Frontal White Matter Lesions and Dementia in Lacunar Infarction

Hitoshi Fukuda, MD, Shotai Kobayashi, MD, Kazunori Okada, MD, and Tokugoro Tsunematsu, MD

We studied the associations of mental deterioration and blood pressure with severity and location of lesions in the cerebral white matter of 35 patients (27 men and eight women) aged 52-84 (mean 70.9) years with multiple lacunar infarcts; 21 had no dementia and 14 were demented. Using magnetic resonance imaging to evaluate lesion severity, we determined that demented patients had more severe lesions than nondemented patients; this difference was especially prominent for lesions in the frontal lobe ($p<0.001$). Score on the dementia rating scale of Hasegawa et al was negatively correlated with severity of the lesions in the frontal lobe. Blood pressure was positively correlated with the severity of white matter lesions. We show that severity of lesions in the white matter, especially in the frontal lobe, is correlated with mental deterioration of patients with multiple lacunar infarcts. Because uncontrolled hypertension is related to the severity of such lesions, careful selection of antihypertensive treatment is important in preventing both the cerebral lesions and the associated mental deterioration. (Stroke 1990;21:1143-1149)

Extensive lesions of the cerebral white matter cause the dementia known as Binswanger's disease. Several investigators have reported that hypertension is a major risk factor for such ischemic lesions. In a clinicopathologic study of the autopsied brains of patients with vascular dementia and a lacunar state, Ishii et al suggested that not only the lacunae but also incomplete softening of the white matter, especially in the frontal lobe, were important causes of the dementia.

The purpose of our study was to investigate the associations of mental deterioration and blood pressure with severity and location of lesions in the cerebral white matter of patients with multiple lacunar infarcts.

Subjects and Methods

We retrospectively evaluated patients who were seen in the Shimane Medical University Hospital from 1987 to 1988 and diagnosed as having multiple lacunar infarcts from their clinical signs and symptoms, laboratory data, and brain images. All patients had a history of stroke. Computed tomography (CT) and magnetic resonance imaging (MRI) using the inversion-recovery method demonstrated multiple ischemic infarcts of restricted size in the deeper parts of the patients' brains; their neurologic deficits could be explained by these lacunae. We excluded patients with obvious cortical lesions, those with acute stroke, those who had been obviously demented before their strokes, and those whose MRI scans were of poor quality (had motion artifacts). After exclusion, there were 35 patients (27 men and eight women) aged 52-84 (mean 70.9) years; 21 (15 men and six women, aged 54-84 [mean 69.3] years) had no dementia, and the other 14 (12 men and two women, aged 52-84 [mean 73.2] years) were demented.

Dementia was diagnosed based on the DSM-IIIR. Fourteen demented patients had an ischemic score of Hachinski et al of >10 points, and their CT and MRI scans demonstrated multiple lacunae without cortical lesions. All 21 demented patients were diagnosed as having multi-infarct dementia. Yoshimura et al reported that the so-called mixed-type dementia with pathologic features of both senile and vascular dementia accounted for only 19 of the 216 autopsied brains from demented persons in Japan. Moreover, those patients with mixed-type dementia had signs of cognitive impairment before their strokes. Therefore, we excluded patients who had been obviously demented before their strokes.

The diastolic, systolic, and mean arterial blood pressures of each patient were the mean of 10 serial measurements obtained several months before MRI. We compared age and blood pressure in the two groups using Student's $t$ test and the incidence of risk...
FIGURE 1. Top left: T1-weighted magnetic resonance image; top right: long spin-echo image; bottom left: inversion-recovery image; and bottom right: schema of axial slice, all at level of basal ganglia. Severity of lesions in white matter was measured on T1-weighted image in regions 1 and 2 shown in schema.

c factors for cerebrovascular disease as documented in the patients' records using the $\chi^2$ test.

The MRI studies were performed using an MRT-15 unit (Toshiba, Tokyo, Japan) with a 0.15-T magnet at Shimane Institute of Health Science. Brain images were obtained approximately parallel to the orbitomeatal line in the transverse plane. Absolute T1-weighted images were obtained by taking inversion-recovery (repetition time [TR] 2,000 msec; echo time [TE] 40 msec; inversion time 400 msec) and spin-echo (TR 1,600 msec; TE 40 msec) scans at the same time (Figures 1 and 2). We evaluated severity of
FIGURE 2. Top left: T1-weighted magnetic resonance image; top right: long spin-echo image; bottom left: inversion-recovery image; and bottom right: schema of axial slice, all at level of body of lateral ventricle. Severity of lesions in white matter was measured on T1-weighted image in regions 3–8 shown in schema.

