Histopathology of the Brain Vascular Network in Moyamoya Disease

MASANORI YAMASHITA, M.D., KAZUNARI OKA, M.D., AND KENZO TANAKA, M.D.

Summary
There is an unusual vascular network at the base of the brain in patients with moyamoya disease. We detected various histologic lesions in the perforating arteries of 22 patients. Vessels showing rupture ranged from 50 to 530 μm in diameter; they were dilated, some had fibrin deposits in the wall, fragmented elastic laminae and attenuated media. Non-ruptured perforating arteries (diameter 200 to 550 μm) revealed microaneurysm formation, focal fibrin deposits and marked attenuation of the wall thickness with diminution of the elastic lamina. These changes seem to predispose to rupture of perforating arteries. Stenotic changes such as fibrous intimal thickening, collapse of the lumen and thrombosis were detected in 14 out of 22 cases. Morphometric analysis of perforating arteries indicated that arteries showing extreme degrees of stenosis or dilatation were more frequent in the patients with moyamoya disease than in the control cases. Dilatative arteries were more frequent in the young patients and stenotic vessels were, in contrast, less frequent in the young patients.

MOYAMOYA DISEASE is a clinical entity with angiographical findings of bilateral stenoses or occlusion of the distal ends of internal carotid arteries and an unusual vascular network at the base of the brain. The disease is characterized by focal stenoses or occlusion at the distal ends of both internal carotid arteries and at the proximal regions of the anterior and middle cerebral arteries. Stenoses are due to eccentric fibrous intimal thickening with laminated elastic fibers. The morphogenesis of these intracranial vascular lesions remains obscure. We report the abnormalities of perforating arteries including lenticulostriate and thalamoperforate arteries in 22 Japanese patients with moyamoya disease.

Materials and Method
Twenty-two cases clinically diagnosed as moyamoya disease and autopsied during the years from 1970 to 1979 were examined pathologically. Nineteen of the 22 cases have already been reported with regard...
to the pathology of intracerebral hemorrhage in moyamoya disease.\textsuperscript{2} Data on a 16-year-old girl, a 32-year-old man and a 48-year-old man were included in the present study. The age and sex of the 22 patients are given in Table 1. The pathological protocol and clinical records on each patient were available. The brain was examined macroscopically by cutting serially on the frontal plane in 21 cases and on the horizontal plane in one. Histologic sections of the brain and blood vessels in the subarachnoid space were routinely stained with hematoxylin and eosin, elastica van Gieson and Mallory’s phosphotungstic acid hematoxylin. In 7 cases, the hematomas and the surrounding cerebral parenchyma were investigated microscopically using serial or semi-serial sections.

In 11 cases, diameter and thickness of the wall (tunica media and intima) of perforating arteries over 30 microns in diameter within basal ganglia, thalami and

<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Sex</th>
<th>Sites of massive hemorrhage</th>
<th>Sites of infarcts</th>
<th>Other vascular lesions</th>
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<tbody>
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<td>8</td>
<td>F</td>
<td>rt. BG, rt. frontal lobe</td>
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<td>16</td>
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<td>rt. TH</td>
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<td>17</td>
<td>M</td>
<td>midbrain, pons</td>
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<td>5</td>
<td>18</td>
<td>F</td>
<td>rt. cerebral peduncle</td>
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<td>rt. BG</td>
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<td>M</td>
<td>rt. TH, midbrain, pons</td>
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<td>48</td>
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<td>rt. BG, TH, temporal lobe</td>
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<td>54</td>
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<td>rt. BG, TH, frontal, parietal, temporal lobes</td>
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<td>M</td>
<td>rt. BG, TH, hypothalamus</td>
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<tr>
<td>22</td>
<td>64</td>
<td>F</td>
<td>pons, cerebral peduncle</td>
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</table>

SAH = subarachnoid hemorrhage; BG = basal ganglia; TH = thalamus; CN = caudate nuclei.
internal capsules were measured microscopically, in each paraffin section. Perforating arteries were also studied in the following nine control cases: 1) a 19-year-old man with spinal injury; 2) a 25-year-old man with malignant lymphoma; 3) a 29-year-old woman with Wernicke’s encephalopathy; 4) a 30-year-old woman with ovarian carcinoma; 5) a 37-year-old woman with valvular heart disease; 6) a 47-year-old man with renal cell carcinoma; 7) a 51-year-old man with anal carcinoma; 8) a 53-year-old man with primary amyloidosis; 9) a 56-year-old man with lung cancer. Four histologic sections containing thalami and basal ganglia of both sides were used for measurement in each of the controls.

