

Relationships of white matter hyperintensity with arterial stiffness and lifestyle in patients with mild cognitive impairment

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Background: Ischemic cerebral lesions and lifestyle are associated with cognitive function and progression of Alzheimer-type dementia.

Objective: The relationships between the grade of white matter hyperintensity (WMH) and the risk factors for vascular disease including lifestyle and arterial stiffness, assessed by the pulse wave velocity test in mild cognitive impairment (MCI) patients, were examined in this study.

Methods: A total of 140 patients diagnosed as having MCI were recruited for this study. Comparisons were made between the high- and low-WMH-grade groups, using the Fazekas classification system, in terms of cognitive function, arterial stiffness, vascular risk factors, and lifestyle-related risk factors.

Results: In MCI patients, the age, prevalence of hypertension, and number of complications were statistically significantly higher and the frequencies of eating fish were statistically significantly lower in the high-WMH-grade group than those in the low-WMH-grade group.

Conclusions: WMH grade was associated with the risk factors for vascular disease in MCI patients. Because WMH grade affects the cognitive function, it is important to recognize the significance of the risk factors for vascular disease and treat the patients from the MCI stage to prevent cognitive function decline.

Key words: mild cognitive impairment, white matter hyperintensity, arterial stiffness, vascular risk factors, lifestyle-related risk factors

Introduction

Recently, the population in Japan has been aging at an unprecedentedly rapid pace and the number of patients with dementia is likewise rapidly increasing. Because the number of patients with Alzheimer-type dementia (AD), which accounts for approximately half of all cases of dementia, will continue to increase, various studies have been carried out on the diagnostic technology for and the treatment and prevention of AD. The development of dementia including AD is affected by physiological factors such as aging, among others; therefore, a diagnostic methodology is needed to identify which and to what extent those factors contribute to the development of AD. Also, there have been many reports about the importance of treating underlying physical diseases, modifying lifestyle, engaging in regular exercise and leisure activities, and having regular eating habits,

which are considered to affect the development of dementia.¹⁻³ Regarding ways to help prevent dementia in Japan, there seem to be various physical activities that are simple and effective. These physical activities may include the prevention and treatment of lifestyle-related diseases that occur after reaching middle age and the maintenance of regular moderate exercise, desirable eating habits, and continuous social interaction.⁴

From this perspective, there is a growing emphasis on the early diagnosis and intervention of dementia. The treatment of mild cognitive impairment (MCI) that occurs prior to the development of dementia including AD has also attracted attention in terms of early intervention. According to a meta-analysis of 19 longitudinal studies, the annual conversion rate from MCI to dementia including AD is 10% on average.⁵ In other reports, the annual reversion rate from MCI to normal cognitive function varies from 15% to 40%.⁶⁻⁸ Such a difference is

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due to various factors including the differences in the study population and follow-up period. It is, therefore, difficult to compare these results simply. However, in terms of ways to help prevent dementia, it is essential to examine the risk factors and other factors contributing to cognitive function decline that may be involved in the progression of MCI to AD. It is well known that lifestyle affects vascular disease. When AD is complicated by ischemic brain lesions, the cognitive function of AD patients further declines.⁹

In clinical practice for treating MCI at a stage prior to AD, it is also important to examine and deal with the factors that affect white matter hyperintensity (WMH), which is an ischemic cerebral lesion associated with cognitive function decline. It is assumed that lifestyle-related risk factors for cerebrovascular disease (CVD) and vascular disease affect the symptoms of MCI. Although there has been a study focusing on the relationship between the presence of WMH and the functional decline in the instrumental activity of daily living and the quality of daily life of patients,¹⁰ only a few reports have detailed this issue in Japan. In the present study, we cross-sectionally examined the relationship between the WMH grade and the risk factors for vascular disease, including lifestyle and arterial stiffness, assessed by the pulse wave velocity (PWV) test, in MCI patients.

Materials and Methods

Subjects

From the medical-record database of 520 patients who attended the dementia diagnosis course at Kitasato University East Hospital from April 2004 to March 2014, the records of 520 patients who agreed to participate in this study were obtained. From these records, those of

140 patients who were diagnosed as having MCI in accordance with the MCI report of the international working group on MCI¹¹ were used in this study.

