SUMMARY Moyamoya disease is a rare but well described entity which has been found in the angiographic investigation of subarachnoid hemorrhage, its most common symptom in adults. We present 4 patients in whom moyamoya disease and an intracranial saccular aneurysm were discovered. In 2 of the 3 patients suffering a hemorrhage, the aneurysm was the source of bleeding. Three of the aneurysms were located at the basilar artery bifurcation. We recommend a careful search for a concomitant aneurysm in all patients with subarachnoid hemorrhage in whom moyamoya disease is found. We believe these patients should be treated as though the aneurysm were the source of bleeding.

MOYAMOYA DISEASE was first described by Nomura and Takeuchi who, on angiography, noted an unusual basal cerebral vascular network in patients suffering strokes. The term, moyamoya, was introduced by Suzuki and Takaku. While patients are reported from other countries, the preponderance are from Japan. In a review of 111 patients, 66 were men and 79 were under 20 years of age. Seizures, paresis, visual or language disturbances and mental retardation are symptoms which indicate possible moyamoya and are attributable to cerebral ischemic events. The angiographic features of moyamoya include: stricture of the carotid bifurcation, narrowing or occlusion of the internal carotid artery in the siphon, stenosis or occlusion of the anterior or middle cerebral arteries, a cloud-like mesh of fine vessels at the base of the brain and prominent ethmoidal and meningeal anastomotic channels. The basilar and posterior cerebral arteries are involved to a lesser degree than the anterior circulation. Thus, moyamoya has features of multiple vessel involvement and includes vascular changes other than the basal telangiectatic network. No consistent pathologic change has been correlated with moyamoya. A variety of abnormalities: thin vessel walls, intimal thickening with cushions, dilated arterioles, necrosis of the media and discontinuity of the internal elastic membrane have been described. The features of moyamoya have been seen on angiography in association with atherosclerosis, tumors, tuberculous meningitis, sickle cell disease, cerebral embolism, and neurofibromatosis, and after radiation therapy.

Subarachnoid hemorrhage may be the initial symptom of moyamoya or may appear in conjunction with above described symptoms; it is the most common symptom leading to the diagnosis of moyamoya in adults. Nishimoto and Takeuchi reported 19 instances of subarachnoid hemorrhage in 35 patients older than 15 years of age. Generally, the initial course of subarachnoid hemorrhage in moyamoya is relatively benign. In a series of 9 patients with moyamoya and subarachnoid hemorrhage, no fatalities occurred and neurologic residuals were only minimal. Hemorrhages do recur. Intraparenchymal hemorrhage is rare. The source of hemorrhage in moyamoya has not been proven, though bleeding from a thin walled collateral vessel is possible. Rare instances of aneurysmal dilatation of collateral vessels and a few cases of saccular aneurysms in association with moyamoya have been reported.

We present 4 patients in whom concomitant moyamoya and an intracranial saccular aneurysm were discovered. In 3 patients, the aneurysm arose from the basilar artery bifurcation. This site of aneurysm development may be related to increased verteobasilar flow induced by an anterior circulation which is compromised by the vascular disease producing the moyamoya. The discovery of a saccular aneurysm and moyamoya in patients with subarachnoid hemorrhage is a diagnostic and therapeutic challenge. The source of the hemorrhage may be either from collateral cerebral channels of the moyamoya or the aneurysm. We suggest that treatment of the patient should focus on the aneurysm as the most likely source of the bleeding.

Case Reports

Case #1
A 35-year-old woman was admitted to the University Hospital, London, Ontario in October, 1974, for operative ligation of a basilar artery aneurysm. In 1969 and 1970, she had recurrent attacks of weakness and vertigo. On one occasion paresis of the left arm persisted for 5 days. Because of increasing frequency of the attacks, angiography was performed in 1972. Stenosis of the left internal carotid artery at the mid-cervical level, a beaded and narrow right internal carotid artery and a basilar artery bifurcation aneurysm were found.

In July, 1973, she was hospitalized for the sudden onset of aphasia and right hemiplegia. Angiography demonstrated occlusion of the left internal carotid artery just above the carotid bifurcation. The right internal carotid artery was narrow. The left middle cerebral artery filled from the left posterior communicating artery and many small basal cerebral arteries were seen (fig. 1). In August, 1973, a left
superficial temporal-middle cerebral artery anastomosis was performed. One year later, the right internal carotid artery was found to be occluded. The right middle cerebral artery was being supplied by extensive collaterals from the right middle meningeal and posterior communicating arteries. The aneurysm appeared unchanged. In October, 1974, the basilar artery aneurysm was clipped. Postoperatively, she developed a left hemiplegia. A right superficial temporal-middle cerebral artery anastomosis was performed but the left hemiplegia persisted.

