Clinical Features and Outcome in North American Adults With Moyamoya Phenomenon

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Background and Purpose—To describe baseline clinical features and outcomes of adults with moyamoya phenomenon treated at a single North American institution.

Methods—We identified 34 adults with moyamoya phenomenon by review of angiographic records. Clinical presentation and baseline stroke risk factors were obtained by chart review. Follow-up was obtained prospectively. A 5-year Kaplan-Meier stroke risk was calculated.

Results—The median age was 42 (range 20 to 79) years. Twenty-five were women. The initial symptom was ischemia, hemorrhage, or asymptomatic in 24, 7, and 3 patients, respectively. Twenty-two had bilateral involvement and 12 had unilateral moyamoya vessels. Baseline stroke risk factors were similar between groups. The median follow-up in 31 living patients was 5.1 (range 0.2 to 19.6) years. Fourteen patients were treated with surgical revascularization (20 total hemispheres). In medically treated symptomatic hemispheres, the 5-year risk of recurrent ipsilateral stroke was 65% after the initial symptom and 27% after angiographic diagnosis. Patients with bilateral involvement presenting with ischemic symptoms were at the highest risk of subsequent stroke (n=17, 5-year risk of stroke with medical treatment after first symptom (P=0.02) but not after angiographic diagnosis.

Conclusion—Moyamoya phenomenon in North American adults is associated with a high risk of recurrent stroke, particularly those with bilateral involvement and ischemic symptoms. These data suggest a potential benefit with surgery if diagnosis could be made earlier.

Key Words: cerebral hemorrhage ■ cerebral infarction ■ cerebral revascularization ■ Moyamoya disease ■ retrospective studies

In some patients with narrowing or occlusion of the distal internal or proximal middle or anterior cerebral arteries, hypertrophy of lenticulostriate arteries may occur and bypass the occlusive segment. The appearance of these multiple tiny channels on catheter angiography was originally described by the Japanese term “moyamoya,” which translates to “a hazy cloud like a puff of cigarette smoke.” Moyamoya collaterals may form in response to a variety of occlusive vasculopathies involving the distal internal carotid, including sickle-cell anemia and atherosclerotic disease.

In Asia, the condition has a well-recognized phenotype. Patients meeting several clinical and radiographic criteria are considered to have moyamoya disease. The cause of the occlusive vasculopathy moyamoya disease remains undefined. A bimodal age distribution of moyamoya disease has been reported with children presenting with ischemic symptoms and adults in the 4th decade of life most often presenting with hemorrhage.

This condition is less well-defined in North America. Limited data suggest notable differences in presentation. Most North American adults, with moyamoya phenomenon are women presenting with ischemic symptoms in their 3rd through 5th decades. In addition, the racial demographics of patients in the United States mirror those of the general population. The risk of subsequent stroke may be as high as 10% per year. Although many patients undergo surgical revascularization procedures, the relative safety and efficacy of surgical revascularization is unproven in adults.

Recent authors have emphasized the lack of data regarding the characteristics and natural history of this condition in the United States. Therefore, we reviewed the clinical features,

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baseline stroke risk factors and long-term outcome of adults with moyamoya phenomenon treated at our institution over the past 9 years.

Materials and Methods

Patient Selection
We identified all adults (age ≥18 years) with moyamoya phenomenon who underwent digital subtraction catheter angiography at our institution from 1996 through 2005. Inclusion criteria included unilateral or bilateral angiographic identification of severe stenosis or occlusion of the distal internal carotid or proximal middle and anterior cerebral arteries with prominent lenticulostriate "moyamoya collaterals" (Suzuki Stages 3, 4 and 5).1,3 Exclusion criteria were presence of any other disease that might be responsible for the observed vasculopathy, including atherosclerosis, systemic vasculitis, neurofibromatosis, meningitis, sickle-cell disease, Down syndrome, and prior skull-base radiation therapy. This included patients with moyamoya phenomenon in association with isolated distal middle cerebral or posterior cerebral artery stenosis or occlusion, and patients with idiopathic stenoses of the distal internal carotid or proximal middle and anterior cerebral arteries without moyamoya phenomenon.

Retrospective Chart Review
Clinical records, including hospital charts, clinic notes, laboratory studies, and radiological studies were reviewed. If necessary, records from outside hospitals were obtained and reviewed. All data were collected through August 2005. The initial symptom was defined as hemorrhage (subarachnoid [SAH], intraparenchymal [IPH], or intraventricular), ischemic stroke, transient ischemic attack (TIA), or incidental (asymptomatic). Stroke was defined as an acute onset of focal neurological deficit lasting >24 hours. TIA was defined as an onset of focal neurological deficit lasting <24 hours. Diagnosis of SAH was made on the basis of blood in a lumbar puncture or on computed tomography. Patients without evidence of stroke, TIA, or hemorrhage at presentation were considered asymptomatic.