Results

Seventeen of 22 patients died following massive intracerebral hemorrhage; intraventricular extension of the hemorrhage was observed in fifteen cases. Sites of hemorrhage and/or infarcts in each patient are shown in table 1. Old infarcts were found in five cases and in one of these five, there was marked cerebral atrophy due to infarction and four presented with multiple cerebral infarcts in association with recent or past subarachnoid hemorrhage, the source of which was not determined at autopsy.

Findings of the Circle of Willis and Main Branches

In all 22 patients, the main vascular lesions were stenoses or occlusion of distal ends of the bilateral internal carotid arteries produced by fibrous thickening in the intima with laminated and reduplicated elastic laminae. In twenty-one out of 22 patients, these histologic lesions were composed of eccentric and focal intimal thickening and resembled the "intimal pads" seen at arterial bifurcations. Both internal carotid arteries in a 7-year-old girl showed segmental and concentric fibromuscular thickening of the intima which resembled the findings seen in intimal hyperplasia of fibromuscular dysplasia. Proximal segments of anterior and middle cerebral arteries revealed an intimal fibrous thickening, in the majority of cases.

In two patients, cerebral dissecting aneurysms were identified. In a 16-year-old girl, dissection beneath the internal elastic lamina was demonstrated histologically along the proximal region of the left anterior cerebral artery. The dissected space was filled with nonclotted blood. In a 48-year-old man, dissecting aneurysm commenced just distal to the bifurcation of the right internal carotid artery and extended to the trifurcation of the middle cerebral artery. The space beneath the internal elastic lamina was filled with a fresh thrombus and communicated with the true lumen through a tear of the elastic lamina.

A ruptured saccular aneurysm identified in a 7-year-old girl was located at the left posterior cerebral-posterior communicating arterial junction and led to a fatal subarachnoid hemorrhage.

Moyamoya Vessels in Angiograms

In twenty-one out of 22 patients, various degrees of unusual vascular network were demonstrated angiographically. In one patient, moyamoya vessels had not been identified angiographically, but abnormal dilated vessels were demonstrated histopathologically. In a 7-year-old patient, the most prominent moyamoya vessels in the angiogram were seen when the patient was five years of age (fig. 1a). Both density and extent of the vascular network were more conspicuous in the patients under 20 years of age. In the older patients, the network was usually identified only to a small extent of the base of the brain. Transdural collaterals were, in turn, more conspicuous (fig. 1b).

Macroscopical Findings of Moyamoya Vessels

The vascular network at the base of the brain consisted of dilated medium- or small-sized muscular arteries which branched off the circle of Willis, anterior choroidal arteries, internal carotid arteries and posteri-
or cerebral arteries. These arteries formed complex channels that usually connected to the distal portion of the anterior and middle cerebral arteries (fig. 2). Numerous small vessels were derived from these channels and entered the base of the brain. These small vessels seemed identical to lenticulostriate and thalamoperforate arteries, except for their dilatation and tortuosity.

An unruptured aneurysm was located in a 64-year-old woman at a dilated perforating artery which had branched off from the posterior communicating artery.

**Morphometric Analysis of Perforating Arteries**

Diameter and thickness of the wall were measured in 2002 perforating arteries; 809 in five young patients under 20 years of age; 663 in six adult patients; 530 in nine control cases.

The ratio of diameter to the thickness of the wall was extremely variable in patients with moyamoya disease, and these perforating arteries could be divided into the following two groups: dilated arteries with a relatively thin wall; thick-walled arteries showing luminal stenoses (fig. 3). For the purpose of statistical analysis, the measured value in the control cases was inverted into that of logarithm. Means of diameter and the thickness of the wall were evaluated as logarithmic values. Each value was re-inverted into the value of the natural number (table 2). In the patients with moyamoya disease and control cases, the number of perforating arteries beyond the value of the mean + 2.5 SD was counted, and statistically analyzed using \( \chi^2 \) test (table 3).

