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Original Research

Plasma MMP-9 Levels as the Future Risk of Conversion to Dementia in ApoE4-Positive MCI Patients: Investigation Based on the Alzheimer's Disease Neuroimaging Initiative Database

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Abstract

BACKGROUND: Matrix metalloproteinase 9 (MMP-9) has been reported to be correlated with declines in hippocampal volume and cognitive function in ApoE4-positive MCI patients.

OBJECTIVES: The present study was aimed to investigate the effects of plasma matrix MMP-9 on the conversion risk between mild cognitive impairment (MCI) patients with and without ApoE4.

DESIGN AND SETTING: Retrospective observational study using the data extracted from the Alzheimer's Disease Neuroimaging Initiative database.

PARTICIPANTS: We included 211 ApoE4-positive MCI subjects (ApoE4+ MCI) and 184 ApoE4-negative MCI subjects (ApoE4- MCI).

MEASUREMENTS: We obtained demographic and data including plasma MMP-9 levels at baseline and longitudinal changes in Clinical Dementia Rating (CDR) up to 15 years. We compared conversion rates between ApoE4+ MCI and ApoE4- MCI by the Log-rank test and calculated the hazard ratio (HR) for covariates including age, sex, educational attainment, drinking and smoking histories, medications, and plasma MMP-9 levels using a multiple Cox regression analysis of ApoE4+ MCI and ApoE4- MCI.

RESULTS: No significant differences were observed in baseline plasma MMP-9 levels between ApoE4+ MCI and ApoE4- MCI. High plasma MMP-9 levels increased the conversion risk significantly more than low plasma MMP-9 levels (HR, 2.46 [95% CI, 1.31-4.48]) and middle plasma MMP-9 levels (HR, 1.67 [95% CI, 1.04-2.65]) in ApoE4+ MCI, but not in ApoE4- MCI.

CONCLUSION: Plasma MMP-9 would be the risk of the future conversion to dementia in ApoE4+ MCI.

Key words: Alzheimer's disease, matrix metalloproteinase 9, mild cognitive impairment, dementia.

Introduction

Mild cognitive impairment (MCI) is an intermediate state between normal cognition and dementia 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. 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 (1).

Alzheimer's disease (AD) is the most predominant cause of MCI and dementia (2). The pathological hallmark of AD is the deposition of amyloid-β (Aβ), neurofibrillary tangles induced by phosphorylated tau (p-tau), and neuronal loss. These pathological changes develop many years before patients manifest subtle cognitive changes (3).

ApoE4 is the most firmly established genetic risk factor for late-onset AD and has been reported to increase the risk of developing AD dementia by 2-12 fold (4, 5). Accumulating evidence has shown that ApoE4 promotes Aβ seeding and aggregation in oligomers and fibrils and reduces its clearance from interstitial fluid, potentially leading to the deposition of Aβ, and also results in tau-induced neurodegeneration (6). Therefore, MCI patients carrying ApoE4 are a high-risk group for the development of AD dementia, and are important targets for early diagnosis and intervention.

No new drug had been approved for the treatment of AD for more than 20 years until Aducanumab was approved this year. With expectations for disease-modifying drugs, the importance of searching biomarkers that identify patients at a higher risk of developing dementia at the prodromal stage and new therapeutic targets is increasing (7, 8). To target this issue, 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 (9).

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Matrix metalloproteinases (MMPs) are calcium-dependent zinc-containing endopeptidases, several of which are expressed in neurons and glial cells. Based on increasing evidence indicating the important, but complex, roles that MMPs play in the regulation of diverse biological processes under normal and pathological conditions, including embryonic development, inflammatory diseases, cancer, and neurodegenerative diseases, including AD, they are attracting attention as novel AD-related biomarkers (10, 11).

