A Radiologic Study of Dynamic Processes in Lacunar Dementia

Yasufumi Tanaka, MD, Osamu Tanaka, MD, Yoshikuni Mizuno, MD, and Mitsuo Yoshida, MD

Using magnetic resonance imaging and digitized brain computed tomography, we evaluated 33 elderly patients with documented lacunar stroke and divided them into three groups (nondemented, n=15; borderline, n=9; and demented, n=9) by neuropsychological assessments and DSM III criteria. We evaluated the extent of white matter lesions and the degree of atrophy of specific anatomic structures, such as the corpus callosum, using magnetic resonance imaging and quantified the volumes of the ventricles, the subarachnoid spaces, and the brain parenchyma using digitized brain computed tomography. Our results show that both borderline and demented patients had significantly more extensive white matter lesions than nondemented patients, indicating a significant relation between the extent of white matter lesions and intellectual decline. In addition, borderline and demented patients had significantly larger ventricles and more brain atrophy than nondemented patients; demented patients also had significantly larger subarachnoid spaces than nondemented patients and more brain atrophy than borderline patients. Our findings suggest that in most patients with lacunar stroke, periventricular and subcortical white matter lesions with subsequent white matter atrophy first induce ventricular enlargement, followed by generalized brain atrophy, resulting in dementia. (Stroke 1989;20:1488-1493)

Vascular dementia and dementia of the Alzheimer type are two main types of dementia. Vascular dementia can be divided into three major subgroups: multiple discrete strokes following thrombotic or embolic occlusion of large cerebral arteries (multi-infarct dementia)1-2; multiple, small, deep subcortical lacunar infarcts, mostly located in the anterior and middle cerebral artery distributions (the lacunar state3-5 or lacunar dementia6'7); and subcortical arteriosclerotic encephalopathy (Binswanger's disease) attributed to arteriosclerosis of the long penetrating cerebral arteries, arterioles, and capillaries.2-6'12 However, it is very difficult to distinguish the lacunar state type from the Binswanger type of vascular dementia on the basis of clinical or radiographic features,4-13 and some investigators claim that the clinical and the pathologic features of these disorders are identical.5-7,10'13

Recently, with the advent of high-resolution computed tomography (CT) and magnetic resonance imaging (MRI), periventricular white matter lesions traditionally associated with Binswanger's disease are being recognized with increasing frequency. Several studies indicate that these lesions are more common in the elderly14-20 and in hypertensive individuals.17,18,20-24 However, the association of these lesions with intellectual impairment remains uncertain.

We performed MRI on 33 elderly patients with lacunar stroke to determine whether there is a relation between white matter lesions and intellectual impairment. Using digitized brain CT, we also quantified the volumes of the ventricles, the subarachnoid spaces, and the brain parenchyma.

Subjects and Methods

We studied 33 patients who had a history of lacunar stroke, a clinical picture consistent with one of the classic lacunar syndromes described by Fisher,25 and CT and/or MRI evidence of lacunar infarcts that appeared responsible for the symptoms. All patients had an ischemic score of ≥7 according to Hachinski et al.26 All 33 patients had >6 years of education and no history of alcohol or drug abuse; renal, hepatic, or pulmonary disease; or heart failure.

For controls, we studied 10 men and two women with no history of neurologic disorders or alcoholism in the same manner as the patient group, except that MRI was not performed. The mean±SEM age and years of education of the controls was 67.4±4.3

From the Departments of Neurology (Y.T., Y.M., M.Y.) and Radiology (O.T.), Jichi Medical School, Tochigi, Japan.

Address for reprints: Yasufumi Tanaka, MD, Department of Neurology, Jichi Medical School, 3311-1 Yakushiji, Minamikawachi, Tochigi 329-04, Japan.

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The Mini-Mental State Examination (MMSE), modified for use in the Japanese, was used to measure overall mental performance. The MMSE is divided into six subtests (orientation, registration, attention and calculation, recall, language, and copying a figure) and has a maximum score of 30. The MMSE score of the controls ranged from 24 to 30 points.

The MMSE has been claimed to correlate well with more extensive assessments of intellectual performance, such as the Wechsler Adult Intelligence Scale. However, not all patients with intellectual impairment have a low score on the MMSE; its sensitivity varies from 76% to 87%. Accordingly, an additional neuropsychological examination was administered to evaluate the degree of intellectual impairment in detail. Since the clinical features of lacunar dementia have been suggested to be due mainly to frontal lobe dysfunction, the modified Wisconsin Card Sorting Test (WCST) was selected from various measures of frontal lobe function. In the WCST, 48 cards with stimuli in various combinations of color, form, and number are sorted according to an unknown and varying sequence of principles using only error feedback. The score on the WCST is the number of categories correctly identified. Controls identified 4-7 categories.

