Impact of White Matter Changes on Clinical Manifestation of Alzheimer’s Disease
A Quantitative Study

Nobutsugu Hirono, MD; Hajime Kitagaki, MD; Hiroaki Kazui, MD; Mamoru Hashimoto, MD; Etsuro Mori, MD

Background and Purpose—There have been conflicting results involving the clinical significance of white matter changes in patients with Alzheimer’s disease (AD). We studied the association between the volume of white matter hyperintensities (WMHs) on T2-weighted images and cognitive, neurological, and neuropsychiatric symptoms.

Methods—The subjects were 76 AD patients who had WMHs but no obvious cerebrovascular diseases. We quantified the volume of WMHs by using fast-fluid–attenuated inversion recovery images and whole brain atrophy by using 3D spoiled gradient-echo images. Effects of WMHs and brain atrophy on dementia severity, cognitive function, neuropsychiatric disturbances, and neurological findings were examined.

Results—Whole brain atrophy was significantly associated with dementia severity and cognitive disturbances, as well as with grasp reflex and some kinds of neuropsychiatric disturbances. After we controlled for the effects of brain atrophy, duration of symptoms, and demographic factors, we found that WMH volume was not associated with global cognitive disturbances or dementia severity but was significantly associated with urinary incontinence, grasp reflex, and aberrant motor behaviors. Brain atrophy and WMH volume were not significantly correlated either before or after controlling for age, sex, education, and duration of symptoms. WMH volume was associated with hypertension, but brain atrophy was not positively correlated with any vascular risk factors.

Conclusions—Our results support the hypothesis that WMHs in AD patients are superimposed phenomena of vascular origin. WMHs contribute to specific neurological and neuropsychiatric manifestations but not to global cognitive impairment, which is more closely associated with brain atrophy. (Stroke. 2000;31:2182-2188.)

Key Words: Alzheimer disease ■ atrophy ■ neurological deficits ■ risk factors ■ white matter

White matter (WM) changes are often found in patients with vascular dementia, especially of small vessel/subcortical subtypes, including Binswanger’s disease, and are generally considered to be a consequence of chronic ischemia associated with microangiopathy.1,2 However, it is also true that the presence of WM changes is not exclusively linked to vascular dementia, because WM changes on neuroimagings are also common in patients with Alzheimer’s disease (AD).3-10 Presently, there is a lack of agreement on the effect of WM changes on the development of dementia.

Some studies have shown a significant relationship between WM changes and certain cognitive functions and/or dementia severity,11-17 whereas others5,10,18-32 have failed to find any such relationships in patients with AD. Different study populations and the heterogeneity of WM changes may explain the inconsistency among these studies. Selection of AD patients without vascular risk factors and/or neurological signs may result in excluding severe WM changes and ignoring the clinical significance of WM changes. Small subcortical infarcts frequently accompanied by WM changes,1,2 which do not necessarily exclude the diagnosis of AD by the clinical diagnostic criteria, obscure the independent effects of WM changes by affecting the strategic sites causing dementia.24 In some studies, periventricular changes in the form of caps or smooth halos were included, with irregular confluent changes in the deep and periventricular WM. The former changes are apparently of nonischemic origin, whereas the latter changes represent ischemic tissue damage.33,34 In addition, the neuroimaging technique used is an important factor. MRI is more sensitive to WM changes than is CT.35-38 Although WM changes have been semi-quantified with a visual rating scale in most studies, none of these scales have been validated, and the concordance of different scales is insufficient.39 Although MRI quantification of WM changes is desirable, a manual outlining of WM changes12,25

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is essentially dependent on visual inspection that may be affected by an arbitrary gray scale used for display and filming. Computer-based thresholding methods for voxel intensities are preferable. Finally, the effect of brain atrophy has rarely been considered, although some studies have analyzed the cerebrospinal fluid space. Because diffuse brain atrophy, which is a main gross pathological feature of AD, is an index of neuronal and synaptic loss, brain atrophy should also be taken into consideration in analyzing the impact of WM changes on cognitive function.

In the present study, we examined a purely selected cohort of patients with AD who had WM changes but no obvious cerebrovascular diseases so as to determine the effect of WM changes on cognitive, neurological, and neuropsychiatric symptoms. We quantified the volume of WM hyperintensities (WMHs) and brain atrophy on MRI by means of computer-based techniques. We also tested the hypothesis that WM changes are associated with vascular risk factors but not with brain atrophy.