Case #2
A 34-year-old man was admitted to Montefiore Hospital and Medical Center in February, 1975. He had a history of labile hypertension. Five days prior to admission he had suffered a generalized convulsion, severe headache and stiff neck. A lumbar puncture confirmed subarachnoid hemorrhage. He was lethargic but had no other neurologic deficits. Evaluation included normal dynamic and static nuclide scans and a normal computerized tomographic study. An electroencephalogram showed diffuse theta activity. Angiography demonstrated marked narrowing and irregularity of the supraclinoid portion of the right internal carotid artery; the right anterior and middle cerebral arteries were not visualized. The anterior cerebral artery filled in a retrograde fashion from the posterior cerebral artery via the pericallosal artery. A diencephalic blush was seen. The Sylvian branches of the right middle cerebral artery filled in a retrograde manner via the posterior choroidal arteries. An aneurysm was present at the junction of the right internal carotid and posterior communicating arteries (fig. 2). The left internal carotid artery was narrowed and irregular in its supraclinoid segment. The left anterior cerebral artery was not visualized, while the origin of the middle cerebral artery was poorly filled. Bilateral extensive external-internal carotid anastomoses were present. The patient was treated with sedation, anticonvulsants and epsilon-aminocaproic acid (EACA). He made a good recovery and was discharged one month later. Subsequent angiography showed no change. In September, 1975, he developed headache and numbness of the left hand. Mild left central facial paresis was evident. Cerebrospinal fluid, radionuclide scan and computerized tomography were normal. In March, 1978 he was reported to be experiencing headaches and intermittent convulsions.

Case #3
A 45-year-old woman was admitted to University Hospital, London, Ontario in February, 1977 for treatment of a subarachnoid hemorrhage which occurred in January, 1977. Angiography demonstrated narrowing of both internal carotid arteries in the neck. Neither vessel was filled above the origin of the ophthalmic artery. Both middle and anterior cerebral arteries were filled by collaterals from the meningeal and posterior communicating arteries. Fine basal vessels were present. Two aneurysms were found — one at the basilar artery bifurcation and a second, larger, aneurysm arising on the first portion of the right posterior cerebral artery (fig. 3). At operation,
FIGURE 3. Lateral view of vertebral angiogram with a basilar artery bifurcation aneurysm (arrow), retrograde filling of collateral vessels and carotid artery. (Case 3)

the basilar aneurysm was packed, while the aneurysm arising on the right posterior cerebral artery was clipped. The larger aneurysm was found to have been the source of the hemorrhage. She did well postoperatively.

Case 4

A 32-year-old woman was admitted to the University of Iowa Hospitals, Iowa City, in August, 1977. She had been well until the night before admission when she complained of a severe headache followed by loss of consciousness. On arrival, she was irritable and stuporous. Bilateral, subhyaloid hemorrhages were present. She had spontaneous movements on the right, but decerebrate posturing of left arm and leg. Oculocerebral reflexes were present. Both pupils were 4 mm in diameter and reacted to light. Increased density in the Sylvian and circum-mesencephalic cisterns and mild dilatation of the third and lateral ventricles were seen on a computerized tomographic study. Angiography showed diffuse narrowing of both common and internal carotid arteries in the neck. The left internal carotid artery was occluded at the siphon. The right middle cerebral artery was poorly filled. Bilateral collateral channels were filled from the ophthalmic and external carotid arteries. Many small caliber beaded vessels arose from the basal portion of the internal carotid and middle cerebral arteries. A basilar bifurcation aneurysm measuring one cm in diameter was visualized (fig. 4). She was initially treated with epsilon aminocaproic acid (EACA) and dexamethasone. Intracranial pressure was measured by a subdural intracranial pressure monitor for 6 days and she was treated with hyperventilation and mannitol, when needed, to control increased intracranial pressure. She remained comatose and on the twentieth hospital day developed sepsis and thrombocytopenia. Klebsiella pneumoniae was cultured in blood and cerebrospinal fluid. The EACA was discontinued and she was treated with intravenous chloramphenicol and gentamicin. Twenty days later she suffered a second subarachnoid hemorrhage. On the forty-sixth hospital day, Staphylococcus aureus was cultured from blood. She continued to deteriorate and died of septicemia on the fifty-fifth hospital day.