MRI was performed using a resistive magnet with a main magnetic field strength of 0.22 T. T2-weighted images in the axial plane were obtained using a spin–echo pulse sequence with a repetition time of 2 seconds and an echo time of 80 msec, T2-weighted images in the sagittal plane were obtained using an inversion–recovery pulse sequence with a repetition time of 2 seconds, an echo time of 30 msec, and an inversion time of 500 msec. We used a 256×256 matrix with one acquisition, and the slice thickness was 10 mm, with no gap between slices.

A radiologist evaluated the MRI scans without the corresponding clinical information. First, the location and extent of white matter lesions by spin–echo pulsing were graded; small triangular foci surrounding the frontal horns were ignored because such foci have been reported to have no pathologic significance by histologic observation. Grade 0 was defined as no white matter lesions except for small triangular foci surrounding the frontal horns; Grade 1 as thin bands surrounding the subependymal region of the ventricles; Grade 2 as thicker bands surrounding the subependymal region of the ventricles, with additional discrete patchy subcortical white matter lesions beside or above the lateral ventricles; Grade 3 as more extensive, confluent subcortical white matter lesions beside and above the lateral ventricles, partially confluent with the bands surrounding the lateral ventricles; and Grade 4 as marked thick, irregular bands completely surrounding the lateral ventricles (Figure 1). The radiologist then graded the degree of atrophy of the corpus callosum by inversion–recovery pulsing as Grade 1, normal or only mild atrophy; Grade 2, moderate atrophy; and Grade 3, severe atrophy (Figure 2).

We also quantified the volumes of the ventricles, the subarachnoid spaces, and the brain parenchyma at the level of Monro’s foramen using digitized brain CT according to the method of Yerby et al. We used Wilcoxon’s test to determine the significance of differences between groups using continuous variables. We compared groups using categorical variables with the χ² test and Yates’ correction.

**Results**

Patients were classified as demented if they satisfied all DSM III criteria for dementia and if they performed abnormally on both assessment instruments (a score of ≤23 on the MMSE and identification of three categories on the WCST). Patients who did not satisfy all DSM III criteria for dementia but who had abnormal scores on one assessment instrument were identified as borderline. Non-demented patients were those who failed to meet DSM III criteria and who scored within the normal range on both assessment instruments. In our series of 33 patients, nine were demented, nine were borderline, and 15 were nondemented. No significant differences were found between the controls and any patient group with respect to mean age or years of education, or between patient groups with respect to mean age, sex, mean years of education, or the presence of risk factors for stroke such as hypertension and diabetes mellitus (Table 1).

On MRI, both borderline and demented patients showed significantly more extensive white matter lesions (Figure 3) than nondemented patients. In addition, demented patients had significantly more extensive atrophy of the corpus callosum than nondemented or borderline patients (Figure 3).

Digitized brain CT showed that both borderline and demented patients had significantly larger ventricles than nondemented patients. In addition, demented patients had significantly larger subarachnoid spaces than nondemented patients. Furthermore, brain atrophy was significantly more marked in borderline than in nondemented patients and in demented than in borderline patients (Figure 3).

**Discussion**

The association of white matter lesions with intellectual impairment is controversial. Some investigators have suggested a close correlation, whereas others have found no difference in the severity of white matter lesions between nondemented and demented patients. Our results support the former view in that both borderline and demented patients had significantly more extensive white matter lesions than nondemented patients. Such differing results may be due to methodologic problems that occur in the assessment of intellectual function or in the grading of white matter lesions.

On digitized brain CT, we also found that both borderline and demented patients had significantly
enlarged ventricles and significantly more extensive brain atrophy than nondemented patients. In addition, demented patients had significantly larger sub-arachnoid spaces than nondemented patients and significantly more extensive brain atrophy than borderline patients.
TABLE 1. Clinical Profiles of 33 Patients With Lacunar Stroke

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (yr)</th>
<th>Male sex</th>
<th>Education (yr)</th>
<th>Mini-Mental State Examination</th>
<th>Wisconsin Card Sorting Test</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demented (n=9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>82</td>
<td>-</td>
<td>9</td>
<td>21</td>
<td>0</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>-</td>
<td>12</td>
<td>19</td>
<td>1</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>+</td>
<td>8</td>
<td>19</td>
<td>0</td>
<td>-</td>
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<tr>
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<td>+</td>
<td>12</td>
<td>18</td>
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<tr>
<td>5</td>
<td>74</td>
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<td>8</td>
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<td>6</td>
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<td>+</td>
<td>12</td>
<td>13</td>
<td>1</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>+</td>
<td>9</td>
<td>11</td>
<td>0</td>
<td>+</td>
<td>+</td>
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<tr>
<td>8</td>
<td>62</td>
<td>-</td>
<td>6</td>
<td>11</td>
<td>0</td>
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<tr>
<td>9</td>
<td>72</td>
<td>+</td>
<td>12</td>
<td>13</td>
<td>1</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Ratio (+/n)</td>
<td>6/9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>69.7±6.4</td>
<td>9.8±2.3</td>
<td>15.6±3.8</td>
<td>0.6±0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Borderline (n=9) |          |          |                |                               |                             |              |                  |
| 10 | 76       | -        | 8              | 26                            | 3                           | -            | -                |
| 11 | 54       | +        | 9              | 23                            | 1                           | +            | -                |
| 12 | 80       | -        | 11             | 24                            | 3                           | +            | -                |
| 13 | 62       | +        | 8              | 23                            | 2                           | +            | -                |
| 14 | 69       | +        | 15             | 26                            | 2                           | +            | -                |
| 15 | 65       | +        | 10             | 25                            | 1                           | +            | -                |
| 16 | 55       | +        | 11             | 27                            | 3                           | +            | -                |
| 17 | 74       | +        | 9              | 26                            | 3                           | +            | +                |
| 18 | 70       | +        | 8              | 22                            | 2                           | +            | -                |
| Ratio (+/n) | 7/9 |          |                |                               |                             |              |                  |
| Mean±SD | 67.2±9.0 | 9.9±2.3 | 24.7±1.7 | 2.2±0.8 |

