Moyamoya Disease in China
Its Clinical Features and Outcomes

Lian Duan, MD, PhD; Xiang-Yang Bao, MM; Wei-Zhong Yang, BS; Wan-Chao Shi, MD; De-Sheng Li, MD; Zheng-Shan Zhang, MM; Rui Zong, MM; Cong Han, MM; Feng Zhao, BS; Jie Feng, BS

Background and Purpose—Here we describe the clinical features and outcomes of patients with moyamoya disease who were surgically treated at a single institution in China.

Methods—Our cohort included 802 patients with moyamoya disease. Demographic and clinical characteristics were obtained by retrospective chart review; follow-up information and outcome were obtained through clinical visits, telephone, or letter interview. We used the Kaplan-Meier methods to estimate stroke risk by treatment status.

Results—The median age for the onset of symptoms was 28 (range, 0.5–77) years. Two definite peaks in age distribution were found. The ratio of women to men was 1:1 (398/404). Familial occurrence of moyamoya disease was 5.2%. The initial symptom was ischemia, hemorrhage, or others in 564, 113, and 125 patients, respectively. Twenty-nine of the 802 patients (3.6%) received conservative management. The remaining 773 patients (96.4%) underwent neurosurgical revascularization procedures, and 502 of these were bilateral. The median follow-up after surgery (n=773) or conservative management (n=26) was 26.3 months (range, 6.0–101.9 months). Most subsequent ischemic events appeared in the first 2 years after surgery. The Kaplan-Meier estimated stroke risk was 10.1% in the first 2 years, and the 5-year-Kaplan-Meier risk of stroke was 12.7% after surgery for all patients treated with surgical revascularization.

Conclusions—This study on the clinical features of moyamoya disease in mainland China indicated bimodal incidence distribution with women-to-men ratios of 1:1 and lower rate of hemorrhages in adults compared with in children. Patients had low rates of postoperative ischemic or hemorrhagic strokes, and the majority of patients had preserved functional status after revascularization. (Stroke. 2012;43:56-60.)

Key Words: moyamoya disease ■ ischemia ■ China

Moyamoya disease (MMD), a chronic cerebrovascular disorder, is defined by the progressive stenosis or occlusion of the intracranial vessels. The stenosis begins with the intracranial carotid arteries and can progress to the anterior, middle, and posterior cerebral arteries (PCA). As these arteries gradually stenose, a collateral network of capillaries develops at the base of the brain, producing the characteristic reticulate appearance (“puff of smoke”) on angiography. The disease was first described in 1957 by Takeuchi and Shimizu1 and later was named by Suzuki and Takaku after the Japanese term “moyamoya” in 1969.2

During the past few decades, many studies have documented the epidemiological and clinical characteristics of the disease.3–8 Some of these studies have indicated a high prevalence of MMD in Asian countries, particularly in Japan, South Korea, and China. The prevalence, clinical features, treatment, and long-term outcome of MMD in Japan and South Korea have been well-documented. However, they lack detailed demographic and clinical data on Chinese patients with MMD.9,10 We aim to evaluate whether MMD in China is different from MMD in other Asian countries, the United States, and Europe in terms of demographic characteristics, clinical presentation, and long-term outcome. We present a consecutive series of 802 patients with MMD admitted and treated during the last 8 years at our institute, a nationwide referral center catering to patients with MMD. Our cohort of patients represents the largest group of patients followed longitudinally from a single institution in China.

Materials and Methods

Patient Selection
We identified all inpatients of bilateral or unilateral MMD, who were diagnosed with angiogram and/or magnetic resonance with magnetic resonance angiography (MRA), at Department of Neurosurgery, 307 Hospital, PLA, Beijing, China, from 2002 to 2010. Inclusion and exclusion criteria were provided in the online supplement.

Retrospective Chart Review
Clinical records, including hospital charts, clinic notes, and radiological studies were reviewed. All data were collected through

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January 2010. The research ethics board at 307 Hospital approved the study design. Initial symptoms were divided into 4 subgroups in the online supplement. Treatment was recorded as bypass surgery or conservative management.

Clinical Follow-Up
After discharge, long-term outcome was obtained through clinical visits, telephone, or letter interview. Stroke status and modified Rankin Scale scores were recorded to evaluate outcomes of the patients. For patients whom we were unable to contact, features and long-term outcomes were determined from the last clinical visit.

Statistics and Data Analysis
Categorical variables were analyzed using the χ² test. Kaplan-Meier methods were used to estimate stroke risk. A probability value of less than 0.05 was considered to indicate statistical significance. All analyses were performed with the use of SPSS software for Windows, version 13.0 (SPSS Inc).

