Relationship among white matter hyperintensity, arterial stiffness, associated diseases, and lifestyle in late-onset Alzheimer's disease patients

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Objective: White matter hyperintensity (WMH) is related to cerebrovascular disease, which deteriorates the cognitive function in Alzheimer's disease (AD) patients. In this study, we examined the association between WMH in AD patients and various vascular factors.

Methods: A total of 107 patients with mild to moderate AD aged 65 years or older were recruited. Comparisons were made between the high- and low-WMH groups, using the Fazekas classification system, in terms of cognitive function, arterial stiffness, vascular risk factors, and lifestyle-related risk factors.

Results: High-WMH were observed in approximately 60% of the AD patients in this study. The high-WMH patients were significantly older than the low-WMH patients. The mean brachial-ankle pulse wave velocity was higher in the high-WMH group than that in the low-WMH group. After correction for age and gender, the diastolic blood pressure (DBP) was significantly higher in the high-WMH group than that in the low-WMH group. The percentage of patients showing white matter lesions significantly increased in correlation with the number of lifestyle-related risk factors as well as in correlation with frequencies of both exercise and fruit consumption.

Conclusions: In the AD patients in the present study, WMH is associated with cognitive impairment, age, arterial stiffness, diastolic blood pressure, and lifestyle-related vascular risk factors.

Key words: Alzheimer's disease, cerebrovascular disease, white matter hyperintensity, arterial stiffness, lifestyle

Introduction

Arterial stiffness can be assessed by a relatively simple method. The severity of arterial stiffness is related to cerebrovascular disease (CVD) and white matter lesions and affects the cognitive functions of the patients.1-3 However, to the best of our knowledge, there are only two reports on arterial stiffness in patients with Alzheimer's disease (AD). One is on the correlation between the morbidity of AD and the severity of arterial stiffness,4 and the other showed that the arterial stiffness in AD patients tended to be milder than that in patients with vascular dementia.5

When AD is complicated by ischemic brain lesions, the cognitive function of AD patients further declines.6 The risk factors for CVD including ischemic lesions have been pointed out to be related to the pathogenesis and prognosis of AD as well as vascular dementia.4,5 Although CVD does not directly cause AD, AD patients tend to be secondarily complicated with CVD because AD and CVD have common risk factors (e.g., hypertension, hyperlipidemia, and diabetes mellitus).6 Because the complication and exacerbation of CVD increase the burden of nursing care, preventive and control methods for CVD are necessary for AD patients as well.

White matter lesions pathologically represent small brain infarctions, myelin degeneration, and expansion of perivascular space.7 Recently, many studies have revealed the association between white matter hyperintensity (WMH) and cognitive decline.8,9 Some reports suggest
an association between WMH and vascular risk factors.\textsuperscript{12,13} It is well known that lifestyle affects vascular disease. However, much remains unclear about the associations among WMH, arterial stiffness, vascular risk factors, and the lifestyles of AD patients. Therefore, we carried out a cross-sectional study to examine the relationships among WMH, risk factors for arterial stiffness, CVD, and the lifestyles of AD patients.

### Materials and Methods

#### Subjects

From the medical-record database of 349 patients who attended the dementia diagnosis course at Kitasato University East Hospital from April 2004 to May 2010, records of 319 patients, who agreed to participate in this study, were obtained. Alzheimer’s Criteria\textsuperscript{14} were extracted from these records of 109 patients aged 65 years or older, who were diagnosed as having AD in accordance with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA). The records of two patients were excluded because of insufficient data. As a result, the records of a total of 107 patients were used in this study. The patients were diagnosed as having mild or moderate dementia using the Clinical Dementia Rating (CDR).\textsuperscript{15}

#### Factors analyzed

The factors analyzed included age, gender, height, body weight, number of complications, the mini-mental state examination (MMSE) score,\textsuperscript{16} education (period of study), pulse wave velocity (PWV) test results, lifestyle-related factors determined by a questionnaire survey, and magnetic resonance (MR) imaging findings. Regarding complications, the presence or absence of hypertension, diabetes mellitus, hyperlipidemia, renal disease, arrhythmia, and ischemic heart disease was examined, and the total number of complications was counted. We selected these complications for which previous studies showed associations to cerebrovascular disorder.\textsuperscript{12,17-19} For CVD-related factors, body mass index (BMI) (=body weight (kg)/[height (m)]\textsuperscript{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. Blood pressure and PWV was measured using a waveform analyzer (PWV/ABI; Colin, Komaki, Japan) after a 5-min rest at dorsal position. Because we did not find more than 10% difference between right and left ABI or PWV values, we used the mean value for comparisons as in previous studies.\textsuperscript{20,21} For lifestyle-related risk factors, the following eight items were surveyed using a questionnaire completed by the family members of the patients: number of meals; frequencies of eating fish, vegetables, and fruit (meal-related habits); drinking, smoking, and exercise habits; and quality of sleep. These eight factors, namely, (1) irregular meals, (2) eating fish once a week or less often, (3) eating vegetables once a week or less often, (4) eating fruit once a week or less often, (5) habitual drinking once a week or less often, (6) habitual smoking, (7) no habit of exercising, and (8) lack of sleep, were regarded as the lifestyle-related risk factors in the present study. The total number of these lifestyle-related risk factors that applied to each patient was counted, and, thus, ranged from 0 to 8.

