Clinical Features of Moyamoya Disease in the United States

David Chiu, MD; Peter Shedden, MSc, MD, FRCSC; Patti Bratina, RN; James C. Grotta, MD

Background and Purpose—We report the clinical features and longitudinal outcome of the largest cohort of patients with moyamoya disease described from a single institution in the western hemisphere. Moyamoya disease in Asia usually presents with ischemic stroke in children and intracranial hemorrhage in adults.

Methods—Our study population included all patients with moyamoya disease evaluated at a university hospital in Houston, Texas from 1985 through 1995 (n=35). We used Kaplan-Meier methods to estimate individual and hemispheric stroke risk by treatment status (medical versus surgical). Predictors of neurological outcome were assessed.

Results—The ethnic background of our patients was representative of the general population in Texas. The mean age at diagnosis was 32 years (range, 6 to 59 years). Ischemic stroke or transient ischemic attack was the predominant initial symptom in both adults and children. Of the 6 patients with intracranial hemorrhage, 5 had an intraventricular site of hemorrhage. The crude stroke recurrence rate was 10.3% per year in 116 patient-years of follow-up. Twenty patients underwent surgical revascularization, the most common procedure being encephaloduroarteriosynangiosis. The 5-year risk of ipsilateral stroke after synangiosis was 15%, compared with 20% for medical treatment and 22% overall for surgery.

Conclusions—Our observations indicate that moyamoya disease may have a different clinical expression in the United States than in Asia, and may demonstrate a trend toward a lower stroke recurrence rate and better functional outcome after synangiosis. (Stroke. 1998;29:1347-1351.)

Key Words: moyamoya disease ■ stroke, ischemic ■ intraventricular hemorrhage ■ epidemiology

Moyamoya disease is a chronic cerebral vasculopathy first described in 1957 by Takeuchi and Shimizu. Progressive occlusion of the arteries of the circle of Willis leads to development of the characteristic collateral vessels after which the disease is named. Suzuki and Takaku observed that the collateral vessels give the appearance of a puff of smoke on arteriography and anointed the name “moyamoya” in 1969.

Since that time, more than 3000 cases of moyamoya disease have been described in Japan. The disease occurs worldwide but is rare outside Asia. A total of 239 cases of moyamoya disease had been reported in the United States as of 1996. Genetic and/or environmental factors that contribute to the prevalence of moyamoya disease in Japan and other Pacific Rim countries are unknown.

In Japan, the onset of moyamoya disease has a bimodal age distribution. The first peak occurs in early childhood, and a second peak affects adults in the fourth decade of life. A predilection for ischemic cerebrovascular events in childhood and hemorrhagic strokes in adults has also been observed. Although no randomized clinical trials have been carried out, surgical revascularization is favored in children.

We set out to investigate whether differences exist between moyamoya disease in the United States and Japan with regard to demographic characteristics, clinical presentation, natural history, or response to surgical treatment. Our cohort of patients represents the largest group of patients followed longitudinally from a single institution in the western hemisphere.

Subjects and Methods

We identified all patients with angiographically proved moyamoya disease evaluated at the University of Texas–Houston Health Sciences Center from 1985 through 1995. Subjects had unilateral or bilateral stenosis or occlusion of the distal internal carotid, proximal middle cerebral, and/or proximal anterior cerebral arteries associated with an abnormal network of fine collateral vessels at the base of the brain. Patients with “secondary” moyamoya disease due to identified etiologies such as atherosclerosis or sickle cell disease were excluded.

Demographic data, clinical history, medical therapy, and surgical interventions for the 35 patients identified with idiopathic moyamoya disease were recorded. Of these, 32 had definite moyamoya disease and 3 had probable moyamoya (unilateral involvement). We were able to obtain clinic or telephone interview with 31 patients (89%), and assessed recurrent stroke symptoms, employment status, and neurological disability based on a modified Rankin scale. Kaplan-Meier methods were used to estimate individual and hemispheric stroke risk stratified by treatment status (medical versus surgical). Cox regression analysis was performed to adjust for confounding clinical variables. Predictors of disability outcome were tested by Fisher’s exact test and multiple logistic regression.
Results

The ethnic distribution of our subjects reflects the population of our referral area (Figure 1). Only 2 patients were of Asian descent—1 Chinese and 1 Indian. The mean age at onset of symptoms was 32 years, ranging from 6 to 59 years (Figure 2). There were 7 patients under age 18 years, but a peak incidence in early childhood was not observed, in contrast to the experience in Japan.41 The female predominance (25 to 10) in our cohort has been noted in previous studies.

The initial symptom was a cerebral ischemic event in 26 patients and a hemorrhagic stroke in 6 patients (Table 1). The literature indicates a preponderance of hemorrhagic stroke in adult patients with moyamoya disease in Japan and South Korea,42 but this is at variance with our US experience. Of our adult patients, 23 presented with ischemic events compared with 3 patients with hemorrhagic strokes. Concurrent arteriographic findings were basilar tip aneurysms in 3 subjects, a posterior communicating artery aneurysm in 1 patient, and a parietal arteriovenous malformation in 1 individual.

