natural log), and MMSE and ADAS-11 scores are shown as means ± standard deviations. Sex and race are shown as the number (percentage) of males and Caucasian participants.
1Y-4Y, years from baseline; N/A, not applicable.

thus, ignored.

To evaluate neurodegeneration, we calculated the ratio of the hippocampal volume to ICV and performed natural log transformation (H/ICV ratio) [18].

Data on WMH volumes were obtained from the file "UCD_ADNI1_WMH", which was also downloaded from the website described above. WMH volumes were evaluated on MRI using a fully-automated method established by Schwarz et al. [19]. Briefly, a binary label for each image voxel that denotes either the presence or absence of a WMH established from a vector of three image intensities at that voxel was obtained using a Bayesian Markov-Random Field (MRF) approach. Details are available in the file "ADNI1_Methods_UCD_WMH_Volumes_Methods" on the website described above.

2.6. Cognitive assessment

To evaluate cognitive function, we obtained the scores of MMSE and Alzheimer's Disease Assessment Scale-11 (ADAS-11) from the files "Mini-Mental State Examination (MMSE) [ADNI1,GO,2,3]" and "Alzheimer's Disease Assessment Scale (ADAS) [ADNI1]", both of which were downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=12&subCategoryId=36).

2.7. Statistical analysis

We initially compared demographic data, MMSE scores, ADAS-11 scores, CSF biomarker levels, H/ICV ratios, and plasma MMP levels between MCI-AD and controls. The Student's *t*-test was used to compare mean values, Mann-Whitney *U* test to compare median values, and chi-square tests to compare categorical values. Shapiro-Wilk test was used to test normality.

We then counted the number of follow-ups for all MCI patients.

We investigated the influence of baseline plasma MMP levels on longitudinal changes in CSF AD biomarkers, hippocampal atrophy, and cognitive function at each annual visit by using a linear mixed regression model. A linear mixed regression analysis, containing fixed and random effects, is widely used in longitudinal studies. The advantages of using this model are that observations within a subject may be correlated and, in addition to estimations of model parameters, between- and within-subject variabilities may be estimated [20]. For example, individuals with one CSF data primarily contribute information to cross-sectional parameters, whereas those with multiple CSF data contribute to cross-sectional and longitudinal parameters (e.g., rates of change over time).

Model selection was performed based on AIC. In the present study, fixed effect variables for dependent variables, including CSF $A\beta_{42}$, CSF t-tau, CSF p-tau, and the H/ICV ratio, were time, age, sex, baseline MMP levels, and interactions between MMP or TIMP levels and time in years from baseline (e.g., MMP-1: High × Time, TIMP-1: Low × Time). Regarding dependent variables, including MMSE and ADAS-11 scores, fixed effect variables were time, age, sex, education attainment, baseline MMP levels, and interactions between MMP or TIMP levels and time in years from baseline. Random intercepts for each subject were employed to account for between- and within-subject correlations. Spearman's rank-order correlations between fixed effect variables included in the models are available in Supporting information (Supplementary Table 1). We performed the F test to evaluate the significance of fixed effects. The significance of differences was set at $p < .05$. All quantitative data were analyzed using the SPSS Version 22.0 statistical package (IBM Corp., Armonk, New York, United States).

3. Results

Demographic and clinical data at each annual follow-up visit are summarized in Table 1. CSF $A\beta_{42}$, t-tau, and p-tau levels and MMSE and ADAS-11 scores were obtained annually for 4 years, and the H/ICV ratio for 3 years. The number of subjects evaluated at each follow-up visit is also shown in Table 1. Fifteen participants were evaluated at baseline only. Participants were followed up on average 1.52 ± 1.14 times (excluding baseline).

3.1. Demographic and clinical findings at baseline

The demographic and clinical data of MCI-AD and controls are summarized in Table 2. No significant differences were observed in age, sex, or education attainment between MCI-AD and controls. MMSE scores and CSF $A\beta_{42}$ were significantly lower in MCI-AD than in controls. ApoE 4, ADAS-11 scores, CSF tau, and p-tau were significantly higher in MCI-AD than in controls. The H/ICV ratio, obtained from 87 out of 95 MCI-AD and 57 out of 58 control subjects, was significantly lower in MCI-AD than in controls. No significant differences were observed in WMH volumes between MCI-AD and controls.

