Moyamoya

Indiana University Medical Center Experience

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Background: Moyamoya usually presents with cerebral ischemia in children and intracranial hemorrhage in adults. Treatment remains controversial.

Design and Objective: We reviewed our experience from June 1995 to August 1999 of 20 adult and pediatric angiographically diagnosed patients with moyamoya to report their clinical presentation, radiological findings, management, and clinical outcomes.

Results: The mean age of patients at symptom onset was 17 years (range, 2-54 years). Patients were divided into 2 age groups (group 1, <18 years; group 2, ≥18 years). There were 13 patients in group 1 and 7 patients in group 2. Ischemic strokes or transient ischemic attacks were the predominant initial presentations in both groups. One patient in group 2 had an intraparenchymal brain hemorrhage. Five patients received medical treatment, and 15 had surgical revascularization. The mean time from symptom onset to surgical procedure was significantly longer for patients in group 1 than for those in group 2 (P=.03). The mean follow-up time was 36 months. One patient in group 1 had an ischemic stroke. There was no difference in stroke recurrence, mortality, or modified Rankin scale score among medically or surgically treated patients.

Conclusions: Moyamoya disease may have a different presentation and more benign natural history in our population than in Asian populations. Our findings emphasize the need to better understand the natural history of patients with moyamoya as well as the clinical benefit of different treatment modalities. Structured multicenter randomized clinical trials are needed to further assess the best treatment modalities for patients with moyamoya in the United States.

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MOYAMOYA disease (MMD) is a nonatherosclerotic, noninflammatory, nonamyloid vasculopathy characterized by chronic progressive stenosis or occlusion of the terminal internal carotid arteries and/or the proximal portion of the anterior cerebral arteries and/or middle cerebral arteries. The diagnosis of MMD is based on angiographic features. In 1957, the abnormal vessels at the base of the brain in MMD were first described as having a “hazy, cloudy puff of smoke” appearance, which led to the term moyamoya.1 The terms moyamoya disease and moyamoya syndrome are often used interchangeably, but most authors reserve the term moyamoya disease for the idiopathic form of this arteriopathy.

While MMD occurs predominantly among individuals of Japanese ancestry, it has also occurred among all races and ethnic groups.2 4 Moyamoya disease has been underrecognized as a cause of ischemic or hemorrhagic stroke in western countries.3 Prior to 1997, only 46 cases of MMD were reported in the United States.6 Since then, additional studies have reported considerably more cases of MMD.7,8 In addition to a much lower incidence in the United States, MMD seems to be distinguished by different demographic and clinical characteristics of patients in the United States than it is in Japan.9

In view of the marked heterogeneity in demographics and natural history of MMD in the United States, institutional experiences from various locations are important. Such features of MMD in the United States will establish guidelines for future management as well as familiarize physicians with this entity in the United States. Therefore, we reviewed our recent experience with 20 adult and pediatric patients with “angiographic moyamoya” and report their clinical presentation, radiological findings, management, and clinical outcomes. We also address differences between patients with MMD in the United States and those in Asian countries.
PATIENTS, MATERIALS, AND METHODS

Between June 1995 and August 1999, 20 patients with catheter or magnetic resonance angiography-proven MMD were diagnosed and treated at Indiana University Hospital and Riley Children’s Hospital in Indianapolis. Diagnosis was based on the findings from catheter cerebral angiography in 15 patients and from magnetic resonance angiography in only 5 patients. All patients had unilateral or bilateral stenosis or occlusion of the first segment of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or the first segment of the anterior cerebral artery with an associated abnormal network of collateral vessels at the base of the brain.

All patients were observed in the neurology outpatient clinic every 4 to 6 months or sooner when clinically indicated. When new symptoms or progression of old neurologic deficits occurred, magnetic resonance imaging was performed. Only 1 patient was lost to follow-up because she moved to another geographical area and could not be reached. Patient outcomes were ranked by functional status using the modified Rankin scale, and statistical analyses were assessed using the Mann-Whitney U test. This study was approved by the institutional review board of all hospitals involved.

RESULTS

Twelve female patients and 8 male patients were diagnosed as having moyamoya. Eighteen patients were white and 2 were African American. Ages ranged from 2 to 54 years. The mean age of patients at symptom onset was 17 years. Patients were divided into 2 groups according to age (group 1, <18 years; group 2, ≥18 years). There were 13 patients in group 1 and 7 patients in group 2. The mean age of patients at symptom onset was 8 years for group 1 and 35 years for group 2. Figure 1 shows the age distribution according to symptom onset.

Events leading to the diagnosis of moyamoya in both groups were mainly ischemic strokes: 11 patients (85%) in group 1 and 5 patients (72%) in group 2 (Table 1). Only 1 patient had an intraparenchymal brain hemorrhage in group 2. Table 2 gives the location of strokes on presentation. Nine patients (69%) in group 1 showed cortical hemispheric infarcts involving the parietal lobes.

