Cerebral Artery Thrombosis and Intramural Hemorrhage

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SUMMARY Thirty-nine thrombosed arterial segments of the branches of the circle of Willis were studied by a complete serial section technique. Twenty-two patients had been hypertensive and 8 had hypercholesterolemia before the onset of cerebral artery thrombosis.

The histological characteristics of the thrombosed arterial segments were intramural hemorrhage in 28 segments, superficial edema of the fibrous cap of the atheroma or fibrous plaque in 4, rupture of the atheromatous plaque in 1, superficial accumulation of foam cells in the atheroma in 1 and an atheroma or fibrous plaque without any other changes in 5. They were many intramural small blood vessels in the atheroma or fibrous plaques of 22 segments with intramural hemorrhage. Fibrinoid degeneration of these small blood vessels was noted in 5.

These findings suggested that intramural hemorrhage from the intramural small blood vessels was the major cause of cerebral artery thrombosis and that persistent hypertension not only promoted cerebral atherosclerosis but also induced hemorrhage from the intramural small blood vessels.

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CEREBRAL ARTERY THROMBOSIS is one of the major causes of death among Japanese. It is usually not clear what kind of pathologic processes participated in cerebral artery thrombosis.

In the pathogenesis of coronary artery thrombosis, rupture or fissure formation of an atherosclerotic plaque has generally been considered to be a major cause of thrombus precipitation, but only a few investigators have suggested that intramural hemorrhage initiated the process leading to thrombosis. No agreement exists on the mechanism of occlusive thrombosis in cerebral arteries. Some consider that it is caused by a break or ulceration of the atherosclerotic intima similar to that in coronary artery thrombosis, and others believe that it is initiated by hemorrhage from intramural capillaries.

The histologic characteristics of the wall of thrombosed cerebral arteries were studied in 39 freshly occluded branches of the circle of Willis after a complete serial section.

Material and Methods

Thirty-three autopsied cases of cerebral artery thrombosis were investigated. The patients died within 4 weeks after the onset of cerebral apoplexy and were admitted during 1964 to 1974 at the hospitals of Kyushu University, Kurume University and Kawasaki University and other hospitals. As more than 2 thrombi were found in 4 cases, 39 thrombosed arterial segments were submitted for examination. Twenty-four thrombi were found in the middle general artery, 6 in the vertebral, 4 in the internal carotid, 2 in the posterior, 1 in the anterior cerebral, 1 in the posterior inferior cerebellar and 1 in the basilar artery.

The 33 patients included 23 men and 10 women, and their ages ranged from 43 to 89 years. The average age was 69 years, 2 months. The elapsed time between the onset of symptoms and death was ascertained.

Twenty-two of 29 patients whose blood pressure was measured before the onset of apoplexy remained hypertensive according to the criteria of the World Health Organization. The total serum cholesterol level was 250 mg/100 ml or more in 8 of 24 patients examined.

In none of the patients were thromboemboli found in the hearts, aortas or carotid arteries.

The occluded arterial segments, including proximal and distal non-occluded areas, were removed and fixed in 10% neutral formalin. The entire arterial specimen was cut serially in segments 5 μm thick, from the beginning to end of the occluded arterial portion. Five to 10 sections were mounted on each slide and stained with hematoxylin and eosin, and elastica Van Gieson in turn. Alcian-blue PAS stain and Berlin-blue stain were used when needed.

Results

The original lumina in 25 of the 39 segments was narrowed 50% or more by atheromatous or fibrous plaques. Calcification was present in only 4 segments.
Calcium was deposited in the deeper portion of fibrous caps or in close proximity to necrotic foci and was found along the internal elastic lamina in part. Alcian-blue-positive material increased in atherosclerotic lesions. The characteristic findings of the occluded arterial segments, which were considered to participate in thrombus formation, are summarized in the table.

The most conspicuous and frequently observed finding in the thrombosed segments was intramural hemorrhage, which was present in 28 out of 39 segments (figs. 1 and 2). The hemorrhage was confined to the superficial layer of the thickened intima in 3 segments. In the other 25 segments, extensive hemorrhage was found in the atheroma or in the outer layer of the fibrous plaques. Twenty-one of these 25 segments showed intramural hemorrhage in the outer layer of the plaque extending to the inner surface, and in 6 cases, through the gap between the lamellar fibrous layers. In almost all instances with intramural hemorrhage, there was edema, swelling of the fibrous component and slight leukocytic infiltration in the inner layer of atheroma or fibrous plaque.

