Effect of the Apolipoprotein E e4 Allele on White Matter Hyperintensities in Dementia

Nobutsugu Hirono, MD; Minoru Yasuda, MD; Satoshi Tanimukai, MD; Hajime Kitagaki, MD; Etsuro Mori, MD

Background and Purpose—The clinical significance of the apoE e4 allele in white matter changes in patients with dementia has been a subject of debate. We studied the association between the apoE e4 allele and white matter hyperintensities (WMHs) before and after control for (1) potential vascular risk factors and (2) the presence of lacunar infarcts in patients with dementia.

Methods—The subjects were 131 patients with dementia who had either Alzheimer’s disease or vascular dementia, or a combination of these 2 types of dementia, with or without WMHs, lacunar infarcts, or both. The association of the e4 allele with WMHs was examined before and after control for age, sex, duration of symptoms, education level, severity of dementia, presence of lacunar infarcts, and potential vascular risk factors, including hypertension, diabetes mellitus, lipid disorders, smoking habit, drinking habit, and cardiac diseases.

Results—WMHs were observed in 73 (55.7%) of the patients. Neither the number of apoE e4 alleles nor their presence was significantly associated with WMHs before or after control for the potential confounding factors. Multiple logistic regression analyses revealed that age, the presence of hypertension, and the presence of lacunar infarcts were independently associated with WMHs.

Conclusions—The apoE e4 allele was not associated with WMHs in patients with dementia. The fact that WMHs were significantly associated with hypertension and lacunar infarcts may indicate an ischemic origin of WMHs. (Stroke. 2000;31:1263-1268.)

Key Words: apolipoproteins■dementia■hypertension■lacunar infarction■white matter

White matter (WM) changes are common in vascular dementia (VaD), especially of small vessel/subcortical subtypes, includingBinswanger’s disease and lacunar infarct, and are generally considered to be a consequence of chronic ischemia associated with microangiopathy.1,2 However, WM changes, which are characterized by attenuation on CT and by white matter hyperintensities (WMHs) on T2-weighted MRIs, have also been reported to be common in patients with Alzheimer’s disease (AD).3–9 Therefore, even though the impact of WM changes in dementia formation is ambiguous and highly controversial, WM changes cannot be considered to be an exclusive feature of VaD.

The apoE e4 allele, which is a genetic risk factor for AD, has been reported to also be a risk factor for atherosclerosis10,11 and coronary heart disease.12–14 Moreover, evidence is accumulating that the presence of the apoE e4 allele increases the risk of cerebral amyloid angiopathy.15–17 These facts suggest an association between the apoE e4 allele and cerebral ischemic insults. A possible association between the apoE e4 allele and ischemic stroke with or without AD has been reported in some studies,18–21 although this association has not been supported in other studies.14,22–25 The association between the apoE e4 allele and WM changes is still controversial, with 1 report supporting an association of the apoE e4 allele with WM changes in demented subjects26 and others refuting such an association in both demented and non-demented subjects.22,27–29 In these studies, however, a possible interaction of the vascular risk factors was not simultaneously taken into consideration, or on the contrary, a selection bias might have yielded a deviant result due to the exclusion of those with vascular risk factors, thereby excluding severe WM changes and ignoring the effects of ischemia. In the present study, we examined the effect of the apoE e4 allele on WMHs in patients with dementia with control of the effects of vascular risk factors.

Subjects and Methods
The present study was conducted at Hyogo Institute for Aging Brain and Cognitive Disorders (HI-ABCD), a research-oriented hospital for dementia. All procedures of this study strictly followed the 1993 Clinical Study Guidelines of the Ethics Committee of HI-ABCD and were approved by the Internal Review Board. After a complete
description of all procedures of this study, written informed consent was obtained from patients or their relatives.

