Cerebral Infarction Due to Moyamoya Disease in Young Adults

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Moyamoya disease was diagnosed as the cause of cerebral infarction in eight young adults (seven women, one man), aged 17–40 (mean 33) years. All had angiographic abnormalities characteristic of moyamoya disease. Single-photon emission tomography showed bilateral carotid circulation hypoperfusion and posterior circulation hyperemia in all seven patients with regional cerebral blood flow studies. All seven women had used oral contraceptives before cerebral infarction. Four patients were treated medically; one died of a second cerebral infarction 9 months after diagnosis. Four patients underwent superficial temporal-to-middle cerebral artery anastomosis; they did well. Moyamoya disease should be included in the differential diagnosis of cerebral infarction as well as intracranial hemorrhage in young adults, particularly women. A possible relation between moyamoya disease and oral contraceptive use deserves investigation. (Stroke 1988;19:826–833)

Moyamoya disease was initially described and defined in Japan, and it remains much more common there than in Western countries.1–2 The main features of moyamoya disease are bilateral stenosis of the internal carotid artery bifurcation and basal telangiectasias comprising dilated collateral lenticulostriate and thalamoperforating arteries.1–3 The name moyamoya was derived from the angiographic appearance of the cerebrovascular abnormalities. On angiography, filling of the basal telangiectasia produces a cloudy image resembling a puff of smoke floating in the air, “moyamoya” in Japanese. Pathologic studies have demonstrated endothelial hyperplasia and fibrosis with no associated inflammatory reaction.2–5 Initial symptoms are due to either cerebral ischemia or intracranial hemorrhage. The hemorrhage may be subarachnoid, intraparenchymal, or intraventricular and is sometimes associated with a saccular aneurysm (usually in the vertebrobasilar system). In children the initial symptoms are usually due to ischemia whereas adults often have hemorrhagic manifestations.1,2

Very few cases of moyamoya disease presenting in adulthood in non-Japanese individuals have been reported6–12; most of such patients have had hemorrhagic events. We studied eight young non-Japanese adults with cerebral infarction who were found to have moyamoya disease. We report these cases because they represent an unusual, but more frequent than previously recognized, form of cerebral vasculopathy.

Subjects and Methods

Patients and Controls

Seven women and one man, aged 17–40 (mean 33) years, diagnosed as having cerebral infarction due to moyamoya disease presented during a 9-year period (1977–1986) to University of Iowa Hospitals and Clinics and the Iowa City Veterans Administration Hospital. These moyamoya patients were included in our prospective registry of cerebral infarctions in young adults (aged 15–45 years),13 which currently includes 210 patients. All eight moyamoya patients underwent cranial computed tomography (CT) and angiography; seven had regional cerebral blood flow (rCBF) studies. Therapy (medical vs. surgical) was decided in each case by the attending physician. Follow-up ranged from 15 months to 10 years (mean 39.5 months). When necessary, patients and their local physicians were telephoned to obtain an up-to-date status.

A control group for the regional cerebral blood flow studies consisted of 22 normal volunteers, aged 22–43 (mean 32) years.
TABLE 1. Clinical Features of Cerebral Infarction Due to Moyamoya Disease in Young Adults

<table>
<thead>
<tr>
<th>Case/age/sex</th>
<th>Vascular risk factors</th>
<th>Interval from first TIA to infarction</th>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/23/F</td>
<td>Smoking, oral contraceptives, peripartum</td>
<td>No TIA</td>
<td>Aphasia, R hemiparesis, B Babinski’s signs</td>
</tr>
<tr>
<td>2/31/F</td>
<td>Hypertension, smoking, oral contraceptives</td>
<td>No TIA</td>
<td>Aphasia, R hemiparesis, B Babinski’s signs</td>
</tr>
<tr>
<td>3/39/M</td>
<td>Hypertension, smoking</td>
<td>5 days</td>
<td>Aphasia, R hemiparesis</td>
</tr>
<tr>
<td>4/26/F</td>
<td>Smoking, diabetes mellitus, oral contraceptives</td>
<td>No TIA</td>
<td>R leg weakness, B simple partial motor seizures</td>
</tr>
<tr>
<td>5/17/F</td>
<td>Smoking, oral contraceptives</td>
<td>1 month</td>
<td>L arm weakness and sensory loss</td>
</tr>
<tr>
<td>6/29/F</td>
<td>Diabetes mellitus, oral contraceptives</td>
<td>2 months</td>
<td>Aphasia, R hemiparesis</td>
</tr>
<tr>
<td>7/40/F</td>
<td>Hypertension, oral contraceptives</td>
<td>1 month</td>
<td>Normal</td>
</tr>
<tr>
<td>8/33/F</td>
<td>Oral contraceptives</td>
<td>No TIA</td>
<td>L hemiparesis and sensory loss</td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack; F, female; M, male; R, right; B, bilateral; L, left.