When the hemorrhage extended to the innermost area of the intima, intimal collagen fibers protruded into the lumen in the manner of an overhead trap door in 3 segments. This observation suggests that the vector of the disruptive force proceeded from within the wall toward the lumen.

In 22 of the 28 segments with intramural hemorrhage, there were many newly-formed small blood vessels in or adjacent to the foci of hemorrhage (fig. 3). Some of these intramural small blood vessels were connected to the arterial lumen (fig. 4). There were platelet thrombi in the small blood vessels of 4 segments (fig. 3), and a thrombus in the small blood vessels continued into the organizing thrombus in the arterial lumen in one segment (fig. 5).

Hypertension was associated with 19 (76.0%) of the 25 cases with intramural hemorrhage. It was present in 16 (72.2%) of the 22 cases with intramural hemorrhage and proliferation of intramural small blood vessels. Fibrinoid necrosis of the small blood vessels was evident in 5 arterial segments among these 16 patients with hypertension (fig. 6). Similar degenerative changes in these intramural small blood vessels were not seen in vessels of normotensives.

Rupture of the fibrous cap of an atheroma was found in one arterial segment (fig. 7). A fissure was formed at the branching portion of the right vertebral artery. Atheromatous material extruded through the fissure, and contained foam cells, cholesterol crystals and fragments of fibrous cap incorporated in the overlying fresh thrombus (fig. 7). Intramural small blood vessels were detected in the periphery of the atheroma. This patient had had severe systolic hypertension (166–220 mm/Hg) prior to his cerebral accident.

Four segments showed marked intimal edema with no other findings responsible for thrombus formation. In 2 segments some hemosiderin-laden macrophages were found around the newly formed small blood vessels of the intimal lesions, but no recent hemorrhage was seen. The lumina were reduced about 20 to 60% by atheroma or fibrous plaque.

The remaining 6 segments of the thrombosed arteries showed no remarkable findings in the atheromatous or fibrous plaques. Foam cells accumulated in the superficial area of the atheromatous plaque in one segment (fig. 8). The arterial lumina were narrowed 38 to 87%. Clinically, 5 of these 6 patients had been hypertensive.

**Discussion**

Our observations clearly suggest that intramural hemorrhage is important in the development of cerebral artery thrombosis. The frequent association of intramural hemorrhage and recent occlusive thrombosis indicates that both of these processes were in some manner causally related, or may be parallel effects, or a combination of effects. The major cause of intramural hemorrhage was most likely bleeding from intramural small blood vessels which were connected with the arterial lumina. In our previous study on the intramural small blood vessels of 22 thrombosed cerebral arteries using postmortem angiography and a serial section technique, these small vessels were found to originate from arterial lumina in 12, from both arterial lumina and adventitial vasa vasorum in 9 and from adventitial vasa vasorum in only one case. These small blood vessels could develop in the course of organization of mural thrombus or progression of atherosclerosis.

It may be that the softening of the supporting stroma and the increased blood pressure induce intra-

<table>
<thead>
<tr>
<th>Type of plaque</th>
<th>Atheromatous</th>
<th>Fibrous</th>
<th>With intramural small blood vessels</th>
<th>With hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage in atheroma or fibrous plaque</td>
<td>25</td>
<td>3</td>
<td>22 78.6%</td>
<td>19/25 76.0%</td>
</tr>
<tr>
<td>Rupture of atheroma</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1/1</td>
</tr>
<tr>
<td>Edema of plaque</td>
<td>3</td>
<td>1</td>
<td>2 50.0%</td>
<td>2/3 66.7%</td>
</tr>
<tr>
<td>Atheroma or fibrous plaque alone</td>
<td>5 (1*)</td>
<td>1</td>
<td>1 16.7%</td>
<td>5/6 83.3%</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>5</td>
<td>26 66.7%</td>
<td>27/35 77.1%</td>
</tr>
</tbody>
</table>

(1*) indicates superficial foam cell accumulation in the atheromatous plaque.
mural hemorrhage. Hypertension, found in high frequency, could predispose to these changes. Russel" reported that microaneurysms in the basal ganglia in the hypertensives seemed to develop due to high blood pressure. Therefore, long-standing high blood pressure was believed to result not only in progression of atherosclerosis but also in an increase in permeability or fibrinoid necrosis of the intramural small blood vessels.