MMP-9 levels have been reported to be elevated in cerebrospinal fluid (CSF) samples from cognitively normal subjects with risk markers of AD (such as low Aβ, high tau, and the ApoE4 genotype) than in those from controls without these markers (12). An animal experiment by Py et al. (13) demonstrated 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 ApoE4, and also that MMP-9 is involved in the pathophysiology of AD at an early stage, even before the development of overt cognitive dysfunction.

We recently investigated patients with ApoE-4-positive MCI due to AD, whose diagnosis of AD was based on a decrease in CSF Aβ42 and/or increase in CSF p-tau (14). The findings obtained showed that high plasma MMP-9 levels were related to significantly faster declines in the hippocampal volumes and faster deterioration of the scores of Mini-Mental State Exam (MMSE) and Alzheimer's Disease Assessment Scale-11 (ADAS-11) of these patients. However, it currently remains unclear whether plasma MMP-9 contributes to clinically significant changes, namely long-term risk of converting to dementia. And the utility of MMP-9 as an AD-related biomarker in MCI patients without ApoE4 has not been evaluated. Therefore, we herein investigated the effects of plasma MMP-9 levels on the conversion risk evaluated on clinical dementia rating (CDR) over up to 15 years of observation between MCI patients with and without ApoE4 using ADNI data.

Methods

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 and led by the 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.

Patients and samples

The diagnosis of MCI was based on subjective or objective memory declines evaluated by education-adjusted scores on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale-Revised. The MMSE score was between 24 and 30, and the Clinical Dementia Rating (CDR) was 0.5 (15).

We confirmed the presence or absence of the ApoE4 allele from the file "ApoE - Results [ADNI1,GO,2,3]", which was downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=11&subCategoryId=33).

In the present study, we included 211 ApoE4-positive MCI subjects (ApoE4+ MCI) and 184 ApoE4-negative MCI subjects (ApoE4- MCI).

To determine the reference levels of plasma MMP-9, we also obtained the data of 52 cognitively normal (CN) subjects whose plasma MMP-9 levels were being examined and registered in the ADNI website. The diagnosis of CN was based on subjective or objective memory declines evaluated by the above-mentioned criteria, the CDR was 0, and ApoE4 was negative.

We obtained demographic and clinical data including plasma MMP-9 levels at baseline and longitudinal changes in CDR up to 15 years. All data used in the present study were downloaded from the ADNI website on 21 June 2021.

Demographic data

We obtained data including age, sex, race, and educational attainment from the file "Key ADNI tables merged into one table", which was downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=16&subCategoryId=43). We also obtained drinking and smoking histories from the file "Medical History [ADNI1,GO,2]" and data on medication that were being administered to subjects at baseline from the file "Medical History [ADNI1,GO,2]", both of which were downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=15&subCategoryId=39). Regarding medication histories, data on 17 drugs taken by more than 5% of MCI subjects were extracted.

MMP-9

We obtained plasma MMP-9 levels 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). This biomarker was 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.

Since the normal range of plasma MMP-9 levels has not been established, we calculated the mean values and standard deviations (SD) of MMP-9 levels in 52 cognitively normal and ApoE4-negative subjects registered in the ADNI website. We then defined baseline MMP-9 levels more than the mean +1SD (2.368 +0.186) as high, less than the mean -1SD (2.368 –0.186) as low, and the range in between as middle.

CSF Aβ42, t-tau, and p-tau

We obtained CSF levels of Aβ42, t-tau, and p-tau 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 Aβ42, 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.

MRI data

Data on bilateral hippocampal and total intracranial volumes (TIV) 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 (HV) were evaluated on MRI using a commercially available high dimensional brain mapping tool (Medtronic Surgical Navigation Technologies, Louisville, Colorado, United States). Details are available in the file "UCSF - SNT Hippocampal Volumes Methods (PDF)" on the website described above. To evaluate hippocampal atrophy, we compared HV, which was calculated as right plus left hippocampal volumes and adjusted by TIV (16).