The mean period of follow-up after diagnosis of moyamoya disease was 40±31 (mean±SD) months. Ten ischemic strokes and 2 subarachnoid hemorrhages occurred in this period, for a crude stroke recurrence rate of 10.3% per year. No individual with an initial presentation of ischemic stroke or transient ischemic attack developed a hemorrhage, and no patient with an index hemorrhage subsequently suffered an ischemic stroke.

Twenty patients underwent surgical revascularization procedures, 11 of which were bilateral. Encephaloduroarteriosynangiosis (EDAS) was the most frequently performed operation, carried out in 24 of 31 hemispheres. EDAS is a nonanastomotic procedure in which a branch of the external carotid artery, usually the superficial temporal artery, is placed intradurally on the brain to allow development of collateral blood supply.46,47 Other surgeries performed were encephaloduroarteriomyosynangiosis (EDAMS), which involves transposing the temporalis muscle with the superficial temporal artery46; direct extracranial-intracranial bypass49, and omental transposition. Perioperative stroke occurred in 4 of 31 cases (13%): 1 of 24 EDAS, 0 of 2 EDAMS, 1 of 2 extracranial-intracranial bypasses, and 2 of 3 omental transpositions, of which one was fatal. The complication rate for the synangiosis operations (EDAS and EDAMS) was 4%.

Kaplan-Meier estimate of recurrent stroke risk after diagnosis of moyamoya disease is 18% in the first year and roughly 5% per year thereafter, for a cumulative 5-year risk of 40% (Figure 3). The 5-year risk of ipsilateral stroke after surgical treatment was 22%, compared with 20% under medical treatment (Figure 4); however, a substantial proportion of the stroke risk in the surgical group is perioperative, and the data suggest that the late stroke risk may be reduced. The 5-year risk of ipsilateral stroke after EDAS or EDAMS was only 15%, owing largely to the low surgical complication rate of these procedures. There was no significant difference in stroke incidence in the surgical and medical groups, which remained true after adjusting for age, sex, race, hypertension, initial clinical presentation (infarct, hemorrhage, or other), and number of strokes prior to diagnosis.

Follow-up information on disability and functional status was available in 31 of 35 patients (89%). Four patients (13%) died, 3 from recurrent strokes (1 perioperative) and 1 from metastatic cancer. Eighteen (58%) had no disability (modified Rankin scale of 0 or 1) and 9 (29%) had mild or moderate disability but were able to walk (modified Rankin scale of 2 or 3). No surviving subject was severely disabled or unable to walk (modified Rankin scale of 4 or 5). Fifteen (48%) were employed or regular full-time students. The functional outcome of patients was not significantly related to age, sex, race, hypertension, initial clinical presentation (infarct, hemorrhage, or other), or number of strokes prior to diagnosis. There was a trend for better outcome in favor of patients undergoing EDAS or EDAMS but not surgery overall (Table 2).

**Table 1. Presenting Symptoms of Study Participants**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>18</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>8</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>1</td>
</tr>
</tbody>
</table>

|          | 35 Total |

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**Figure 1.** Pie chart shows ethnic background of study participants (n=35).

**Figure 2.** Graph shows age of study participants at onset of symptoms.

**Figure 3.** Kaplan-Meier estimate of recurrent stroke risk.
Moyamoya disease has been described on every continent and in all ethnic groups, but remains rare outside Japan and other countries of the Far East. The etiology of the disorder is obscure, and the reason for the large number of cases observed at our institution relative to other centers in the United States is also unclear. Since the diagnosis of moyamoya disease is based on its angiographic features, case detection hinges on the performance of angiography. Although angiography is part of the standard diagnostic workup of subarachnoid hemorrhage, the use of angiography in the evaluation of ischemic stroke varies widely in practice. Moyamoya disease is thus particularly underrecognized as a cause of ischemic stroke.

Several differences between moyamoya disease in the United States and Japan are notable. First, we observed a predominance of ischemic rather than hemorrhagic stroke in adult cases. Only 13% of our adult patients had intracranial hemorrhages (17% overall). A recent US multicenter study by Numaguchi et al revealed a similarly low prevalence of intracranial hemorrhage (14%). In Hawaii, the proportion of moyamoya patients with intracranial hemorrhage is higher (29%), but the majority are of Asian ethnicity. Second, an age peak in childhood was absent in our study. Numaguchi et al found a high incidence in the first decade of life, but 2 of the contributing institutions were children’s hospitals. We recognize the possibility of referral bias at our center as well. The best way to minimize referral bias is through a population-based survey. In such a study in Hawaii, only 4 of 21 patients were under 18 years of age, a percentage very similar to that in our study. Moyamoya disease may be a heterogeneous syndrome rather than a single disease. Moyamoya-like vascular changes are associated with conditions as diverse as sickle cell disease, neurofibromatosis, Down’s syndrome, and cranial irradiation. Whether a different form of moyamoya disease is prevalent in the United States or its expression altered by genetic or environmental cofactors is unknown.

