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Association of White Matter Hyperintensity Progression with Cognitive Decline in Patients with Amnestic Mild Cognitive Impairment

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Abstract.
Background: White matter hyperintensities (WMH) on MRI have been reported to increase the risk of conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD). However, effects of the progression of WMH on the cognition of patients with MCI remains unclear to date.
Objective: To investigate the association between WMH progression and cognitive decline in amnestic MCI patients.
Methods: Thirty-eight subjects with amnestic MCI were analyzed prospectively every year for 2 years. Fourteen MCI subjects dropped out on the final visit, and therefore 24 subjects with MCI were analyzed for the entire duration. The volumes of periventricular hyperintensities (PVH) and deep WMH (DWMH) were measured on T2 FLAIR using the 3D-slicer. The associations between PVH/DWMH progression and cognitive decline were investigated.
Results: An increase in DWMH volume significantly correlated with changes in Mini-Mental State Examination and category verbal fluency scores, whereas an increase in PVH volume did not correlate with changes in any item.
Conclusion: DWMH progression was closely associated with a decline in frontal lobe function and semantic memory, suggesting that WMH progression might affect some AD pathophysiologies in amnestic MCI patients.

Keywords: Deep white matter hyperintensities, mild cognitive impairment, periventricular hyperintensities

INTRODUCTION

In recent years, the contribution of white matter abnormalities to cognitive dysfunction has been increasingly gaining interest. White matter hyperintensities (WMH) on magnetic resonance imaging (MRI) have been increasingly recognized to be a risk factor for the conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD). Several recent studies have reported the associations of WMH, such as periventricular and parietal white matter regions, with the risk of future development of AD [1–4], although MCI is a heterogeneous disorder with a variety of clinical outcomes (amnestic MCI, nonamnestic MCI, etc.). We recently reported the association of periventricular hyperintensities (PVH)

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volume with frontal lobe dysfunction and serum cystatin C (CysC) level in amnestic MCI patients [5]. However, we did not assess the association of an increase in WMH volume with cognitive decline. There have only been a few longitudinal studies analyzing the association between an increase in WMH volume and cognitive decline [3, 6]. Therefore, in this study, we investigated the association between WMH progression and cognitive decline, blood levels of various molecules, and the presence of vascular risk factors in MCI patients. Furthermore, we investigated whether the presence of vascular risk factors, such as hypertension (HT), dyslipidemia (DL), and diabetes mellitus (DM), and WMH progression is associated with the conversion from MCI to AD during a 2-year period by logistic regression analysis.

MATERIALS AND METHODS

Subjects

Outpatients (aged > 60 years and < 90 years) who were enrolled at the memory clinic or outpatient clinic of Tokyo Medical University were prospectively recruited between 2015 and 2018. Written informed consent was obtained from all subjects before the study. The study design was approved by the ethics review board of Tokyo Medical University. Thirty-eight subjects with amnestic MCI were prospectively analyzed every year for 2 years. Fourteen MCI subjects dropped out on the final visit, and therefore 24 subjects with amnestic MCI were analyzed for the entire duration. Every year, all patients underwent detailed general physical, neurological, and psychiatric examinations and extensive laboratory tests, including MRI and single-photon emission computed tomography (SPECT). SPECT images were analyzed using Neurological Statistical Image Analysis software, which are three-dimensional stereotactic surface projections developed by Minoshima et al. for evaluating the spatial distribution of abnormal perfusion, to exclude other potential causes of dementia, including dementia with Lewy bodies, frontotemporal lobar degeneration, etc. [7] A decrease in regional cerebral blood flow (rCBF) in the parietotemporal association cortex on SPECT has been recognized as a diagnostic pattern of prodromal AD [8].

The subjects were diagnosed as having MCI due to AD according to the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria [9] and their Mini-Mental State Examination (MMSE) scores were 24 and above. Subjects were excluded from the study if they did not show any reduction in rCBF in the parietotemporal association areas. Subjects were also excluded if they had territorial or cortical infarctions, or if they showed severe white matter disease in which both PVH and deep WMH (DWMH) were grade 3 on the Fazekas scale [10]. During the follow-up period, if the subjects met the criteria of probable AD according to the NIA-AA criteria [11], we defined the case as a conversion from MCI to AD. We excluded from the study one subject who was diagnosed as having probable dementia with Lewy bodies using additional neuroimaging techniques, such as ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane dopamine transporter single-photon emission computed tomography and ^{123}I-metaiodobenzyl-guanidine myocardial scintigraphy, and one subject who had a stroke during the follow-up period. Cognitive functions and depressive symptoms were assessed by various neuropsychological tests, such as the MMSE, Frontal Assessment Battery, Trail Making Test (TMT)-A/B, Wechsler Memory Scale-Revised-Logical Memory I, category verbal fluency (VF), and Geriatric Depression Scale-15.