Associated medical conditions (some were probably coincidental while others represented generally accepted associations) that occurred in a single patient were Down syndrome and hypothyroidism, Turner syndrome, developmental delay associated with hydrocephalus and microcephaly, aortic coarctation, sickle cell disease, sickle cell trait, neurofibromatosis 1, use of oral contraceptives, asthma, activated protein C resistance, and migraine headaches. Two patients were siblings. None of our patients had arterial hypertension, diabetes mellitus, hyperlipidemia, or family history of stroke.

MANAGEMENT APPROACH

Eight patients (62%) of group 1 were treated surgically compared with all 7 patients in group 2. The most common revascularization procedure was an encephaloduroarteriosynangiosis (EDAS) followed by superficial temporal artery to middle cerebral artery (STA-MCA) bypass. In group 1, 7 patients had bilateral and 6 had unilateral moyamoya (Figure 2). Among those patients with bilateral involvement, 3 patients were medically treated only, and 4 had surgical revascularization procedures. The most common surgical procedure was EDAS in 5 hemispheres and EDAS followed by STA-MCA bypass in 2 hemispheres. Among 6 patients with unilateral moyamoya, 2 patients were treated medically only, and 4 were surgically treated (EDAS in 3 hemispheres and STA-MCA bypass in 1). Patients in both medical and surgical groups received aspirin therapy for secondary stroke prevention.

Table 1. Initial Clinical Manifestations

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Group 1, No. (%)</th>
<th>Group 2, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>4 (31)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Ischemic stroke and headaches</td>
<td>3 (23)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Ischemic stroke and seizures</td>
<td>4 (31)</td>
<td>0</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>2 (15)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0</td>
<td>1 (14)</td>
</tr>
</tbody>
</table>

*Group 1 patients were younger than 18 years; group 2, 18 years of age or older.

Table 2. Location of Infarctions on Presentation

<table>
<thead>
<tr>
<th>Location of Infarctions</th>
<th>Group 1, No. (%)</th>
<th>Group 2, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal lobe</td>
<td>9 (69)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>5 (38)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>3 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>2 (15)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>2 (15)</td>
<td>2 (29)</td>
</tr>
</tbody>
</table>

*Group 1 patients were younger than 18 years; group 2, 18 years of age or older.

Figure 1. Age distribution at symptom onset.
Of the 7 patients in group 2 (Figure 3), 5 had bilateral, and 2 had unilateral moyamoya. The most common surgical procedure was STA-MCA, which was performed in 4 hemispheres; an occipital artery to middle cerebral artery bypass was performed in 1 hemisphere. Encephaloduroarteriosynangiosis was done in 4 hemispheres. In the unilateral group, STA-MCA bypass was carried out in 1 hemisphere and EDAS (for the patient with hemorrhagic stroke) in the other. Post-surgically, all patients were treated with aspirin.

The mean interval between symptom onset and surgery was 18 months for patients in group 1, and 4 months for patients in group 2. All patients received aspirin therapy until the time of surgery. The mean time from symptom onset to surgical procedure was significantly longer for patients in group 1 than for those in group 2 (P=.03). No patient had a complication in either group.

LONG-TERM OUTCOME

Follow-up information was available in 19 of 20 patients (group 1, 13 of 13 patients; group 2, 6 of 7 patients). The mean follow-up time was 36 months, ranging from 2 to 58 months. One patient among the medically treated in group 1 had an ischemic stroke. One patient in group 1 who had a unilateral STA-MCA bypass subsequently had a normal pregnancy and delivery. At the end of the follow-up period, there was no significant difference in the modified Rankin scale score between patients in the surgically treated group (mean modified Rankin scale score, 2) and those in the medically treated group (mean modified Rankin scale score, 1.8).

Management of moyamoya remains controversial. In the United States, about 300 cases of definite or probable MMD have occurred among nearly all ethnic groups. In our study, we report 20 patients with moyamoya from a single institution. Compared with other US studies, this is the second largest study with a long-term assessment of different management approaches.

In our study, patients with moyamoya were clustered at ages 0 to 17 years (13 patients) and 30 to 54 years (5 patients). A prominent peak was observed in the first decade and another clustering was found in the second and third decades. Age distribution characteristics as well as female predominance (12 female patients to 8 male patients) resembled those of previous US studies. Our patient population was 90% white (18 patients) and 10% African American (2 patients). In the largest US review, ethnic background was identified in only 55% of the cases. An unexpected finding in our study was the high percentage (90%) of white patients compared with the percentages in other US studies as given in Table 3.