Factors analyzed

The factors analyzed included age, gender, height, body weight, number of complications, PWV, lifestyle-related factors determined by a questionnaire survey, and magnetic resonance (MR) imaging findings. For complications, the presence/absence of hypertension, diabetes mellitus, hyperlipidemia, renal disease, arrhythmia, ischemic heart disease, and collagen disease was examined, and the total number of complications was counted. For CVD-related factors, body mass index (BMI) = body weight (kg)/[height (m)]², systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the upper arm obtained in the PWV test, mean ankle-brachial pressure index (mABI) (mean of the left and right mABIs), and mean brachial-ankle pulse wave velocity (mbaPWV) were extracted from the medical-record database. We selected these items that would be associated with atherosclerosis or arteriosclerosis. For lifestyle-related risk factors, the following eight items were examined using a questionnaire completed by family members of the patients: number of meals; frequency of eating fish, vegetables, and fruit (meal-related habits); drinking, smoking, and exercise, and quality of sleep. Eight factors: 1. irregular meals, 2. eating fish at least once a week, 3. eating vegetables at least once a week, 4. eating fruits at least once a week, 5. habitual drinking once or more a week, 6. habitual smoking, 7. no habit of exercising, and 8. lack of sleep are regarded as lifestyle-related risk factors. We selected these items that would be associated with cognitive function. The total number of lifestyle-related risk factors that apply to each patient was counted, which ranged between 0 and 8.

Table 1. Demographic data of high-WMH-grade and low-WMH-grade groups

	High-WMH grade n = 58	Low-WMH grade n = 82	P
Age (y)	74.7 ± 5.8	72.5 ± 7.0	0.042*
Female n, (%)	33 (56.9)	60 (73.2)	0.048*
Education (y)	11.7 ± 3.0	11.8 ± 2.5	0.869
MMSE	25.2 ± 2.5	25.6 ± 2.3	0.386
Total number of complications	1.3 ± 1.2	0.8 ± 0.9	0.005*

*P < 0.05; P values calculated using Student's *t*-test or Fisher's exact test
WMH, white matter hyperintensity; MMSE, Mini-Mental State Examination
Data are shown as mean ± SD.

Evaluation of WMH

The lesions that appear as WMH areas were graded visually from FLAIR (fluid-attenuated inversion recovery) MR images of the brain using the Fazekas classification system.¹² The patients were divided into two groups: patients with WMH grade ≥ 2 (high-WMH-grade group, n = 58) and those with a WMH grade of 0 or 1 (low-WMH-grade group, n = 82). The clinical background characteristics of these patients are summarized in Table 1.

Ethical consideration

This study was carried out with the approval of the Ethics Committee of Kitasato University on September 15, 2005, Number: B05-33.

Statistical analyses

Student's *t*-test and Fisher's exact test were performed to compare the results between the two groups. The factors related to arterial stiffness, e.g., BMI, blood pressure, mABI, mbaPWV, and the total number of lifestyle-related risk factors, were compared. The results obtained were corrected for age and gender using a generalized estimation equation. In addition, the number and percentage of patients who were judged at risk were determined for each lifestyle-related risk factor, and logistic regression analysis was carried out to obtain the relative risk (relative odds ratio) of each factor by correcting the data for age and gender. $P < 0.05$ was considered to indicate a statistically significant difference. No correction for multiple comparisons was carried out in this study because the number of subjects was small and the study was exploratory. SPSS version 17.0 was used for statistical analyses.

Results

Comparison of clinical background characteristics between high- and low-WMH-grade groups

Approximately 41% of the patients who were diagnosed as having MCI at the time of attending the dementia diagnosis course held at our hospital had high WMH grades. Table 1 shows the clinical characteristics of patients in the high- and low-WMH-grade groups. The mean age and the number of complications in the high-WMH-grade group were significantly higher than that in the low-WMH-grade group. The proportion of female patients in the high-WMH-grade group was significantly lower than that in the low-WMH-grade group. There was no significant difference in the Mini-Mental State Examination score between the two groups.

Comparison of CVD-related complications between high- and low-WMH-grade groups

Table 2 shows the number of patients with the complications that were reported being related to CVD and the prevalences of such complications in the high- and low-WMH-grade groups. The number of patients with hypertension was significantly higher in the high-WMH-grade group than that in the low-WMH-grade group. The relative risk of high WMH grade in patients with each complication was calculated and corrected for age and gender. The relative risk of high WMH grade in patients with hypertension was approximately three times higher than that in patients without hypertension. There was a possibility that the relative risks of high WMH grade in patients with diabetes mellitus and in those with ischemic heart disease were twice or higher than that in patients without these complications; however, the differences were not statistically significant.