Levels of serum CysC, 25-hydroxyvitamin D, and homocysteine were measured using colloidal gold agglutination, radioimmunoassay, and high-performance liquid chromatography, respectively. The levels of other cerebrovascular risk factors, including total cholesterol, low-density lipoprotein cholesterol, glucose, hemoglobin A1c, vitamin B12, blood urea nitrogen, creatinine, estimated glomerular filtration rate, aspartate transaminase, and alanine aminotransferase were also measured.

Magnetic resonance imaging and volumetric analysis

Brain MRI scans (3D-T1 and T2 fluid-attenuated inversion recovery (FLAIR) imaging) were performed using a 1.5-Tesla scanner (Magnetom; Siemens Medical Systems, Erlangen, Germany) together with T1 gradient echo images and FLAIR sequences. FLAIR sequences were obtained using the following parameters: TR 9,000 ms; TE 104 ms; slice thickness 4.0 mm; gap 0.0 mm. For quantitative analysis of WMH volumes, FLAIR images were registered. WMH was defined as the presence of hyperintensity in the white matter area. PVH and DWMH lesions were outlined by a neurologist, using the semiautomated freeware 3D-slicer, which is a freely available, open-source software package for visualization,

registration, segmentation, and quantification of medical data (http://www.slicer.org) [12]. Furthermore, intracranial volumes (ICVs) were calculated using VBM toolbox, which was implemented in Statistical Parametric Mapping software (SPM8, Wellcome Institute of Neurology, University College London, UK), and the ratios (%) of PVH and DWMH volumes to ICV were used for rating white matter abnormalities. Correlations between changes in the ratio (%) of PVH/DWMH volumes to ICV and cognitive decline, blood levels of molecules, and the presence of vascular risk factors, such as HT, DL, and DM were investigated.

Statistical analysis

Demographic and laboratory data were calculated as means ± SD. Statistical analyses (the Student *t*-test, Pearson test, linear multiple regression, and logistic regression analysis) were performed using SPSS 26.0 software.

RESULTS

A summary of the characteristics of the MCI patients who were initially enrolled ($n = 38$) and those who were followed for 2 years ($n = 24$) is shown in Table 1. There were no significant differences in any of the items between the entire MCI group ($n = 38$) and those who were followed for 2 years ($n = 24$). Table 2 shows a comparison of the clinical characteristics, blood biochemistry data, and WMH volume ratios of the 24 patients between the initial and the final visit. In Table 2, the paired *t*-test showed that both PVH and DWMH volumes of the MCI patients on the final visit were significantly greater than those on the initial visit, whereas both neuropsychological test scores and CysC levels were not significantly different between the visits. Nine out of the 38 MCI subjects who were initially enrolled and 4 out of the 24 subjects who were followed for 2 years eventually converted to AD within 2 years, and the annual conversion rate to AD was approximately 12% and 8.5%, respectively. There were no MCI subjects who eventually developed vascular dementia during the follow-up period. Table 3 shows the initial characteristics and the changes in PVH and DWMH volume ratios of the MCI patients who eventually converted to AD and those who did not. We found that CysC level was significantly higher in the converters than in the non-converters, whereas there were no significant differences between the two groups regarding the initial and changes in both PVH and DWMH volume ratios during the 2 years. Although we do not show the results of logistic regression analysis, we did not find any associations of the presence of vascular risk factors, such as HT, DL, and DM, and PVH/DWMH progression with the conversion to AD. Table 4 shows that initial DWMH volume significantly correlated with changes in TMT-B score and CysC level, although initial PVH volume did not correlate with any of the items. Changes in DWMH volume significantly correlated with changes in MMSE and VF (category) scores by Pearson's analysis, whereas changes in PVH volume did not correlate with changes in any of the items. We found that changes in both PVH and DWMH volumes did not correlate with the presence of vascular risk factors or change in CysC levels by multiple linear regression analysis (data not shown).

