Leukoaraiosis and Dementia in Hypertensive Patients

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Background and Purpose: Although our previous study demonstrated that dementia of the Binswanger type may be a disconnection dementia caused by leukoaraiosis, some hypertensive patients with marked leukoaraiosis do not develop dementia. The goal of the present study is to elucidate the pathophysiology of nondemented hypertensive patients with leukoaraiosis.

Methods: We performed clinical and neuroradiological studies, including positron emission tomography, in eight hypertensive patients with leukoaraiosis.

Results: Four patients were demented, and two among the other four who were not demented at the first examination developed dementia during the follow-up period. Digital subtraction angiography of the cervical and intracranial arteries demonstrated stenotic lesions in only one patient. Cerebral blood flow and oxygen metabolism in patients with dementia were markedly reduced in the white matter (59–67% of control values). In contrast, cerebral blood flow in the white matter of patients without dementia was reduced less markedly (74% of control), oxygen extraction fraction in the white matter was significantly increased (130% of control), and oxygen metabolism remained at almost-normal levels not only in the white matter but also in the cortical area.

Conclusions: Hypertension-caused arteriosclerotic changes of the long penetrating medullary arteries may cause misery perfusion and later ischemic damage in the periventricular white matter. Preserved oxygen metabolism in hypertensive patients with leukoaraiosis may represent the early stage of vascular dementia of the Binswanger type.

KEY WORDS • cerebral blood flow • dementia • hypertension • white matter

Leukoaraiosis or periventricular white matter lesions is a characteristic finding of Binswanger’s disease or subcortical arteriosclerotic encephalopathy. Periventricular white matter lesions are also observed in clinically normal individuals and in non-demented patients with vascular risk factors and minor neurological deficits. Recently, Shimada et al demonstrated that the grade of leukoaraiosis or silent stroke is significantly associated with advancing age and hypertension and suggested that white matter lesions of this type could be the basis for vascular dementia. However, it is not clear why some hypertensive patients with leukoaraiosis develop dementia whereas others do not. To elucidate the relation between white matter lesions and cognitive function, we investigated cerebral blood flow (CBF) and oxygen metabolism in hypertensive patients with apparent white matter lesions but without dementia compared with those in patients in vascular dementia of the Binswanger type (VDBT) using positron emission tomography (PET).

Subjects and Methods

From April 1987 to February 1991, we performed 10 PET studies in eight patients (six men and two women; mean±SEM age, 63±4 [range, 41–77] years) who had prominent white matter lesions that reached confluency in the periventricular regions on magnetic resonance imaging (MRI) and vascular risk factors such as hypertension, often with a history of minor stroke. Despite marked periventricular hyperintensities on T2-weighted MRI in four patients, there was no diagnosis of dementia; two of these patients developed dementia at the time of the second PET study, approximately 1 year after the first. Two of the patients who underwent repeat scans when they developed dementia and four who were demented originally composed the VDBT group. Dementia was diagnosed and its severity was rated according to the revised version of the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III-R). 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 VDBT were assessed by careful physiological and neurological examinations, including a clinical history of long-standing hypertension, minor stroke, and gradual intellectual decline. Laboratory and neuroradiological studies included electroencephalography, cerebrospinal fluid examination, brain computed tomographic (CT) scan (TCT 60A or TCT 900S, Toshiba Inc., Tokyo), MRI.
For the PET study, each patient was placed in a supine position with eyes open and ears unplugged in a dimly lit PET scanning room. One femoral artery was cannulated for the measurement of radioactivity in the blood and analysis of arterial blood gases. Regional CBF, oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen (CMRO$_2$) were measured by the $^{15}$O steady-state technique described by Frackowiak et al. Both OEF and CMRO$_2$ were corrected with cerebral blood volume measured by single inhalation of $^{15}$O-labeled carbon monoxide gas. A HEADTOME-III device (Shimadzu Inc., Kyoto, Japan) with a spatial resolution of 8.2 mm full-width at half-maximum was used as previously described. Four slices were analyzed in each brain parallel to the orbitomeatal line at 35, 50, 65, and 80 mm above orbitomeatal line. Regions of interest were placed by one of the authors to minimize the partial volume effect. The regions of interest (18x14 mm) were placed on the bilateral cerebral cortical areas (frontal, temporal, parietal, and occipital cortices) and white matter (anterior and posterior parts), as described in our previous study. The regions of interest for white matter were placed at the midpoints between the cortex and the edge of the lateral ventricle on the slice 65 mm above the orbitomeatal line using the brain CT image corresponding to each PET slice as a reference. The values of all pixels within a region of interest were averaged to demonstrate regional CBF, OEF, CMRO$_2$, and cerebral blood volume.

