Comprehensive and histological evaluations of intracranial atherosclerosis in hypertensive and normotensive subjects

Goro Araki, M.D., Hiroshi Mihara, M.D., Masahiro Mizukami, M.D., Hiroshi Kin, M.D., Michiharu Nishijima, M.D., and Yoji Yoshida, M.D.

Summary: Cerebral atherosclerosis without luminal narrowing has been found macroscopically and by angiographic examinations in some patients with cerebral hemorrhage. In order to clarify the histology of non-stenotic atherosclerosis of the cerebral vessels, we examined cleared specimens and serial sections of the main trunks of the cerebral arteries. The middle cerebral artery was selected in 20 cases of cerebral hemorrhage and 7 cases of cerebral infarction. Non-stenotic atherosclerosis was found frequently in cases of cerebral hemorrhage, while most patients with cerebral infarction showed stenotic cerebral atherosclerosis. We counted the numbers of medial smooth muscle cells in 10 autopsied cases of cerebral hemorrhage and 6 of cerebral infarction.

The mean numbers of smooth muscle cells per unit area in the patient with cerebral hemorrhage were less than those in cerebral infarction. In cerebral hemorrhage, the main trunks of the cerebral arteries were dilated, probably as a result of the damage to medial muscle cells and higher blood pressure during the course of intimal thickening. It is considered that arterial hypertension spreads to the peripheral, small arteries through the main trunks without luminal narrowing of the cerebral vessels.

At present, no in vivo method exists, other than angiography, to evaluate cerebral atherosclerosis. It is unjustified to conclude that there is no cerebral atherosclerosis when stenotic findings are not demonstrable by cerebral angiography. We have frequently encountered cerebral atherosclerosis during autopsy of patients with cerebral hemorrhage who showed no abnormalities in cerebral angiograms.

The present study describes differences and similarities between angiographic and histologic evaluation of the cerebral arteries, in patients with cerebral hemorrhage and cerebral infarction.

Materials and Methods

Twenty autopsied patients with cerebral hemorrhage and 7 patients with cerebral infarction, excluding cerebral embolism, were examined. The patients had been admitted to Mihara Memorial Hospital between 1972 and 1974. There were 12 males and 8 females with cerebral hemorrhage (age range, 29 to 77; mean, 56.6 years), and 3 men and 2 women with cerebral infarction (age range, 51 to 80; mean, 66.4 years).

Of the 20 with cerebral hemorrhage, putaminal hemorrhage occurred in 13, thalamic hemorrhage in 4, pontine hemorrhage in 2, and cerebellar hemorrhage in 1. Two also had occlusion of the internal carotid artery. In 5 no vascular occlusion was found angiographically. Sixteen of the 20 patients with cerebral hemorrhage had a history of hypertension. Only 1 had normal pressure. The blood pressures of the other 3 patients were unknown.

Comparison of the average blood pressure was made between patients with cerebral hemorrhage and those with cerebral infarction. The former showed higher blood pressure than the latter (table).

After fixing the brain in 10% buffered formaldehyde solution, the circle of Willis and main trunks of the cerebral arteries were removed from the base of the brain and examined macroscopically for degree and extent of atheromatous changes. The cerebral arteries were dehydrated with alcohol and prepared as cleared specimens with tetralin. Using a dissecting microscope, the thickness of the arterial walls and degree of luminal narrowing were estimated for comparison with cerebral angiographic findings. Atheromatous lesions from the arteries were cut transversely or longitudinally, embedded in paraffin, sectioned serially and stained with hemotoxylin eosin, Weigert or Mallory stain, for light microscopic study. In 10 patients with cerebral hemorrhage and 6 with cerebral infarction, specimens were obtained from 3 sites, i.e., the origin of the middle cerebral artery, and the anterior or posterior portions, respectively, of the bifurcation of the middle cerebral artery (fig. 1).

The number of muscle cell nuclei per unit area of media were counted in the cross sections using a photo pattern analyzer (PPA 250, Lesca Co. Ltd.). Areas of the media without secondary atrophy and having little or no thickening of the intima were selected.

Results

A. Comparative Angiographic and Pathologic Findings in Cerebral Artery

1) Atherosclerosis Without Luminal Narrowing in the Arteriogram (Non-stenotic Atherosclerosis).

Figure 2a shows the cerebral arteriogram of a patient with a left putaminal hemorrhage. No narrow-
TABLE Comparison of Average Blood Pressure between Patients with Cerebral Hemorrhage and Cerebral Infarction

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<tr>
<td>pressure</td>
<td>159</td>
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<td><strong>Diastolic blood</strong></td>
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<tr>
<td>pressure</td>
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Figure 3a shows the cerebral arteriogram of a patient with putaminal hemorrhage. Severe atherosclerosis was observed in the left middle cerebral artery (M1), or the left anterior cerebral artery (A1). Atherosclerosis could not be diagnosed on the basis of the cerebral arteriographic findings. However, atherosclerosis was observed in the left middle cerebral artery on macroscopic examination (fig. 2b). This indicates that atherosclerosis may not always cause luminal narrowing.