Regional Cerebral Blood Flow Studies

During hospitalization for acute cerebral infarction and before superficial temporal-to-middle cerebral artery (STA-MCA) anastomosis, all rCBF studies were acquired with xenon-133 inhalation using a dynamic tomography technique. A dedicated single-photon emission computed tomography (SPECT) system (Tomomatic-64, Medimatic Inc., Copenhagen, Denmark) was modified to obtain five contiguous slices of brain simultaneously. The instrument acquires four sequential 1-minute images of brain while 133Xe is inhaled during the first minute and while radioxenon is cleared during the next 3 minutes of the study. rCBF values were derived from the rate of xenon arrival and washout in each pixel after deconvolution with the lung time–activity curve. Resolution of the SPECT slices is 16 mm within the image plane and 20 mm axially. We have verified that valid rCBF quantifications can be derived with this technique from brain regions of ≥3 cm diameter.14

Subjects were studied in a resting supine position with eyes open. The examination room was quiet and dimly lit, and an attendant was present throughout the study to minimize patient anxiety. Five contiguous slices centered at 2, 4, 6, 8, and 10 cm above the orbitomeatal line were obtained in each subject.

Areas of abnormality were diagnosed where perfusion was <45 ml/100 g brain/min, or less than two-thirds of the mean rCBF in the five brain slices in that hemisphere. These criteria are based on our previous study of 20 normal subjects and 30 stroke patients.15 A frontal rCBF value for each hemisphere was obtained by averaging all the focal areas of abnormality in the frontal region. For each subject, a frontal and an occipital rCBF value was obtained by averaging the rCBF values in the corresponding regions in the two hemispheres. The two-sided Wilcoxon rank sum nonparametric test was used to analyze differences in rCBF between moyamoya patients and normal controls.

Results

Clinical features, vascular risk factors, and preceding transient ischemic attacks (TIAs) for the eight moyamoya patients are summarized in Table 1. All patients were white. None had a family history of early-onset vascular disease; none had a history of central nervous system infection, radiation therapy, or neurofibromatosis; none had evidence of atherosclerosis, vasculitis, hypercoaguoble state, hyperviscosity state, fibromuscular dysplasia, cardiac source of emboli, or intracranial tumor. All TIAs were manifested by symptoms the same as although usually milder than the subsequent infarction. No patient experienced amaurosis fugax. Two patients (Cases 3 and 5) complained of severe diffuse headache that developed gradually in association with their neurologic deficit; in Case 3 the headache subsided over 5 days and in Case 5 it continued to be a major problem but without neurologic deterioration. Simple partial motor seizures developed in one patient (Case 4) at the time of her initial stroke. No patient had dizziness or other neurologic symptoms associated with rapid arising from lying or sitting positions or with exertion.

Results of CT, rCBF studies, and angiography are summarized in Table 2. On CT, low-density areas consistent with cerebral infarctions were usually found bilaterally, even when only unilateral cerebral dysfunction or no abnormalities were found on examination (Cases 3, 6, 7, and 8). Infarctions were found predominantly in watershed territories between the anterior, middle, and posterior cerebral arteries and in the centrum semiovale in distal beds of supply of the penetrating branches of the anterior and middle cerebral arteries (Figure 1). No patient had evidence of intracranial hemorrhage.
### TABLE 2. Results of Neuroimaging Studies in Eight Patients With Moyamoya Disease