3.2. Baseline MMP and TIMP-1 levels in MCI-AD

As shown in Table 2, no significant differences were observed in baseline plasma MMP and TIMP-1 levels between MCI-AD and controls, except for MMP-10, which was significantly lower in MCI-AD than in controls.

Table 2
Comparison of demographic and clinical data at baseline between MCI-AD patients and control subjects.

	MCI-AD (n = 95)	Control (n = 58)
Demographics		
Age[b]	73.30 (69.60–78.20)	73.15 (71.05–79.08)
Sex (male)	58 (61.1%)	30 (51.7%)
ApoE 4[**]	homo: 20 (21.1%)	homo: 0 (0.0%)
	hetero: 75 (78.9%)	hetero: 5 (8.6%)
	null: 0 (0.0%)	null: 53 (91.4%)
Education[b]	16.00 (14.00–18.00)	16.00 (13.00–18.00)
MMSE[b,*]	27.00 (25.00–28.00)	29.00 (28.00–29.00)
ADAS-11[b,*]	12.00 (9.67–15.67)	6.00 (3.67–8.00)
CSF biomarker		
$A\beta_{42}$ (pg/ml)[b,*]	133.00 (114.00–147.00)	252.50 (229.25–265.25)
t-tau (pg/ml)[b,*]	105.00 (82.00–152.00)	59.50 (48.00–76.25)
p-tau (pg/ml)[b,*]	39.00 (30.00–53.00)	18.55 (14.75–24.00)
MRI findings		
^{Log} H/ICV ratio[a,c,*]	−5.46 ± 0.14	−5.29 ± 0.10
WMH (cm^3)[b,d]	0.29 (0.09–0.66)	0.18 (0.08–0.40)
Plasma MMP		
^{Log} MMP-1 (ng/ml)[b]	0.04 (−0.12–0.20)	0.00 (−0.07–0.15)
MMP-2 (ng/ml)[b]	3.56 (3.48–3.64)	3.57 (3.48–3.66)
MMP-7 (ng/ml)[b]	0.15 (0.04–0.23)	0.18 (0.08–0.26)
MMP-9 (ng/ml)[b]	2.16 (1.98–2.28)	2.12 (1.99–2.28)
^{Log} MMP-10 (ng/ml)[b,*]	−1.36 (−1.48 - -1.25)	−1.28 (−1.39 - -1.17)
TIMP-1 (ng/ml)	2.00 ± 0.09	2.01 ± 0.10

Demographic and clinical data of MCI-AD patients and control subjects at baseline are summarized.
Age, education, MMSE and ADAS-11 scores, $A\beta_{42,}$ t-tau, p-tau, WMH, and plasma MMP levels are shown as median (25% quartile - 75% quartile). H/ICV ratio and TIMP-1 levels are shown as means ± standard deviations. Sex and the ApoE 4 genotype are shown as a number (percentage).
MCI-AD, mild cognitive impairment due to Alzheimer's disease,
[a] Compared by Students' *t*-test.
[b] Compared by Mann-Whitney *U* test.
[*] Significant difference with $p < .05$ (FDR adjusted).
[**] Significant difference with $p < .01$ (FDR adjusted).
[c] The H/ICV ratio was calculated in 87 out of 95 MCI-AD subjects and 53 out of 58 controls.
[d] WMH was obtained in all MCI-AD patients and 57 out of 58 controls.

3.3. Results of the linear mixed regression analysis

Correlations of absolute magnitude exceeding 0.50 were not observed between any pair of selected variables (Supporting information, Supplementary Table 1), indicating no multicollinearity. Therefore, we included all of the selected variables in the linear mixed regression model. The results of the F test to evaluate the significance of the fixed effects are summarized in Table 3.

