Multiple Progressive Intracranial Arterial Occlusions
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Abstract:
A 30-year-old woman experienced a series of strokes over a period of three months. Radiographical studies showed evidence of occlusive disease of the cerebral arteries and a rich collateral circulation typical of multiple progressive intracranial arterial occlusive disease. At autopsy, the involved cerebral arteries showed marked fibrosis of the intima, media and adventitia, degeneration of the internal elastic lamina, and evidence of old and recent thrombosis. These findings are interpreted as a late stage of the disease and give no indication as to its pathogenesis. It is suggested that the vascular disease may have had its onset in childhood with the terminal strokes related to institution of oral contraceptive therapy.

Additional Key Words: moyamoya disease  rete mirabile
stroke in children and young adults

Multiple progressive intracranial arterial occlusive disease is an unusual cerebrovascular disorder occurring in children and young adults. The disease also has been designated by some authors as progressive cerebral arterial occlusive disease, spontaneous occlusion of the circle of Willis, and cerebral “moyamoya” disease.1-12 It is characterized clinically by a syndrome of multiple strokes and by radiographical evidence of multiple and progressive occlusions of the cerebral arteries. The internal carotid artery distal to the origin of the posterior communicating artery and the proximal portions of the anterior and middle cerebral arteries are involved early and there is often striking narrowing of the carotid artery below the level of the occlusion, perhaps due to diminished flow in the vessel.10 A rich collateral circulation develops in the region of the basal ganglia and upper brain stem from vessels arising from the posterior cerebral, basilar and internal carotid arteries and the major trunks of the anterior and middle cerebral arteries. Transdural anastomoses between the external and internal carotid arteries are often spectacular and have been referred to as rete mirabile and “moyamoya,” a Japanese word meaning something hazy or fuzzy. Although the clinical and radiographical features have been well documented in the literature, pathological study of the cerebral arteries has been reported in only a few cases. This report describes the pathological findings in a young woman who had multiple strokes and radiographical evidence of the progressive occlusions of the cerebral arteries characteristic of this disease.

Case Report
This 30-year-old woman was hospitalized on January 26, 1971, because of nightmares, night sweats and progressive confusion of ten days’ duration. She appeared unable to comprehend or communicate and her actions were often inappropriate. Her history was not remarkable except for visual impairment of the left eye since childhood. She had been taking an oral contraceptive for six weeks prior to the onset of her illness. The general physical examination was not remarkable except for visual impairment of the left eye since childhood. She had been taking an oral contraceptive for six weeks prior to the onset of her illness. The general physical examination was not remarkable except for a temperature of 102.2°. The patient was obviously confused and had mild aphasia and paresis of the right lower face and right arm. The left optic fundus was difficult to visualize because of a complicated cataract and showed a diffuse white peripapillary and macular scarring. Laboratory studies were within normal limits except for erythrocyte sedimentation rates of 52 mm per hr and 100 mm per hr on two occasions. The cerebrospinal fluid contained 24 red cells per cubic millimeter but was otherwise normal. Electroencephalography was abnormal due to delta slowing in the left frontotemporal area. Biopsy of the left temporal artery showed no histological abnormality.

The patient’s aphasia and right arm and face paresis improved by the second day of hospitalization but weakness of the right arm recurred two weeks later and was accompanied by right leg weakness, headache and nausea. She was treated with Decadron and these
symptoms improved sufficiently so that the patient was able to return to her home. She re-entered the hospital on February 20, 1971, with slight expressive aphasia, right lower facial paresis, diffuse weakness of the right arm and leg, distal weakness of the left leg, hyperactive tendon reflexes in the right arm and both legs, a Babinski sign on the left side and diminished pinprick sensation in the right leg. Laboratory findings were similar to those on her previous admission. The right temporal artery was biopsied and was normal. Three days following admission the first of a series of seizures occurred. These were relatively well controlled until April 5, 1971, when the patient began experiencing repeated seizures and became poorly responsive and incontinent. On the following day her temperature rose to 106°F and the right pupil became dilated and nonreactive. She died approximately three months after the onset of her illness.