Baseline epidemiological stroke risk factors at initial presentation were obtained, including a self-reported history of hypertension, hypertensive heart disease, coronary artery disease, congestive heart failure, diabetes mellitus, hyperlipidemia, significant alcohol use, tobacco use, oral contraceptive use, and parental stroke death. Laboratory studies at the time of presentation were documented (if performed), including hemoglobin, anticardiolipin antibodies, homocysteine, and C-reactive protein. All angiographic reports were analyzed for sites of involvement, sources of collateral flow, and other cerebrovascular abnormalities. Treatment was recorded as medical (antiplatelet or anticoagulation) or surgical. Surgical treatments included superficial temporal artery to middle cerebral artery bypass, encephaloduralysangiosis (EDAS), and encephaloduralmalloyangiosis (EDAMS).

Clinical Follow-Up
In living patients diagnosed with moyamoya phenomenon <1 year before data collection, stroke status and modified Rankin scores were obtained from recent clinical visits. In living patients diagnosed >1 year before data collection, we attempted phone contact and interview to obtain long-term follow-up data. Informed verbal consent was obtained before interview in a script approved by the Human Studies Committee. Stroke status since last clinical follow-up was determined by the Questionnaire for Verifying Stroke-Free Status.14,15 Current functional status and quality of life were assessed using modified Rankin Scale, Barthel index, and stroke specificity-quality of life questionnaires (SS-QOL).16–18 In patients whom we were not able to contact directly, stroke-free status and Rankin scores were determined from the last clinical visit.

Statistics and Data Analysis
Comparisons of baseline data were made between patients experiencing ischemic and hemorrhagic symptoms, between patients with unilateral and bilateral disease, between nonsurgically and surgically treated patients, and between nonsurgically treated patients that remained stroke-free and those that experienced subsequent stroke or death. Comparisons were made using χ² or t tests.

All risks of subsequent stroke and death were determined using the Kaplan-Meier (KM) technique, with comparisons made using the Log-rank statistic. The risk of any subsequent stroke was determined from the initial onset of symptoms (stroke, TIA, or hemorrhage; before or at initial presentation) to the first acute stroke in the territory of the affected vessels (ipsilateral or contralateral). Overall survival was determined from symptom onset (or diagnosis, if asymptomatic) to death (uncensored) or last follow-up (censored). Comparisons of stroke risk were made between nonsurgically and surgically treated symptomatic hemispheres. In nonsurgically treated hemispheres, stroke risk was determined from symptom onset to subsequent ipsilateral stroke (uncensored), whereas hemispheres not experiencing stroke were censored through last follow-up or until ipsilateral surgery was performed. A second analysis of stroke risk was performed in nonsurgically treated hemispheres using time of angiographic diagnosis to subsequent ipsilateral event. In surgically treated hemispheres, stroke risk was determined from the time of surgery to perioperative stroke (ipsilateral or contralateral stroke <30 days from surgery date) or any subsequent ipsilateral stroke (both uncensored), whereas hemispheres not experiencing stroke were censored at last follow-up.

Results

Patients
Thirty-four patients were identified with unilateral (n=12) or bilateral (n=22) idiopathic moyamoya phenomenon. Patient characteristics are detailed in the Table and clinical timelines for each patient are shown in Figure 1A and 1B. The median (range) age at symptom onset was 42 (20 to 79) years for all patients. There was a trend toward a younger age at diagnosis.
Figure 1. Clinical timelines. Panel A shows patients initially presenting with ischemic events. Panel B shows patients initially presenting with hemorrhage and patients who were asymptomatic (incidental).
among patients with bilateral moyamoya phenomenon versus those with unilateral involvement (mean age 39.7 versus 46.8; \( P = 0.15 \)). Twenty-five patients were women. The initial symptom was ischemia, hemorrhage, or asymptomatic in 24, 7, and 3 patients, respectively. Of the 7 patients presenting with acute hemorrhage, 2 had IPH only, 3 had IPH with intraventricular extension, and 2 had SAH. In 3 patients the moyamoya phenomenon was an incidental finding on angiography.

Of the 22 patients with bilateral involvement, 3 presented with hemorrhage (2 IPH and 1 SAH). One patient was asymptomatic. Eighteen of the 22 presented with ischemia (6 TIAs and 12 strokes). Four presented with bilateral symptoms. Fourteen patients had angiography within a month of their first event. The remaining 7 were studied after a recurrent event. Twelve patients presented with unilateral moyamoya phenomenon. Two were incidental findings on angiography. Of the 10 symptomatic patients, 6 presented with ischemic symptoms (3 TIAs and 3 strokes). The remaining 4 patients presented with hemorrhage (Table).