**Figure 1.** a. Diagram of middle cerebral artery from which cross sections were obtained. b. Number of muscle cell nuclei calculated in media with little or no thickening of intima.

**Figure 2.** a. (Upper) No stenosis of left middle cerebral artery was observed on cerebral angiogram of a patient with putaminal hemorrhage. b. (Lower) Arrow shows atherosclerosis of middle cerebral artery found at postmortem in same patient.
sclerosis without obvious stenosis was demonstrated at the origin of the anterior cerebral artery. The cleared specimen showed no luminal narrowing but the outer diameter was increased by the thickening of the wall (fig. 3b). This change differed from a dilatation of the vessel. Serial sections parallel to the long axis of the artery revealed remarkable thickening of the intima without luminal narrowing. The muscle cells were decreased, and there was laceration of the internal elastic lamina and infiltration by foamy cells into media.

Absence of arterial narrowing on cerebral angiography does not always indicate an absence of atherosclerosis since in spite of a marked thickening of the arterial wall, no significant luminal narrowing may be evident.

2) Atherosclerosis with Luminal Narrowing in Cerebral Arteriogram (Stenotic Atherosclerosis)

Figures 4 and 5 illustrate instances of cerebral infarction. Figure 4a shows the cerebral arteriogram of a patient with cerebral infarction. Severe stenotic alterations were observed in the right middle cerebral artery (M). Figure 4b is a lateral view showing narrowing of a branch (M2) of the right middle cerebral artery. Figure 5a and b illustrates a cleared specimen of the main trunk of the right middle cerebral artery (M). In contrast with non-stenotic atherosclerosis, the lumen shows a marked narrowing corresponding to angiographically demonstrated stenosis. Microscopic examination of a transverse section of the artery in this patient revealed a marked thickening of the intima (fig. 5c). An atheroma was found deep in the intima, and the lumen was reduced to less than one-third of its original diameter. The media and part of the internal elastic lamina were destroyed. The muscle cells in the section of media without atheromatous changes in the intima remained unchanged.

B. Incidence of Non-stenotic and Stenotic Atherosclerosis in Cerebral Hemorrhage and Cerebral Infarction

The incidence of non-stenotic and stenotic atherosclerosis in 20 patients with cerebral hemorrhage is shown in figure 6. The ratio of non-stenotic to stenotic...
Cerebral Atherosclerosis was 58:19. In 11 patients with putaminal hemorrhage, the relative incidence of non-stenotic and stenotic atherosclerosis of the middle cerebral artery (M1) was examined. There were 10 sites with non-stenotic atherosclerosis on the side of the lesions, and 4 on the opposite side. In all 7 patients with cerebral infarction, various degrees of stenotic atherosclerosis were observed (fig. 7). In 2 of these, non-stenotic atherosclerosis was seen in addition to stenotic atherosclerosis. The incidence of non-stenotic atherosclerosis in cerebral hemorrhage was higher than in cerebral infarction.

C. Medial Muscle Cells in Middle Cerebral Artery of Patients with Cerebral Hemorrhage and Cerebral Infarction

In an attempt to explain the higher incidence of non-stenotic atherosclerosis in cerebral hemorrhage as compared to cerebral infarction, the number of muscle cells in the middle cerebral artery was compared. The mean number of muscle cell nuclei per unit area (mm²) of the media was 48 in 10 cases of cerebral hemorrhage, and 65 in 6 cases of cerebral infarction (fig. 8). This suggests that the damage to medial muscle cells is more severe in cerebral hemorrhage than in cerebral infarction.

Discussion

Histologic evaluation of cerebral arteries revealed that in cases of cerebral hemorrhage cerebral atherosclerosis was frequent and often failed to appear in arteriograms. Simple assessment of atherosclerosis by cerebral arteriography is thus not totally accurate. The reason for this is that the lumen may remain unchanged despite sub-intimal thickening.

Histologic examination revealed severe degeneration, necrosis, disappearance of medial muscle cells, and laceration of the internal elastic lamina. Atherosclerosis without luminal narrowing may develop as a
Cerebral infarction (7 cases)

\[\text{non-stenotic} \quad \text{stenotic 25-50%} \quad \text{stenotic 50-75%}\]

\[\text{Distribution of stenotic atherosclerosis and non-stenotic atherosclerosis in patients with cerebral infarction.}\]

result of dilatation of the media and adventitia eccentrically. An artery which becomes stenotic by subintimal thickening first may gradually dilate.

Although the degeneration and necrosis of smooth muscle cells usually reflect severe changes in the intima, the possibility exists that in cerebral hemorrhage primary damage to the media occurs. The numbers of medial muscle cells were calculated in the arterial wall without thickening of the intima. The numbers of medial muscle cells in patients with cerebral hemorrhage were less numerous than in cerebral infarction. In cerebral hemorrhage, the cerebral arteries showed no luminal narrowing and were enlarged due to damage to the medial muscle cells.

Ooneda\textsuperscript{1-4} has reported that fibrinoid degeneration, often with cerebral hemorrhage, is due to necrosis of the medial muscle cells of the cerebral arteries. Furthermore, it has been demonstrated in experimental studies that hypertension may induce medial muscle cell necrosis.\textsuperscript{5-10}

References

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