### Subjects and Methods

The present study was conducted at the Hyogo Institute for Aging Brain and Cognitive Disorders (HI-ABCD), a research-oriented hospital for dementia

### Subjects

All procedures of the present 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 the present study, written informed consent was obtained from patients or their relatives.

On the basis of the following inclusion/exclusion criteria, 76 AD patients were selected from a consecutive series of 391 patients with dementia who were given a short-term admission for examination to the HI-ABCD infirmary between April 1997 and March 1999. All patients were examined by both neurologists and psychiatrists with standardized medical history inquiries, neurological examinations, routine laboratory tests, electroencephalography, magnetic resonance (MR) images of the brain, and MR angiography of the head and neck. The inclusion criteria were those identified by (1) the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, revised for dementia; (2) the presence of WM changes, which were defined as irregular periventricular, early confluent deep, or confluent deep WMH on T2-weighted MRI according to Fazekas and colleagues; and (3) the National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer’s Disease and Related Disorders Association, for AD when disregarding WM changes.

Although 234 patients fulfilled the inclusion criteria, 158 patients were excluded from the present study in accordance with the exclusion criteria. Excluded were patients (1) with medical illnesses possibly causing cognitive impairment or WM lesions, including demyelinating diseases, thyroid diseases, vitamin deficiencies, and malignant diseases with or without antineoplastic agents (n=23); (2) with focal brain lesions, including lacunar infarcts and hematoma (n=84); (3) with complication of developmental abnormalities, mental diseases, substance abuse, or significant neurological antecedents, such as brain trauma, brain tumor, epilepsy, and inflammatory disease (n=21); (4) with evidence of severe intracranial or cervical arterial occlusive lesions on MR angiography (n=1); and (5) whose informed consent was not obtained (n=29).

The subjects consisted of 64 women and 12 men; the mean±SD age at examination was 75.6±7.1 years, and the mean educational attainment was 8.8±2.0 years. The mean duration of symptoms, determined through an interview with the primary caregiver and defined as the time between the first appearance of symptoms of sufficient severity to interfere with social or occupational functioning and the admission, was 30.8±19.4 months. The functional severity was very mild in 7 patients, mild in 41 patients, moderate in 22 patients, and severe in 6 patients, as determined by the Clinical Dementia Rating Scale (CDR). No patient had a history of stroke.

### Assessment of Vascular Risk Factors and Neurological Disturbances

Hypertension, diabetes mellitus, lipid disorder, smoking habit, drinking habit, and cardiac diseases were evaluated as vascular risk factors. Hypertension was judged as present when either a systolic pressure of >160 mm Hg or a diastolic pressure of >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 when a history of treatment for diabetes mellitus was present. 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 ≥1 cigarette/d for ≥1 year, and drinking habit was defined as ≥30 mL ethanol equivalent per day for ≥1 year sometime in life. Cardiac diseases were assumed to be present whenever there was a known history or clinical demonstration of any kind of heart disease, including myocardial infarction, angina pectoris, and arrhythmia.

A careful neurological examination was given to document the presence or absence of hemiparesis, sensory loss, visual field defects, postural instability (gait disturbance and/or paresis), pyramidal signs (hyperreflexia, spasticity, and/or extensor plantar responses), extrapyramidal signs (resting tremor, bradykinesia, and/or rigidity), pseudobulbar palsy, ataxia, grasp reflexes, and urinary incontinence. No attempt was made to grade the severity of these risk factors or neurological abnormalities.

### Assessment of Cognitive Function and Neuropsychiatric Status

We assessed the cognitive function of the patients with the Mini-Mental State Examination, Wechsler Adult Intelligence Scale–Revised, and Alzheimer’s Disease Assessment Scale–Cognitive Part. The 10-word list recall subtest of the Alzheimer’s Disease Assessment Scale was also analyzed separately. The patients’ behavioral changes were assessed semiquantitatively during an interview with the caregiver by using the Neuropsychiatric Inventory (NPI). In the NPI, the following 10 behavioral changes in dementia were rated on the basis of the condition of the patients in the previous month before the interview: delusions, hallucinations, depression (dysphoria), anxiety, agitation and aggression, disinhibition, euphoria, irritability and lability, apathy, and aberrant motor activity. According to the criterion-based rating scheme, the severity of each manifestation was classified into 4 grades (from 0 to 3), and the frequency of each manifestation was classified into 5 grades (from 0 to 4). The NPI score (severity×frequency) was calculated for each manifestation (range of possible scores 0 to 12). All clinical measures were taken with the investigators blinded to the inclusion of subjects in the present study.