RADIOPHICAL FINDINGS
Left carotid angiography performed during the first admission demonstrated a markedly hypoplastic internal carotid artery with an irregular and severely narrowed supraclinoid segment. The ophthalmic artery was well visualized and transdural anastomoses from the distal branches of the ophthalmic artery to a frontal branch of the anterior cerebral artery were seen. Tiny dilated collateral vessels in the region of the basal ganglia were poorly filled with contrast medium. Later in the study these filled small branches of the middle cerebral artery. The horizontal portion of the anterior cerebral artery was occluded. Right carotid angiography demonstrated leptomeningeal anastomotic filling of the left anterior cerebral artery and some branches of the left middle cerebral artery. During the patient's second hospitalization right brachial angiography showed extensive collateral circulation through numerous hypertrophied vessels in the region of the basal ganglia; these filled branches of the left middle cerebral artery.

AUTOPSY FINDINGS
The viscera were not remarkable except for bronchopneumonia, pulmonary edema and hepatomegaly with moderate centrolobular fatty metamorphosis. There were no changes of note in the systemic arteries.

The right cerebral hemisphere was swollen and softened, particularly those areas supplied by the right middle cerebral artery. There was mild herniation of the right uncus accompanied by multiple small secondary hemorrhages in the midbrain and pons. The arteries at the base of the brain (fig. 1) showed severe alterations, particularly the left internal carotid artery and the proximal segment of the left middle cerebral artery. The walls of these vessels were unusually firm, markedly thickened, and nodular in places. The left internal carotid artery was surrounded by thickened leptomeninges which were firmly adherent to the left optic nerve; its lumen was pinpoint in size and

FIGURE 1
The arteries of the anterior circulation of the brain show diffuse thickening of their walls. Note the pinpoint lumen (solid arrow) and nodular appearance of the left internal carotid artery. The right middle cerebral artery (open arrow) is distended by recent thrombus.
contained organized thrombus. These changes extended into the left middle and anterior cerebral arteries and their major branches. The walls of the distal branches of these vessels were only slightly thickened. The right internal carotid artery showed only mild thickening of its wall and its lumen was patent. The proximal 2-cm segment of the right middle cerebral artery was distended and its wall slightly thickened; the lumen was entirely filled by a firm, dark red-brown thrombus. The distal branches of the artery appeared normal. The proximal segment of the right anterior cerebral artery also was markedly thickened with a pinpoint lumen which was occluded at its origin by thrombus. The vertebral, basilar and posterior cerebral arteries showed only mild diffuse thickening of their walls. The posterior perforating arteries arising from the basilar and posterior cerebral arteries appeared larger and more numerous than usually seen in this region. Extensive recent encephalomalacia was noted in the cortex, white matter and basal ganglia in the distribution of the right middle cerebral artery. In addition, the cortex appeared moderately narrowed and granular in some areas, indicating areas of old infarction. In the left cerebral hemisphere, there were multiple small foci of old encephalomalacia in the cortex and white matter in almost all lobes.

Microscopic examination of the left internal carotid artery (fig. 2) revealed intense fibrosis of the media and adventititia, marked fraying, duplication and fragmentation of the elastica and focal intimal thickening by poorly cellular connective tissue with narrowing of the lumen. In places, the elastic tissue appeared to be redundant and formed coils in the fibrosed wall of the vessel. In some sections, small occluded arteries were found in the markedly thickened adventitia. The changes in the right internal carotid artery were similar but much less severe. In the left anterior and middle cerebral arteries, the lumens were virtually obliterated in places by loose-meshed connective tissue. Focal calcification was noted in the intima and elastica, and the media and adventitia showed striking fibrosis. The right anterior cerebral artery (fig. 3) also showed occlusion of its lumen by organized, recanalized thrombus which contained hemosiderin. The distal branches of these vessels showed mild fibrosis of the adventitia but the media, elastica and intima appeared relatively normal. The changes in the right middle cerebral artery were somewhat different. The lumen was occluded by a recent thrombus and the intima was considerably thickened by fibrous and smooth muscle cells. There was focal degeneration of the thickened intima with cyst formation in some areas (fig. 4). The elastic tissue and media also showed focal degeneration with particularly severe fibrosis in the

