Cerebral Blood Flow and Oxygen Metabolism in Patients With Vascular Dementia of the Binswanger Type

Hiroshi Yao, MD, Seizo Sadoshima, MD, Yasuo Kuwabara, MD, Yuichi Ichiya, MD, and Masatoshi Fujishima, MD

We performed clinical and neuroradiologic studies, including positron emission tomography, in five patients with vascular dementia of the Binswanger type. The clinical features of these cases consisted of slowly progressive dementia, together with vascular risk factors such as hypertension and often a history of minor stroke, and characteristic white matter lesions on brain computed tomograms or magnetic resonance images. Digital subtraction angiography of the cervical and intracranial arteries demonstrated no occlusive lesion in any patient. Both cerebral blood flow and the cerebral metabolic rate for oxygen were markedly reduced in the white matter (54–77% of control values), and both were decreased in the parietal (73% of control), frontal (74–80%), and temporal (74–83%) cortices, where no abnormalities were detected by brain computed tomography or magnetic resonance imaging. We conclude that vascular dementia of the Binswanger type may be caused by disconnection between the cerebral cortex and subcortical structures due to ischemic damage in the white matter. (Stroke 1990;21:1694–1699)

Binswanger's disease has recently been described as a type of vascular dementia, the most common feature of which is slowly progressive dementia with characteristic periventricular white matter lesions on computed tomography (CT) or magnetic resonance imaging (MRI). In patients with vascular dementia, intellectual decline is often associated with ischemic brain damage in the form of white matter lesions with multiple lacunes. Thus, it seems important to measure cerebral blood flow (CBF) and brain metabolism of patients with Binswanger-type dementia to elucidate the pathophysiology of vascular dementia. Measured by the intravenous xenon technique, CBF has been reported to be reduced in patients with subcortical arteriosclerotic encephalopathy. However, this technique could not distinguish white matter blood flow from cortical blood flow. Using positron emission tomography (PET), we investigated regional CBF and the cerebral metabolic rate for oxygen (CMRO₂) in patients with vascular dementia of the Binswanger type (VDBT) and examined whether derangement of brain metabolism, especially in the cortical or white matter regions, contributes to the development of VDBT.

Subjects and Methods

From January 1988 to June 1989, we examined five male patients (mean ± SEM age 61 ± 7 years) who were diagnosed with VDBT. Dementia was diagnosed and its severity was rated according to the revised version of the Diagnostic and Statistical Manual of Mental Disorders, third edition. The level of dementia was also graded using the Hasegawa Dementia Rating Scale, the Mini-Mental State Examination, and the Wechsler Adult Intelligence Scale. Clinical characteristics of the patients were assessed by careful physiologic and neurologic examinations, including a clinical history of long-standing hypertension with or without minor stroke and gradual intellectual decline. Laboratory and neuroradiologic studies included electroencephalography, cerebrospinal fluid examination, brain CT (TCT 60A or TCT 900S, Toshiba Inc., Tokyo, Japan), MRI (Sigma system, 1.5 T, GE Co., Freemont, Calif.), and intra-arterial (intravenous in one patient) digital subtraction angiography (Angiotron, Siemens Inc., Erlangen, F.R.G.).

For the PET study, each patient was placed in a supine position, with his eyes open and his ears unplugged, in a dimly lit PET scanning room.
Yao et al

**PET in Binswanger-Type Dementia**

**TABLE 1. Clinical Features of Five Men With Vascular Dementia of Binswanger Type**

<table>
<thead>
<tr>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64</td>
<td>74</td>
<td>77</td>
<td>50</td>
<td>41</td>
</tr>
<tr>
<td>Dementia</td>
<td>+ to ++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hasegawa Dementia Rating Scale</td>
<td>12.5</td>
<td>4</td>
<td>14</td>
<td>19.5</td>
<td>24</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>16</td>
<td>9</td>
<td>19</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>Wechsler Adult Intelligence Scale</td>
<td>62</td>
<td>&lt;60</td>
<td>77</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Emotional incontinence</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pseudobulbar palsy</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Blood pressure on admission (mm Hg)</td>
<td>156/118</td>
<td>124/88</td>
<td>160/96</td>
<td>232/150</td>
<td>146/96</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>History of stroke</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hachinski's ischemic score</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>