Stenotic or dilative arteries were more frequent in the patients with moyamoya disease than in the control cases. Among the patients, dilative arteries were more prominent in the young than in the adult patients. Stenotic vessels were, in contrast, less frequent in the young patients (table 3).

**Pathological Findings of Moyamoya Vessels**

Various histologic lesions were demonstrated in the cerebral parenchyma. There were various degrees of luminal stenoses with intimal thickening and reduplication of the elastic lamina, partial dilatation with discontinuity of the elastic lamina, microaneurysm formation, dilative change of the vessels with medial fibrosis and rupture of the vascular wall, with or without fibrin deposits.

**Stenotic Vascular Lesions**

Concentric thickening of the intima and luminal narrowing by loose fibrous connective tissue, suggestive of a secondary collapse of the vessels were frequently found in 13 cases. The involved arteries ranged from one to ten or more in number, in one paraffin section of the respective case. These stenotic arteries were usually associated with moderate to marked thickening and reduplications of the internal elastic lamina, fibrosis of the tunica media and fibroelastosis of the vascular wall (fig. 4a). Three vessels in 2 cases were occluded by fibrous connective tissue containing numerous capillaries, thereby indicating recanalization in an organized thrombus (fig. 4b).

Partial dilatation with discontinuity of the elastic lamina was noted in 3 vessels in 2 patients.

**Dilatation With or Without Serious Vascular Degeneration and Microaneurysm Formation**

The majority of dilated arteries revealed moderate to serious vascular degeneration and microaneurysm formation. Various histologic lesions were demonstrated in the cerebral parenchyma. There were various degrees of luminal stenoses with intimal thickening and reduplication of the elastic lamina, partial dilatation with discontinuity of the elastic lamina, microaneurysm formation, dilative change of the vessels with medial fibrosis and rupture of the vascular wall, with or without fibrin deposits.

**TABLE 2 Diameter and Thickness of the Wall of Perforating Arteries in Control Cases**

<table>
<thead>
<tr>
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<th>Mean - 2.5 SD</th>
<th>Mean + 2.5 SD</th>
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<tr>
<td>Diameter (( \mu m ))</td>
<td>100</td>
<td>25.3</td>
<td>422.7</td>
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<tr>
<td>Thickness of the wall (( \mu m ))</td>
<td>9.2</td>
<td>2.7</td>
<td>31.6</td>
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</table>

**TABLE 3 Number of Perforating Arteries Beyond Mean + 2.5 SD**

<table>
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<tr>
<th></th>
<th>Control</th>
<th>Young patients</th>
<th>Adult patients</th>
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<tr>
<td>No. of stenotic arteries</td>
<td>[2]</td>
<td>53</td>
<td>71</td>
</tr>
<tr>
<td>No. of dilated arteries</td>
<td>5</td>
<td>53</td>
<td>22</td>
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(Overall no. of perforating arteries) (530) (809) (663)

Stenotic arteries = under 422.7 \( \mu m \) in diameter, beyond 31.6 \( \mu m \) in wall thickness; dilated arteries = beyond 422.7 \( \mu m \) in diameter, under 31.6 \( \mu m \) in wall thickness.

Bars indicate significant differences (*p < 0.001; †p < 0.005).
marked fibrosis of the media, attenuation of the wall, moderate increase in elastic fibers and occasionally discontinuity or segmentation of elastic lamina (fig. 5a). Three vessels presented more serious alterations and which might predispose to disruption of the dilated arteries.

A focal protrusion in an area of a dilated vessels was present in the periphery of a hematoma of the left basal ganglia in a 41-year-old woman. The involved part, probably near a small branch of the dilated artery, showed discontinuity of the internal elastic lamina and had fibrin deposits on the wall (fig. 5b). The parent artery with a diameter of 550 x 1350 microns revealed medial fibrosis and segmentation of the elastic lamina.

A dilated artery of 550 x 730 microns in diameter found in the cerebral parenchyma adjacent to a right putaminal hematoma of a 54-year-old woman showed irregular intimal thickening, marked fragmentation of the elastic lamina, medial fibrosis and extravasation of red blood cells. Part of the wall was markedly attenuated (fig. 5c).