**FIGURE 2**

A segment of the left internal carotid artery shows focal fibrous thickening of the intima, degeneration of elastica and fibrosis of the media. Several small occluded vessels (arrows) are embedded in the fibrosed adventitia. (Verhoef stain, X 50)
Marked intimal thickening and old thrombosis of the right anterior cerebral artery is present. A small slit-like lumen is surrounded by clumps of dark-staining hemosiderin pigment. (Verhoeff stain, X 50)

latter. The proximal portions of the right and left posterior cerebral arteries and the distal portion of the basilar artery showed changes similar to those in the carotid vessels. The more proximal portions of the basilar artery and the vertebral arteries showed mild focal intimal thickening. The distal branches of the anterior, middle and posterior cerebral arteries were relatively normal. Some of the small leptomeningeal arteries contained emboli or thrombi but only rarely were changes noted in the walls of these vessels. Many unusually large vessels were noted on and near the surface of the pulvinar and in the basal ganglia. The left optic nerve was severely degenerated with marked fibrosis of the leptomeninges and of the connective tissue septa of the nerve and optic chiasm. There was a prominent fibrosis around small vessels in the chiasm and optic tracts, particularly near the surface.

Comment

The case of multiple progressive intracranial occlusive disease described here is similar to many of those reported in the literature. The patient was a young female. Her illness, like many previously reported, began suddenly with a febrile episode and she had various neurological deficits indicating involvement of both cerebral hemispheres. Radiographical studies showed progressive occlusive disease in the internal carotid and anterior and middle cerebral arteries and a rich collateral circulation. The only other laboratory abnormality was an elevated sedimentation rate, a finding reported in many cases in the literature.

The recent reports describing this unusual type of arterial occlusive disease have dealt primarily with the clinical and radiographical findings. In general, the disease appears to be more common in the Japanese people than in Caucasians and most reports indicate a predominance in females. Kudo* and Suzuki and Takaku have noted that the juvenile cases tend to present with fever and transitory repetitive cerebral ischemic attacks including paroxysmal hemiplegia and a variety of neurological signs and symptoms. In the adult cases, the onset of neurological symptoms is generally more abrupt, the symptoms are more severe, and there is less tendency to recur. Subarachnoid hemorrhage may be somewhat more common in the adult cases than in the juvenile ones. In most cases, the disease radiographically appears to involve the distal portion of the internal carotid artery, the proximal portions of the anterior and middle cerebral arteries and, at times, the basilar artery and the proximal portions of the posterior cerebral arteries. The initial changes appear to occur at the carotid fork distal to the posterior communicating artery with progression to

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The intima of the right middle cerebral artery is thickened due to proliferation of connective tissue and smooth muscle cells. Note the cystic degeneration in the deeper portion of the intima on the right side. There is mild fibrosis of the media and adventitia. Thrombus is seen in the lumen at the top of the photograph. (Hematoxylin and eosin stain, × 200)

Involvement of the right and left circulation may be asymmetrical in severity and may occur at differing times. The prognosis, particularly in the juvenile form, is relatively good with most of the patients surviving with variable degrees of neurological and mental impairment.