An additional other seven nondemented patients (five men and two women; mean±SEM age, 64±2 years), who had either dizziness or vertigo secondary to a peripheral vestibular disorder, a history of transient amaurosis or amnesia, or hypertension without leukoaraiosis, also underwent PET. Although these patients were not completely normal volunteers, they were cognitively and neurologically normal on careful examination. The scores for the Wechsler Adult Intelligence Scale, the Mini-Mental State Examination, and the Hasegawa Dementia Rating Scale were not completely normal volunteers, they were cognitively normal, and showed no significant stenosis of the main cerebral and intracranial arteries on angiography; thus the indices (CBF, CMRO$_2$, and OEF) were used as control values. Informed consent was obtained from all patients and control subjects before the PET study.

All results were presented as mean±SEM. We considered all the gray matter and all the white matter regions together as two mean values and analyzed the significance of differences in CBF, CMRO$_2$, and OEF between patients with VDBT and nondemented hypertensive patients with leukoaraiosis and control patients using the unpaired t test. Because of multiple comparisons, the Bonferroni correction principle was used with the level of significance set at $P<0.004$.

**Results**

The scores for the Wechsler Adult Intelligence Scale, the Mini-Mental State Examination, and the Hasegawa Dementia Rating Scale of patients with VDBT and nondemented hypertensive patients with leukoaraiosis are shown in Table 1. Moderate-to-slight dementia was present in VDBT according to DSM-III-R. Neurological examination revealed gait disturbances in four nondemented hypertensive patients with leukoaraiosis and five patients with VDBT, respectively. Emotional incontinence was present in three and urinary incontinence in four patients with VDBT but in no nondemented hypertensive patient with leukoaraiosis. One VDBT patient had pseudobulbar palsy. Because hypertension was present in all eight patients and a history of minor stroke in all but one, the ischemic scores$^9$ were high (mean±SEM, 9±1; range, 5–11). Blood pressure readings on admission were 181±19/95±9 mm Hg and 175±19/111±9 mm Hg in VDBT and nondemented hypertensive patients with leukoaraiosis, respectively. One of the nondemented hypertensive patients with leukoaraiosis had non-insulin-dependent diabetes mellitus.

All VDBT patients and nondemented hypertensive patients with leukoaraiosis had normal hematologic and biochemical findings. The tests for syphilis were also negative. Cerebrospinal fluid examination in VDBT patients revealed normal values except for slight elevation in total protein concentration: total protein, 51±4 mg/dl; glucose, 62±3 mg/dl; lactate, 1.65±0.15 mmol/l; lactate/pyruvate ratio, 15.3±1.6; opening pressure, 142±9 mm H$_2$O; and cell count, <3/mm$^3$. Noncontrast CT showed extensive and heterogenous bilateral decreases in density of the deep white matter in the periventricular regions and the white matter anterior to the frontal horns of the lateral ventricles. Generalized dilatation of the ventricular system was seen in contrast to less atrophy in the cortical area. Multiple subcortical lacunar infarcts were frequently seen in the basal ganglia and the corona radiata. In Figure 1, typical brain CT and MRI scans in a nondemented hypertensive patient show confluent periventricular hyperintensities with a relatively well-preserved cortical area. Significant stenosis of the cervical and intracranial arteries on digital subtraction angiography was found in one nondemented hypertensive patient with leukoaraiosis who developed dementia and border zone infarction during antihypertensive therapy.

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**Table 1. Neuropsychological Testing in Patients With Vascular Dementia of the Binswanger Type (Demented) and Nondemented Hypertensive Patients With Leukoaraiosis (Nondemented)**

<table>
<thead>
<tr>
<th>Test</th>
<th>Nondemented patients (n=4)</th>
<th>Demented patients (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wechsler Adult Intelligence Scale</td>
<td>94 (90–98)</td>
<td>68 (60–77)</td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>24 (22–28)</td>
<td>18 (9–25)</td>
</tr>
<tr>
<td>Hasegawa Dementia Rating Scale</td>
<td>25 (17–32.5)</td>
<td>14 (4–24)</td>
</tr>
</tbody>
</table>

Mean±SEM ages: nondemented patients, 67±4 years; demented patients, 61±6 years.
In two patients, PET studies were repeated before and after the development of dementia. A 57-year-old man with renovascular hypertension, mentioned above, developed dementia during the course of antihypertensive therapy; this case was previously reported. The other patient, a 73-year-old man, became demented without any specific causes during the 1-year follow-up period. Changes in CMRO$_2$ demonstrated by PET in the latter case are shown in Figure 2.