Table 1
Demographic, clinical, blood biochemistry, and MRI characteristics of patients with MCI on their initial visit

	All MCI ($n = 38$)	Followed-up MCI ($n = 24$)
Sex (M/F)	13/25	9/15
Age	77.4 ± 5.6	76.7 ± 5.8
Education (y)	13.4 ± 2.3	13.5 ± 2.6
MMSE	27.3 ± 1.6	27.2 ± 1.6
FAB	13.0 ± 2.2	12.9 ± 2.3
TMT-A (s)	52.7 ± 20.8	50.3 ± 20.0
TMT-B (s)	156.9 ± 80.8	155.4 ± 83.4
WMS-R-Logical Memory (immediate)	13.6 ± 6.7	14.4 ± 7.0
VF (category)	14.5 ± 3.4	14.5 ± 3.5
GDS-15	3.8 ± 3.1	4.2 ± 3.7
Cystatin C (mg/L)	1.0 ± 0.2	1.0 ± 0.2
25(OH)VitD (ng/ml)	25.0 ± 11.9	25.7 ± 13.4
Homocysteine (nmoL/mL)	10.5 ± 3.5	10.5 ± 3.1
PVH volume (mm^3)	8,905 ± 7,678	10,450 ± 9,087
DWMH volume (mm^3)	4,529 ± 9,223	5,839 ± 11,495
PVH volume ratio (%)	0.70 ± 0.60	0.76 ± 0.66
DWMH volume ratio (%)	0.30 ± 0.70	0.43 ± 0.85
Hypertension, n (%)	21 (55)	12 (50)
Diabetes mellitus, n (%)	7 (18)	4 (17)
Dyslipidemia, n (%)	20 (53)	10 (42)
Coronary artery disease, n (%)	3 (8)	1 (4)
Antihypertensives, n (%)	20 (53)	12 (50)
Antidiabetic medications, n (%)	3 (8)	2 (8)
Statins, n (%)	11 (29)	5 (21)

MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; TMT, Trail Making Test; WMS-R, Wechsler Memory Scale-Revised; VF, verbal fluency; GDS, Geriatric Depression Scale; 25(OH)VitD, 25-hydroxyvitamin D; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities; MCI, mild cognitive impairment.

DISCUSSION

In the present study, we focused on the associations between changes in PVH/DWMH volumes and cognitive decline, blood levels of molecules, and the presence of vascular risk factors in patients with amnestic MCI. We found a significant negative correlation between DWMH progression and changes in MMSE and category VF scores, whereas changes in PVH volume did not correlate with any of the items. These results suggest that DWMH progression increases the risk of the decline of cognition in MCI, such as frontal lobe function and semantic

Table 2
Comparison of clinical characteristics, blood biochemistry data, and WMH volume ratios of MCI subjects between the initial and the final visit ($n = 24$)

	Initial visit	Final visit
MMSE	27.2 ± 1.6	26.9 ± 3.0
FAB	12.9 ± 2.3	13.4 ± 2.4
TMT-A (s)	50.3 ± 20.0	48.9 ± 24.2
TMT-B (s)	155.4 ± 83.4	167.1 ± 95.1
WMS-R-Logical Memory (immediate)	14.4 ± 7.0	15.9 ± 6.8
VF (category)	14.5 ± 3.5	14.7 ± 4.3
GDS-15	4.2 ± 3.7	3.9 ± 3.3
HbA1c (%)	5.8 ± 0.5	5.7 ± 0.5
T-Cho (mg/dL)	199.5 ± 35.1	192.0 ± 27.2
LDL-Cho (mg/dL)	109.9 ± 26.3	104.4 ± 21.6
eGFR (mL/min/1.73 m^2)	66.0 ± 11.4	65.0 ± 13.6
Cystatin C (mg/L)	1.0 ± 0.2	1.0 ± 0.2
Systolic blood pressure (mmHg)	130.0 ± 14.2	130.0 ± 22.0
Diastolic blood pressure (mmHg)	71.2 ± 14.0	70.6 ± 12.9
PVH volume ratio (%)	0.76 ± 0.66	1.04 ± 0.84*
DWMH volume ratio (%)	0.43 ± 0.85	0.59 ± 0.98*
Hypertension, n (%)	12 (50)	12 (50)
Diabetes mellitus, n (%)	4 (17)	4 (17)
Dyslipidemia, n (%)	10 (42)	10 (42)