3.3.1. Baseline plasma MMP and TIMP-1 levels and longitudinal changes in CSF AD biomarkers

As shown in Table 3, no correlations were observed between any baseline levels of MMP and TIMP-1 and longitudinal changes in CSF $A\beta_{42}$, t-tau, and p-tau. The results of the linear mixed regression analysis to estimate longitudinal changes in CSF $A\beta_{42}$, t-tau, and p-tau at each annual visit based on fixed effects are available in Supporting information (Supplementary Tables 2–4).

3.3.2. Baseline MMP and TIMP-1 levels and longitudinal changes in the H/ICV ratio

As shown in Table 3, a correlation was observed between MMP-1, −9, and TIMP-1 levels at baseline and longitudinal changes in hippocampal volumes evaluated by the H/ICV ratio at each annual visit. The results of the linear mixed regression analysis to estimate the H/ICV ratio based on fixed effects are summarized in Supporting information (Supplementary Table 5).

A significant difference was observed in the estimate of the H/ICV ratio between “MMP-1: Middle × Time” and “MMP-1: High × Time”, “MMP-9: Middle × Time” and “MMP-9: High × Time”, “MMP-9: Low × Time” and “MMP-1: High × Time”, and “TIMP-1: Low × Time” and “TIMP-1: High × Time”.

The relationship between baseline MMP-1, −9, and TIMP-1 levels and longitudinal changes in the H/ICV ratio are shown in Fig. 1(a-c).

3.3.3. Baseline MMP and TIMP-1 levels and longitudinal changes in cognitive function

As shown in Table 3, correlations were observed between MMP-1, −9, and − 10 levels at baseline and longitudinal changes in the MMSE score. MMP-9 levels at baseline also correlated with longitudinal changes in the ADAS-11 score.

The results of the linear mixed regression analysis to estimate the MMSE score and ADAS-11 score based on fixed effects are summarized in Supporting information (Supplementary Tables 6–7).

Significant differences were noted in the estimate of the MMSE score between “MMP-1: Middle × Time” and “MMP-1: High × Time”, “MMP-9: Middle × Time” and “MMP-9: High × Time”, and “MMP-9: Low × Time” and “MMP-9: High × Time”. The estimated MMSE score did not significantly differ between “MMP-10: Low × Time” and “MMP-10: High × Time” or “MMP-10: Middle × Time” and “MMP-10: High × Time”.

The relationship between baseline MMP-1 and -9 levels and longitudinal changes in the MMSE score is shown in Fig. 1(d-e).

A significant difference was observed in the estimate of the ADAS-11 score between “MMP-9: Middle × Time” and “MMP-9: High × Time” and between “MMP-9: Low × Time” and “MMP-9: High × Time”. The relationship between baseline MMP-9 levels and longitudinal changes in the ADAS-11 score is shown in Fig. 1(f).

4. Discussion

In the present study, we compared the levels of 5 subtypes of plasma MMPs and TIMP-1 between MCI-AD and controls. We also investigated the effects of baseline plasma MMP and TIMP-1 levels on longitudinal changes in AD-related biomarkers, hippocampal volumes, and cognitive function in MCI-AD using a linear mixed regression model.

We found that plasma MMP-10 levels were significantly lower in MCI-AD than in controls. Declines in both hippocampal volumes evaluated by the H/ICV ratio and cognitive function evaluated by MMSE and ADAS-11 were significantly faster in MCI-AD with high MMP-9 levels than in those with middle and low MMP-9 levels. This is the first study to report the effects of plasma MMP-9 levels on predictions of future neurodegeneration and cognitive decline in MCI-AD.

4.1. Plasma MMP-9 levels and its effect on longitudinal changes in AD biomarkers and cognitive function

No significant differences were observed in MMP-9 levels between MCI-AD and controls. Consistent with the present results, Lim et al. [21] reported no significant difference in plasma MMP-9 levels among AD dementia, MCI, and controls. They retrospectively confirmed that the prevalence of the ApoE 4 genotype and the uptake of amyloid PET were significantly higher in AD dementia and MCI patients than in controls. On the other hand, Lorenzl et al. [10] reported that plasma MMP-9 levels were significantly higher in patients with AD dementia than in those with MCI and controls. They diagnosed AD dementia and MCI using clinical criteria, such as cognitive assessments with the Consortium to Establish a Registry for AD battery and Peterson criteria. Whelan et al. [22] also showed that plasma MMP-9 levels were significantly higher in Aβ-positive and Aβ-negative MCI patients than in Aβ-negative controls. In the present study, MCI-AD were all ApoE 4-positive, as confirmed by low Aβ or high tau in CSF, whereas controls were defined based on normal cognition and may have included both Aβ-positive and Aβ-negative cases. Differences in the recruitment

Table 3
Results of the F test on fixed effects.