#### Evaluation of WMH

All MRI studies were performed using a 1.0- or 1.5-tesla scanner. The lesions that appear as WMH areas were

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>High-WMH n = 64</th>
<th>Low-WMH n = 43</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>77.5 ± 5.0</td>
<td>74.4 ± 6.3</td>
<td>0.006*</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>24 (37.5)</td>
<td>12 (27.9)</td>
<td>0.303</td>
</tr>
<tr>
<td>Education (y)</td>
<td>10.7 ± 2.9</td>
<td>10.9 ± 3.1</td>
<td>0.746</td>
</tr>
<tr>
<td>MMSE</td>
<td>19.3 ± 4.4</td>
<td>21.3 ± 3.3</td>
<td>0.013*</td>
</tr>
<tr>
<td>Total number of complications</td>
<td>1.2 ± 1.0</td>
<td>0.9 ± 1.0</td>
<td>0.181</td>
</tr>
</tbody>
</table>

*P < 0.05

WMH, white matter hyperintensity; MMSE, mini-mental state examination

Data are shown as mean ± SD.

P values were calculated using the t-test or the chi-square test.
graded visually (the WMH grade) from fluid-attenuated inversion recovery (FLAIR) MR images of the head using the Fazekas classification system. The grades were determined by at least three psychiatrists. The patients were classified into two groups: patients with a WMH grade ≥2 (the high-WMH group, n = 64) and those with a WMH grade of 0 or 1 (the low-WMH group, n = 43). WMH grade 1 is defined as an aging related change, so we classified WMH grade 0 and 1 as the low-WMH group. 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.

**Statistical analyses**

The t-test and chi-square test were performed to compare the results between the two groups. The factors related to arterial stiffness were compared, e.g., BMI, blood pressure, mABI, mbaPWV, and the total number of lifestyle-related risk factors. To obtain an estimated mean value corrected for age and gender, a generalized estimation equation (GEE) approach was used because the GEE is applicable for obtaining an estimated mean value of a group in the event that there are some missing data. In addition, the number and percentage of patients who were judged to be at risk were determined for each lifestyle-related risk factor, and logistic regression analysis was performed to obtain the relative risk (relative odds ratio) of each factor by correcting the obtained data for age and gender. P values of <0.05 were considered to

<table>
<thead>
<tr>
<th>Disease</th>
<th>High-WMH n = 64</th>
<th>Low-WMH n = 43</th>
<th>P</th>
<th>Relative odds ratio</th>
<th>(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>34 (53.1)</td>
<td>15 (34.9)</td>
<td>0.063</td>
<td>1.81</td>
<td>(0.79, 4.13)</td>
<td>0.161</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>15 (23.4)</td>
<td>5 (11.6)</td>
<td>0.139</td>
<td>2.10</td>
<td>(0.68, 6.52)</td>
<td>0.198</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4 (6.3)</td>
<td>7 (16.3)</td>
<td>0.113</td>
<td>0.38</td>
<td>(0.10, 1.42)</td>
<td>0.149</td>
</tr>
<tr>
<td>Renal disease</td>
<td>4 (6.3)</td>
<td>2 (4.7)</td>
<td>1.000</td>
<td>1.53</td>
<td>(0.24, 9.89)</td>
<td>0.658</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>8 (12.5)</td>
<td>5 (11.6)</td>
<td>0.777</td>
<td>0.86</td>
<td>(0.25, 2.98)</td>
<td>0.815</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>10 (15.6)</td>
<td>5 (11.6)</td>
<td>0.777</td>
<td>0.77</td>
<td>(0.24, 2.50)</td>
<td>0.662</td>
</tr>
</tbody>
</table>

*P < 0.05

WMH, white matter hyperintensity

Data are shown in (%).