Table 2. Comparison of complications between high-WMH-grade and low-WMH-grade groups

	High-WMH-grade n = 57	Low-WMH-grade n = 81	P ^a	Relative odds ratio ^b	(95% CI)	P
Hypertension	33 (57.8)	25 (30.9)	0.002	2.75	(1.32, 5.71)	0.007*
Diabetes mellitus	10 (17.5)	7 (8.6)	0.187	2.13	(0.65, 7.00)	0.213
Hyperlipidemia	11 (19.3)	13 (16.0)	0.653	1.56	(0.60, 4.04)	0.358
Renal disease	3 (5.3)	4 (4.9)	1.000	1.51	(0.31, 7.33)	0.604
Arrhythmia	10 (17.5)	11 (13.6)	0.632	1.20	(0.44, 3.27)	0.720
Ischemic heart disease	10 (17.5)	7 (8.6)	0.187	2.28	(0.72, 7.23)	0.160

* $P < 0.05$

Data shown in (%)

^aCalculated using Fisher's exact test

^bCVD positivity relative odds ratio of risk-factor-positive group corrected for age and gender

Comparison of factors related to arterial lesions between high- and low-WMH-grade groups

BMI, SBP, DBP, mABI, mbaPWV, and the number of lifestyle-related risk factors were compared between the high- and low-WMH-grade groups as the factors related to arterial lesions (Table 3). The mbaPWV and the number of lifestyle-related risk factors before correction for age and gender were higher in the high-WMH-grade group than in the low-WMH-grade group, although the differences were not statistically significant. The number of lifestyle-related risk factors after correction for age and gender was significantly higher in the high-WMH-grade group than in the low-WMH-grade group. The differences in BMI and mABI between the two groups were not statistically significant.

Comparison of lifestyle-related risk factors between high- and low-WMH-grade groups

Table 4 shows the number and percentage of patients in the high- and low-WMH-grade groups who were positive for each of the eight lifestyle-related risk factors examined in this study. The frequency of habitual drinking tended to be high in the high-WMH-grade group. When the relative risk of a high WMH grade in patients with each risk factor was calculated and corrected for age and gender, the relative risks of a high WMH grade were about 4.3 times and 2.2 times in the patients who ate fish less frequently and in those who drank frequently, respectively.

Table 3. Comparison of factors related to arterial lesions between high-WMH-grade and low-WMH-grade groups

	High-WMH grade n = 58		Low-WMH grade n = 82		P	High-WMH grade		Low-WMH grade		P
	Mean	(95% CI)	Mean	(95% CI)		Estimated mean ^a	Estimated (95% CI)	mean ^a	(95% CI)	
BMI	22.2	(21.5, 22.9)	22.3	(21.5, 23.1)	0.878	22.3	(21.5, 22.9)	22.6	(21.7, 23.4)	0.5
SBP (mmHg)	141.6	(137.0, 146.2)	136.4	(130.7, 146.2)	0.104	140.8	(137.0, 144.6)	135.4	(130.2, 140.6)	0.119
DBP (mmHg)	78.7	(76.3, 81.6)	76.7	(74.5, 79.0)	0.248	79.0	(76.7, 81.4)	77.0	(74.6, 79.5)	0.257
mABI	1.12	(1.11, 1.14)	1.12	(1.10, 1.14)	0.788	1.12	(1.11, 1.14)	1.13	(1.12, 1.15)	0.554
mbaPWV (cm/s)	1,750.8	(1,669.0, 1,832.6)	1,661.6	(1,600.1, 1,723.1)	0.088	1,723.7	(1,645.6, 1,801.8)	1,684.7	(1,624.2, 1,745.3)	0.432
Lifestyle-related risk factors	1.5	(1.2, 1.9)	1.1	(0.9, 1.3)	0.055	1.6	(1.2, 1.9)	1.1	(0.9, 1.3)	0.03*

*P < 0.05

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; mABI, mean ankle-brachial pressure index; mbaPWV, mean brachial-ankle pulse wave velocity

^aEstimated mean calculated using general equal estimation corrected for age and gender

Table 4. Comparison of lifestyle-related risk factors between high-WMH-grade and low-WMH-grade groups