White matter hyperintensities (WMH), which reflect the vascular pathologies, are known to contribute to the development of AD, and has recently been reported to be associated with the ApoE4 status (17). To assess the extent of vascular pathologies, 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. (18). Details are available in the file "ADNI1_Methods_UCD_WMH_Volumes_Methods" on the website described above.

Cognitive assessment

To evaluate cognitive function, we obtained the scores for MMSE and CDR from the files "Mini-Mental State Examination (MMSE) [ADNI1,GO,2,3]" and "Clinical Dementia Rating Scale (CDR) [ADNI1,GO,2,3]", both of which were downloaded from the ADNI website (https://ida.loni.usc.edu/pages/access/studyData.jsp?categoryId=12&subCategoryId=36). We defined conversion when the CDR scores of subjects consistently reached 1 or greater during the observation period.

Statistical analysis

We initially compared the demographic data, MMSE scores, CSF biomarker levels, HV, WMH, plasma MMP-9 levels, and conversion rates between ApoE4+ MCI and ApoE4- MCI. The Student's t-test was used to compare mean values, the Mann-Whitney U test to compare median values, and the chi-squared test to compare categorical values. The Log-rank test was used to compare conversion rates.

To investigate the effects of plasma MMP-9 levels on the conversion risk in ApoE4+ and ApoE4- MCI subjects, we divided subjects into 3 groups according to plasma MMP-9 levels (high, middle, and low), and compared conversion rates in each group. We calculated the hazard ratio (HR) for covariates including age, sex, educational attainment, drinking and smoking histories, usage of NSAIDs and cholinesterase inhibitors (ChEI), and baseline plasma MMP-9 levels using a multiple Cox regression analysis of ApoE4+ MCI and ApoE4- MCI.

The significance of differences was set at $p < 0.05$. All quantitative data were analyzed using JMP® Pro 15.0.0 (SAS Institute Inc).

Results

Demographic and clinical findings at baseline

The demographic and clinical data of ApoE4+ MCI and ApoE4- MCI are summarized in Table 1. No significant differences were observed in sex, race, educational attainment, MMSE scores, drinking and smoking histories, plasma MMP-9 levels, or WMH volumes between ApoE4+ MCI and ApoE4-MCI. Furthermore, no significant differences were noted in the percentage of subjects taking medications, except for NSAIDs, HMG CoA reductase inhibitors, and ChEI. Age, CSF tau, and p-tau were significantly higher in ApoE4+ MCI than in ApoE4- MCI. CSF Aβ42 and HV were significantly lower in ApoE4+ MCI than in ApoE4- MCI.

Table 1. Comparison of demographic and clinical data at baseline between ApoE4+ MCI and ApoE4- MCI