In patients with VDBT, both CBF and CMRO$_2$ of cortical gray matter were decreased to 71–74% of control values, whereas CBF and CMRO$_2$ were not different between nondemented hypertensive patients with leukoaraiosis and control subjects. There were no differences in OEF among VDBT patients, nondemented hypertensive patients with leukoaraiosis, and control subjects. In the white matter, both CBF and CMRO$_2$ in VDBT were decreased to 59–67% of control. In contrast, CBF in nondemented hypertensive patients with leukoaraiosis was decreased less markedly (74% of control), and OEF in the white matter was increased significantly to 0.52±0.02 (130% of control); thus, CMRO$_2$ remained almost normal (Figure 3).

**Discussion**

Our previous PET study in VDBT patients revealed widely and significantly suppressed brain metabolism not only in the white matter but also in the cortical areas. In contrast, the present study found that brain oxygen metabolism was well preserved in both the white matter and cortical area of hypertensive patients with leukoaraiosis if dementia was not evident. Therefore,
mental dysfunction or VDBT may develop closely associated with a decline in brain oxygen metabolism.

Binswanger's disease, a type of vascular dementia, is thought to be a disconnection dementia, in which disconnection between the cortex and subcortical structures causes cortical dysfunction and dementia. Some studies have indicated that Binswanger's disease is essentially identical to dementia with multiple lacunar stroke. Ishii et al have found that diffuse and incomplete softenings of the white matter and multiple lacunes were predominant in the frontal lobes of patients with vascular dementia, producing prominent fronto 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 the subcortical structure.

Among hypertensive patients with marked leukoaraiosis, there are clinically normal–appearing individuals and some who exhibit dementia. In this study, the Wechsler Adult Intelligence Scale scores were clearly different between the patient groups although there was some overlap in terms of the Mini–Mental State Examination and the Hasegawa Dementia Rating Scale. Furthermore, in contrast to the decreased CMRO₂ in VDBT, cerebral oxygen metabolism in nondemented hypertensive patients with leukoaraiosis was not decreased in any regions of interest. Rao et al and Schmidt et al reported that the differences observed on neurological testing between subjects with and without leukoaraiosis were not significant. Thus, we assume that cognitive function does not directly correlate with the severity of white matter lesions demonstrated on MRI or CT scans but rather with the disturbed brain metabolism determined with PET.

Although the changes in CBF and brain oxygen metabolism in patients with prominent white matter lesions with or without dementia are still controversial, some studies revealed that white matter lesions such as periventricular lucency are related to impaired cerebral circulation. Meguro et al reported that reduced CBF with increased OEF was observed in patients with severe periventricular hyperintensities and vascular risk factors but without neurological abnormalities. Although there was no increase in OEF in any area in VDBT, which suggested no evidence for misery perfusion in VDBT, OEF was significantly increased in the white matter of nondemented hypertensive patients with leukoaraiosis in the present study. We assume, therefore, that misery perfusion exists in the white matter at the very early stage of leukoaraiosis associated with vascular risk factors such as hypertension.

In hypertensive individuals, the hemodynamic reserve is reduced, which may predispose them to cerebral ischemia even during small decreases in cerebral perfusion pressure. Cerebral hyperperfusion is observed in cases with leukoaraiosis as well as silent lacunar lesions, and hypertension is one of the most significant contributory factors. 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 a border zone or a watershed area of these arteries. Long-standing hypertension, which causes arteriosclerotic change of these long penetrating arteries, may lead to misery perfusion and subsequently to incomplete infarction in the periventricular white matter, resulting in VDBT.

In conclusion, our present study revealed that periventricular white matter lesions in our hypertensive patients have a vascular etiology, and progression of ischemic derangement in the white matter results in a disconnection dementia or VDBT. Brain circulation and metabolism should be further investigated in nondemented hypertensive individuals with leukoaraiosis.

Acknowledgments

We thank Dr. Hiroshi Sugimori, MD, for his assistance in evaluating the impact of ventricular size on cerebral blood flow and oxygen metabolism; and Drs. Jen Yueh Chang, PhD, and Kyoshi Takagi, MD, for their valuable advice.

References


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Stroke. 1992;23:1673-1677
doi: 10.1161/01.STR.23.11.1673

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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