Baseline Stroke Risk Factors
Baseline stroke risk factors were documented in 33 of 34 patients. One patient was found unconscious with hemorrhage, and baseline risk factors could not be obtained. This patient died as a result of this hemorrhage. Risk factors were compared between hemorrhagic and ischemic patients, surgically treated and nonsurgically treated patients, and bilateral and unilateral patients; no significant \( P < 0.05 \) differences were observed. Baseline risk factors among nonsurgically treated patients were not significantly different \( P < 0.05 \) in those experiencing subsequent stroke versus those not experiencing subsequent stroke (data not shown).

Surgery
Fourteen patients underwent surgical revascularization, 6 for both hemispheres. Three procedures were direct arterial anastomoses, 3 were EDAMS, and the remainder EDAS. Two perioperative ischemic strokes occurred, both minor and after unilateral EDAS procedures in patients with bilateral disease \( (2/20 = 10\% \text{ procedural stroke risk}) \). One patient treated by EDAS had a stroke 8 months after surgery. The remainder remained stroke-free in the treated hemisphere.

Outcome
Timelines for each individual patient are shown in Figure 1A (ischemic symptoms) and 1B (hemorrhage or asymptomatic). Two patients died as a consequence of their presenting ischemic stroke \( (n = 1) \) or hemorrhage \( (n = 1) \). None of the 3 asymptomatic patients experienced an ischemic or hemorrhagic event during follow-up of over 5 years duration. None of the 5 surviving patients presenting with hemorrhage had a recurrent event. Two of the 10 medically treated patients with unilateral involvement had ischemic strokes after diagnosis. None developed contralateral symptoms.

Eleven of the 17 patients with bilateral involvement and ischemic symptoms had 1 or more ischemic strokes after presentation. The duration from first symptomatic event to last symptomatic event (TIA or stroke) with medical treat-
ment is shown in Figure 2A. Most subsequent events occurred in the first 2 years after presentation and 1 after six years. These patients had a high risk of developing contralateral symptoms (Figure 2B). Nine of the 17 patients developed symptoms in the initially asymptomatic contralateral hemisphere.

Three of the 17 patients were treated initially with surgical revascularization of the symptomatic hemisphere. One of the 3 developed contralateral symptoms and underwent a contralateral EDAS. Of the 14 patients initially treated medically, 4 had no further events, including 2 with bilateral symptoms on presentation. Ten of the 14 medically treated patients had a recurrent ipsilateral stroke (mean 24 months after first event). Six of these patients underwent subsequent surgical revascularization. Four of these patients developed contralateral symptoms, and 3 of the 4 underwent surgical revascularization of the contralateral hemisphere. Four of the 10 medically treated patients with recurrent ipsilateral stroke were treated medically. None had a second ipsilateral stroke, but 2 of the 4 developed new contralateral symptoms. Both were treated medically and 1 had a second contralateral stroke.

In medically treated symptomatic hemispheres, the 5-year KM risk of recurrent ipsilateral stroke was 65% after the initial symptom and 27% after angiographic diagnosis. The stroke risk was highest in the 17 surviving patients with bilateral involvement presenting with ischemic symptoms (5-year KM risk for stroke 82%; Figure 3A). In surgically treated hemispheres, the 5-year KM risk of perioperative or subsequent ipsilateral stroke or death was 17% (Figure 3B). This was significantly different compared with medical treatment after first symptom (P=0.02) but not after angiographic diagnosis (Figure 3B).

**Functional Outcome**

Thirty-one patients were alive at last follow-up. Of the 25 living patients diagnosed >1 year before data collection, we...
were able to contact 19 patients by phone. The remaining 6 patients were alive at last contact by report of a primary care physician (4 patients) or a relative.2 Of these 6 patients, 5 had undergone surgical revascularization and 1 had not.

There were no differences (P<0.05) in modified Rankin, Barthel, or SS-QOL scores between surgically treated and nonsurgically treated patients or between patients presenting with ischemia or hemorrhage. The percentage of patients with a modified Rankin score of 0 or 1 was greater in patients with unilateral moyamoya disease versus those with bilateral disease (83% versus 48%; P=0.04).