the white matter lesions on T1-weighted images as distance from the nearest margin of the lateral ventricle to the point at which the T1 value exceeded 400 msec on a television monitor; distance was measured using commercially available software for the MRI unit. In this study, the T1 value of normal white matter was <300 msec. The area in which the T1 value exceeds 400 msec is nearly equal to the area of hyperintensity shown by the T2-weighted method. This area shows not only the lacuna but also the so-called periventricular hyperintensity.
We measured severity of the white matter lesions in eight regions: the right and left frontal lobe on an axial slice at the level of the basal ganglia (Figure 1) and the right and left anterior (frontal), middle (frontoparietal), and posterior (parieto-occipital) portions on an axial slice at the level of the body of the lateral ventricle (Figure 2). It was difficult to measure severity of the white matter lesions in posterior areas on an axial slice at the level of the basal ganglia because white matter in those areas was narrow, especially when brain atrophy was severe, and contamination of the white matter with the cortex and the subarachnoid space could not be excluded. We compared severity between groups for each region individually and for the sum of all eight regions using Student's t test. We investigated the relations of the sum of severities with diastolic, systolic, and mean arterial blood pressures for all 35 patients and for each group separately using linear regression analysis.

We studied interrater reliability of the severity measure using MRI scans from 10 of the 35 patients analyzed by three observers. We evaluated interrater agreement using Pearson's correlation coefficients.

Using the dementia rating scale of Hasegawa et al, we evaluated the mental abilities of 26 of the 35 patients, 12 (nine men and three women) without dementia and the 14 (12 men and two women) who were demented. This dementia rating scale is a useful bedside method of scoring cognitive impairment and consists of five subtests to measure orientation, general information, calculation, memory recall, and memorization. The maximum score is 32.5 points, with low scores reflecting more cognitive impairment. We investigated the relations of severity and location of the white matter lesions with score on the dementia rating scale for the 26 patients using linear regression analysis. Data are presented as mean±SD. Statistical significance was tested using Student's t distribution with a probability value of 0.05.

Results

Table 1 shows the clinical characteristics of the two groups. There were no significant differences in age, blood pressure, or the incidence of risk factors for cerebrovascular disease between groups.

In the comparison of lesion severity as measured by three observers, high levels of interrater agreement were obtained. Correlations ranged from 0.9320 (p<0.001) to 0.9978 (p<0.001) and averaged 0.9760.

Severity of the white matter lesions in each region for the two groups is shown in Figure 3. White matter lesions in the demented patients were significantly more severe than those in the nondemented patients in all regions, especially in the frontal lobe around the anterior horns of the lateral ventricles. The sum of severities of the white matter lesions for all eight regions was also higher in the demented group than in the nondemented group (100±25 and 47±25 mm, respectively; p<0.001).

The correlations between severity of the white matter lesions in all eight regions and score on the dementia rating scale for 26 patients appear in Table 2. Severity was significantly correlated with score in the anterior half of the brain, namely, the frontal lobe. The correlation was strongest in the frontal lobe around the anterior horns (Figure 4).

Diastolic, systolic, and mean arterial blood pressures in all 35 patients and in each group individually were significantly correlated with the sum of severities of the white matter lesions (Table 3). Diastolic

![figure 3](attachment:image URL)
TABLE 2. Correlation Coefficients and Probabilities for Severity of White Matter Lesions and Score on Dementia Rating Scale for 26 Patients

<table>
<thead>
<tr>
<th>Region</th>
<th>Location</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior horns</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>R frontal lobe</td>
<td>-0.701</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>anterior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>L frontal lobe</td>
<td>-0.790</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>anterior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body of lateral ventricle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R anterior</td>
<td>-0.621</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L anterior</td>
<td>-0.538</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R middle</td>
<td>-0.626</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L middle</td>
<td>-0.363</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R posterior</td>
<td>-0.189</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L posterior</td>
<td>-0.273</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>-0.682</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

R, right; L, left; NS, not significant.

blood pressure was most strongly correlated with severity of the white matter lesions (Figure 5).

Discussion

Several investigators have suggested an association between dementia and extensive lesions in the white matter of patients with multiple lacunar infarcts. Positive relations of white matter lesions to a history of stroke and to atherosclerogenic risk factors such as hypertension and diabetes mellitus have been reported. The area surrounding the anterior horns is a common site for the lacunae. Ishii et al described a clinicopathologic study of 30 autopsied brains of patients with vascular dementia and a lacunar state and suggested that not only the lacunae but also incomplete softening of the white matter, especially in the frontal lobe, were important causes of the dementia. Kameyama studied 700 autopsied brains and reported that persons with frontal cerebrovascular lesions, especially multiple infarcts in the bilateral white matter of the frontal lobe, cingulate gyrus, and anterior part of the corpus callosum, had a higher incidence of dementia. Our findings agree with these previous reports.