A true microaneurysm of 470 microns in diameter was demonstrated in the thalamus adjacent to the massive hematoma in a 48-year-old man. The parent artery of 200 microns in diameter showed diminution of the elastic lamina and medial fibrosis. The wall of the aneurysm was attenuated without disruption (fig. 5d).

Rupture of Perforating Arteries

Apparent rupture of the arterial wall was demonstrated in 13 vessels in six patients. The diameter and the sites of each of the arteries are shown in figure 6. These arteries ranged from 50 to 530 microns in diameter (mean: 250 µm), and presented moderate to severe fibrosis in the media (fig. 7a). Only one artery had focal fibrin deposits at the disrupted site (fig. 7b). Ten of 13 arteries were accompanied by a fresh massive cerebral hemorrhage and with fresh thrombi around these vessels. Three vessels were organized in old hemorrhagic foci in the thalamus. These ruptured arteries were located within or around massive hemorrhagic foci and usually near the base of the brain.

Arterio-venous malformation and hemangioma were never detected during this study.

Discussion

Although it had been reported that intraparenchymal hemorrhage was rare in moyamoya disease,1-4,5 the main causes of death were intracerebral hemorrhage followed by extension to intraventricular and subarachnoid spaces.2 There are few reports in which vascular changes leading to intracerebral hemorrhage have been verified, histopathologically. The thalamoperforate arteries in a 51-year-old Japanese man had four identical microaneurysms (100 to 2500 µm) located within the thalamic hemorrhagic foci and showed apparent disruption of the wall (Mauro et al6). Lipohyalinosis of the wall as another type of vascular lesion was identified among small perforating arteries ranging from 100 to 500 microns in diameter and which showed focal disintegration of elastic lamina with marked hyalinization of the vascular wall and accumulation of foam cells. These investigators concluded that
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FIGURE 4. a.) Small artery showing fibroelastosis of the wall in the basal ganglia of a 7-year-old girl. The lumen is markedly stenosed by edematous intimal thickening. Elastica van Gieson stain × 188. b.) Small artery in the base of the brain of a 43-year-old woman. The lumen is occupied by fibrous connective tissue containing numerous capillaries. Elastica van Gieson stain × 175.

Lipohyalinosis and miliary aneurysms were the source of a fatal intracerebral hemorrhage.6

Saccular aneurysms in the circle of Willis, other main branches and dilated moyamoya vessels with or without rupture were recently reported.7,8 These aneurysms, it was concluded, were not uncommon but rather important causative lesions of fatal intracranial hemorrhage.

FIGURE 5. a.) Dilated artery in the basal ganglia of a 46-year-old woman showing attenuation of the wall, fragmentation of the elastic lamina and focal intimal fibrous thickening. Elastica van Gieson stain × 124. b.) Focal protrusion of the small arterial wall in a 41-year-old woman. Discontinuity of the elastic lamina and fibrin deposits in the wall are noted. Elastica van Gieson stain × 84. c.) Dilated artery of 550 microns in diameter in a 54-year-old woman showing marked medial attenuation and diminished elastic lamina. Elastica van Gieson stain × 82. Inset: High power of the vascular wall shows fragments of the elastic lamina (arrowheads). × 177. d.) Microaneurysm of 470 microns in diameter without rupture in a 48-year-old man (arrowheads). Elastica van Gieson stain × 151.
RUPTURED ARTERIES; DIAMETER AND SITES

Kodama et al.\textsuperscript{9,10} reported microaneurysms at the distal portion of the posterior choroidal artery, as demonstrated angiographically in patients with moyamoya disease. They speculated that the microaneurysm resulted from fragility and localized disruption of the vascular wall due to continuous and insidious ischemic conditions in the cerebral parenchyma around the lateral ventricles. Further disruption of the pseudoaneurysm caused an intracerebral hemorrhage followed by intraventricular extension and subarachnoid hemorrhage.

In our investigation, two saccular aneurysms within the subarachnoid space were identified among 22 patients. One was unruptured and the other, located at the posterior cerebral-posterior communicating arterial junction, was ruptured and led to fatal subarachnoid hemorrhage. Saccular aneurysms rarely occur in childhood, moreover aneurysms of the posterior part of the circle of Willis are extremely uncommon.\textsuperscript{11-14} In this case, aneurysm formation was perhaps due to hemodynamic stress against the vertebro-basilar system secondary to progressive stricture of the bilateral internal carotid arteries.