Dependent variables	$A\beta_{42}$		t-au		p-tau		H/ ICV ratio		MMSE		ADAS-11	
Parameter	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Constant	16.697	< 0.001	0.283	0.596	2.804	0.098	682.937	< 0.001	55.877	< 0.001	1.966	0.165
Time	0.000	0.998	1.067	0.303	0.186	0.667	19.105	< 0.001	3.423	0.066	6.790	0.010
Age	0.206	0.651	0.711	0.402	0.004	0.948	5.305	0.024	0.027	0.870	0.032	0.860
Sex	0.028	0.868	4.230	0.043	2.930	0.091	3.728	0.057	0.625	0.431	0.304	0.583
Education	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.027	0.869	0.004	0.950
MMP-1	4.552	0.013	0.017	0.983	0.173	0.841	0.099	0.906	0.586	0.558	1.028	0.361
MMP-2	0.783	0.460	1.169	0.316	0.108	0.898	1.451	0.241	1.079	0.343	0.932	0.397
MMP-7	0.734	0.483	0.160	0.852	0.323	0.725	0.137	0.873	0.713	0.492	0.700	0.499
MMP-9	1.014	0.367	0.303	0.739	0.000	1.000	2.316	0.105	0.164	0.849	1.609	0.204
MMP-10	0.371	0.691	0.868	0.424	0.717	0.490	0.860	0.427	0.287	0.751	3.030	0.052
TIMP-1	0.735	0.483	0.086	0.918	0.236	0.791	0.751	0.475	0.440	0.645	0.706	0.496
MMP-1 × Time	0.067	0.935	0.354	0.703	0.290	0.749	11.221	< 0.001*	3.335	0.038*	1.479	0.231
MMP-2 × Time	0.197	0.821	1.943	0.147	0.056	0.946	1.806	0.170	1.154	0.318	1.195	0.306
MMP-7 × Time	0.486	0.616	2.290	0.105	0.311	0.733	1.312	0.275	0.194	0.824	0.012	0.988
MMP-9 × Time	1.184	0.309	0.379	0.685	0.120	0.887	11.938	< 0.001*	13.223	< 0.001*	15.061	< 0.001*
MMP-10 × Time	0.015	0.985	0.103	0.903	0.185	0.831	2.178	0.119	5.930	0.003*	0.899	0.409
TIMP-1 × Time	0.066	0.936	0.008	0.992	2.309	0.103	3.278	0.042*	1.730	0.180	2.468	0.088

The results of the F test to evaluate the significance of fixed effects are summarized.
F, F value; *p*, *p*-value; N/A, not applicable; *, significant difference with $p < .05$*.