*Calculated using the chi-square test

*CVD, cerebrovascular disease positivity relative odds ratio of risk-factor-positive group corrected for age and gender

<table>
<thead>
<tr>
<th>Variables</th>
<th>High-WMH (n = 64)</th>
<th>Low-WMH (n = 43)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>22.2 (21.4, 23.0)</td>
<td>21.8 (20.6, 23.0)</td>
<td>0.517</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>143.3 (138.1, 148.5)</td>
<td>136.4 (130.7, 142.1)</td>
<td>0.079</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>78.2 (75.5, 80.9)</td>
<td>75.1 (72.4, 77.8)</td>
<td>0.125</td>
</tr>
<tr>
<td>mABI</td>
<td>1.13 (1.10, 1.16)</td>
<td>1.12 (1.10, 1.14)</td>
<td>0.777</td>
</tr>
<tr>
<td>mbaPWV (cm/s)</td>
<td>1869.1 (1783.1, 1955.1)</td>
<td>1709.5 (1602.8, 1816.2)</td>
<td>0.021*</td>
</tr>
<tr>
<td>No. of lifestyle-related risk factors</td>
<td>1.6 (1.3, 1.9)</td>
<td>1.1 (0.8, 1.4)</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

*Estimated mean calculated using a general equal estimation corrected for age and gender

*P < 0.05

WMH, white matter hyperintensity; 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

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

**Table 3. Comparison of factors related to arterial lesions between the high- and low-WMH groups**
indicate statistically significant differences. The correction for multiple comparisons was not done in the present study because the number of subjects was small, and because it was an exploratory study. The SPSS version 17.0 was used for statistical analyses.

Results

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

High-WMH were observed in approximately 60% of the patients aged 65 years or older who attended the dementia diagnosis course and who were diagnosed as having AD (Table 1). The clinical background characteristics of the high- and low-WMH groups are summarized in Table 1. The mean age of the high-WMH group was significantly higher than that of the low-WMH group. The score of the mini-mental state examination (MMSE) of the high-WMH group was lower than that of the low-WMH group. There were no significant differences in the number of years of education, number of complications, or gender between the two groups.

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

Table 2 shows a summary of the number of patients and prevalences of diseases that were reported to be related to CVD in the high- and low-WMH groups. The prevalences of hypertension and diabetes mellitus were higher in the high-WMH group than those in the low-WMH group; however, these differences were not statistically significant. The relative odds ratios for each disease were calculated using data corrected for age and gender. The relative odds ratios for hypertension and diabetes mellitus were approximately 2.0 but not statistically significant.

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

The factors related to arterial lesions, BMI, SBP, DBP, mABI, mbaPWV, and the number of lifestyle-related risk factors were compared between the two groups (Table 3). Before correction, mbaPWV and the number of lifestyle-related risk factors of the high-WMH group were higher than those of the low-WMH group. After correction for age and gender, DBP and the number of lifestyle-related risk factors of the high-WMH group were significantly higher than those of the low-WMH group. BMI and mABI were similar between the two groups.

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

Table 4 shows a summary of the number and percentage of patients who were determined at risk of CVD on the basis of the presence of the eight lifestyle-related risk factors in the two groups. The percentage of patients who do not have a habit of exercising was significantly high in the high-WMH group compared with that in the low-WMH group. After correction for age and gender, the relative odds ratios for the low frequency of fruit consumption and not having a habit of exercising increased to approximately 5 and 2.5, respectively.

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

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>High-WMH</th>
<th>Low-WMH</th>
<th>P&lt;br&gt;</th>
<th>Relative Odds ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of meals</td>
<td>3 (5.0)</td>
<td>1 (2.3)</td>
<td>0.638</td>
<td>5.04</td>
<td>(0.39, 64.0)</td>
<td>0.214</td>
</tr>
<tr>
<td>Fish consumption</td>
<td>14 (23.3)</td>
<td>6 (14.0)</td>
<td>0.235</td>
<td>1.75</td>
<td>(0.59, 5.24)</td>
<td>0.317</td>
</tr>
<tr>
<td>Vegetable consumption</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit consumption</td>
<td>10 (16.7)</td>
<td>3 (7.0)</td>
<td>0.229</td>
<td>4.77</td>
<td>(1.09, 20.86)</td>
<td>0.038*</td>
</tr>
<tr>
<td>Drinking</td>
<td>16 (29.1)</td>
<td>15 (34.9)</td>
<td>0.541</td>
<td>0.82</td>
<td>(0.32, 2.08)</td>
<td>0.669</td>
</tr>
<tr>
<td>Smoking</td>
<td>2 (3.4)</td>
<td>3 (7.0)</td>
<td>0.648</td>
<td>0.43</td>
<td>(0.06, 2.94)</td>
<td>0.387</td>
</tr>
<tr>
<td>Exercise</td>
<td>29 (47.5)</td>
<td>11 (25.6)</td>
<td>0.023*</td>
<td>2.52</td>
<td>(1.03, 6.15)</td>
<td>0.042*</td>
</tr>
<tr>
<td>Sleep</td>
<td>21 (35.6)</td>
<td>11 (26.2)</td>
<td>0.317</td>
<td>1.67</td>
<td>(0.66, 4.20)</td>
<td>0.278</td>
</tr>
</tbody>
</table>

*P < 0.05

WMH, white matter hyperintensity

Data are shown as number (%).