A disrupted artery was demonstrated in the subarachnoid space in a 48-year-old patient. Such a type and site of arterial rupture have not been detected in patients with moyamoya disease.

Angioneurosis of lenticulostriate arteries (50 to 200 \( \mu \text{m} \) in diameter) and subsequent single or multiple disruption of the involved vessels were thought to be the main causes of massive cerebral hemorrhage in hypertensives.\textsuperscript{15} Fisher,\textsuperscript{16,17} Russell,\textsuperscript{18} Ooneda,\textsuperscript{19} and Cole and Yates\textsuperscript{20} supported the conclusion and considered respectively that hypertensive cerebral hemorrhage resulted from single or multiple rupture of microaneurysms ranging from 50 to 2500 \( \mu \text{m} \) in diameter. The vascular lesions in hypertensives involved usually the entire circumference of the vessel wall and displayed a diminution in the number of smooth muscle cells in the tunica media, fibrosis, hyalinosis, fibrinoid necrosis and lipohyalinosis of tunica media followed by dilatation of the involved segment and discontinuity or segmentation of elastic lamina.

Finally, the involved segment formed a microaneurysm, as the source of hemorrhage. While these concepts have been well confirmed, there have been few reports of histopathological evidence of the rupture of arteries or microaneurysms within massive hemorrhagic foci in hypertensives.\textsuperscript{16-19}

Our present study on moyamoya disease revealed that the initial vascular lesion of small perforating arteries which could predispose to the rupture of the wall might consist of fibrosis and attenuation of tunica media, in association with luminal dilatation. Focal fibrin deposits and a true microaneurysm were considered to be further advanced lesions predisposing to rupture. Lipohyalinosis of the vascular wall was not evidenced in our materials.

Disrupted arteries were 50 to 530 \( \mu \text{m} \) in diameter (mean: 250 \( \mu \text{m} \)), and were larger than the necrosed arteries of 50 to 200 \( \mu \text{m} \) in diameter in hypertensives.\textsuperscript{15,16,19} Elastic laminae were usually well preserved except for focally disrupted sites in the moyamoya vessels. Tunica media showed focal fibrin deposits only at the disrupted site, in one patient. In the other patients, the wall of the vessels was ruptured.
without fibrinoid necrosis but was associated with fibrosis and attenuation of the medial smooth muscle cells. These findings indicate that the rupture of the vessels in moyamoya disease could occur in the absence of microaneurysm or fibrinoid necrosis. Increase in blood supply would lead to hemodynamic stress to these moyamoya vessels, as a collateral pathway. In addition, the progressive stenoses of moyamoya vessels, in severity and distribution, may induce further stress against the remaining vessels and finally disruption of the wall would occur. The disrupted and organized small arteries within old hemorrhagic foci indicate that the rupture of moyamoya vessels may even occur repeatedly.

We concluded that medial fibrosis and attenuation of the wall were probably primary and were closely related to the rupture of the moyamoya vessels, on the basis of the following: 1) Since the ruptured arteries and small number of the unruptured dilated vessels showing serious alteration were mainly located in the periphery of the hematoma or in the brain parenchyma adjacent to the hematoma, the histological alteration should be less prominent than alteration within the hematoma. However, almost all the dilated arteries, even within the hematoma, showed a well preserved elastic lamina. 2) Dilated arteries in the basal ganglia free from hemorrhage showed various degrees of medial fibrosis and attenuation of the wall, of the same degree seen in cases of hematoma. Therefore, the rupture of these arteries is probably responsible for the formation of the hematoma.