On postmortem examination, numerous small collateral vessels were present at the base of the brain. A 6 mm aneurysm, surrounded by hematoma, was present at the bifurcation of the basilar artery. A perforation was found at the apex. No atherosclerotic changes were noted and no specific changes were noted on microscopic examination of the vessels.

Discussion

Reports of concomitant moyamoya and intracranial aneurysm are few. While it is possible that coincidence accounts for the occurrence of both in a patient, Kodoma and Suzuki found aneurysms in 5 of 35 adults with moyamoya.17 Several of the aneurysms have consisted of small peripheral ectasias on abnormal vessels or collaterals. One patient in the series of Lee and Cheung12 and 3 of the 5 patients reported by Kodoma and Suzuki17 had nonsaccular aneurysms located on peripheral, collateral cerebral arteries. Follow up angiography did not re-visualize the aneurysm in the 3 patients of Kodoma and Suzuki.17

The literature contains 8 other reports of saccular aneurysms and the diffuse vascular changes consistent with moyamoya which are summarized in the table.
Galligioni et al. presented 2 patients with angiographic evidence of moyamoya and an intracranial aneurysm. A 34-year-old woman suffered an intracranial hemorrhage and right arm paresis. A left temporal lobe mass, moyamoya, and a small right internal carotid artery aneurysm originating from below the ophthalmic artery were demonstrated on angiography. She was medically treated and recovered. A 44-year-old woman presented with intermittent episodic dizziness and left hemiparesis. Angiograms demonstrated moyamoya and a small saccular aneurysm arising from the intracavernous portion of the right internal carotid artery. In both instances, the aneurysms likely were asymptomatic. Debrun and Lacour reported an 18-year-old man with recurrent subarachnoid hemorrhage and hemiparesis. Moyamoya and 2 large, possibly saccular aneurysms arising from the intracavernous portion of the left internal carotid artery were found. The patient survived and was not operatively treated. The source of the hemorrhage was not proven. The fourth patient was a 31-year-old woman who suffered a fatal subarachnoid hemorrhage. While angiography demonstrated moyamoya, no aneurysm was visualized. At autopsy, mirror (2.5 and 3.5 mm in size) unruptured aneurysms were discovered on the internal carotid arteries at the origin of the anterior choroidal arteries. Two patients with moyamoya, a saccular aneurysm and subarachnoid hemorrhage were operatively treated by Yasargil and Smith. One had recurrent hemorrhages and a large fusiform aneurysm at the origin of the right fronto-orbital artery. While they noted scarring and fibrosis at operation, Yasargil and Smith in neither case specifically mentioned the aneurysm as the source of hemorrhage. Two patients of Kodoma and Suzuki had saccular aneurysms in the posterior circulation. One patient had headache, but a cerebrospinal fluid examination was not performed. Sequential angiography demonstrated the moyamoya and an enlarging basilar artery bifurcation aneurysm. The other patient of Kodoma and Suzuki had a subarachnoid hemorrhage. At operation, 2 aneurysms, one arising at the basilar artery bifurcation and the other from the junction of the basilar and right superior cerebellar arteries were found to have bled.

Our 4 patients were all adults with angiographic evidence of moyamoya and a saccular aneurysm. Three presented with subarachnoid hemorrhage while the fourth had intermittent symptoms which were felt to be ischemic events. In 2 of our patients, the aneurysm was found to be the site of bleeding and in one the illness was fatal. Two of our patients had operative therapy of the aneurysm with a complicating stroke occurring in one.

Even though the number of patients is small, an unusual distribution in the location of the aneurysm is apparent. Both of the patients of Kodoma and Suzuki and 3 of our patients had aneurysms at the basilar artery bifurcation. The unusual prominence of this site is indicated by McCormick and Nofzinger's study in which only 2 of 206 aneurysms found in an autopsy series, were located at the basilar artery bifurcation. The vascular disease which produces the