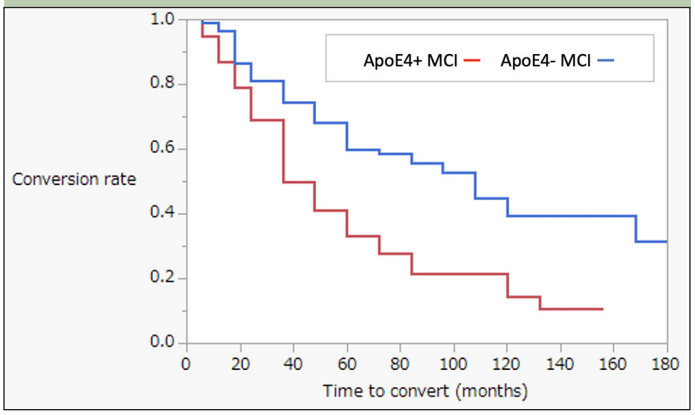
	ApoE4+ MCI (n = 211)	ApoE4- MCI (n = 184)
Demographics		
Age *	73.83 ± 6.72	75.72 ± 7.98
Sex (male)	133 (63.0%)	122 (66.3%)
Race (Caucasian)	198 (93.8%)	171 (92.9%)
BMI	25.85 ± 3.79	26.31 ± 4.05
Education	15.64 ± 2.99	15.67 ± 3.11
MMSE	26.93 ± 1.78	27.13 ± 1.76
Alcohol abuse	9 (4.27%)	7 (3.80%)
Smoking	114 (54.03%)	118 (64.13%)
Medications		
NSAIDs **	115 (54.5%)	124 (67.4%)
Acetaminophen	17 (8.1%)	21 (11.4%)
Thiazides	40 (19.0%)	30 (16.3%)
β-blockers	43 (20.4%)	41 (22.3%)
Dihydropyridine derivatives	22 (10.4%)	21 (11.4%)
ACE inhibitors	34 (16.1%)	39 (21.1%)
Angiotensin II antagonists	24 (11.4%)	24 (13.0%)
Vasodilator agents	52 (24.6%)	39 (21.2%)
Other cardiac preparations	23 (10.9%)	18 (9.8%)
HMG CoA reductase inhibitors **	117 (55.5%)	71 (38.6%)
Fish oils	36 (17.1%)	28 (15.2%)
Other lipid modifying agents	17 (8.1%)	9 (4.9%)
Thyroid hormone receptor agonists	23 (10.9%)	24 (13.0%)
Muscle relaxants	11 (5.2%)	9 (4.9%)
Anti-anxiety agents	12 (5.7%)	13 (7.1%)
Anti-depressants	65 (30.8%)	42 (22.8%)
Anti-cholinesterases **	110 (52.1%)	63 (34.2%)
Plasma MMP-9 (ng/ml)	2.35 ± 0.23	2.32 ± 0.20
CSF biomarker¶		
$A\beta_{42}$ (pg/ml) **	141.72 ± 43.25	187.50 ± 59.30
t-tau (pg/ml) **	115.09 ± 68.54	84.35 ± 48.35
p-tau (pg/ml) **	40.31 ± 18.13	29.71 ± 16.26
MRI findings		
HV (mm^3) †**	6334.42 ± 987.65	6612.57 ± 1105.17
WMH (cm^3) ‡	0.74 ± 2.28	1.11 ± 3.24

Demographic and clinical data of ApoE4+ MCI and ApoE4- MCI at baseline are summarized. Age, BMI, education, MMSE scores, Aβ42, t-tau, p-tau, HV, WMH, and plasma MMP-9 levels are shown as means ± standard deviations. Sex, race, the presence or absence of drinking and smoking histories, and the presence or absence of specific medications are shown as a number (percentage). *, significant difference with $p < 0.05$; **, significant difference with $p < 0.01$. ¶, CSF biomarkers (Aβ42, t-tau, and p-tau) were obtained from 106/211 (50.2%) ApoE4+ MCI and 92/184 (50.0%) ApoE4- MCI subjects. †, HV was calculated in 206/211 (97.6%) ApoE4+MCI subjects and 180/184 (97.8%) ApoE4- MCI subjects, and adjusted by total intracranial volume for comparison. ‡, WMH was obtained in all ApoE4+ MCI subjects and 180/184 (97.8%) ApoE4- MCI subjects.

Conversion rates in ApoE4+ and ApoE4- MCI

Among ApoE4+ MCI and ApoE4- MCI, 118 (55.9%) and 64 (34.8%) subjects, respectively, converted to dementia ($p < 0.01$). As shown in Figure 1, the average time to conversion was significantly shorter in ApoE4+ MCI (57.6 months) than in ApoE4- MCI (101.6 months) ($p < 0.01$).