**Patients**

Based on the following inclusion/exclusion criteria, 131 patients were recruited from a consecutive series of 452 patients with dementia who underwent a short-term admission for examination at the HI-ABCD infirmary between April 1997 and June 1999. All patients were examined by both neurologists and psychiatrists with the use of standardized medical history inquiry, neurological examinations, routine laboratory tests, electroencephalography, MRIs of the brain, and MR angiography of the head and neck. All patients also were tested with the Wechsler Adult Intelligence Scale-Revised, the Wechsler Memory Scale-Revised, the Mini-Mental State Examination (MMSE), the cognitive portion of the Alzheimer’s Disease Assessment Scale, the Neuropsychiatric Inventory, and the Clinical Dementia Rating Scale; the results were incorporated into the diagnosis of dementia. The inclusion criteria were obtained from (1) the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) for dementia and National Institute of Neurological and Communicable Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association (NINCDS/ADRDA) criteria for probable AD when WM changes were specified as lesions with diameters of $\geq 5$ mm and an intersection gap of 2.5 mm covering the area from the base of the cerebellum to the vertex. In all acquisitions, the field of view was 200$\times$200 mm and the matrix size was 256$\times$256. WMHs were defined as irregular periventricular, early confluent deep, and confluent deep on T2-weighted and FLAIR images according to Fazekas et al. Pertiventricular changes in the forms of caps or smooth halos were not included because these changes were reported to be of nonischemic origin. The test-retest reliability among 3 neuroradiologists for this classification was examined with randomly selected 30 patients, and a high $r$ coefficient was obtained ($r=0.82$). Lacunar infarcts were specified as lesions with diameters of $\leq 15$ mm with (1) hyperintensity on T2-weighted images, (2) distinct hypointensity on T1-weighted images, and (3) hyperintensity with central hypointensity on FLAIR images. With the use of these criteria, lacunar infarcts can be distinguished from the état criblé or punctuate hyperintensity form of WMHs. MRI were examined by 1 neuroradiologist without knowledge of the patients’ clinical data, including apoE status.

**Assessment of Vascular Risk Factors**

Hypertension, diabetes mellitus, lipid disorders, smoking habit, drinking habit, and cardiac diseases were evaluated as vascular risk factors. Hypertension was judged as present when either systolic pressure of $\geq 160$ mm Hg or diastolic pressure of $\geq 95$ mm Hg was demonstrated on repeated examinations or when a history of treatment for hypertension was present. Diagnosis of diabetes mellitus was made when the fasting blood glucose level was $>7.770$ mmol/L (140 mg/dL) or there was a history of treatment for diabetes mellitus. Lipid disorder was judged as present when laboratory examination of the serum at presentation showed a total cholesterol level of $>5.698$ mmol/L (220 mg/dL), a triglyceride level of $>1.695$ mmol/L (150 mg/dL), or an HDL cholesterol level of $<1.036$ mmol/L (40 mg/dL) or when a history of treatment was present. Smoking habit was defined as $\geq 1$ cigarettes per day for $\geq 1$ years, and drinking habit was defined as $\geq 0.30$ mL ethanol equivalent per day for $\geq 1$ years sometime in life. Cardiac diseases were defined as a known history or clinical demonstration of any heart disease, including myocardial infarction, angina pectoris, and arrhythmia.

**MRI Acquisition**

MRI was performed with a 1.5-T superconducting magnet (Signa Advantage; General Electric Medical Systems). Axial double-echo fast spin echo T2-weighted images (3000/105/2 [repetition time/ effective echo time/excitations]), spin-echo T1-weighted images (550/15/2), and fast fluid attenuated inversion recovery (FLAIR) images (9002/147/2200/1 [repetition time/effective echo time/inversion time/excitations]) were obtained for 14 locations parallel to the anteroposterior commissure plane with a section thickness of 5 mm and an intersection gap of 2.5 mm covering the area from the base of the cerebellum to the vertex. In all acquisitions, the field of view was 200$\times$200 mm and the matrix size was 256$\times$256. WMHs were defined as irregular periventricular, early confluent deep, and confluent deep on T2-weighted and FLAIR images according to Fazekas et al. Pertiventricular changes in the forms of caps or smooth halos were not included because these changes were reported to be of nonischemic origin. The test-retest reliability among 3 neuroradiologists for this classification was examined with randomly selected 30 patients, and a high $r$ coefficient was obtained ($r=0.82$). Lacunar infarcts were specified as lesions with diameters of $\leq 15$ mm with (1) hyperintensity on T2-weighted images, (2) distinct hypointensity on T1-weighted images, and (3) hyperintensity with central hypointensity on FLAIR images. With the use of these criteria, lacunar infarcts can be distinguished from the état criblé or punctuate hyperintensity form of WMHs. MRI were examined by 1 neuroradiologist without knowledge of the patients’ clinical data, including apoE status.