*$p < 0.05$ between the initial and the final data. MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; TMT, Trail Making Test; WMS-R, Wechsler Memory Scale-Revised; VF, verbal fluency; GDS, Geriatric Depression Scale; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities; MCI, mild cognitive impairment; HbA1c, hemoglobin A1c; T-Cho, total cholesterol; LDL-Cho, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Table 3
Comparison of initial clinical characteristics, blood biochemistry data, WMH volume ratios, and ratio changes between AD converters and non-converters among MCI subjects ($n = 24$)

	AD converters ($n = 4$)	Non-converters ($n = 20$)
MMSE	26.3 ± 0.5	27.4 ± 1.6
HbA1c (%)	6.0 ± 0.5	5.8 ± 0.5
T-Cho (mg/dL)	213.3 ± 37.1	196.8 ± 35.1
LDL-Cho (mg/dL)	119.5 ± 28.8	106.7 ± 26.3
eGFR (mL/min/1.73 m^2)	61.3 ± 12.5	66.9 ± 11.3
Cystatin C (mg/L)	1.1 ± 0.2*	0.97 ± 0.1
25(OH)VitD (ng/mL)	26.0 ± 7.7	25.6 ± 14.4
Homocysteine (nmoL/mL)	9.4 ± 2.7	10.7 ± 3.2
PVH volume ratio (%)	1.2 ± 0.7	0.7 ± 0.6
DWMH volume ratio (%)	0.4 ± 0.6	0.4 ± 0.9
PVH volume ratio changes(%)	0.37 ± 0.48	0.26 ± 0.32
DWMH volume ratio changes(%)	0.31 ± 0.30	0.13 ± 0.17
Hypertension, n (%)	2 (50)	10 (50)
Diabetes mellitus, n (%)	1 (25)	3 (15)
Dyslipidemia, n (%)	2 (50)	8 (40)

*$p < 0.05$ between AD converters and non-converters. MMSE, Mini-Mental State Examination; HbA1c, hemoglobin A1c; T-Cho, total cholesterol; LDL-Cho, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; 25(OH)VitD, 25-hydroxyvitamin D; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities; AD, Alzheimer disease; MCI, mild cognitive impairment.

Table 4
Associations between the initial ratio or the ratio changes in PVH/DWMH volumes to ICV, and changes in neuropsychological test scores and blood biochemistry data

	Initial PVH vol. ratio		Changes in PVH vol. ratio		Initial DWMH vol. ratio		Changes in DWMH vol. ratio	
Changes in measurement	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*	Coefficient	*P*
MMSE	–0.32	0.13	–0.2	0.35	–0.15	0.5	–0.5*	0.01
FAB	0.27	0.21	0.003	0.99	–0.02	0.93	0.11	0.62
TMT-A	0.07	0.76	0.25	0.26	–0.08	0.73	0.08	0.74
TMT-B	0.18	0.43	–0.04	0.85	0.5*	0.02	0.33	0.14
WMS-R	0.35	0.1	0.41	0.05	0.2	0.37	0.29	0.17
VF	–0.35	0.12	–0.43	0.05	–0.21	0.36	–0.46*	0.04
GDS-15	–0.11	0.61	–0.28	0.2	0.4	0.06	0.02	0.93
Cystatin C	–0.14	0.51	–0.25	0.25	0.55**	0.005	0.18	0.41

*$p < 0.05$, significant correlation with the initial ratio or ratio changes of DWMH volume to ICV. **$p < 0.01$, significant correlation with the initial ratio of DWMH volume to ICV. MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; TMT, Trail Making Test; WMS-R, Wechsler Memory Scale-Revised; VF, verbal fluency; GDS, Geriatric Depression Scale; PVH, periventricular hyperintensities; DWMH, deep white matter hyperintensities; ICV, intracranial volume.

memory, although there were no significant differences in DWMH progression between AD converters and non-converters, and we did not observe a significant increase in the risk of conversion to AD [13, 14]. The reason for the progression of frontal lobe dysfunction may be that WMH is more pronounced in the frontal region and may hence mainly impair frontal lobe function by disrupting cortico-cortical and cortico-subcortical connections [15–17], because initial DWMH volume was found to also be associated with changes in TMT-B score. In our previous study, we found that frontal lobe dysfunction was associated more closely with PVH volume than DWMH volume in patients with MCI. Considering these results, DWMH volume may become a useful indicator of the progression of cognitive dysfunction in the near future, and PVH volume may become a useful marker for assessing cognitive dysfunction in patients with MCI.