Figure 1. Comparison of conversion rates between ApoE4+ MCI and ApoE4- MCI



Conversion rates of ApoE4+ and ApoE4- MCI by plasma MMP-9 levels

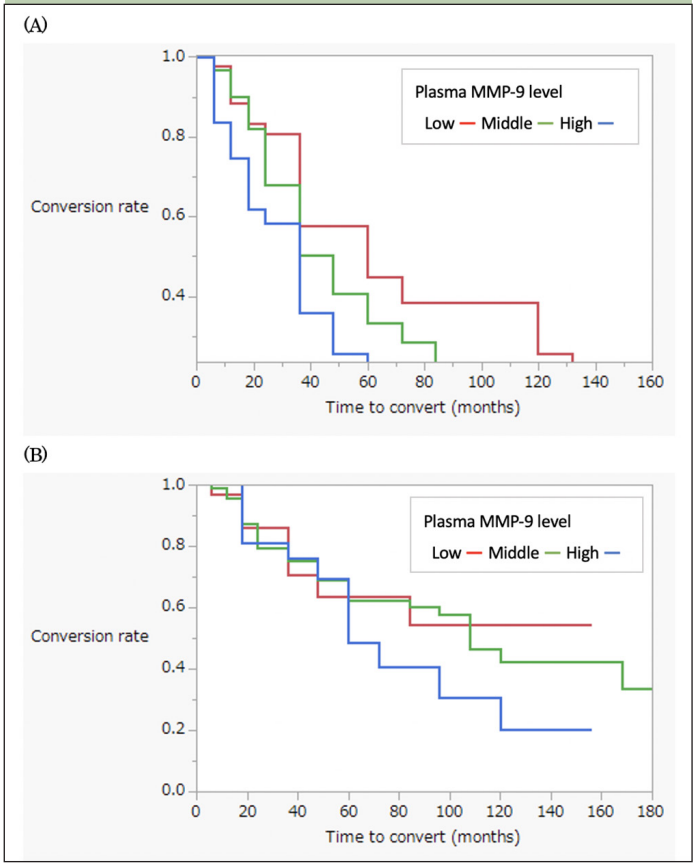
Conversion rates were significantly different among the MMP-9 high, middle, and low groups in ApoE4+ MCI (Figure 2A), but not in ApoE4- MCI (Figure 2B). Higher plasma MMP-9 levels correlated with higher conversion rates in ApoE4+ MCI.

The results of the Cox regression analysis are summarized in Table 2. Sex (female) (HR, 1.69 [95% CI, 1.08-2.65]) and high plasma MMP-9 levels (vs middle MMP-9: HR, 1.67 [95% CI, 1.04-2.65], vs low MMP-9: HR, 2.46 [95% CI, 1.31-4.48]) significantly increased the conversion risk in ApoE4+ MCI. On the other hand, plasma MMP-9 levels did not correlate with an increased risk of conversion in ApoE4- MCI. ChEI (HR, 1.74 [95% CI, 1.04-2.90]) significantly increased the conversion risk in ApoE4- MCI.

Discussion

In the present study, we initially compared demographic and biological data, including plasma MMP-9 levels and medications, between 211 ApoE4+ MCI and 184 ApoE4- MCI. We then compared the effects of plasma MMP-9 levels on conversion rates over up to 15 years of observation between ApoE4+ MCI and ApoE4- MCI. Although no significant differences were observed in baseline plasma MMP-9 levels between ApoE4+ MCI and ApoE4- MCI, high plasma MMP-9 levels significantly increased the conversion risk in ApoE4+ MCI, but not in ApoE4- MCI.

Figure 2. Comparison of conversion rates by plasma MMP-9 levels. Comparison of conversion rates by plasma MMP-9 levels in (A) ApoE4+ MCI and (B) ApoE4- MCI



Plasma MMP-9 levels in ApoE4+ MCI and ApoE4- MCI

No significant differences were observed in MMP-9 levels between ApoE4+ MCI and ApoE4- MCI. Consistent with the present results, Whelan et al. reported no significant differences in plasma MMP-9 levels between Aβ-positive and Aβ-negative MCI patients (19). On the other hand, Ringland et al. showed that MMP-9 levels in cerebrovascular samples were significantly higher in ApoE4-positive humans and mice than in ApoE4-negative controls (20). Previous findings on MMP-9 levels by the disease stage of AD are also inconsistent (14, 21, 22).