**Statistical Analysis**

We used the $\chi^2$ test for nominal variables and the 2-tailed $t$ test or 1-way ANOVA for continuous variables for unadjusted comparisons. Because a dose effect of the apoE $e4$ alleles has been shown, the effect of the number of apoE $e4$ alleles on WMHs was analyzed with multiple logistic analysis. Each analysis was repeated with and without control for the effects of potentially confounding variables by incorporating age, sex, duration of symptoms, educational level, MMSE as a measure of the severity of dementia, the aforementioned vascular risk factors, and the presence of lacunar infarcts into the model. The presence/absence–based analysis of the $e4$ allele was also tested as a secondary analysis. For all analyses, the statistical $\alpha$ level was set at 0.05.
Results

The apoE genotyping was ε3/ε3 in 62 patients, ε3/ε4 in 59 patients, and ε4/ε4 in 10 patients. Seventy-three (55.7%) of the patients were positive for WMHs. Although there were 5 patients with a history of stroke supposedly caused by lacunar infarcts, none of the patients had an obvious relationship between stroke and dementia. Therefore, on the basis of the infarcts, none of the patients had an obvious relationship patients with a history of stroke supposedly caused by lacunar

The apoE genotyping was classified as having possible VaD. Forty-four 11 of the patients who had both dementia and pseudobulbar palsy, extensor planter response, and extrapyramidal signs, or who had both dementia and a history of stroke without a relationship between each other, were classified as having possible VaD. On the basis of the ADDTC, 11 of the patients who had both dementia and ≥2 lacunar infarcts were classified as having probable VaD, and 26 patients who had both dementia and a single lacunar infarct or had both dementia andBinswanger’s syndrome defined as the presence of early-onset urinary incontinence or gait disturbance, vascular risk factors, and WMHs, were classified as having possible VaD. Only 13 patients were classified as having probable or possible VaD on the basis of both criteria. Table 1 summarizes background characteristics, vascular risk factors, apoE genotypes, lacunar infarcts, and WMHs for each subgroup. The frequencies of apoE genotypes were comparable among the subgroups reassigned according to either criterion. The patients who fulfilled the ADDTC criteria for VaD more frequently had lacunar infarcts, WMHs, hypertension, lipid disorder, and drinking habit and were significantly older than those who did not fulfill the criteria. Regarding the NINDS/AIREN criteria, a significant difference was noted only for hypertension; those who fulfilled the VaD criteria more frequently had hypertension than did those excluded on the basis of this criterion.

The frequencies of apoE genotypes, lacunar infarcts, background characteristics, and vascular risk factors are summarized in Table 2 according to the presence or absence of WMHs. The distribution of apoE genotypes was comparable between the WMH-positive and WMH-negative groups (Table 2). The frequency of the apoE ε4 allele was 30.2% in the WMH-positive group and 30.1% in the WMH-negative group. Sixteen WMH-positive patients but only 3 WMH-negative patients had coexisting lacunar infarcts. Moreover, WMH-positive patients were significantly more hypertensive and older and were of lower education level than WMH-negative patients. The number of apoE ε4 alleles was not a significant predictor for WMHs before (OR 1.00, 95% CI 0.58 to 1.73 for 1 increase in ε4 allele) and after control for the demographic factors, dementia severity, vascular risk factors, and the presence of lacunar infarcts in a multiple logistic regression analysis (OR 1.06, 95% CI 0.53 to 2.14 for 1 increase in ε4 allele). The logistic regression analysis also demonstrated that advanced age (OR 3.03, 95% CI 1.63 to 5.62 for 10-year increase), hypertension (OR 3.83, 95% CI 1.35 to 10.90 for presence to absence), and lacunar infarcts (OR 4.91, 95% CI 1.07 to 22.62 for presence to absence), but

### Table 1. Background Characteristics of the Patients Who Fulfilled or Did Not Fulfill the Criteria of Vascular Dementia