Aneurysms and arteriovenous malformations, detected in 11% of our cases, have a recognized association with moyamoya disease. We observed aneurysms at locations of increased flow: the basilar tip and posterior communicating artery. Moyamoya disease causes shunting of flow from the vertebrobasilar circulation to the carotid territory. We found a predilection for an intraventricular location of hemorrhage. Five of our 6 patients with intracranial hemorrhage had an intraventricular site. Moyamoya disease should be suspected in such patients.

The surgical treatment performed most frequently at our institution and associated with the lowest complication rate (4%) was EDAS. EDAS has been the favored procedure at our center since 1993. Surgical management includes strict maintenance of normotension, euvolectria, and normocapnia and the use of nimodipine perioperatively. Individuals with spontaneous transdural collateral vessels were not considered for synangiosis. Patients undergoing bilateral procedures were given a hiatus of several weeks between operations. Medical interventions included antiplatelet agents (aspirin and ticlodipine), rheologic therapy (pentoxifylline), and calcium channel antagonists (nimodipine and nicardipine), although the efficacy of these treatments has not been proven. We avoided the long-term use of anticoagulation because of the concern for hemorrhagic stroke.

Improvement of cerebral blood flow and even resolution of moyamoya vessels following surgical treatment for moyamoya disease have been demonstrated in previous studies, but long-term data on clinical end points are scarce and the risk of recurrent stroke heretofore undefined. We found that the stroke recurrence risk was highest in the first year after diagnosis (18%) and that it decreased to 5% per year thereafter into the fifth year. The 5-year stroke recurrence risk is similar for medical and surgical treatment overall, although the data suggest that stroke incidence may be reduced by surgery after the first year. EDAS and EDAMS were associated with a lower complication rate and a lower 5-year stroke risk. We were unable to detect a difference in functional outcome between medical and surgical patients overall, but once again there was a trend favoring patients undergoing EDAS or EDAMS (Table 2). The tendency for patients with high-grade disease to be treated surgically creates a bias that could obscure a benefit of surgery, but statistical adjustment

**TABLE 2. Characteristics and Functional Outcome of Surgical vs Medical Patients**

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Female</th>
<th>White</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical</strong></td>
<td>12/15</td>
<td>13/15</td>
<td>8/15</td>
<td>7/15</td>
</tr>
<tr>
<td><strong>EDAS/EDAMS</strong></td>
<td>13/16</td>
<td>9/16</td>
<td>12/16</td>
<td>5/16</td>
</tr>
<tr>
<td><strong>Other surgery</strong></td>
<td>3/4</td>
<td>3/4</td>
<td>2/4</td>
<td>1/4</td>
</tr>
<tr>
<td><strong>P</strong>*</td>
<td>0.96</td>
<td>0.17</td>
<td>0.39</td>
<td>0.59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Initial Symptom Infarct</th>
<th>Initial Symptom Hemorrhage</th>
<th>Two or More Strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical</strong></td>
<td>5/15</td>
<td>5/15</td>
<td>5/15</td>
</tr>
<tr>
<td><strong>EDAS/EDAMS</strong></td>
<td>10/16</td>
<td>1/16</td>
<td>10/16</td>
</tr>
<tr>
<td><strong>Other surgery</strong></td>
<td>3/4</td>
<td>0/4</td>
<td>1/4</td>
</tr>
<tr>
<td><strong>P</strong>*</td>
<td>0.16</td>
<td>0.08</td>
<td>0.18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Good Outcome–Modified Rankin 0 or 1 (No Disability)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical</strong></td>
<td>7/13</td>
</tr>
<tr>
<td><strong>EDAS/EDAMS</strong></td>
<td>11/15</td>
</tr>
<tr>
<td><strong>Other surgery</strong></td>
<td>0/3</td>
</tr>
<tr>
<td><strong>P</strong>*</td>
<td>0.06</td>
</tr>
</tbody>
</table>

EDAS indicates encephaloduroarteriosynangiosis; EDAMS, encephaloduroarteriomyosynangiosis.

*Pearson’s χ² test for homogeneity.
for the number of strokes prior to diagnosis and the type of clinical presentation did not alter our findings. Further refinements in anesthesia, surgical technique, and perioperative care should lower surgical morbidity and enhance the potential benefit of revascularization.

The role of surgical treatment in moyamoya disease needs further evaluation with a focus on long-term clinical outcome and stroke recurrence. Is the response similar in adults and children? Does surgery reduce the risk of both hemorrhagic and ischemic stroke? Is there a plateau phase after which the disease may be considered quiescent or “burned out”? A randomized clinical trial is warranted and will likely be feasible only in Japan. At the same time, investigations into the mechanisms of disease are planned that will explore differences between Asian and US moyamoya patients. The answers to these questions will gain importance as moyamoya disease is increasingly recognized in young patients with stroke.

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