As reported by Ringland et al. and other research groups, ApoE4 has a number of functions for MMP-9. It has been shown to increase the secretion of MMP-9 from brain endothelial cells and activates pro-MMP-9. On the other hand, ApoE4 dose-dependently inhibited the function of MMP-9 (11, 20, 23). Slight differences in recruitment criteria and/or the disease stages of MCI subjects may have contributed to the inconsistencies observed in previous findings on plasma MMP-9 levels. Demographic and biological factors affecting plasma MMP-9 levels need to be examined in future studies.

Higher MMP-9 levels correlated with higher conversion rates in ApoE4+ MCI

Higher plasma MMP-9 levels correlated with higher conversion rates in ApoE4+ MCI, but not in ApoE4- MCI (Figure 2A, B). Among ApoE4+ MCI, high plasma MMP-9 levels increased the conversion risk significantly more than low plasma MMP-9 levels (HR, 2.46 [95% CI, 1.31-4.48]) and middle plasma MMP-9 levels (HR, 1.67 [95% CI, 1.04-2.65]). On the other hand, plasma MMP-9 levels did not correlate with conversion rates in ApoE4- MCI.

In our previous study (14), we investigated the effects of several MMPs on longitudinal changes in AD-related biomarkers in CSF, brain atrophy, and cognitive function evaluated on MMSE and ADAS-11 in patients with MCI due to AD (MCI-AD), who were confirmed to have ApoE4 and low Aβ42 and/or high phosphorylated-tau (p-tau) in CSF. Patients with high plasma MMP-9 levels showed significantly faster declines in hippocampal volumes and cognitive function. On the other hand, no relationship was observed between plasma MMP-9 levels and longitudinal changes in CSF Aβ42 and tau.

Montagne et al. (24) reported that blood-brain barrier (BBB) damage in the hippocampus and parahippocampal gyrus was significantly more severe in ApoE4 carriers than in ApoE4 non-carriers, even from cognitively normal stages, and significantly predicted future cognitive declines in ApoE4 carriers, but not in ApoE4 non-carriers. Furthermore, they verified whether BBB disruption in ApoE4 carriers was downstream of amyloid and tau accumulation by analyzing amyloid and tau PET findings to show that BBB breakdown started from the medial temporal lobe independently of AD pathologies and correlated with the activation of the CypA-MMP-9 pathway. The CypA-MMP-9 pathway was previously demonstrated to be activated by ApoE4, which lead to the breakdown of BBB and, as a result, the neuronal uptake of multiple blood-derived neurotoxic proteins and microvascular and cerebral blood flow reductions in the pericytes of mice, and these changes preceded neuronal and synaptic dysfunction and may initiate neurodegenerative changes (25). Consistent with previous findings (14, 24), the present study found no correlation between plasma MMP-9 levels and AD pathologies (Supplementary Table 1).

Collectively, previous findings and the present results implicate BBB dysfunction via the CypA-MMP-9 pathway activated by ApoE4 in the promotion of neurodegeneration and clinical conversion to dementia independently of AD pathologies. This supports that plasma MMP-9 is a useful biomarker to predict the future risk of conversion for ApoE4+ MCI and detect targets for early interventions at the prodromal phase.