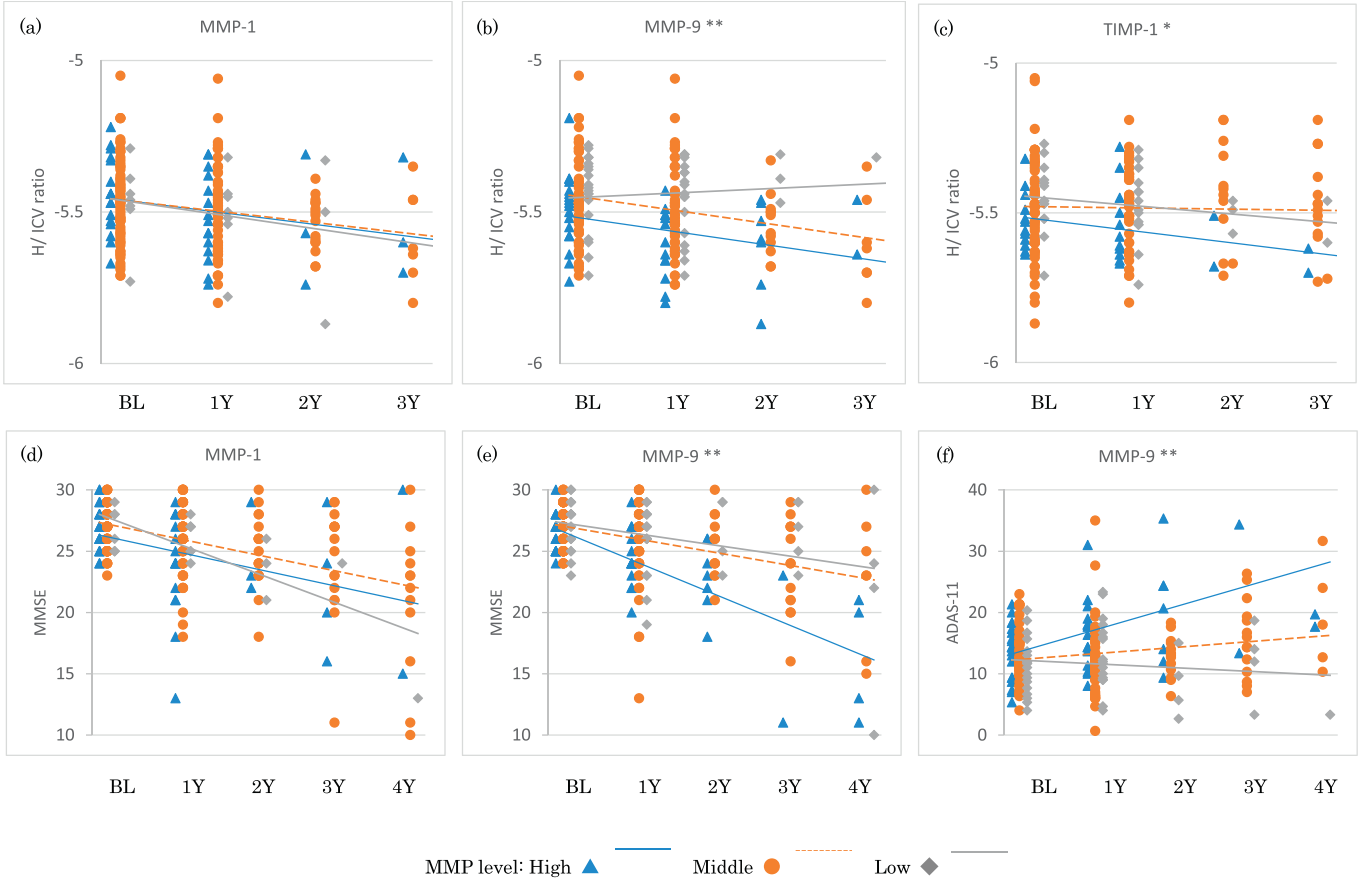

Fig. 1. Relationship between baseline MMP and TIMP-1 levels and longitudinal changes in H/ICV ratios, MMSE scores, and ADAS-11 scores.
Longitudinal changes in the H/ICV ratio, MMSE score, and ADAS-11 score for each baseline MMP and TIMP-1 level are dot-plotted. The approximately straight lines show the slope of longitudinal changes. The vertical axis shows the dependent variable, and the horizontal axis shows the time from baseline. Each MMP level was categorized by dot color and shape.
(a) Relationship between MMP-1 levels and the H/ICV ratio, (b) relationship between MMP-9 levels and the H/ICV ratio, (c) relationship between TIMP-1 levels and the H/ICV ratio, (d) relationship between MMP-1 levels and the MMSE score, (e) relationship between MMP-9 levels and the MMSE score, and (f) relationship between MMP-9 levels and the ADAS-11 score.
BL, baseline; Y, year; *, significant difference between High and Low; **, significant difference between High and Middle and between High and Low.

criteria of MCI and controls may have contributed to the inconsistent results on plasma MMP-9 levels.