*Calculated using the chi-square test

*CVD, cerebrovascular disease positivity relative odds ratio of risk-factor-positive group corrected for age and gender
Discussion

In this study, moderate or severe white matter lesions were observed in approximately 60% of AD patients aged 65 years or older. Kuo et al.\textsuperscript{13} reported that about 20% of elderly patients without dementia showed moderate to severe WMH. Fazekas et al.\textsuperscript{22} reported that 4 of 12 AD patients and 3 of 9 subjects in the control group had ischemic lesions. Compared with these figures, the prevalence of moderate or severe white matter lesions obtained in the present study was high. Our finding is in agreement with previous findings that the percentage of patients having white matter lesions is higher in AD patients than in control subjects.\textsuperscript{25,26} According to Krishnan et al.,\textsuperscript{27} moderate subcortical ischemic lesions were observed in the MR images of 54% of the patients with depression aged 60 years or older—a prevalence similar to that observed in the present study. It is very interesting that the prevalence of CVD, as indicated by the presence of white matter lesions, in the patients with depression, is equivalent to that in the AD patients, considering that depression is a risk factor for dementia.\textsuperscript{28,29}

It has also been reported that WMH is a risk or an exacerbation factor for AD.\textsuperscript{10,31} and that the severity of WMH is a significant predictor of lesion progression in AD patients.\textsuperscript{25} Therefore, the prevention and control of the progression of WMH are particularly important to suppress cognitive function decline in patients. In the present study, similarly, the MMSE score of the high-WMH group was significantly lower than that of the low-WMH group, suggesting a relationship between WMH and cognitive function decline. Recently, a relationship between white matter lesions and brain atrophy has been pointed out\textsuperscript{12}; therefore, psychiatrists should pay special attention to white matter lesions, particularly in AD patients.

Age is an important factor for the onset of white matter lesions.\textsuperscript{20,35} In the present study, the mean age of the patients in the high-WMH group was significantly higher than that in the low-WMH group. Moreover, the effects of hypertension, diabetes mellitus, cardiac disorder, metabolic syndrome, and deterioration in renal function on white matter lesions have been reported.\textsuperscript{12,17,19} In the present study, we expected the number of complications in the high-WMH group would be higher than that in the low-WMH group, and detected the tendency of such, but without statistical significance. In this study, although we were unable to clarify any relationships between white matter lesions and any particular diseases, the presence of hypertension and diabetes mellitus tended to increase the risk of having high WMHs. Regarding the relationship between high WMHs and other diseases, the number of patients was small so that the reliability of these results was considered to be too low to determine any definitive relationships.

Blood pressure, arterial stiffness, and high BMI are reported to be factors related to CVD.\textsuperscript{18,21,34,35} Results of this study showed that both SBP and DBP tended to be higher in the high-WMH group than those in the low-WMH group; however, these differences were not statistically significant. When the obtained results were corrected for age and gender, DBP in the high-WMH group was significantly higher than that in the low-WMH group. Brickman et al.\textsuperscript{36} reported that wide fluctuations of blood pressure affect the progression of WMH in elderly patients, and suppression of fluctuations of blood pressure is also important to inhibit the progression of WMH. Hirono et al.\textsuperscript{37} showed that WMH volume is associated with hypertension in AD patients. These results indicate that appropriate control of blood pressure is important for AD patients.

Ochi et al.\textsuperscript{21} reported that the blood pressure and mbaPWV of the patients with a small asymptomatic brain infarction were significantly higher than those of the control group. Hatanaka et al.\textsuperscript{35} reported that the prevalence of WMH tended to increase with increasing mbaPWV. In the present study, mbaPWV, an index of arterial stiffness, was significantly higher in the high-WMH group than that in the low-WMH group; after data correction for age and gender, no significant differences were observed. Age is considered to be the predominant factor for the development of arterial stiffness. It has been reported that arterial stiffness is affected by aging\textsuperscript{20} and blood pressure and is related to WMH,\textsuperscript{35,38} which is in agreement with our results. In the present study, we used mbaPWV as an index of arterial stiffness. Kearney-Schwartz et al.\textsuperscript{3} obtained similar results using carotid-femoral PWV as an index. In this study, we were unable to show that a high PWV is a risk factor for white matter lesions from the results corrected for age and gender. Chalmers et al.\textsuperscript{39} showed that frontal white matter damage in AD patients is closely related to parenchymal beta-amyloid load, but they found no associations between white matter damage and atherosclerosis or arteriosclerosis using a neuropathological technique. Thus, the possibility of amyloid deposits and arterial stiffness exacerbating WMH with age should be taken into account in AD patients.

The high-WMH group had more lifestyle-related habits that were risk factors for vascular disease in this study. Eating fruit, vegetables, fish, and low-fat foods is...
References


