Medullary Arteries in Aging and Dementia
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We examined sclerotic changes of the medullary arteries in 110 nonneuropsychiatric patients ranging in age from the second to the ninth decades, in 20 patients with subcortical arteriosclerotic encephalopathy (Binswanger's disease), and in 20 patients with dementia of the Alzheimer type. The principal sclerotic change was fibrohyaline thickening of the wall, which began to appear during the late fourth decade, increased in incidence gradually with age, and was most severe in patients with subcortical arteriosclerotic encephalopathy. Morphometry showed that the sclerotic changes of the medullary arteries were most prominent in the frontal lobe, followed by the parietal, occipital, and temporal lobes, in both the nonneuropsychiatric and demented groups. The sclerotic rate in the frontal lobe of patients with dementia of the Alzheimer type was slightly higher than that in the nonneuropsychiatric patients (p<0.05) but far less than that in the patients with subcortical arteriosclerotic encephalopathy (p<0.001). The sclerotic rate correlated well with the degree of ischemic white matter changes as well as with blood pressure. (Stroke 1991;22:442–446)

Medullary arteries are small arteries and arterioles in the cerebral white matter arising from cerebral surface branches of the anterior, middle, and posterior cerebral arteries and penetrating into the cerebral cortex perpendicularly. At the subcortical U fiber, they change their direction toward the nearer lateral ventricle. The main branches measure 100–200 μm in diameter where they penetrate into the white matter and then gradually decrease in diameter. They are end-arteries without anastomoses.

The development of diagnostic procedures such as computed tomography (CT) and magnetic resonance imaging (MRI) has created interest in diffuse white matter lesions of the elderly and patients with vascular dementia. Recent progress in functional imaging has made it possible to assess the regional cerebral blood flow of these patients, but pathological studies on the medullary arteries supplying the cerebral white matter are scarce. This study elucidates relations between sclerotic medullary arteries and ischemic white matter changes as well as aging and hypertension among demented patients.

Materials and Methods
We examined 150 brains necropsied at four different hospitals from 1965 to 1987. Of these, 110 were from nonneuropsychiatric patients of different ages (10 each from the second to the sixth decades and 20 each from the seventh to the ninth decades). The cause of death in this group was malignant neoplasm of visceral organs in 73, inflammatory disease in 12, collagen disease in five, liver failure in three, accident in three, and other in 14.

Twenty brains from patients with subcortical arteriosclerotic encephalopathy, 12 men and eight women aged 60–90 (mean 74.9) years, were selected from clinically and pathologically typical cases. The cardinal signs and symptoms of these patients were dementia, lack of volition, dysarthria, emotional lability, urinary incontinence, and gait difficulties. Hachinski's ischemic score in this group ranged from 7 to 15 (mean±SD 10.1±3.54). Following its introduction in our hospital in 1977, CT was performed on 11 of the 20 patients. All 11 showed periventricular lucency as well as ventricular dilatation. Diffuse and patchy white matter changes with sparing of U fibers were observed pathologically in addition to multiple lacunar infarcts and sclerosis of the medullary arteries (Figure 1). Neurofibrillary tangles and senile plaques were minimal in this group, as in age-matched nondemented controls.

We also studied 20 brains from patients with the Alzheimer type of presenile and senile dementia (five men and 15 women aged 61–90 [mean 78.3] years). Clinical manifestations included disorientation to time and place, visual-spatial agnosia, memory disturbance, wandering, and restlessness. Pathological
Evans et al. CT-Verified Cerebral Infarction

addition to CT-verified infarcts, older age, black race, hypertension, diabetes, and ischemic cardiac disease were significantly related to an increased risk of death in the full model.