Risk factor	High-WMH grade n = 55	Low-WMH grade n = 77	P ^a	Relative odds ratio	(95% CI)	P
Meals/day	1 (1.8)	3 (3.9)	0.640	0.58	(0.05, 6.41)	0.653
Fish consumption	8 (14.5)	4 (5.4)	0.123	4.28	(1.20, 15.25)	0.025*
Vegetable consumption	2 (3.6)	0 (0.0)	0.177	na		
Fruit consumption	6 (11.3)	5 (6.7)	0.524	2.46	(0.62, 9.83)	0.202
Drinking	24 (44.4)	21 (27.3)	0.061	2.18	(0.97, 4.45)	0.06
Smoking	5 (9.6)	4 (5.3)	0.484	2.29	(0.56, 9.32)	0.249
Exercise	16 (29.1)	19 (25.3)	0.691	1.28	(0.58, 2.83)	0.55
Sleep	21 (37.5)	34 (45.3)	0.379	0.78	(0.38, 1.61)	0.503

*P < 0.05

Data shown in (%)

^aCalculated using Fisher's exact test

na, not available

Discussion

WMH in MCI patients

In patients with vascular dementia (VD), early intervention of underlying diseases such as hypertension, diabetes mellitus, and hyperlipidemia, which are risk factors for vascular disease, can slow the progression of symptoms. Also, WMH, which is an ischemic lesion, is often observed on brain MR images of VD patients owing to their clinical conditions.

Regarding WMH in AD patients, we previously reported that approximately 60% of AD patients who attended the dementia diagnosis course held at our hospital had a high WMH grade (high-WMH-grade group).¹³ Kuo et al.¹⁴ reported that about 20% of elderly patients without dementia showed moderately high to very high grades of WMH. Fazekas et al.¹² reported that 4 of 12 AD patients and 3 of 9 control subjects had ischemic lesions. In the present study, approximately 41% of patients who were diagnosed as having MCI had moderate to high WMH grades.

Factors related to WMH grade and vascular disease in MCI patients

Age is considered an important factor related to the pathogenesis of WMH.^{15,16} Consistent with previous reports, the mean age in the high-WMH-grade group was significantly higher than that in the low-WMH-grade group.

As for gender difference, the percentage of females was higher than that of males among all MCI patients in this study, but the proportion of females in the high-WMH-grade group was significantly lower than that in the low-WMH-grade group. It has been reported that WMH was more common in females than in males.¹⁷ The results in the present study were affected by the subjects' age range, which included young patients. It has been suggested that MCI is strongly associated with cardiovascular risk factors such as hypertension, among others.¹⁸

In the present study, the number of patients with hypertension in the high-WMH-grade group was significantly higher than that in the low-WMH-grade group. The relative risk of high WMH grade in patients with each complication was calculated and corrected for age and gender. The relative risk of high WMH grade in patients with hypertension was approximately threefold higher than in patients without hypertension. The relative risk of high WMH grade in patients with diabetes mellitus and ischemic heart disease may be twofold or higher than that in patients without these complications;

however, the differences were not statistically significant. The effects of hypertension, diabetes mellitus, cardiac disorder, metabolic syndrome, and deterioration in renal function on white matter lesions have been reported.¹⁹⁻²² It is necessary to recognize the presence of hypertension and other underlying diseases and to provide the appropriate treatment for patients while still in the MCI stage.

In this study, five items related to arterial lesions, namely, BMI, SBP, DBP, mABI, and mbaPWV were compared between the high- and low-WMH-grade groups as the risk factors for CVD. Also, eight items in four areas, namely, meal-related habits, drinking and smoking habits, exercise, and sleep, were surveyed as the lifestyle-related risk factors that were considered related to arterial lesions. The number of applicable items was compared with the number of lifestyle-related risk factors between the high- and low-WMH-grade groups. As a result, mbaPWV and the numbers of lifestyle-related risk factors before correction for age were higher in the high-WMH-grade group than those in the low-WMH-grade group, although the differences were not statistically significant. The number of lifestyle-related risk factors after correction for age and gender was statistically significantly higher in the high-WMH-grade group than that in the low-WMH-grade group. Hanon et al.²³ studied the relationship between PWV and cognitive function in the elderly and reported that PWV was higher in the elderly with normal cognitive function, MCI, AD, and VD in this order. There was a significant negative correlation between the Mini-Mental State Examination score and the PWV.²³ Hatanaka et al.²⁴ reported that the prevalence of WMH tended to increase with the increasing mbaPWV.