The definition of moyamoya varies in the US literature. In the largest review from 8 US institutions and the US literature, MMD was classified into definite (n=46), presumptive (n=52), possible (n=10), and doubtful (n=6) groups. In the Midwest study, MMD was grouped as definite MMD (n=30); probable MMD (n=9); and akin MMD (n=12). In the Hawaiian MMD study, 21 patients had definite MMD, and 5 patients had probable MMD. In the Houston study, all patients had definite MMD (n=35). In the Virginia review of 18 young adult patients, 11 patients met the criteria of definite MMD. All 18 patients had idiopathic supraclinoid and internal carotid bifurcation stenotic and/or occlusive disease. As mentioned above, various diagnostic criteria for moyamoya has been used in the US literature. Hence, understanding the etiology and assessing the subsequent outcome is difficult.

Because we sought to further understand the natural history and subsequent outcome of MMD in the United States, we included all patients with moyamoya, including those with moyamoya syndrome, angiographic moyamoya, probable moyamoya, and definite moyamoya because these most likely share the same underlying
pathological process. Medical disorders found in association with moyamoya suggest that moyamoya patterns of vascular changes may be common in a variety of insults. In addition, diagnostic guidelines of moyamoya syndrome are not clearly established so that reliability depends on the availability and consistency of the diagnostic tests. Furthermore, cases of unilateral moyamoya in children often progress to MMD.12 Hirotsune et al13 reported new contralateral lesions in 6 of 12 pediatric patients with unilateral moyamoya within 20 months. If we had required bilateral disease to define MMD for inclusion in our study, 8 patients with unilateral MMD would have been excluded, and long-term possible progression might have been underdiagnosed. Notably, all 8 patients with unilateral moyamoya remained asymptomatic in our study and did not develop contralateral neurologic symptoms during the 29 months of follow-up. However, in one US series, 1 of 3 pediatric patients who presented with unilateral disease later developed contralateral disease.14 Unilateral moyamoya may have a more benign course in US patients than in Japanese patients. Although data from US studies supporting the above observation are limited, this difference seems to be intriguing and deserves further delineation.

Hemorrhagic strokes are more prevalent in adult patients with moyamoya in Japan and Korea.15 Although our adult patient population is small and the follow-up period is brief, only 1 (14%) of 7 adults had a hemorrhagic stroke. Chiu et al9 had a similar clinical experience; in their adult series, 12% presented with a hemorrhagic stroke.

Many studies report successful revascularization results in patients with moyamoya. However, much debate has centered on the safety and efficacy of various revascularization procedures.16 In adults, direct revascularization, and in children, indirect revascularization are considered the preferred surgical treatments.2 In Japanese adults, a reduction in ischemic events following direct revascularization surgery has been reported.17 Karasawa et al18 investigated 104 patients who had STA-MCA anastomosis and/or encephalomyosynangiosis. After a mean follow-up of 115 months, complete or marked neurologic improvement occurred in 84% of patients, while only 6% had cognitive deterioration. In another Japanese study, activities of daily living scores were improved in 61% of those treated surgically compared with 26% of those patients treated medically.19 However, in contrast to these results, other reports suggest that surgical treatment is not needed.20 Chiu et al21 described 20 patients who had surgical revascularization and 13 who were treated medically and found no statistical difference in the 5-year stroke recurrence rate between these 2 groups. Interestingly, within the first year following diagnosis, the risk of recurrent stroke was 18% and then decreased to 5% per year, also suggesting a relatively benign course of the disease process. This observation is in agreement with the results of our study. We found no statistically significant difference in the rate of stroke or transient ischemic attack or in the functional outcome among the 2 treatments at the end of the follow-up period. However, no surgically treated patient and only 1 medically treated patient developed cerebral ischemia.

Moyamoya disease causes a 60% decline in IQ 5 to 9 years after symptom onset.22 Early surgical intervention may be beneficial, delaying a decline in cognitive performance and activities of daily living score.23,24 In our study, the mean interval from initial attack to surgery was longer in group 1. Among the possible factors that may have played a role in this delay were the severity of initial presentation, associated medical diseases, and a possible delay in making the decision whether to perform surgery, particularly in children.

Our study has several limitations. First, we recognize the potential for referral bias as well as treatment selection bias. The latter may be because patients with mild and transient neurologic deficits and minimum disability might have had medical treatment while patients with more severe deficits and moderate disability might have been treated with surgery. Second, while no differences in the severity of neurologic deficits and disability were present between the 2 groups, a difference in the long-term neuropsychological outcome might have occurred. Third, our patient population was more heterogeneous than that in other studies and included all patients with angiographic moyamoya.

The results of our study, together with the results of other published US studies, suggest that moyamoya may have a different presentation and a more benign natural history in US populations than in Asian populations. The greater percentage of whites along with the benign course of the disease among our patients suggests that this US population may have a relatively benign form of moyamoya. If true, factors influencing the course of moyamoya in the United States remain unknown. Despite our limited patient population, our findings emphasize the need to better understand the natural history of moyamoya as well as the clinical benefit of different treatment modalities. Structuring a nationwide study that combines neurologic, neurodiagnostic, and neuropsychological evaluation as study end points will help answer this question. Until that time, the best treatment will remain unclear and will probably vary according to institutional experience.

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REFERENCES