Description of the pathological changes in the cerebral arteries of autopsied cases has been limited. Narrowing of the lumens of the arteries and intimal thickening with no alteration of the media and adventitia have been encountered in several cases1-3 and slight fibrosis of the media in others.11 No evidence of angiitis or arteriosclerotic change has been encountered in these cases. In the present case the cerebral vessels were examined in detail in an attempt to detect the earliest pathological changes. Some differences were noted in the right internal carotid and middle cerebral arteries which clinically and pathologically appeared to be more recently involved. In the right middle cerebral artery, the thickened intima contained fairly numerous smooth muscle elements which were not seen in the older lesions in the left internal carotid and middle cerebral arteries. In addition, focal cystic degeneration and edema were noted in the thickened intima. These features, however, might represent reactive changes to the recent thrombosis rather than an earlier stage of the disease. The degenerative changes in the elastica and media also were somewhat less marked than in the left cerebral vessels. The changes in the posterior cerebral and basilar arteries, which were not clinically detected as being involved, were similar to those in the internal carotid and middle cerebral arteries and appeared to be long-standing and static. It would appear that in this case the vascular process is one involving all of the layers of the vessel with striking proliferation of connective tissue in the intima, media and adventitia. These findings probably represent a late stage of the disease and give no indication as to the pathogenesis of the lesion. An inflammatory basis for the vascular
intracranial arterial occlusion

disease has been mentioned frequently in the literature\textsuperscript{5, 7, 12} but has not been substantiated. The absence of inflammatory changes in the cerebral vessels in the present case does not necessarily eliminate the possibility of a remote infectious process. The fibrosis of the vessel walls might well represent a healed stage of an arteritis. The marked adhesion of the left internal carotid artery to the optic nerve and chiasm in the present case also might be the result of an old inflammatory process. Vascular diseases such as giant cell and granuloma-tous arteritis and polyarteritis can be excluded by the lack of the distinctive pathological changes usually found at autopsy and fibromuscular dysplasia, which also occurs predominantly in young women, by its distinctive angiographical appearance.\textsuperscript{18} The predominance of cases in Japanese females also suggests a link with Takayasu's arteritis, but the latter involves the extracranial rather than intracranial vessels.

It has been suggested by Kudo\textsuperscript{4} that in those cases presenting in adulthood the changes in the blood vessels may actually have occurred in childhood. The abundant collateral circulation which develops may provide sufficient blood to the brain under normal circumstances. When the cerebral circulation is further compromised by local or systemic factors, neurological symptoms may become manifest. The present case may support this theory. This patient had loss of vision in the left eye in childhood, the details of which are not known. The marked involvement of the left internal carotid artery and its adhesions to the left optic nerve and chiasm found at autopsy suggest that the occurrence of the visual loss may have coincided with the onset of the vascular disease. Whether the changes in the cerebral vessels occurred during childhood and remained static or gradually progressed over the ensuing years is a matter of speculation. It is of interest that the onset of clinical symptoms occurred approximately six weeks after the patient was started on oral contraceptive therapy. Although the relationship of oral contraceptives and thromboembolic phenomena remains controversial, the data in the literature suggest that these drugs are related to a slight increase in thromboembolism and pulmonary embolism.\textsuperscript{14} This may be due to a hypercoagulable state induced by an increase in blood coagulation constituents\textsuperscript{15, 17} or to actual changes in the vessel walls such as endothelial proliferation and intimal thickening.\textsuperscript{18} It is possible that the vascular lesions in the present case, which may have been present since childhood, either were aggravated by the oral contraceptive therapy or an increase in coagulability of the blood led to thrombosis of previously diseased arteries. It is unlikely, in view of the clinical and pathological findings, that the vascular disease was due to the oral contraceptive therapy alone.

Summary

A case of multiple progressive intracranial arterial occlusive disease has been described with a review of the clinical, radiographical and pathological findings. The pathological changes in the arteries appeared to be long-standing and suggest that in this instance the disease may have begun in childhood and remained quiescent until the patient's terminal illness. The relationship of the latter to oral contraceptive therapy is discussed. The pathogenesis of the degenerative changes in the blood vessels, however, remains obscure.

References


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