**TABLE Saccular Aneurysms in Patients with Moyamoya Syndrome**

<table>
<thead>
<tr>
<th>Author</th>
<th>Age</th>
<th>Sex</th>
<th>Signs</th>
<th>Aneurysm(s) location</th>
<th>Aneurysmal rupture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galligioni et al., 1971</td>
<td>34</td>
<td>F</td>
<td>SAH</td>
<td>Left intra-cerebral hemorrhage</td>
<td>(1) Right internal carotid-ophthalmic artery</td>
</tr>
<tr>
<td>Debrun and Lacour, 1974</td>
<td>44</td>
<td>F</td>
<td>Strokes</td>
<td>(1) Right internal carotid artery</td>
<td>?</td>
</tr>
<tr>
<td>McCormick and Schochet, 1977</td>
<td>31</td>
<td>F</td>
<td>SAH</td>
<td>(1) Left internal carotid artery</td>
<td>?</td>
</tr>
<tr>
<td>Yasargil and Smith, 1976</td>
<td>38</td>
<td>M</td>
<td>SAH</td>
<td>(1) Right internal carotid artery</td>
<td>?</td>
</tr>
<tr>
<td>Kodoma and Suzuki, 1978</td>
<td>35</td>
<td>M</td>
<td>SAH</td>
<td>(1) Left internal carotid artery</td>
<td>?</td>
</tr>
<tr>
<td>Present report, 1979</td>
<td>34</td>
<td>M</td>
<td>SAH</td>
<td>(1) Basilar artery bifurcation</td>
<td>?</td>
</tr>
<tr>
<td>Galligioni et al., 1971</td>
<td>34</td>
<td>F</td>
<td>SAH</td>
<td>(1) Basilar artery bifurcation</td>
<td>?</td>
</tr>
<tr>
<td>Kodoma and Suzuki, 1978</td>
<td>35</td>
<td>M</td>
<td>SAH</td>
<td>(1) Left internal carotid-posterior communicating artery</td>
<td>?</td>
</tr>
<tr>
<td>Present report, 1979</td>
<td>34</td>
<td>M</td>
<td>SAH</td>
<td>(1) Basilar artery bifurcation, right posterior cerebral artery</td>
<td>?</td>
</tr>
<tr>
<td>Galligioni et al., 1971</td>
<td>34</td>
<td>F</td>
<td>SAH</td>
<td>(1) Basilar artery bifurcation</td>
<td>?</td>
</tr>
</tbody>
</table>

SAH - subarachnoid hemorrhage; + = documented aneurysm rupture; - = documented aneurysm non-rupture; ? = unknown source of bleeding; Surgery/autopsy = method of documentation.
moyamoya may compromise the anterior circulation and thus alter circulatory dynamics in the vertebro-basilar system in such a way as to induce the development of aneurysms at the basilar artery bifurcation. It may also be responsible for the unusual number of aneurysms arising from the intracavernous portion of the internal carotid artery and for the absence of any aneurysms from the middle cerebral artery or its branches.

Pilz and Hartjes have reported a case with fibromuscular dysplasia, intracranial moyamoya and dissecting aneurysms.20 While the aneurysms described in their patient were not saccular, aneurysms are more common in patients with fibromuscular dysplasia of the carotid.21 No reliable figures of the number of individuals with moyamoya exist, however, 12 instances in which an aneurysm was identified in conjunction with the diffuse vascular disease producing moyamoya may be more than coincidence. Keeping in mind that, pathologically, moyamoya is a nonspecific entity, possible interrelationships between saccular aneurysms and moyamoya should be considered. Further patients similar to those of Pilz and Hartjes may solidify the role of a dysplasia in moyamoya.

All patients with subarachnoid hemorrhage and moyamoya should be thoroughly investigated for a possible aneurysm. A careful angiographic search for an aneurysm of the posterior circulation, in particular the basilar artery bifurcation, is necessary. Moyamoya is not likely to be confused with spasm secondary to the hemorrhage. The prominent anastomoses and narrowing of extracranial vessels, (including carotid hypoplasia or carotid fibromuscular dysplasia), are not seen in spasm from a ruptured aneurysm.

While most patients with moyamoya and subarachnoid hemorrhage have recovered from their initial hemorrhage,22 bleeding from a ruptured aneurysm automatically carries a guarded prognosis. We believe these patients should be treated as if the aneurysm is the source of the hemorrhage. We have evidence that the aneurysm had bled in 2 of our patients. The cooperative aneurysm study has demonstrated a beneficial therapeutic effect from the administration of antifibrinolytic agents in patients with subarachnoid hemorrhage from saccular aneurysms.23 Because of increased risk of cerebral ischemia, Dillon et al. recommended that antifibrinolytic agents not be given to patients with moyamoya who suffered a subarachnoid hemorrhage.24 However, we believe it is reasonable to use this therapy in patients where moyamoya and a saccular aneurysm coexist. We used EACA in 2 of our patients without complications and one had a subsequent hemorrhage after the agent was discontinued.