In a study of multi-infarct dementia using oxygen-15 positron emission tomography, Ujike et al reported that decreases in cerebral blood flow and metabolism were most prominent in the frontal lobe. We suggest that their results correspond with a predominant lesion in the white matter of the frontal lobe in persons with multi-infarct dementia.
Extensive frontal white matter lesions are closely related to the severity of white matter lesions, especially lacunar infarcts. Because uncontrolled hypertension is correlated with multiple lacunae and incomplete softening may enlarge to hypertensive vasculopathy of small arteries and arterioles in the white matter. Ishizaki reported the cases of subcortical arteriosclerotic encephalopathy reported by Olszewski were attributed to hypertensive vasculopathy of small arteries and arterioles in the white matter. Ishizaki reported that multiple small infarcts around the basal ganglia (état lacunaire) may be associated with subcortical arteriosclerotic encephalopathy in the brains of elderly patients with a history of hypertension. Multiple lacunae and incomplete softening may enlarge more easily in those patients with multiple lacunar infarcts and uncontrolled hypertension. Ischemic lesions elongate both the T1 and T2 values on MRI. Many studies have shown that white matter lesions on MRI correspond to demyelination, such conditions as etat crible, and lacunar or gliosis. Although we used T1 values, the area in which the T1 value exceeds 400 msec is nearly equal to the high-intensity area shown by the T2-weighted method. Therefore, we consider the white matter lesions in our study to be ischemic lesions, especially lacunar and areas of incomplete softening.

The positive correlation between blood pressure and severity of white matter lesions suggests that uncontrolled hypertension accelerates the progression of white matter lesions. An association between hypertension and white matter lesions has been reported. Hypertension is a major risk factor for lacunae. The cases of subcortical arteriosclerotic encephalopathy reported by Olszewski were attributed to hypertensive vasculopathy of small arteries and arterioles in the white matter. Ishizaki reported that multiple small infarcts around the basal ganglia (état lacunaire) may be associated with subcortical arteriosclerotic encephalopathy in the brains of elderly patients with a history of hypertension. Multiple lacunae and incomplete softening may enlarge more easily in those patients with multiple lacunar infarcts and uncontrolled hypertension. Ischemic lesions elongate both the T1 and T2 values on MRI. Extensive frontal white matter lesions are closely related to mental deterioration.

Although a difference between demented and nondemented patients in the severity of white matter lesions was prominent in our study, mean arterial blood pressure did not differ significantly between groups. We speculate that there are differences in the history of hypertension such as severity, duration, therapy, and episodes of transient hypotension. However, these factors cannot be accurately determined in a retrospective study. More detailed prospective studies are necessary to investigate this possibility.

Our study shows that severity of white matter lesions, especially in the frontal lobe, is correlated with mental deterioration in patients with multiple lacunar infarcts. Because uncontrolled hypertension is related to the severity of white matter lesions, selection of appropriate antihypertensive therapy is important in preventing both white matter lesions and mental deterioration.

To what level must we reduce blood pressure in a hypertensive patient to prevent white matter lesions? We acknowledge the technical contributions of Akira Besho, Shimane Institute of Health Science. Thanks are also due to Dr. Shuhei Yamaguchi, Dr. Hiromi Koide, Dr. Nobuo Suyama, and Dr. Hirokazu Bokura for much help.

This question is very difficult to answer, especially during the later stages of uncontrolled hypertension when vasculopathy may already be severe. During this stage, overreduction of blood pressure may lead to ischemic brain lesions. Autoregulation of the cerebral circulation also changes in hypertensive patients. The lower limit of cerebrovascular autoregulation is higher among persons with hypertension than among those who are normotensive, and the extent of the change varies among patients. Therefore, optimal blood pressure, which not only maintains sufficient cerebral blood flow but also prevents the formation of hypertensive vasculopathy, may also differ in each case.

### References

5. McQuinn BA, O'Leary DH: White matter lucencies on computed tomography, subacute arteriosclerotic encephalopathy (Binswanger's disease), and blood pressure. Stroke 1987; 18:900–905

### Table 3. Correlation Coefficients and Probabilities for Sum of Severities of White Matter Lesions and Blood Pressure

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Blood pressure (mm Hg)</th>
<th>Nondemented (n=21)</th>
<th>Demented (n=14)</th>
<th>Total (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td>0.711</td>
<td>&lt;0.001</td>
<td>0.600</td>
</tr>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td>0.528</td>
<td>&lt;0.025</td>
<td>0.607</td>
</tr>
<tr>
<td>Mean arterial</td>
<td></td>
<td></td>
<td>0.634</td>
<td>&lt;0.005</td>
<td>0.634</td>
</tr>
</tbody>
</table>
17. Awad IA, Johnson PC, Spetzler RF, Hodak JA: Incidental subcortical lesions identified on magnetic resonance imaging in the elderly: II. Postmortem pathological correlations. Stroke 1986;17:1090–1097

KEY WORDS • dementia • hypertension • lacunar infarction
Frontal white matter lesions and dementia in lacunar infarction.
H Fukuda, S Kobayashi, K Okada and T Tsunematsu

Stroke. 1990;21:1143-1149
doi: 10.1161/01.STR.21.8.1143

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/21/8/1143

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/