Thrombi in the small blood vessels extending into the arterial lumen appeared to be equally important in forming arterial thrombi.

The thrombosed segments with intramural hemorrhage showed edema, swelling of fibrous components, slight leukocytic infiltration and/or increase of Alcian-blue-positive material in the superficial area of the intima. These changes might lead to exposure of subendothelial tissue, particularly collagen fibers, activation of Factor XII, release of tissue thromboplastin and release of ADP by destruction of endothelial cells and erythrocytes, which are all thought to be important factors for adhesion and aggregation of platelets and fibrin deposition. Paterson suggested that hemorrhage in the intima induced the release of thromboplastic substances into the lumen, and that necrosis of the intima involving the endothelium might occur and be followed by exposure of a raw surface. The abrupt increase in intimal thickening by hemorrhage would also reduce the arterial lumina.

A significant finding in the thrombosed arterial wall was that only one thrombus originated on the fissure of an atheroma. In contrast to our findings, a similar study carried out by Constantinides revealed that all 10 cerebral artery thrombi were attached to a break in the atherosclerotic or fibrosed arterial wall. Constantinides was convinced that the break preceded and caused thrombus formation, though the mechanism of the formation of plaque fissure was not identified.

Generally, coronary arteries show more severe atherosclerosis than cerebral arteries and they receive relatively higher blood pressure and are always exposed to the heart beat. It is understandable why a high frequency of rupture of the fibrous cap of an atheroma, might be more likely to cause thrombus precipitation in a coronary artery. Our previous study

**FIGURE 1.** Occlusive thrombus in a cerebral artery with hemorrhage in the atheroma.

**FIGURE 2.** Fresh occlusive thrombus in a cerebral artery with a narrowed lumen due to markedly thickened intima. Hemorrhage in the inner layer of the thickened intima is prominent.

**FIGURE 3.** Many small blood vessels in the markedly thickened intima. There are some platelet thrombi in the lumina of these small vessels (arrows). H & E. $\times 54$.

**FIGURE 4.** Intramural small blood vessel connected to the arterial lumen. Elastica Van Gieson. $\times 90$.

**FIGURE 5.** Fibrin thrombus in a small blood vessel. Hemorrhage is found in the peripheral area of the atheroma. The thrombus is continuous with the organizing thrombus in the arterial lumen. H & E. $\times 170$.

**FIGURE 6.** Fibrinoid necrosis of the small blood vessels in the periphery of an atheroma. Hemorrhage and hemosiderin deposition are associated. H & E. $\times 230$.

**FIGURE 7.** A thrombus precipitated on the ruptured area of atheroma. Foam cells, cholesterin crystals and a small amount of atheromatous gruel escape into the thrombus. H & E. $\times 80$.

**FIGURE 8.** A thrombus precipitated on the thickened intima on which superficial area foam cells accumulate. Slight hemorrhage and cellular infiltration are associated. H & E. $\times 110$. 
on occlusive coronary artery thrombosis supported this opinion.\(^{15}\)

A comparative study by Resch et al.\(^ {18}\) showed that cerebral atherosclerosis was more severe among Japanese than among Caucasians. This was considered to be one of the factors which explained the high frequency of cerebrovascular disorders among Japanese. However in our observations of autopsy cases in the Hisayama survey,\(^ {6}\) the severity of atherosclerosis, estimated by Gore's method, of cerebral arteries was not as high as described. It is our assumption that severe atherosclerotic changes, such as complicated lesions, were more frequent among Caucasians, and that rupture or fissure formation of atherosclerotic lesions might be found in higher frequency in Caucasians than in Japanese. It is suggested that geographic or racial differences might influence the clinical risk factors, such as hypertension, hypercholesterolemia, emotional stress and others, in the morphogenesis of cerebral artery thrombosis.

The mechanisms of thrombus formation in the 6 cases which showed no conspicuous changes in the cerebral arterial wall, except for a fibrous plaque or atheroma formation, were difficult to explain, but 5 of these 6 cases had long-standing hypertension. Hypertension not only promotes cerebral atherosclerosis,\(^ {11}\) but also increases glycosaminoglycans,\(^ {17}\) collagen and elastin,\(^ {18}\) and participates in the degenerated smooth muscle cells of the arterial wall.\(^ {19}\) These alterations in the arterial wall, associated with overstretching or spasm due to elevated blood pressure,\(^ {20,21}\) could surely be important factors which preceded cerebral artery thrombosis.

References