TABLE 1. Estimates of Proportional Hazard Ratio (Risk of Death) in TIA Patients After Controlling for All Other Factors Listed

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computed tomographically verified infarction</td>
<td>1.70</td>
<td>0.035</td>
</tr>
<tr>
<td>Clinical history</td>
<td>1.03</td>
<td>0.924</td>
</tr>
<tr>
<td>Age*</td>
<td>1.53</td>
<td>0.0002</td>
</tr>
<tr>
<td>Ischemic cardiac disease</td>
<td>1.87</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.80</td>
<td>0.032</td>
</tr>
<tr>
<td>Black race</td>
<td>1.94</td>
<td>0.042</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.53</td>
<td>0.046</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.46</td>
<td>0.143</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.37</td>
<td>0.233</td>
</tr>
<tr>
<td>TIA distribution</td>
<td>...</td>
<td>0.503</td>
</tr>
<tr>
<td>Carotid/vertebrobasilar</td>
<td>1.12</td>
<td>...</td>
</tr>
<tr>
<td>Both/vertebrobasilar</td>
<td>1.53</td>
<td>...</td>
</tr>
<tr>
<td>Admission date†</td>
<td>1.09</td>
<td>0.094</td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack.
*Per decade of age.
†Per year of admission.

FIGURE 1. Effect of infarction verified by cranial computed tomography (CCT) and clinical history of stroke on survival following transient ischemic attack (TIA).

For the 98 patients evaluated by CT who died during follow-up, the odds of death attributed to stroke were 2.19 times greater for patients with CT-verified infarcts than for patients without tomographic evidence of infarction (Table 2). Given the relatively few deaths, however, the association between cause of death and CT-verified infarct was not significant, whether we controlled for clinical history of stroke (Mantel-Haenszel $\chi^2=1.322$, $p=0.25$) or not (Pearson's $\chi^2$ with $2 df=3.181$, $p=0.204$).

Discussion

Our results clearly demonstrate that CT-verified infarcts are associated with an excess risk of premature death in TIA patients. Even after adjustment for other covariates, the effect of CT-verified infarction was comparable to that of established risk factors such as hypertension, diabetes, and ischemic cardiac disease. In contrast, after controlling for CT-verified infarction the effect of a clinical history of stroke on prognosis was marginal at best.

Among patients with CT-verified infarcts, there was little difference in the risk of premature death between patients with asymptomatic infarction and those whose stroke was clinically pronounced. Of the 95 strokes documented in this study, fully one third

KEY WORDS: cerebral ischemia, transient, mortality, tomography, x-ray computed
anol, embedded in Epon 812 (Nacalai, Kyoto, Japan), and examined with electron microscopy.

Results

Normal medullary arteries had a few thin layers of medial muscle fibers and vestigial fibrous adventitia on light microscopy (Figure 2a). Width of the arterial walls in vessels approximately 50 μm in external diameter ranged from 7 μm to 9 μm. Sclerotic changes of the medullary arteries were uniform compared with those of perforating arteries in the basal ganglia. Figures 2b and 2c show the characteristic features of these changes. The most prominent findings were concentric lamellar arrangements of collagen fibers with deposition of a fibrohyaline substance, mainly in the subadventitia; in contrast, changes in the media were not prominent. In medullary arteries ≥100 μm in external diameter, some medial muscle bundles had degenerated instead of showing proliferative changes. In the intima, elastica-van Gieson staining frequently showed splitting and fibroelastosis of the internal elastic lamina but no prominent thickening of the intima or occlusion of the lumen. Other pathological changes such as angionecrosis were rarely seen in the white matter, and atherosclerosis and amyloid angiopathy were not observed in the medullary arteries. As for localization, sclerotic change of the medullary arteries was detected more prominently and frequently in the periventricular white matter than in the convolutional white matter.

Electron microscopy of the sclerotic medullary arteries in patients with subcortical arteriosclerotic encephalopathy disclosed proliferation of collagen fibers, accumulation of cell debris, and deposition of amorphous materials in the subadventitia (Figures 2d and 2e). These findings corresponded with the fibrohyaline thickening of the wall on light microscopy. The basal laminae were thickened and became multilayered. Occasionally, medial muscle cells degenerated and were split by the basal lamina-like substance. This sclerotic change appeared late during the fourth decade and increased in degree and incidence with age. The change was most prominent in patients with subcortical arteriosclerotic encephalopathy but was not different in quality from that in elderly nonneuropsychiatric patients.