### MR Acquisition

MR was performed on a 1.5-T superconducting magnet (Signa Advantage, General Electric Medical Systems). Axial double-echo fast-spin echo T2-weighted images (3000/105/2 [replication time/ effective echo time/excitations]), spin-echo T1-weighted images (550/15/2), and fast-fluid–attenuated inversion recovery (FLAIR) images (9002/147/22001 [replication 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 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 200×200 mm, and the matrix size was 256×256. All scans were...
Measurement of Volume of WMH Areas

Original images (top) and processed images (bottom). The volume of WMH areas was obtained by automatic count of the number of voxels of values higher than the threshold (shown in blue) within the regions of interest determined by a manually driven mouse cursor (white line).
TABLE 1. Risk Factors, Neurological Signs, and Scores of Cognitive Tests and NPI

<table>
<thead>
<tr>
<th>Risk factors: cognitive test scores</th>
<th>Frequency, n (%)</th>
<th>Score</th>
<th>Mean ± SD Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>30 (39.5)</td>
<td>MMSE</td>
<td>19.1 ± 4.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (9.2)</td>
<td>ADAS total</td>
<td>23.8 ± 9.7</td>
</tr>
<tr>
<td>Lipid disorder</td>
<td>35 (46.1)</td>
<td>ADAS recall</td>
<td>3.5 ± 1.3</td>
</tr>
<tr>
<td>Smoking</td>
<td>12 (15.8)</td>
<td>WAIS VIQ</td>
<td>78.4 ± 11.5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>12 (15.8)</td>
<td>WAIS PIQ</td>
<td>75.7 ± 13.5</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>10 (13.2)</td>
<td>WAIS FIQ</td>
<td>75.4 ± 12.1</td>
</tr>
<tr>
<td>Neurological disturbances: NPI scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyramidal sign</td>
<td>12 (15.8)</td>
<td>Delusions</td>
<td>2.5 ± 3.5</td>
</tr>
<tr>
<td>Extrapyramidal sign</td>
<td>10 (13.2)</td>
<td>Hallucinations</td>
<td>0.2 ± 0.9</td>
</tr>
<tr>
<td>Grasp reflex</td>
<td>7 (9.2)</td>
<td>Agitation</td>
<td>2.2 ± 3.5</td>
</tr>
<tr>
<td>Postural instability</td>
<td>19 (25)</td>
<td>Dysphoria</td>
<td>1.2 ± 2.5</td>
</tr>
<tr>
<td>Pseudobulbar palsy</td>
<td>1 (1.3)</td>
<td>Anxiety</td>
<td>1.1 ± 2.5</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>18 (23.7)</td>
<td>Euphoria</td>
<td>0.1 ± 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apathy</td>
<td>4.6 ± 3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disinhibition</td>
<td>1.4 ± 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irritability</td>
<td>1.8 ± 3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aberrant motor behavior</td>
<td>2.4 ± 2.4</td>
</tr>
</tbody>
</table>

MMSE indicates Mini-Mental State Examination; ADAS, Alzheimer’s Disease Assessment Scale–Cognitive Part; WAIS, Wechsler Adult Intelligence Scale–Revised; VIG, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient; and FIQ, Full Scale Intelligence Quotient.

Results

The mean ± SD WMH volume was 38.4 ± 23.3 cm³. The mean WBV was 1009 ± 96 cm³, TIV was 1394 ± 103 cm³, and nWBV was 0.725 ± 0.048. No significant correlation was noted between the volume of WMHs and nWBV before \( r = -0.002, P = 0.99 \) or after \( r = 0.12, P = 0.31 \) controlling for the effects of age, sex, and education. A significant correlation was present between nWBV and the risk factors. WMH volume was positively correlated with hypertension. nWBV was positively correlated with smoking (nWBV was larger in smokers). Table 4 summarizes the partial Spearman rank correlation coefficients of volume of WMHs and nWBV with neurological disturbances, CDR, cognitive test scores, and NPI scores after controlling for the effects of the confounding variables. The volume of WMHs was significantly correlated with incontinence and grasp reflex and with the NPI aberrant motor behavior scores but not with cognitive test scores or CDR. On the other hand, nWBV was significantly correlated with all cognitive test scores and CDR, with grasp reflex, and with NPI disinhibition and aberrant motor behavior scores.