Discussion

The data from this large cohort of patients both confirms prior observations regarding North American moyamoya phenomenon and extends our knowledge of the prognosis of this disorder. It primarily affects young women. It most often presents with ischemic symptoms, and the risk for subsequent stroke is extremely high, particularly in those patients with bilateral involvement and ischemic symptoms. The highest risk is in the first few years after presentation. The risk for symptomatic progression in the contralateral hemisphere is high in those with angiographic evidence of bilateral disease and low in those with unilateral angiographic disease. Patients with incidental moyamoya phenomenon appear to have a very good outcome.

The racial demographics of patients in our cohort were similar to those of our region, with 69% of patients being white and 29% being black, consistent with prior observations.6–10 Most of our patients were women between the ages of 30 and 50 who presented with ischemic symptoms. This is also consistent with observations from smaller previous studies.6–10 These data support the hypothesis that North American and Asian forms of moyamoya are different, because most adults with Asian moyamoya disease present with hemorrhage.4,6–10

These differences in presentation between North American and Asian patients may be related to the timing of onset of the occlusive vasculopathy. It is likely that ischemic symptoms develop soon after the onset of the arterial narrowing or occlusion. In Asia, this most frequently occurs in childhood. In North America, this may be more frequent in young adults. The increased hemorrhage risk in Asian adults may be a function of the fragility of the moyamoya collaterals and a late consequence of the process. The temporal pattern of symptoms also supports this hypothesis of a later onset of occlusive vasculopathy. We observed a higher risk for recurrent symptoms or development of contralateral symptoms in the first few years after symptom onset (Figure 2A and 2B). This pattern is similar to patients with symptomatic atherosclerotic carotid disease22 and may reflect an improvement in collateral flow over time.20

In the current study, the development of contralateral symptoms did not occur in patients with unilateral disease or those with incidental, asymptomatic bilateral disease. This appears to be another difference between the clinical manifestations of moyamoya phenomenon in North America and Asia. In a recent study by Kuroda et al, 63 adult patients with 86 unoperated hemispheres were followed for a mean of 73 months.22 Three of the 11 patients with initially unilateral disease developed contralateral symptoms (2 TIAs and 1 hemorrhage).

In the series reported by Chiu et al, no patient initially presenting with an ischemic stroke experienced a subsequent hemorrhage and no patient initially presenting with a hemorrhage experienced a subsequent ischemic stroke.7 In addition, Asian adults presenting with hemorrhage have a high risk for subsequent hemorrhage.21 Our experience was different. None of the 7 patients presenting with hemorrhage had a subsequent hemorrhage and only 1 experienced a subsequent ischemic stroke.

Surgical revascularization procedures are often performed on patients with moyamoya phenomenon; however, surgery is associated with a risk of perioperative stroke.13 In 21 patients undergoing surgical revascularization at the University of Texas, most of whom were adults, Chui et al, observed a perioperative stroke risk of 13% per operated hemisphere (4 of 31) and a 5-year risk of ipsilateral postoperative stroke of 22% per hemisphere,7 similar to data from the present study.

The present data suggest that surgery may be of benefit in patients with moyamoya disease, despite the risk of ischemic complications. However, the sample size of the present study is small and the study design is retrospective. Our data also suggest that earlier diagnosis must be accomplished for surgery to be proven effective (Figure 3B). Methods of hemodynamic assessment may also play a role in patient selection for surgery.26 Impaired hemodynamics likely play a major role in the risk for future stroke in these patients,23 similar to atherosclerotic carotid stenosis and occlusion.24,25

Several limitations of the present study must be noted. This was a retrospective study from a single center. The analysis was limited to patients with typical moyamoya phenomenon: stenosis or occlusion of the distal internal carotid or proximal middle and anterior cerebral arteries and moyamoya phenomenon. Direct clinical follow-up was incomplete, although all were confirmed to be alive. Finally, follow-up anatomic imaging was not obtained in most of these patients. Medically treated patients without recurrent symptoms were not studied further and angiographic follow-up of surgically treated patients was incomplete. Therefore, the relationship between the clinical course and angiographic changes over time is not known.

In conclusion, this study expands the current base of knowledge on moyamoya phenomenon in adults in the United States. Most patients are young women who likely develop idiopathic narrowing or occlusion of the distal internal carotid arteries or its proximal branches and consequent ischemic stroke. The etiology of this occlusive vasculopathy remains unknown and maybe different than the Asian childhood disorder. Patients presenting with bilateral symptomatic involvement had a worse functional outcome than those with unilateral involvement. They were at extremely high risk for future stroke, both ipsilateral to the side of initial symptoms and in the contralateral hemisphere. This risk appears to abate over time. Surgery may be of benefit to these patients, particularly if the diagnosis of moyamoya could be made earlier in the course of their disease. Further prospective studies are warranted.
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