In the morphometric study, 30.5% of the medullary arteries were ≤49 μm, 49.1% were 50–99 μm, and 20.4% were ≥100 μm in external diameter. The sclerotic rate of the medullary arteries in these three classes tended to increase with age in all lobes. The medullary arteries 50–99 μm in diameter were most frequently observed and showed constant sclerotic changes. Table 1 shows the sclerotic rate of this class. In the nonneuropsychiatric patients of the ninth decade as well as in the subcortical arteriosclerotic encephalopathy and dementia of the Alzheimer type groups, the sclerotic rates were highest in the frontal lobe, followed by the parietal, occipital, and temporal lobes. Sclerotic rates of the frontal lobe in both the subcortical arteriosclerotic encephalopathy and dementia of the Alzheimer type groups were significantly higher than that in age-matched controls (p < 0.001 by Welch's t test and p < 0.05 by Student's t test, respectively) (Figure 3).

Table 2 shows the blood pressure level and degree of white matter changes in 99 cases >60 years of age. There were significant correlations between the sclerotic rate in the frontal lobe and the degree of white matter changes (none versus mild using Student's t test, p < 0.01; none versus moderate using Student's t test and none versus severe using Welch's t test, p < 0.001; mild versus moderate and moderate versus severe, p < 0.05 by Student's t test, as well as between sclerotic rate and blood pressure using Welch's t test (normal versus borderline, p < 0.05; normal versus hypertension, p < 0.01) (Table 3).

Discussion

Pathological changes of the medullary arteries seem different from those of the perforating arteries in the basal ganglia and thalamus or the cortical arteries. In medullary arteries, amyloid deposition is not observed and angiomegrosis is seldom seen. The
principal sclerotic change of the medullary arteries is fibrohyaline thickening of the wall. There exists a considerable literature on angioneurosis or amyloid angiopathy in cerebral arterioles, but little work has been reported on the changes of medullary arteries accompanying normal aging and dementia. Our light and electron microscopic findings of sclerotic medullary arteries showed an accumulation of collagen fibers in the subadventitia and a fibrous medial change without obstruction of the lumen. These were seen rather uniformly and corresponded with the "adventitial proliferation" and "medial fibrosis" described by Baker and Iannone.

Ravens postulated that one cause of adventitial proliferation was a change of vascular permeability due to damage to the endothelium and blood-brain barrier. However, no definite pathogenesis of this change has been elucidated. Baker and Iannone reported an excellent correlation between age and the severity of arteriolar change in the brain, and our morphometry showed that sclerotic rate of the medullary arteries increases with age. Thus, aging seems to be the most influential factor inducing sclerosis of the medullary arteries.

Caplan and Schoene emphasized persistent hypertension in the clinical features of subcortical arteriosclerotic encephalopathy. Recently, Fukuda et al. reported that blood pressure was positively correlated with the severity of white matter lesions in CT and MRI findings, and we found a significant correlation between sclerotic rate and blood pressure. Hypertension may therefore accelerate the pathologic process in the medullary arteries of the senile brain. However, two of 20 patients with subcortical arteriosclerotic encephalopathy were normotensive in our series, which showed a high sclerotic rate of the medullary arteries. We conclude that hypertension may not be a direct cause of sclerotic changes of the medullary arteries. Sclerotic medullary arteries are not specific for subcortical arteriosclerotic encephalopathy or any other disease entity but are commonly seen among aged people with hypertension. We can say that some arteriosclerotic medullary arteries are associated with diffuse ischemic white matter change, consistent with subcortical arteriosclerotic encephalopathy.

Oeda morphometrically evaluated the sclerotic changes in cerebral arteries and pointed out that the media of small white matter arteries in patients with subcortical arteriosclerotic encephalopathy was significantly thicker than that in patients with hypertensive encephalopathy and intracerebral hemorrhage. Tomonaga et al. reported that the incidence of arteriolar changes increased with the severity of white matter lesions in patients with subcortical arteriosclerotic encephalopathy. We have demonstrated a significant correlation between the severity of ischemic white matter changes and sclerotic rate of

TABLE 2. Blood Pressure and White Matter Changes in Cases >60 Years Old

<table>
<thead>
<tr>
<th>Group</th>
<th>Blood pressure</th>
<th>White matter changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>B</td>
</tr>
<tr>
<td>Nonneuropsychiatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>61–70 yr</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>71–80 yr</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>81–90 yr</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>SAE</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>DAT</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>32</td>
</tr>
</tbody>
</table>

Values are number of cases. N, normal; B, borderline; H, hypertension; −, none; +, mild; ++, moderate; ++++, severe; SAE, subcortical arteriosclerotic encephalopathy; DAT, dementia of Alzheimer type.