<table>
<thead>
<tr>
<th></th>
<th>NINDS/AIREN Possible (n=37)</th>
<th>NINDS/AIREN Negative (n=54)</th>
<th>P*</th>
<th>ADDTC Probable (n=11)</th>
<th>ADDTC Possible (n=28)</th>
<th>ADDTC Negative (n=94)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>apoE ε4 dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (56.8)</td>
<td>41 (43.6)</td>
<td>0.39</td>
<td>6 (54.5)</td>
<td>13 (50.0)</td>
<td>43 (45.7)</td>
<td>0.91</td>
</tr>
<tr>
<td>1</td>
<td>14 (37.8)</td>
<td>45 (47.9)</td>
<td></td>
<td>4 (36.4)</td>
<td>12 (46.2)</td>
<td>43 (45.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (5.4)</td>
<td>8 (8.5)</td>
<td></td>
<td>1 (9.1)</td>
<td>1 (3.8)</td>
<td>8 (8.6)</td>
<td></td>
</tr>
<tr>
<td>Lacunar infarcts, n</td>
<td>6 (16.2)</td>
<td>13 (13.8)</td>
<td>0.73</td>
<td>11 (100)</td>
<td>8 (30.8)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WMHs, n</td>
<td>23 (62.2)</td>
<td>50 (53.2)</td>
<td>0.35</td>
<td>11 (100)</td>
<td>23 (88.5)</td>
<td>39 (41.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>74.2±8.9</td>
<td>73.3±8.2</td>
<td>0.56</td>
<td>77.5±4.3</td>
<td>78.5±6.4</td>
<td>71.7±8.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>27 (73.0)</td>
<td>74 (78.7)</td>
<td>0.48</td>
<td>8 (72.7)</td>
<td>19 (73.1)</td>
<td>74 (78.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>M</td>
<td>10 (27.0)</td>
<td>20 (21.3)</td>
<td></td>
<td>3 (27.3)</td>
<td>7 (26.9)</td>
<td>20 (21.3)</td>
<td></td>
</tr>
<tr>
<td>Duration, mo</td>
<td>39.8±28.5</td>
<td>31.8±20.1</td>
<td>0.07</td>
<td>18.5±14.3</td>
<td>40.5±30.6</td>
<td>34.1±20.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Education, y</td>
<td>8.9±2.0</td>
<td>9.2±2.7</td>
<td>0.55</td>
<td>8.0±1.5</td>
<td>8.6±2.5</td>
<td>9.4±2.5</td>
<td>0.11</td>
</tr>
<tr>
<td>MMSE</td>
<td>18.8±4.9</td>
<td>18.2±4.9</td>
<td>0.53</td>
<td>19.6±7.1</td>
<td>16.6±5.5</td>
<td>18.7±4.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypertension, n</td>
<td>16 (43.2)</td>
<td>23 (24.5)</td>
<td>0.03</td>
<td>7 (63.6)</td>
<td>10 (38.5)</td>
<td>22 (23.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>5 (13.5)</td>
<td>11 (11.7)</td>
<td>0.78</td>
<td>2 (18.2)</td>
<td>5 (19.2)</td>
<td>9 (9.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Lipid disorder, n</td>
<td>24 (64.9)</td>
<td>48 (51.1)</td>
<td>0.15</td>
<td>5 (45.5)</td>
<td>20 (76.9)</td>
<td>47 (50.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Drinking habit, n</td>
<td>9 (24.3)</td>
<td>19 (20.2)</td>
<td>0.60</td>
<td>5 (45.5)</td>
<td>8 (30.8)</td>
<td>15 (16.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Smoking habit, n</td>
<td>7 (18.9)</td>
<td>17 (18.1)</td>
<td>0.91</td>
<td>2 (18.2)</td>
<td>4 (15.4)</td>
<td>18 (19.2)</td>
<td>0.91</td>
</tr>
<tr>
<td>Cardiac disease, n</td>
<td>5 (13.5)</td>
<td>14 (14.9)</td>
<td>0.84</td>
<td>3 (27.3)</td>
<td>4 (15.4)</td>
<td>12 (12.8)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Values are mean±SD or number of patients with percentages in parentheses.

*χ² test for nominal variables and the 2-tailed t test or 1-way ANOVA for continuous variables.
TABLE 2. Demographic Factors, Dementia Severity, Frequencies of the apoE Genotype, and Vascular Risk Factors in Patients With and Without WMHs

<table>
<thead>
<tr>
<th></th>
<th>WMH Positive</th>
<th>WMH Negative</th>
<th>Statistical Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>apoE ε4 dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>35 (48.0)</td>
<td>27 (46.6)</td>
<td>χ² = 0.14</td>
<td>0.93</td>
</tr>
<tr>
<td>1</td>
<td>32 (43.8)</td>
<td>27 (46.6)</td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>6 (8.2)</td>
<td>4 (6.8)</td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>Lacunar infarcts, n</td>
<td>16 (21.9)</td>
<td>3 (5.2)</td>
<td>χ² = 7.31</td>
<td>0.007</td>
</tr>
<tr>
<td>Age, y</td>
<td>76.5±6.5</td>
<td>69.8±9.0</td>
<td>t = 4.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>56 (76.7)</td>
<td>45 (77.6)</td>
<td>χ² = 0.014</td>
<td>0.91</td>
</tr>
<tr>
<td>M</td>
<td>17 (23.2)</td>
<td>13 (22.4)</td>
<td></td>
<td>...</td>
</tr>
<tr>
<td>Duration, mo</td>
<td>33.3±23.7</td>
<td>34.9±22.3</td>
<td>t = 0.40</td>
<td>0.69</td>
</tr>
<tr>
<td>Education, y</td>
<td>8.8±2.2</td>
<td>9.6±2.8</td>
<td>t = 1.82</td>
<td>0.029</td>
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<tr>
<td>MMSE</td>
<td>18.1±5.1</td>
<td>18.8±4.7</td>
<td>t = 0.78</td>
<td>0.44</td>
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<tr>
<td>Hypertension, n</td>
<td>30 (41.1)</td>
<td>9 (15.5)</td>
<td>χ² = 10.1</td>
<td>0.002</td>
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<tr>
<td>Diabetes, n</td>
<td>10 (13.7)</td>
<td>6 (10.3)</td>
<td>χ² = 0.34</td>
<td>0.56</td>
</tr>
<tr>
<td>Lipid disorder, n</td>
<td>35 (47.9)</td>
<td>37 (63.8)</td>
<td>χ² = 3.28</td>
<td>0.07</td>
</tr>
<tr>
<td>Drinking habit, n</td>
<td>18 (24.7)</td>
<td>10 (17.2)</td>
<td>χ² = 1.06</td>
<td>0.30</td>
</tr>
<tr>
<td>Smoking habit, n</td>
<td>13 (17.8)</td>
<td>11 (19.0)</td>
<td>χ² = 0.029</td>
<td>0.86</td>
</tr>
<tr>
<td>Cardiac disease, n</td>
<td>9 (12.3)</td>
<td>10 (17.2)</td>
<td>χ² = 0.63</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Values are mean±SD or number of patients with percentages in parentheses.