In the longitudinal analysis, declines in the H/ICV ratio and MMSE and ADAS-11 scores were significantly faster in MCI-AD subjects with high MMP-9 levels at baseline than in those with middle and low MMP-9 levels at baseline.

Stomrud et al. [15] previously reported that MMP-9 levels were significantly higher in CSF samples from controls with risk markers of AD (such as low Aβ, high tau, and the ApoE4 genotype) than in those from controls without these markers. Py et al. [23] showed that the expression of MMP-9 was significantly stronger in transgenic 5xFAD AD model mice at the prodromal phase of neuronal disturbance than in those at the asymptomatic and symptomatic phases. These findings suggest a relationship between MMP-9 and AD biomarkers, such as Aβ, tau, or ApoE 4, and also that MMP-9 is involved in the pathophysiology of AD at an early stage, even before the development of overt cognitive dysfunction. The results of the present study indicate that plasma MMP-9 is a useful biomarker for detecting MCI-AD at higher risk of converting to dementia.

The mechanisms by which MMP-9 affects neurodegeneration and cognitive decline currently remain unclear. Bruno et al. [24] reported that increases in the activity of MMP-9, which was observed in the postmortem brains of MCI and AD patients, negatively correlated with MMSE scores and Global Cognitive Scores (GCS). Based on previous findings showing that nerve growth factor (NGF) receptors decline in the early stage of AD and correlate with cognitive dysfunction measured by GCS and MMSE and also that MMP-9 inactivates NGF, [25,26] a reduction in mature NGF as a consequence of MMP-9-mediated degradation appears to contribute to the pathogenesis of cognitive deficits in MCI and AD.

However, MMP-9 has been shown to play a beneficial role in learning, memory formation, and neuronal plasticity under normal conditions [27–33]. In human subjects, the doxycycline-mediated blockade MMP-9 activity reduced fear memory [34]. Moreover, the mRNA and protein levels of MMP-9 were lower in patients with depression with lower performance in cognitive tasks than in healthy subjects. Furthermore, within a healthy control group, a positive correlation was observed between the mRNA level of MMP-9 and performance in cognitive tasks [35]. On the other hand, Mizoguchi et al. [36] demonstrated that cognitive impairment induced by an injection of Aβ was alleviated in MMP-9 knockout mice.

Since the tasks and effects of MMPs are complex and the same MMP may exert opposite effects on the brain depending on the underlying conditions, location, and time point at which it is being expressed [8,9], MMP-9 may have unusual functions under the influence of the AD pathology.

Although there was no significant association between MMP-9 level and CSF biomarkers in the present study, some previous studies reported that MMP-9 had preventive effects on progression of Aβ pathology [37,38]. On the other hand, other research groups reported that MMP-9 activity was correlated with increased tau oligomer formation and Braak stage, which evaluates the extent of tau pathology [14,24]. These findings imply that the faster decline of hippocampal volume and cognitive function observed in high MMP-9 subjects in the present study might be more relevant to tau-induced neurodegeneration rather than amyloid-related pathology.

To obtain a more detailed understanding of the pathogenesis of AD, the National Institute on Aging-Alzheimer's Association proposed that MCI needs to be biologically classified based on the presence or absence of the deposition of Aβ, pathological tau, and neurodegeneration [39]. The correlation between MMP-9 levels and amyloid and tau PET findings in MCI-AD needs to be investigated in future studies in order to clarify the role of MMP-9 in the disease progression of AD. Furthermore, since the levels of MMP-9 are elevated in the CSF of healthy elderly subjects with risk markers of AD [15], targeting those who are cognitively normal, but at high risk of developing AD in the future warrants further study.

4.2. Plasma MMP-1 levels and its effect on longitudinal changes in AD biomarkers and cognitive function

MCI-AD with high MMP-1 levels at baseline showed a significantly more rapid decline in the H/ICV ratio and MMSE score than those with middle MMP-1 levels at baseline. However, no significant differences were observed in the estimated H/ICV ratio or MMSE score between MCI-AD with high MMP-1 levels and those with low MMP-1 levels at baseline.