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
<th>Case 6</th>
<th>Case 7</th>
<th>Case 8</th>
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<td>Right</td>
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<td>Right</td>
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<tr>
<td>CT</td>
<td>Superficial frontal in watershed region, multiple deep frontal in centrum semiovale</td>
<td>Two superficial frontal including watershed region, multiple deep frontal in centrum semiovale</td>
<td>Normal</td>
<td>Superficial frontal and parietal in watershed regions</td>
<td>Superficial frontal parietal in watershed regions</td>
<td>Deep frontal (40:80)</td>
<td>Two superficial frontal including watershed region, multiple deep frontal in centrum semiovale</td>
<td>Massive hemispheric, sparing only anterior frontal area</td>
</tr>
<tr>
<td>rCBF</td>
<td>Diffuse frontal (40:100)</td>
<td>Diffuse frontal (40:100)</td>
<td>Frontal in watershed region (50:90)</td>
<td>Normal (45:130)</td>
<td>Normal (50:90)</td>
<td>Normal (75:120)</td>
<td>Superficial frontal including watershed region, multiple deep frontal in centrum semiovale</td>
<td>Head of caudate</td>
</tr>
<tr>
<td>Angio</td>
<td>Narrowed supraclinoid ICA, occluded proximal ACA and MCA</td>
<td>Narrowed supraclinoid ICA, severely stenotic ACA, occluded proximal MCA</td>
<td>Ocularized MCA at origin</td>
<td>Occluded ACA, severely stenotic proximal MCA</td>
<td>Occluded MCA, 50% stenosis in proximal MCA</td>
<td>Occluded supraclinoid ICA</td>
<td>Superficial frontal including watershed region, multiple deep frontal in centrum semiovale</td>
<td>Occluded supraclinoid ICA</td>
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</table>

CT, location of infarctions on computed tomography; rCBF, location of abnormal low blood flow areas and frontal/occipital flow values in parentheses; Angio, summary of angiographic findings; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCoA, posterior communicating artery.

On rCBF studies, focal areas of decreased blood flow corresponded closely with low-density areas seen on CT (Table 2). Low-flow regions in general were more extensive than the corresponding low-density areas. In all seven patients with rCBF studies, a striking bilateral fronto-occipital blood flow gradient was found (Figure 2, Table 2). Mean frontal blood flow was significantly decreased ($p<0.01$) and mean occipital blood flow was significantly increased ($p<0.01$) compared with controls (Figure 3).

On angiography all patients had bilateral stenotic lesions involving the internal carotid artery bifurcation and dilated collateral basal vessels (telangiectasias) (Figure 4, Table 2). Distal segments of the anterior and middle cerebral arteries usually filled
Bruno et al  Infarction Due to Moyamoya Disease


FIGURE 2. Regional cerebral blood flow study of Case 1 demonstrates bilateral frontal hypoperfusion and occipital hyperemia.
via at least one of the following collateral pathways: 1) basal telangiectasia, 2) transdural collaterals from the external carotid circulation, and 3) leptomeningeal collaterals from the posterior cerebral artery. The proximal portion of the internal carotid artery was stenotic in only 2 of 16 carotid studies (Cases 2 and 7). No patient had abnormalities suggestive of fibromuscular dysplasia, arteritis, an arteriovenous malformation, or an aneurysm. The vertebrobasilar system appeared normal in all patients.

The brain of Case 2 was available for pathologic examination. Histologic examination of cerebral vessels disclosed concentric intimal hyperplasia,
duplication, fragmentation and lamination of the internal elastic lamina, and segmental medial thinning in the anterior and middle cerebral arteries and their major branches (Figure 5). Neither atherosclerosis nor inflammatory reaction was seen. Organized thrombi were present in several meningeal arteries overlying cerebral convexities. The vertebral and basilar arteries were normal.

Therapy and outcome are summarized in Table 3. All patients received antiplatelet agents; none were treated with anticoagulants. Four patients received a short course (3 days to 3 weeks) of steroids at the time of their acute cerebral infarction. Four patients were treated surgically with STA-MCA anastomosis; one (Case 6) had bilateral operations. One of the four surgically treated patients (Case 3) developed recurrent ischemic events 3 months after his initial stroke while taking 1,300 mg aspirin daily. STA-MCA anastomosis was performed on the symptomatic side and his attacks stopped. The other three surgically treated patients underwent prophylactic STA-MCA anastomosis when they were in stable condition.