not education level (OR 1.03, 95% CI 0.84 to 1.27 for 1-year increase), were independent significant predictors for WMHs. A secondary multiple logistic regression analysis of apoE ε4 allele presence/absence basis also revealed that the effect of apoE ε4 allele on WMHs was not significant (OR 0.87, 95% CI 0.36 to 2.08 for the presence relative to the absence) and that the effects of age (OR 3.07, 95% CI 1.64 to 5.71 for 10-year increase), hypertension (OR 3.76, 95% CI 1.33 to 10.60 for presence to absence), and lacunar infarcts (OR 4.82, 95% CI 1.05 to 22.18 for presence to absence) were independently significant.

Discussion

In the present study, by using multivariate statistics, we investigated the possibility of an interaction of the potential vascular risk factors for WMHs in a large number of patients with dementia. Our results clearly demonstrated that the apoE ε4 allele was not associated with WMHs and strongly support the view that the apoE ε4 allele has no effect on WM changes.22,27–29 It is noteworthy that the apoE ε4 allele frequency in the WMH-positive patients (30.1%) was as high as it was in the WMH-negative patients (30.0%), who completely fulfilled the criteria for probable AD. These figures were also quite similar to those reported in patients with AD and higher than those reported in the general population.54 The fact that the apoE ε4 allele frequency in the WMH-positive patients corresponded to that of AD patients might indicate that the majority of these patients had AD pathology regardless of the presence of WMHs, because all of these patients actually fulfilled the NINCDS/ADRDA criteria for probable AD when the changes in WM and lacunar infarcts were disregarded.

Our finding that WMHs were significantly associated with hypertension is compatible with previous reports55,56 and supports the concept of an underlying hypertensive microangiopathy and chronic cerebral ischemia.57 Lacunar infarcts in the basal ganglia, thalamus, and WM were usually accompanied with WM changes inBinswanger’s disease. Therefore, several authors have proposed the term “microangiopathy-related cerebral damage” (MARCD), which includes both WM changes and lacunar infarcts.58,59 Our result that WMHs were significantly associated with lacunar infarcts is consistent with this hypothesis. Schmidt et al59 examined 280 individuals without neuropsychiatric diseases through the use of a multiple logistic regression analysis and demonstrated that age and hypertension, but not the apoE ε4 allele, were independent significant predictors for MARCD (ie, for early confluent or confluent WMHs or lacunar infaracts). Their result is consistent with ours and may indicate that age and hypertension, but not the apoE ε4 allele, are independent risk factors for MARCD in both patients with and patients without dementia. Their study also demonstrated a significant effect of the apoE ε2/ε3 allele. However, because the prevalence of the apoE ε2/ε3 allele is very rare in the population with dementia,60,61 it is quite difficult to examine the effect of this allele in patients with dementia.

In conclusion, in patients with dementia, the apoE ε4 allele was not associated with WMHs, whereas advanced age, the presence of hypertension, and the presence of lacunar infarcts were independently associated with WMHs. The frequency of the apoE ε4 allele in the WMH-positive patients was quite similar to that in the WMH-negative patients. These findings suggest that WMHs were of ischemic origin and that WMHs were superimposed on the AD pathology in the majority of our patients. The effect of the apoE ε2 allele should be assessed in patients with dementia. However, the very low prevalence of this allele in the dementia population makes such studies difficult.

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