Limited information is currently available on the relationship between MMP-1 and AD [40]. One research group reported the up-regulated expression of MMP-1 in the postmortem brains of AD patients. Since MMP-1 acts on collagen within the vasculature, MMP-1 may be a causative factor for the disruption of the blood-brain barrier, which is a common finding in AD patients. More evidence is required to elucidate the role of MMP-1 in the pathogenesis of AD.

4.3. Plasma MMP-10 levels and its effect on longitudinal changes in AD biomarkers and cognitive function

In the present study, plasma MMP-10 levels at baseline were significantly lower in MCI-AD than in controls (Table 2) and showed a weak correlation with plasma MMP-9 at baseline (Supplementary table 1). Although the results of the F test indicated that plasma MMP-10 levels at baseline correlated with longitudinal changes in MMSE scores, no significant differences were observed in longitudinal changes in MMSE scores among the groups of MCI-AD with different baseline MMP-10 levels.

A previous study comparing 14 AD patients and 14 healthy controls reported that plasma MMP-10 levels remained unchanged in AD patients and there was no correlation between MMP-10 and MMP-9 levels [41].

In the central nervous system, MMP-10 has been implicated in the pathogenesis of multiple sclerosis and brain tumors. However, limited information is currently available on the relationship between MMP-10 levels and the AD pathology. Further studies on MMP-10 in MCI and AD patients are needed to elucidate the role of MMP-10 and its interaction with other MMPs in the pathogenesis of AD.

4.4. Plasma TIMP-1 levels and its effect on longitudinal changes in AD biomarkers and cognitive function

MCI-AD with high TIMP-1 levels at baseline showed a significantly more rapid decline in the H/ICV ratio than those with low TIMP-1 levels at baseline. However, TIMP-1 levels were not associated with longitudinal changes in CSF AD biomarkers or cognitive function.

TIMP-1, which generally forms a complex with MMP-9, is also induced by Aβ [11]. In contrast to the present results, Stomrud et al. reported that the decrease in the TIMP-1/MMP-9 ratio in AD patients was associated with high levels of CSF t-tau, which is a marker of neurodegeneration [15]. More evidence is required to elucidate the exact role of TIMP-1 in the pathogenesis of AD and evaluate the predictive value of plasma TIMP-1 levels to estimate future neurodegeneration.

4.5. Limitations

The present study was missing important values. Fifteen out of 95 patients (15.8%) were only evaluated at baseline. Since the second year, the number of subjects has dropped to around 20. In the linear mixed regression analysis, missing values were not imputed. Therefore, the present results showing a correlation between baseline plasma MMP-9 levels and longitudinal changes in hippocampal atrophy and cognitive function may be false positives. It is also possible that the effects of missing data masked the relationship between other MMP levels at baseline and longitudinal changes in AD biomarkers. However,

difficulties are associated with the long-term follow-up of MCI-AD patients, more than 10% of whom convert to dementia each year. Since ADNI is one of the most extensive multicenter clinical observational studies worldwide, the dataset examined in the present study was large. The results of the present study need be validated in further studies using data obtained from other large cohorts.

In the present study, only 5 subtypes of MMPs and 1 subtype of TIMPs available at the ADNI database are considered. There remains the possibility that MMPs and TIMPs other than MMP-9 or − 10 are involved in the pathogenesis of AD. Therefore, in future studies, it is necessary to include other subtypes of MMP and TIMP family that were not examined in this study.

5. Conclusion

We investigated several types of plasma MMP and TIMP-1 levels in MCI-AD patients confirmed by CSF $A\beta_{42}$ and tau, and examined the longitudinal effects of MMP and TIMP-1 levels on AD-related biomarkers. We revealed that a high plasma MMP-9 level in patients with MCI-AD might enhance neurodegeneration and cognitive decline. To elucidate the role of MMPs and TIMPs in MCI-AD in more detail, the present results need to be validated in further studies using the biomarker-based classification of MCI-AD.

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Declaration of Competing Interest

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2020.116989.

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