The risk of interrupting anastomotic channels during approach to the aneurysm may be a significant factor in the operative management of these patients. Several cases of successful aneurysm surgery are reported. The aneurysms in 2 of our patients were surgically treated; however, one of our patients had a complicating cerebral infarction. Instances of successful operative superficial temporal-middle cerebral artery anastomoses are reported.25 Creation of extracranial-intracranial anastomosis prior to operative therapy of the aneurysm may be warranted in selected patients.

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Adrenergic Control of Cerebral Blood Flow and Energy Metabolism in the Rat

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SUMMARY Studies in rats were designed to separate and define the roles of the intrinsic and extrinsic adrenergic neurons in the control of cerebral blood flow (CBF) and cerebral energy metabolism. The data suggest several conclusions:

1. Arterial sympathetic innervation plays a role in the autoregulation of cerebral circulation.
2. The central adrenergic neurons have several functions: a) They enhance cerebral vascular tone by action on alpha receptor sites. b) They play an important role in the metabolic control of CBF. The proton-sensitive receptor sites on blood vessel walls require beta-adrenergic input in order to function. c) They influence metabolic rate of brain tissue by acting on beta-receptor sites on the cell membrane.

Evidence now exists that there are at least 2 types of adrenergic innervation of cerebral vessels, one from the cervical sympathetic plexus innervating mainly extracerebral arteries, but also reaching cerebral arterioles of 15 μm diameter1–2 and the other originating in the locus ceruleus and impinging directly on the walls of intramedullary arterioles.3–4 The influences of these vascular neurogenic systems on cerebral circulatory physiology or metabolism are still not understood.

Results of recent physiologic studies of the cerebral sympathetic system have been inconsistent,7–10 probably reflecting the variety of animal models and methodology. There is evidence, however, that the sympathetic innervation of cerebral vessels influences vascular reactivity to changes in Paco2 and Pao2 and in some way functions to help maintain autoregulation.11–13 Harper recently proposed that the sympathetic nervous system is the coarse adjuster of cerebral blood flow (CBF), as contrasted to the fine control exerted by tissue metabolism.14

The concept that mechanisms intrinsic to the brainstem, and probably neurogenic in character, are capable of influencing CBF and cerebral metabolic rate is supported by a variety of studies. Pial and cortical flow, as well as cerebral metabolism, may be increased by electrical stimulation of many areas in the brainstem15–17 and hypothalamicus.11, 18, 19 In addition, localized brainstem lesions cause a reduction in CBF and metabolism20, 21 as well as an altered respon-
siveness of cerebral vessels to CO2.21 It has been suggested that these phenomena have a neurogenic origin, mediated by intramedullary neurons whose axons exit the brainstem in the fifth or seventh cranial nerves and eventually innervate cortical arteries.22, 24 The recent discovery by immunofluorescence studies of an intramedullary adrenergic system speaks for direct neuronal action on parenchymal vessels as one basis for intrinsic control of CBF and metabolism.4–6 The present experiments were designed to separate and define the roles of the intrinsic and extrinsic cerebral adrenergic neurons in the control of CBF and cerebral energy metabolism. Extrinsic adrenergic neurons are concerned with cerebral vascular autoregulation; the intrinsic (parenchymal) adrenergic system is essential to the metabolic regulation of CBF.

Methods

Studies were performed on groups of male Wistar rats weighing between 250 and 350 grams and were designed to examine the effects of unilateral cervical sympathetic denervation on homolateral CBF and vascular resistance and the effects of certain drugs which alter both central and peripheral neuronal monoamine metabolism (reserpine) or block specific actions of monoamines on alpha and beta receptors of cerebral neurons and blood vessels (phenoxybenzamine, propranolol). In order to accomplish this, it was necessary to devise a system of internal controls to minimize the variables. Two major groups of animals were studied: one received no drugs and the other received reserpine, phenoxybenzamine, or propranolol. The animals in group 1 were divided into
Intracranial saccular aneurysm and moyamoya disease.
H P Adams, Jr, N F Kassell, H S Wisoff and C G Drake

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