Discussion

WM changes, when defined as irregular periventricular hyperintensities, early confluent deep WMHs, and confluent deep WMHs, had a significant relationship with hypertension, as expected. An association between WM changes and high blood pressure or hypertension and/or the other vascular risk factors has been demonstrated in a number of clinical studies,7,13,18,44 and the relationship between these WM changes and ischemic vascular changes has been documented in pathological studies.33,34 On the other hand, we found no significant correlation between brain atrophy and vascular risk factors. Furthermore, brain atrophy was not correlated with WMH volume either with or without controlling for age, sex, education, and the duration of symptoms. Using quanti-
TABLE 4. Association of volume of WMHs and nWBV With Neurological, Cognitive, and Neurobehavioral Symptoms

<table>
<thead>
<tr>
<th>Neurological findings</th>
<th>WMH Volume</th>
<th>nWBV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rs</td>
<td>P</td>
</tr>
<tr>
<td>Pyramidal sign</td>
<td>-0.005</td>
<td>0.97</td>
</tr>
<tr>
<td>Extrapyramidal sign</td>
<td>-0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>Incontinence</td>
<td>0.26</td>
<td>0.027</td>
</tr>
<tr>
<td>Grasp</td>
<td>0.32</td>
<td>0.007</td>
</tr>
<tr>
<td>Postural instability</td>
<td>-0.019</td>
<td>0.88</td>
</tr>
</tbody>
</table>

Cognitive tests

<table>
<thead>
<tr>
<th></th>
<th>rs</th>
<th>P</th>
<th>rs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.022</td>
<td>0.86</td>
<td>0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADAS</td>
<td>-0.001</td>
<td>0.99</td>
<td>-0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADAS recall</td>
<td>0.11</td>
<td>0.35</td>
<td>0.30</td>
<td>0.011</td>
</tr>
<tr>
<td>WAIS VIQ</td>
<td>0.025</td>
<td>0.84</td>
<td>0.35</td>
<td>0.003</td>
</tr>
<tr>
<td>WAIS PIQ</td>
<td>-0.11</td>
<td>0.38</td>
<td>0.48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WAIS RQ</td>
<td>-0.039</td>
<td>0.75</td>
<td>0.47</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CDR</td>
<td>0.11</td>
<td>0.36</td>
<td>-0.26</td>
<td>0.028</td>
</tr>
</tbody>
</table>

NPI scores

<table>
<thead>
<tr>
<th></th>
<th>rs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusion</td>
<td>-0.005</td>
<td>0.97</td>
</tr>
<tr>
<td>Hallucination</td>
<td>-0.069</td>
<td>0.57</td>
</tr>
<tr>
<td>Aggression</td>
<td>0.11</td>
<td>0.37</td>
</tr>
<tr>
<td>Depression</td>
<td>0.032</td>
<td>0.79</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.16</td>
<td>0.18</td>
</tr>
<tr>
<td>Euphoria</td>
<td>0.063</td>
<td>0.60</td>
</tr>
<tr>
<td>Apathy</td>
<td>0.14</td>
<td>0.23</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>0.14</td>
<td>0.25</td>
</tr>
<tr>
<td>Irritability</td>
<td>0.056</td>
<td>0.64</td>
</tr>
<tr>
<td>Aberrant motor behavior</td>
<td>0.28</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Values are PValues or partial Spearman rank correlation coefficients (rs) after controlling for effects of age, sex, education, duration of symptoms, and either nWBV or volume of WMHs.

Neurological, Cognitive, and Neurobehavioral Symptoms

- Pyramidal sign
- Extrapyramidal sign
- Incontinence
- Grasp
- Postural instability

Cognitive tests

- MMSE
- ADAS
- ADAS recall
- WAIS VIQ
- WAIS PIQ
- WAIS RQ
- CDR

NPI scores

- Delusion
- Hallucination
- Aggression
- Depression
- Anxiety
- Euphoria
- Apathy
- Disinhibition
- Irritability
- Aberrant motor behavior

Values are PValues or partial Spearman rank correlation coefficients (rs) after controlling for effects of age, sex, education, duration of symptoms, and either nWBV or volume of WMHs.