Discussion
A Japanese research committee on the spontaneous occlusion of the circle of Willis proposed the following guidelines for the diagnosis of moyamoya disease: 1) stenosis primarily involving the region of the internal carotid artery bifurcation, 2) presence of dilated basal collateral arteries (usually the lenticulostriate and the thalamoperforating), and 3) bilateral abnormalities. Occasionally such abnormalities are found in association with one of many conditions, such as neurofibromatosis, tuberous sclerosis, fibromuscular dysplasia, vasculitis, radiation-induced arteritis, sickle cell anemia, Fanconi's anemia, or cerebral glioma. Therefore, the committee recommended that if any of these conditions is present, the angiographic abnormality should be termed moyamoya syndrome rather than moyamoya disease. In addition, the moyamoya angiographic pattern is sometimes found on one side only, and none of the above-mentioned risk factors are present. The committee recommended that such cases be termed probable moyamoya disease.

In adults, moyamoya disease has been more commonly recognized as a cause of intracranial hemorrhage than of cerebral infarction. Among 660 non-Japanese young adults included in nine recent studies on brain infarction conducted at...
other medical centers (three in the United States, two in India, two in England, one in Canada, one in Switzerland) only one case of moyamoya disease was reported. The finding of moyamoya disease more frequently in adults with hemorrhagic than with ischemic stroke may reflect a higher rate of cerebral angiography recommended for the former group. Young adults who suffer a nontraumatic hemorrhagic stroke are often thought to have a potentially curable condition, such as an aneurysm or an arteriovenous malformation, and frequently undergo angiography; on the other hand, young adults who develop an infarction undergo angiography less frequently. Perhaps an aggressive diagnostic approach regarding cerebral angiography is partly responsible for our frequent diagnosis of moyamoya disease (8 of 210, 4%). Angiographic criteria for diagnosis of moyamoya disease, as described above, were fulfilled in all eight patients. No patient had evidence of any of the specific conditions associated with moyamoya syndrome. Although most patients had hypertension or diabetes or smoked, the relation of these vascular risk factors to moyamoya disease has not been reported.

Another potential vascular risk factor present in all seven female patients was a history of oral contraceptive use. Several cases of angiographically and/or pathologically documented intracranial arterial occlusive disease in women using oral contraceptives have been reported. The distribution of vasculopathy in those cases was variable. Angiographic moyamoya syndrome was found in only three cases; one had a unilateral moyamoya vasculopathy. Histologic appearance of these vasculopathies was very similar to that of stenotic moyamoya disease. The main findings included endothelial hyperplasia, duplication of the internal elastic lamina, and absence of an inflammatory reaction. The exact relation of oral contraceptive use to intracranial occlusive disease remains unknown. However, since oral contraceptive use is very prevalent and documented instances of cerebral vasculopathy in women using oral contraceptives very rare, their coexistence may be incidental.

Cerebral angiography is needed to confirm the diagnosis of moyamoya disease, but abnormalities seen on CT and rCBF study can be very suggestive. On CT we found a predilection for infarctions to occur in watershed regions between the anterior, middle, and posterior cerebral arteries as well as in distal beds of supply of the penetrating branches of the anterior and middle cerebral arteries. CT studies of patients with moyamoya disease and ischemic complications also demonstrated multiple and bilateral cerebral infarctions. Presence of multiple bilateral cerebral infarctions in hemodynamically compromised regions in a young adult should alert the physician to the possibility of moyamoya disease.

The technique of 133Xe inhalation and SPECT has not been reported previously in the study of moyamoya disease. We noted a striking bilateral fronto-occipital blood flow gradient, with frontal hypoperfusion and occipital hyperemia, in all seven patients with rCBF studies. Such studies using 133Xe inhalation and superficial detectors, intravenous 133Xe injection, and stable xenon-enhanced CT have also demonstrated a fronto-occipital blood flow gradient with relative occipital hyperemia.

The best therapy for moyamoya disease remains unknown. The outcome in our patients with moyamoya disease was good. All seven surviving patients remain in stable condition on daily aspirin therapy. Some have been followed for many years (Table 3). Several cerebral revascularization procedures for the treatment of moyamoya disease have been introduced in Japan; however, randomized treatment trials have not been reported. Since virtually the entire Japanese literature on the treatment of moyamoya disease is concerned with surgical therapies, the natural history of this disease is unknown. However, it has been noted that a better prognosis is associated with later age of onset of symptoms.

In summary, moyamoya disease may be a more common cause of cerebral infarction in non-Japanese adults than has previously been reported. A large proportion of patients are women who have used oral contraceptives. Whether a relation exists between moyamoya disease and the use of oral contraceptives remains to be determined. Prognosis appears to be good for both surgically and medically treated patients.

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References


KEY WORDS: cerebral infarction, contraceptives, oral, moyamoya disease
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