Grades of dementia: ++, moderate; +, slight.5

Femoral artery was cannulated for the measurement of radioactivity in the blood and for the analysis of arterial blood gases. Regional CBF, oxygen extraction fraction, and CMRO2 were measured by using the oxygen-15 steady-state technique described by Frackowiak et al.2 Both oxygen extraction fraction and CMRO2 were corrected for cerebral blood volume as measured by a single inhalation of oxygen-15-labeled CO gas.8 A Headtome-III device (Shimazu Inc., Kyoto, Japan) with a spatial resolution of 8.2 mm full width at half maximum was used as previously described.9 In each brain, four slices parallel to the orbitomeatal line (35, 50, 65, and 80 mm above it) were analyzed. As shown in Figure 1, 18x14=mm regions of interest were placed bilaterally on the cerebral cortical areas (frontal, temporal, parietal, and occipital cortices), deep gray matter (striatum and thalamus), and white matter (anterior and posterior parts) using the brain CT image corresponding to each PET slice as a reference. These regions of interest were placed by one of the authors so as to minimize the partial volume effect. The values of all pixels within a region of interest were averaged to determine regional CBF, oxygen extraction fraction, CMRO2, and cerebral blood volume. Five nondemented men (mean±SEM age 62±2 years) who had either vertigo or dizziness secondary to a peripheral vestibular disorder or a history of amaurosis or amnesia also underwent PET. Because these men were cognitively and behaviorally normal on careful examination and showed no major stenosis of the main cervical and intracranial arteries on DSA, their values for CBF, oxygen extraction fraction, and CMRO2 were used as the control values. Informed consent was obtained from all patients and controls before PET study.

We presented all results as mean±SEM. The two hemispheres were analyzed separately; the data were not pooled. We used two-way analysis of variance to test for significant differences in CBF, oxygen extraction fraction, and CMRO2 in the eight regions of interest between the VDBT patients and the nondemented controls. We used Student's unpaired t test to compare the average CBF and CMRO2 in each region of interest between the VDBT patients and the nondemented controls.

**Results**

The clinical features of the VDBT patients are summarized in Table 1. Dementia was moderate in case 2, slight to moderate in case 1, and slight in cases

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**Figure 1. Schematic drawings of locations of regions of interest placed symmetrically on each hemisphere. Numerals below each slice indicate distance from orbitomeatal (OM) line in millimeters.**
3–5. The dementia had lasted 1–4 years. Remarkable hypertension on admission was present in cases 1 and 4. A history of hypertension and minor stroke was present in all patients so that their ischemic scores were high. No patient had diabetes mellitus. Neurologic examination revealed motor deficit in cases 4 and 5; ataxia in case 3; gait disturbance in cases 1, 2, 4, and 5; emotional incontinence in cases 1, 2, and 4; and urinary incontinence in cases 1 and 2. No patient had pseudobulbar palsy.

All VDBT patients had normal hematologic and biochemical findings: total protein, 7.4±0.2 (normal range 6.3–8.4) g/dl; albumin, 4.1±0.1 (normal range 4.0–5.0) g/dl; blood urea nitrogen, 18±3 (normal range 7–20) mg/dl; creatinine, 1.2±0.3 (normal range 0.5–1.2) mg/dl; fasting blood sugar, 93±6 (normal range 65–110 mg/dl); cholesterol, 201±17 (normal range 120–250) mg/dl; triglycerides, 112±5 (normal range 30–150) mg/dl; and hematocrit, 47±2%. None of these values differed significantly from those of control group. Tests for syphilis were also negative. In all patients cerebrospinal fluid examination was normal except for a slight elevation in the total protein concentration: total protein, 50±11 mg/dl; glucose, 65±3 mg/dl; opening pressure, 136±19 mm H2O; and cell count, <3/mm³.

Brain CT findings in cases 1–5 are demonstrated in Figure 2. Noncontrast CT showed extensive and heterogeneous bilateral decreases in density of the deep white matter in the periventricular regions and of the white matter anterior to the frontal horns in the lateral ventricles. Generalized dilatation of the ventricular system was seen in contrast to less atrophy in the cortical areas. Multiple subcortical lacunar infarcts were frequently seen in the basal ganglia and corona radiata. A typical MRI scan (that for case 1) is presented in Figure 3, showing confluent areas of periventricular hyperintensity with well-preserved cortical areas. No significant stenosis of the cervical or intracranial arteries was found in any VDBT patient or control on DSA.