Although no significant difference was observed in the mbaPWV between the high- and low-WMH-grade groups, the mbaPWV in the high-WMH-grade group tended to be high in this study. Because the PWV test is not invasive and is also easy to perform, it may be helpful to refer to the results of the PWV test in clinical practice for patients at an early stage prior to dementia in order to assess the risk of CVD and to provide appropriate instructions to patients. The SBP and DBP tended to be higher in the high-WMH-grade group than in the low-WMH-grade group, but the differences were not statistically significant in this study. Blood pressure control at an early stage of MCI is important because it has recently been suggested that MCI is strongly associated with cardiovascular risk factors such as hypertension.¹⁸ Moreover, Brickman et al.²⁵ reported that the progression of WMH in elderly patients was affected by blood pressure fluctuation and suggested that

the reduction of blood pressure fluctuation was important to prevent the progression of WMH. Because the prevalence of WMH was high in MCI patients in this study, it is necessary to pay attention to the relationship between blood pressure and WMH in MCI patients.

There was no significant difference in BMI between the high- and low-WMH-grade groups in this study. It was considered that the WMH grade is more strongly affected by blood pressure and arterial stiffness than body weight because severe obesity is less common in Japan than in Europe and the United States.

Relationships of WMH grade with lifestyle and meal-related habits in MCI patients

Regarding to lifestyle and meal-related habits, eating fruit, vegetables, fish, and low-fat foods is considered to decrease the risk of CVD.^{26,27} In this study, the frequencies of eating fish were significantly lower in the high-WMH-grade group than in the low-WMH-grade group. Also, the relative risk of high WMH grade corrected for age and gender was 4.3 times high in the patients who ate fish less frequently. As for the relationship between AD and fish intake, there have been reports that the amount of fish intake inversely correlated with the incidence of AD²⁸ and that fish intake prevented the development of AD.²⁹ In the longitudinal research on the relationship between fish intake and cognitive function, Hashimoto et al. showed importance of the erythrocyte membrane docosahexaenoic acid levels.³⁰ It has also been reported that fish intake was associated with the prevention of stroke or a decrease in the incidence of cerebral thrombosis and that these effects were due to eicosapentaenoic acid in fish oil.³¹

Maintenance of motor function and engagement in physical activities are likely to be effective in preventing AD and should be recommended for the elderly, although their effects were not clarified in this study. The effects of exercise on elderly patients with MCI have been examined in limited trials, which indicated that aerobic exercise was effective in improving or maintaining cognitive function.^{32,33} However, because the effects of exercise on the cognitive function in elderly patients with MCI have not yet been clarified,³⁴ and some elderly patients cannot exercise owing to their complications or physical limits, the effectiveness of exercise should be determined for each patient. Recently, it has been reported that the presence or absence of apparent WMH resulted in the differences in the decline in activity of daily living, the risk of falling, and the behavioral changes in patients in the MCI stage and that the differences affected the amount of care required by the patients.¹⁰ The subjects

of this study seemed to be very conscious of their health because they attended the dementia diagnosis course on their own will, which could be a reason why there was no significant difference in the habit of exercising between the high- and low-WMH-grade groups.

The results of this study showed that the frequency of drinking was associated with the relative risk of high WMH grade corrected for age and gender. As for the relationship between alcohol consumption and dementia, it was reported that the relative risk of dementia in patients who drank a small amount of alcohol was lower than that in patients who did not drink at all.³⁵ However, it was also reported that the risk of dementia in heavy drinkers was higher than in mild to moderate drinkers.³⁶ The results varied from study to study.

The factors associated with WMH of MCI patients were examined in this study. The results showed that lifestyle-related risk factors for CVD might be associated with WMH. The results also indicated that the use of WMH as a marker of progression of vascular disease will be effective in MCI patients. However, because the living environment, physical disorders, and social background vary from patient to patient, it is important to improve the lifestyle of patients and to take a multifaceted and balanced approach to dealing with the risk factors for vascular disease rather than to focus on some specific factors.

The limitations of this study are as follows. 1. The number of patients was small and the statistical results were not highly reliable. 2. The study subjects were patients who attended the dementia diagnosis course to detect dementia at an early stage. 3. There is a possibility that the study subjects were highly interested in health and maintained a good lifestyle, which may have led to the finding of a large number of lifestyle-related risk factors showing insignificant differences between the low- and high-WMH-grade groups.

Because this study was a cross-sectional study, we were unable to determine how the risk factors affected WMH progression. We will clarify the factors associated with WMH progression by conducting a future large-scale longitudinal study.

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Conflicts of Interest

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