As shown in Figure 2, it is noteworthy that not only in ApoE4+ but also in ApoE4-, the conversion ratio tends to be high after 60 months (much later than ApoE4+ MCI) in the subjects with high MMP-9 levels. From

Table 2. Results of the Cox regression analysis

	ApoE4+ MCI			ApoE4- MCI		
	HR	95% CI	p	HR	95% CI	p
Age	2.49	0.95-6.55	0.06	1.03	0.99-1.06	0.14
Sex (Female/Male)	1.69	1.08-2.65	0.02	1.53	0.92-2.56	0.10
Education	1.13	0.49-2.69	0.77	1.07	0.98-1.17	0.16
Alcohol abuse	1.21	0.37-4.02	0.75	0.35	0.05-2.62	0.32
Smoking	1.15	0.77-1.71	0.50	1.34	0.78-2.29	0.29
NSAIDs	1.04	0.71-1.53	0.82	1.24	0.72-2.16	0.44
ChEI	1.41	0.96-2.08	0.08	1.74	1.04-2.90	0.03
MMP-9						
High/Low	2.43	1.31-4.48	<0.01	1.37	0.55-3.37	0.50
High/Middle	1.67	1.04-2.65	0.03	1.63	0.84-3.16	0.15

The results of the Cox regression analysis are summarized; HR, hazard ratio; ChEI, cholinesterase inhibitors.

these results, we derived the following hypotheses. (1) MMP-9 values have thresholds that begin to promote neurodegeneration, and (2) ApoE4-related factors regulate the timing at which MMP-9 begins to promote neurodegeneration (in other words, in ApoE4 carrier, MMP-9 begins to drive the neurodegeneration earlier than ApoE4 non-carriers). These are consistent with the results that no difference was found in baseline MMP-9 values between ApoE4+ MCI and ApoE4- MCI. They also raise the question whether plasma MMP-9 could be a "disease driver", which means that it may be a therapeutic target of neurodegenerative dementia. Future research will be needed to clarify (1) demographic or genetic factors that elevate MMP-9 in the pre-dementia stage, and (2) factors affecting the conversion to dementia through CypA-MMP-9 pathway.

ChEI use was associated with a higher conversion risk in ApoE- MCI

Among ApoE4- MCI, the use of ChEI significantly increased the conversion risk (HR, 1.74 [95% CI, 1.04-2.90]). Previous studies on the administration of ChEI to patients with MCI did not obtain convincing findings (26–31). The relationship between the ApoE genotype and responses to ChEI has been examined. Bizzaro et al. reported that ApoE4 was a factor associated with better responsiveness to treatment using ChEI (32). However, other researchers reported contrasting findings (33, 34). ChEI have not yet been shown to exacerbate cognitive function in ApoE4 non-carriers; however, further studies are warranted to clarify the responses of MCI with non-AD pathologies to ChEI.

Strengths and limitations

The strength of the present study is that a large number of subjects including both ApoE4+ and ApoE4- MCI patients were observed for a long period up to 15 years. As a result, we have shown that measuring plasma MMP-9 levels is useful in predicting the clinically significant outcome, conversion to dementia. These results also indicate that MMP-9 may be involved in driving neurodegeneration of ApoE4 carriers, and thus sheds light on the possibility that MMP-9 might be a new therapeutic target.

As limitations of the present study, the relationship between the activities of the CypA-MMP-9 pathway and the extent of the AD pathology and BBB disruption was not investigated. Therefore, it was not possible to verify whether plasma MMP-9 is really acting as a "disease driver" of dementia only from this study. However, it is very difficult to collect subjects, such as ApoE4-negative patients with the AD pathology or ApoE4-positive patients without the AD pathology, from ADNI data. Basic research using AD model mice and further clinical trials are required in the future to investigate whether the inhibition of MMP-9 in ApoE4 carriers is an effective therapeutic strategy for preventing BBB breakdown and, as a result, cognitive decline. Moreover, data on parameters related to BBB permeability (e.g., the IgG index and Q albumin) have not been collected and need to be investigated in future studies.

In conclusion, plasma MMP-9 would be the long-term risk of conversion of ApoE4+ MCI patients. Further studies are needed to verify whether MMP-9 promotes neurodegeneration in patients with ApoE4+ MCI and is also useful as a therapeutic target.

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Conflict of interest: None of the authors have conflicts of interest.

Ethical standard: The present study was approved by the Institutional Ethics Committee of Yokohama City University Hospital (B190900010).

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