FIGURE 3. Bar graph of sclerotic rate in medullary arteries 50–99 μm in external diameter. Sclerotic rates of frontal lobe in subcortical arteriosclerotic encephalopathy (SAE) and dementia of Alzheimer type (DAT) groups are significantly higher than that of age-matched controls. **p<0.001 by Welch’s t test, *p<0.05 by Student’s t test. Mean ages of SAE and DAT groups given in parentheses.

TABLE 3. Correlations Between Sclerotic Rate in Frontal Lobe and Blood Pressure or White Matter Changes in Cases >60 Years Old

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>n</th>
<th>Mean age (yr)</th>
<th>Sclerotic rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>42</td>
<td>75.3</td>
<td>39.76±7.60</td>
</tr>
<tr>
<td>Borderline</td>
<td>32</td>
<td>76.4</td>
<td>45.39±12.0*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25</td>
<td>76.1</td>
<td>47.50±11.7†</td>
</tr>
<tr>
<td>White matter changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>32</td>
<td>75.4</td>
<td>37.30±6.97</td>
</tr>
<tr>
<td>Mild</td>
<td>32</td>
<td>75.5</td>
<td>42.22±7.73$$</td>
</tr>
<tr>
<td>Moderate</td>
<td>23</td>
<td>77.5</td>
<td>47.07±10.2$$</td>
</tr>
<tr>
<td>Severe</td>
<td>12</td>
<td>74.8</td>
<td>56.90±12.8$$</td>
</tr>
</tbody>
</table>

$$p<0.05, 0.01, respectively, different from normal using Welch’s t test.
$$p<0.001, 0.01, respectively, different from none (none vs. mild and none vs. moderate using Student’s t test, and none vs. severe using Welch’s t test).
$$p<0.05 different from moderate using Student’s t test.
medullary arteries in the frontal lobe in groups of demented and nondemented elderly subjects.

The short arcuate fibers in the subcortical white matter are usually spared in subcortical arteriosclerotic encephalopathy because they are irritated by short, penetrating arteries that arise from superficial cortical branches of the cerebral arteries. Kawahara termed the arteries "subcortical arteries" in his injection study. We observed no significant sclerotic changes of the subcortical arteries in our subcortical arteriosclerotic encephalopathy or nonneuropsychiatric groups.

In Binswanger's original description of a single case, white matter atrophy was most prominent in the occipital and temporal lobes. However, this observation was only macroscopic. Recently, predominance of the frontal lesion in vascular dementia has been emphasized. Ishii et al. reported that the predominance of frontal symptoms and signs in patients with vascular dementia correlated with frontal pathological changes including lacunar infarcts and ischemic white matter lesions. Clinical observations of CT and MRI findings in patients with subcortical arteriosclerotic encephalopathy showed that white matter changes were frequently encountered as periventricular abnormalities in the frontal lobe. Based on the findings in positron emission tomography and xenon CT, blood flow of the frontal lobe decreased most in the patients with vascular dementia. Our results support these radiological and clinicopathologic investigations. It is interesting that non-demented senile patients also had a tendency for a high sclerotic rate in the frontal lobe.

Brun and Englund reported that white matter lesions in patients with dementia of the Alzheimer type were regularly related to neither the severity nor the regional appearance of the cortical Alzheimer process. The sclerotic rate in our group with dementia of the Alzheimer type was slightly higher than that in age-matched controls and was highest in the frontal lobe, where cortical changes such as plaques and tangles are usually less severe than in the temporal and parietal cortex. We consider that dementia of the Alzheimer type with white matter lesions and markedly sclerotic medullary arteries may be consistent with a combined form of dementia of the Alzheimer type and subcortical arteriosclerotic encephalopathy. Both diseases are rather common among aged people, so their coincidence is not unlikely.

References
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KEY WORDS: • aging • dementia • leukoencephalopathy
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