We found that the changes in both PVH and DWMH volumes did not correlate with the presence of vascular risk factors or with changes in CysC level, when measurements were made under well-controlled conditions. Furthermore, the presence of any of the vascular risk factors, i.e., HT, DL, or DM, was not associated with the risk of conversion to AD. Our findings in terms of HT and DL were consistent with the previous reports in the literature showing that vascular risk factors, such as HT and DL increase the likelihood of cognitive decline in midlife, but not in late life [18, 19]. On the other hand, our finding in terms of DM was inconsistent with some previous reports [20, 21]. We believe that a 2-year observation period is not sufficient to fully analyze the associations of WMH volume changes and vascular risk factors with the risk of conversion to AD. However, we believe that AD pathology has a strong effect on the progression of MCI to AD, and thus additional effects of WMH progression and vascular risk factors on MCI due to AD are not expected [19, 22]. We found that initial CysC level was significantly higher in AD converters than in non-converters, and a significant positive correlation between changes in CysC level and initial DWMH volume in MCI was observed, although CysC level was not associated with the conversion to AD by logistic regression analysis. This is probably why CysC level is associated with not only white matter abnormalities but also AD pathology [5, 23–25]. Although the presence of vascular risk factors was not associated with the WMH progression and the conversion from MCI to dementia in the present study, vascular risk factors have been reported to affect cognitive decline as well as white matter abnormalities. In addition, a reduction in the rate of conversion to dementia and improvement of cognition, even in dementia, has been reported to be possible using the appropriate therapies and care [21, 26–29]. In the present study, most MCI subjects with vascular risk factors were receiving some treatment, such as antihypertensives, antidiabetic medications, statins, etc., and hence the measurements were made under conditions in which the vascular risk factors were well controlled. We hence believe that the negative findings of this study regarding vascular risk factors may be owing to the patients receiving optimal treatments, because we did not prescribe anti-dementia drugs, such as cholinesterase inhibitors and an N-methyl-D-aspartate receptor antagonist, unless the subjects converted to AD during the follow-up period.

In the present study, the underlying pathology of the MCI patients was not confirmed. We consider that it is important to analyze other biomarkers in the future, to clarify the association between WMH progression and AD pathology. A previous study showed that WMH and cerebrospinal fluid (CSF) levels of amyloid and phosphorylated tau (p-tau) appear to be independent and nonsynergistic indicators of the risk of progression to MCI in preclinical AD patients and may hence be useful as disease biomarkers [6]. However, the subjects that were analyzed included relatively young patients, and in terms of the methods, the assessment of WMH was done by full automatic segmentation of whole WMH. On the other hand, in our present study, only older subjects with amnestic MCI were included, and we used semi-automatic segmentation for the assessment of WMH volume, which is thought to be more accurate than the methods used in the previous study. Therefore, we are planning to further analyze CSF $A\beta_{42}$ and p-tau protein levels as potential biomarkers in the future.

This study has some limitations. First, the sample size was small, and the follow-up duration was short for clarifying the association between vascular risk factors and the conversion to AD. However, it is clear from the results that WMH progression was associated with cognitive decline in amnestic MCI. Second, we excluded subjects showing severe white matter diseases, and hence we should take caution in interpreting the results. Third, the underlying pathology in MCI patients was not confirmed in this study. However, neuroimaging data were used as part of the diagnostic process; in particular, decreases in rCBF in the parietotemporal association cortex on

SPECT is recognized as a diagnostic pattern of MCI due to AD [8]. Therefore, we are confident that most MCI patients in the present series did indeed have AD pathology. Fourth, we did not assess the association between regional WMH volume and cognitive decline. Therefore, we are planning to investigate this association in the near future.

In conclusion, we found that DWMH progression is closely associated with a decline of cognition, such as frontal lobe function and semantic memory, which suggests that WMH progression might affect some AD pathophysiologies in amnestic MCI patients.

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