Nondemented (n=15) |          |          |                |                               |                             |              |                  |
| 19 | 69       | +        | 11             | 30                            | 6                           | +            | -                |
| 20 | 62       | +        | 12             | 30                            | 6                           | +            | -                |
| 21 | 84       | -        | 11             | 28                            | 7                           | +            | -                |
| 22 | 72       | +        | 9              | 26                            | 5                           | +            | -                |
| 23 | 63       | +        | 15             | 29                            | 5                           | -            | +                |
| 24 | 76       | +        | 9              | 27                            | 5                           | +            | -                |
| 25 | 60       | +        | 11             | 28                            | 5                           | +            | -                |
| 26 | 69       | +        | 8              | 27                            | 6                           | +            | -                |
| 27 | 67       | +        | 8              | 28                            | 6                           | +            | -                |
| 28 | 66       | -        | 6              | 26                            | 4                           | +            | -                |
| 29 | 77       | +        | 8              | 24                            | 4                           | +            | -                |
| 30 | 58       | -        | 8              | 24                            | 4                           | -            | +                |
| 31 | 68       | -        | 11             | 26                            | 5                           | +            | -                |
| 32 | 73       | +        | 8              | 26                            | 6                           | +            | -                |
| 33 | 69       | -        | 8              | 26                            | 5                           | +            | -                |
| Ratio (+/n) | 10/15 |          |                |                               |                             |              |                  |
| Mean±SD | 68.9±6.9 | 9.5±2.3 | 27.0±1.9 | 5.3±0.9 |

Taken together, these findings suggest that, in most patients with lacunar stroke, periventricular and subcortical white matter lesions play a significant role in the progression of intellectual decline and that white matter atrophy, secondary to white matter lesions, first induces ventricular enlargement, then generalized brain atrophy, resulting in dementia.

However, we also noticed that some demented patients did not have these typical radiographic changes but, rather, had relatively mild periventricular white matter lesions and/or brain atrophy. In such demented patients, the most salient finding on MRI was atrophy of the corpus callosum. However, the role of this structure in cognition is controversial.41-42 Callosectomy does not produce a clini-
All of our demented patients exhibited more or less extensive subcortical white matter lesions immediately above the lateral ventricles. This subcortical white matter region probably corresponds to that underlying the cingulate gyrus. Since this region is close to the corpus callosum, lesions here, even if not too widespread, would cause more extensive callosal atrophy than lesions in other areas. Based on an autopsy study on 700 patients with documented ischemic strokes, Kameyama47 indicated that patients with lesions involving the white matter underlying the cingulate gyrus and the anterior corpus callosum were significantly more demented than patients without such lesions. This suggests that involvement of specific anatomic structures, such as the cingulate gyrus and the underlying white matter, play an important role in the progression of intellectual deterioration.

A relation between callosal degeneration and dementia has also been reported in patients with multiple sclerosis.48,49 Thus, the presence of callosal atrophy as well as white matter lesions on MRI should alert physicians to the possibility of dementia, especially in patients with lesions in the deep white matter.

Finally, white matter changes similar to those in our patients, designated “leuko-araiosis” by Hachinski et al., have also been described recently in patients with dementia of the Alzheimer type18,21,22,38,39,51-55 although the lesions were not as pronounced as those in vascular dementia.38,39 The pathogenesis and clinical significance of these lesions remain uncertain.52 Recently, Steigart et al.54 indicated a highly significant trend for the association of leukoaraiosis with increased dementia scores in cases of early Alzheimer’s disease. These patients may also show atrophy of the corpus callosum. Further accumulation of relevant data is necessary to clarify these points.

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Key Words • dementia, multi-infarct • lacunar infarction • magnetic resonance imaging
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Y Tanaka, O Tanaka, Y Mizuno and M Yoshida

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