Both CBF and CMRO₂ were reduced in the VDBT patients compared with the controls (p<0.001). There was no significant difference in oxygen extraction fraction between the VDBT patients (mean values 0.37–0.48) and the controls (0.37–0.44). Figure 4 demonstrates the average values of CBF and CMRO₂ in the VDBT patients and the controls. In the right and left frontal, temporal, and thalamic regions of interest of the VDBT patients CMRO₂ was decreased to 73–82% of the control value. Furthermore, CBF and CMRO₂ in the right and left parietal regions of interest of the VDBT patients were reduced to 72–73% of those in the controls. In the white matter of the VDBT patients, especially the anterior part, CBF and CMRO₂ were markedly reduced to 54–77% of the control values. The occipital cortex and striatum were less severely affected in the VDBT patients, with a 9–20% reduction in CBF and a 16–25% reduction in CMRO₂. A typical PET scan (Figure 5) shows decreased CBF and CMRO₂ in the white matter and frontal cortex.
Discussion

Recently, extensive clinical and pathologic studies have focused on a type of vascular dementia believed to be associated with Binswanger's disease or subcortical arteriosclerotic encephalopathy. Because the clinical features and neuroradiologic findings in our five patients agree with those described in previous reports on Binswanger's disease, we diagnosed our cases as having VDBT. In these patients PET revealed widely and significantly suppressed brain metabolism not only in the white matter, but also in the cortical areas. There was no increase in the oxygen extraction fraction in any region of interest, which suggests no evidence for misery perfusion in VDBT.

Pathologic studies of patients with Binswanger's disease have emphasized the role of long-standing hypertension as the most essential causative factor for the development of this disease. The cerebral cortex and the short arcuate fibers in the subcortical white matter are supplied by short penetrating arteries. The deep hemispheric white matter is perfused by long penetrating medullary arteries, and thus the periventricular white matter is considered to be a border zone or watershed area of these arteries. Long-standing hypertension, which causes arteriosclerotic change of these long penetrating arteries, may lead to incomplete infarction of the periventricular white matter.

Some studies have indicated that Binswanger's disease is essentially identical to dementia with multiple lacunar strokes. Ishii et al. found that diffuse and incomplete softening of the white matter, together with multiple lacunes, occurred predominantly in the frontal lobes of patients with vascular dementia, producing prominent frontal lobe symptoms. Ischemic lesions such as incomplete infarction or lacunes in the white matter may induce disconnection of the neuronal network between the cerebral cortex and subcortical structures.

The changes or regional differences in CBF and CMRO2 in patients with vascular dementia are still controversial. Some studies using single-photon emission computed tomography have demonstrated re-
FIGURE 5. Positron emission tomograms showing (top) regional cerebral blood flow (CBF) and (bottom) cerebral metabolic rate for oxygen (CMRO₂) in case 1. Reduction of both CBF and CMRO₂ is seen in bilateral white matter and frontal cortex. Numerals below each slice indicate distance from orbitomeatal (OM) line in millimeters. This 64-year-old Japanese man was found to be hypertensive (diastolic blood pressure 100–110 mm Hg) at age 30. At age 45, he suffered abrupt onset of right hemiparesis, which resolved in 1 month. At age 59, he was admitted to our clinic because of slowly progressive dementia. His wife had noted his gradual intellectual decline but could not accurately define when it started. His blood pressure on admission was 158/110 mm Hg. He had slight weakness with hyperreflexia on the right side. Over the next 4 years his clinical course was uneventful, but his wife commented that he became quieter and less outgoing.

Reduced CBF in the frontal lobe, but other studies show no specific regional pattern in patients with vascular dementia. Jagust et al. also demonstrated bilaterally reduced CBF in the frontal cortex of two patients with Binswanger’s disease. Both CBF and CMRO₂ were decreased predominantly in the frontal lobe or else scattered defects were observed in PET studies. Frackowiak et al. reported nine cases with vascular dementia (four with VDBT) in whom generalized declines in CBF and CMRO₂ were seen throughout the hemispheric brain. The depression of cortical CMRO₂ was most severe in the parietal cortex.

Our study revealed marked decreases in both CBF and CMRO₂ in the parietal, frontal, and temporal cortices in addition to the large reductions in CBF and CMRO₂ in the white matter. The hypodense or hyperintense areas on brain CT or MRI scans, respectively, in patients with VDBT indicate morphologic abnormalities; thus, the decreased CBF and CMRO₂ in these regions are attributed to “ischemic” tissue damage. On the other hand, the decreased CBF and CMRO₂ in the cortical areas seem to be due to secondary hypometabolism through a remote metabolic effect (diachisis) or functional suppression rather than to primary tissue damage because cortical structures were well preserved on CT or MRI. Disconnection between the cortex and subcortical structures as mentioned above, may cause a reduction in cortical metabolism, contributing to the development of dementia in patients with VDBT.

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