The stenosing and obstructive process in moyamoya vessels may be related to ischemic events. Despite a high frequency in stenotic lesions, only one patient presented progressive and finally fatal cerebral infarction without a hemorrhagic accident. Why there is a discrepancy between the high frequency in stenosing lesions and relatively rare occurrence of serious ischemic events in the clinical history remains unclear. Fatal hemorrhagic accidents may be caused by an increasing hemodynamic overload before ischemic events became apparent and complete and the gradual development of a transdural collateral pathway could compensate for the decrease in blood supply of the cerebral parenchyma through the moyamoya vessels. It is speculated, in turn, that owing to a rich blood flow in the basal ganglia through the moyamoya vessels, hemorrhagic accidents would more readily occur in patients free from ischemic events. At present, we have no adequate explanation for both the high incidence of ischemic events and relatively rare occurrence of hemorrhage in the pediatric patients presenting well developed moyamoya vessels. Aging processes in moyamoya vessels may influence the rupture of dilated vessels, as suggested by Mauro et al.6

The morphometric analysis of moyamoya vessels showed a more variable ratio of the diameter to the thickness of the wall in the patients with moyamoya disease than in the control cases. In addition, dilated arteries were more prominent in the young patients and stenotic arteries were less prominent in these young patients. These results correspond to the angiographical findings of moyamoya vessels, and indicate that with aging, dilated moyamoya vessels progressively become attenuated and decrease in numbers, in contrast with the increase of stenotic arteries. The simultaneous presence of both extremely dilated and stenotic arteries in the brain parenchyma may be characteristic of moyamoya disease.

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We wish to thank the following pathologists and doctors who contributed data on the autopsies related to this investigation: Prof. T. Nakashima (Kurume), Prof. H. Nakamura (Yonago), Prof. S. Seno (Okayama), Prof. K. Nakata (Osaka), Prof. R. Maeda (Osaka), Prof. Y. Hamashima (Kyoto), Prof. A. Oshima (Wakayama), Prof. N. Komai (Wakayama), Prof. M. Takahashi (Gifu), Prof. G. Ohba (Kanazawa), Dr. Y. Kodama (Kure), Dr. T. Kitaioka (Hiroshima), Dr. Y. Nishihara (Fukukoka), Dr. H. Uchida (Kobe), Dr. T. Masuo (Sumoto), Drs. K. Kotoh and M. Sasaki (Osaka).
We thank M. Ohara for comments on the manuscript.

References
Delayed TIAs Distal to Bilateral Occlusion of Carotid Arteries — Evidence for Embolic and Hemodynamic Mechanisms

JULIEN BOGOUSSLAVSKY, M.D. AND FRANCO REGLI, M.D.

SUMMARY We studied 4 patients with bilateral carotid artery occlusion who suffered delayed TIAs in one of the occluded internal carotid or common carotid areas. Hemodynamic mechanisms were prominent in two patients, in head turning and orthostatic hypotension. In the other two cases, embolic phenomena through the homolateral external carotid collateral pathways were probable, because this artery (or the common carotid artery) showed atheromatous stenosis and major collateral supply to the brain and retina. Different mechanisms may be responsible for further ischemia after bilateral occlusion of carotid arteries.

BILATERAL CAROTID ARTERY OCCLUSION (BCO) — most often internal carotid artery (ICA) — is not a common finding in clinical neurology. For a long time it was thought to be incompatible with life, but a few studies showed that patients may survive this condition, sometimes with a fairly benign outcome.1-3 A few studies dealt with the diagnosis of BCO,4,5 but little attention has been paid to the occurrence of further ischemic events in the areas supplied by the occluded carotid arteries. We now report 4 patients with BCO, demonstrated on angiography who later suffered delayed TIAs in one of the occluded artery areas. Different mechanisms, either embolic or hemodynamic, appear to be responsible for further acute ischemia in BCO.

Case Reports

Case 1

This 59-year-old man suddenly lost consciousness without warning symptoms. After one day the patient regained consciousness, but was aphasic and hemiparetic on the right side of the body. When hospitalized 5 weeks later he showed a right-sided facio-brachial weakness and a moderate expressive speech disturbance. Archography and bilateral carotid arteriography showed bilateral ICA occlusion, with stenosis of left external carotid arteries (ECA) and left common carotid artery (CCA) (fig. 1). ECA collateral pathways to the brain and retina were well developed on both sides. Intracerebral arteries did not show significant changes. Doppler ultrasonography showed reversal of ophthalmic flow bilaterally. There was no heart disturbance. During the next 6 months the patient experienced three times amaurosis fugax in the left eye and once numbness of the right face and arm, of 5' duration. Acetylsalicylic acid was begun, but the patient was not seen again.
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