Although WMHs are sometimes reported as being significantly more frequent in AD patients than in control subjects, the increase is attributed to mild periventricular changes of probably nonischemic origin, including caps, halos, and thin lining. Moreover, Scheltens et al reported that compared with WMH in control subjects, WMH was more intense in patients with senile onset AD but not in patients with presenile onset AD and suggested that additional microvascular factors are involved in elderly patients with senile onset AD. Together with those findings in the recent studies, our results suggest that WM changes in AD patients, when they are defined as irregular periventricular or confluent deep WMHs, are superimposed phenomena of ischemic origin. It is also interesting that our results demonstrated that a smoking habit had a modest but significant protective effect against brain atrophy. Smoking has been reported to prevent AD, and our findings might support this hypothesis.

In the present study, WMH volume was not correlated with the severity of dementia, global cognitive impairment, or memory impairment. This finding is compatible with the findings of our previous study, in which we demonstrated that WMHs were associated with decreased cerebral blood flow but not with decreased oxygen metabolism in patients with AD. Brain atrophy, but not reduced cerebral blood flow, was significantly associated with cognitive impairments. These findings suggest that the cognitive impairment in our patients is not attributable to WM changes but to brain atrophy, although WM changes are reported to impair some cognitive functions that were not evaluated in the present study. Although WMHs associated with more severe small-vessel diseases might affect cognitive functions in patients with AD, Snowdon et al reported that in subjects with pathological evidence of AD, those lacunar infarcts in the basal ganglia, thalamus, or deep white matter had poorer cognitive function and a higher prevalence of dementia than those without infarcts. However, even in patients who were diagnosed as having vascular dementia, the association between WM changes and global cognitive impairment is unconvincing. Although Binswanger’s disease reportedly causes dementia without a cortical degenerative process, the pathological features of this disorder include not only WM changes but also lacunar infarcts in the basal ganglia and thalamus. Coexistent lacunar infarcts may affect the strategic sites, causing dementia. Inzitari et al pointed out that a strong association between WM changes and dementia was an epiphenomenon that could be explained by a history of stroke. In a longitudinal study of patients with lacunar infarcts, Loeb et al found that the development of dementia was significantly associated with cerebral atrophy and new focal cerebrovascular episodes but not with WM changes. These findings, together with those in the present study, suggest that cognitive impairment, both in AD and vascular dementia, is not principally attributable to WM changes.

On the other hand, the present study clearly demonstrated that WM changes and brain atrophy were independently associated with certain neurological and neurobehavioral signs. Urinary incontinence, grasp reflexes, and aberrant motor behaviors were significantly correlated with WMH volume even after controlling for brain atrophy, although the latter 2 were also correlated with brain atrophy after controlling for WMH volume. Urinary incontinence is considered to be one of the central clinical features of Binswanger’s disease, and an involvement of WM changes in its development has been shown in previous studies. Primitive reflexes have also been reported to be associated with WM changes in elderly people and in patients with dementia. Positive associations between WM changes and psychiatric symptoms have been reported in subjects without dementia. Although previous studies have failed to find a relationship between WM changes and neurobehavioral signs in patients with dementia, the present study clearly demonstrated that WM changes were involved in the development of aberrant motor behaviors. Aberrant motor behaviors, including wandering, pacing, and rummaging, belong to repetitive and excessive behaviors, which are likely to be caused by frontal lobe dysfunction. Our findings indicate that WM changes would
at least add frontal lobe–related neurological and neurobehavioral features as manifestations of dementia.

In conclusion, WM changes in AD patients without any obvious cerebrovascular diseases are related to hypertensive microangiopathy and are independent of brain atrophy that would be attributable to a degenerative process. WM changes contribute to the development of some frontal lobe–related neurological and neurobehavioral signs but not to the development of a global cognitive impairment, which is more closely associated with brain atrophy. Further studies are needed to generalize our findings to include AD patients with more severe vascular disease.

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References


Quantitative Study of WM Hyperintensities


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