Results
Demographic Data
We identified 802 patients with MMD. The majority of the patients (792/802) were Han Chinese, 2 patients were Korean, 3 patients were Manchu, 3 patients were Mongolian, 1 patient was Hani, and 1 patient was Bai. One hundred forty-nine patients were from Henan province; 128 patients from Shandong province; 118 patients from Hebei province; 51 patients from Beijing; 357 patients from the other 25 provinces; 11 patients were of Chinese origin from the United States, Europe, and Africa (Figure 1). There were 404 men and 398 women. The ratio of female to male patients was 1:1.

The median age at symptom onset was 28 (range, 0.5–77) years for all patients. The percentage of patients younger than age 10 years and that of patients older than age 18 years was 26.9% and 61.6%, respectively. Age distribution of the patients with MMD was found to have a bimodal occurrence: the highest peak of detection rate was observed at age 5 to 9 years, and a smaller peak was observed at age 35 to 39 years. Both women and men followed the same pattern in age distribution (Figure 2A).

Disease Type
In our cohort, transient ischemic attack was the most common initial clinical manifestation (48%). The others were infarction (22%), hemorrhage (14%), headache (12%), seizure (1.5%), no symptoms (1.1%), and syncope (0.9%; Supplemental Table, http://stroke.ahajournals.org). The percentage of ischemia as the initial symptom was significantly higher than that of hemorrhage, regardless of age. Hemorrhage as an initial manifestation mostly occurred in the third and fourth decades of life. The percentage of hemorrhage was significantly higher in adult patients than in patients younger than age 10 years (P<0.01), whereas ischemia occurred more often in pediatric patients compared with adults (Figure 2B).

Figure 1. Distribution of 802 cases with moyamoya disease in China. Numbers in parentheses indicate the number of cases from each region.
Diagnostic Features
A total of 795 patients underwent cerebral angiography, including bilateral internal and external carotid arteriography, and unilateral or bilateral vertebral arteriography. Seven patients underwent magnetic resonance with MRA. We identified 78 unilateral and 724 bilateral MMD patients. Although MMD has long been regarded as a disease of the anterior circulation, there were steno-occlusive changes of the PCA in 252 patients (31.4%) in our cohort.

Familial Occurrence
Familial history was observed in 5.2% of patients (42/802). Fourteen of 42 cases have siblings diagnosed with MMD, 6 cases with mothers diagnosed, 14 cases with fathers diagnosed, 5 cases with daughters diagnosed, 1 cases with paternal cousin diagnosed, and 2 cases with maternal aunt diagnosed. The family members mentioned above were all confirmed by cerebral angiography and/or MRA.

Treatment
Twenty-nine of the 802 patients (3.6%) received conservative management. Twenty-five of the 29 patients received medical treatment only, using anticonvulsant agents, antihypertensive agents, antifibrinolytic agents, and vasodilators. Two patients received decompressive craniectomy for large brain area infarction, whereas the remaining 2 patients with intraventricular hemorrhage on admission received extraventricular drainage. Two of the 29 conservatively managed patients received revascularization procedures in other hospitals later. Of the 29 patients, 4 patients experienced an ischemic stroke, 2 patients experienced 1 (n=1) or 2 (n=1) hemorrhagic strokes in hospital. Three patients died as a consequence of their presenting ischemic stroke (n=2) or hemorrhage (n=1) before discharge.

A total of 773 patients (96.4%) underwent neurosurgical revascularization procedures. Given that 502 patients received bilateral procedures, the total procedures performed were 1274. The most common type of bypass surgery performed was encephaloduroarteriosynangiosis using the superficial temporal artery. They made up 90.6% (1154/1274) of the bypass operations performed. Fifty-two encephaloduroarteriosynangioses were performed using the occipital artery as donor vessel in patients with PCA involved. The remainder received other types of bypass surgery including superficial temporal artery/middle cerebral artery anastomosis (n=45) and burr holes (n=75). Forty-five patients (5.8%) revascularized (3.6% of procedures performed), experienced ischemic strokes (n=44), or experienced hemorrhage strokes (n=2) in the postoperative period (defined as the first 30 days after the revascularization procedure). No patient died because of surgical complications in the postoperative period.

Follow-Up
The median follow-up after surgery (n=773) or conservative management (n=26) was 26.3 months (range, 6.0–101.9 months). Of the 799 living patients by discharge, 56 patients could not be contacted by phone or letter for data collection. A total of 84 strokes occurred in 77 patients during follow-up: 57 of the 77 patients with strokes had 1 (n=52) or 2 (n=5) ischemic strokes, 18 patients had 1 hemorrhagic stroke, and 2 patients had an ischemic stroke followed by a hemorrhagic stroke. None of the 26 conservatively treated patients had an ischemic or hemorrhagic stroke during follow-up. Sixty-two ischemic and 15 hemorrhagic strokes occurred in the first 2 years after revascularization surgery, including 46 postoperative strokes. Only 2 ischemic and 5 hemorrhagic strokes occurred more than 2 years after surgery.

The Kaplan-Meier estimate of postoperative or subsequent stroke was 10.1% (95% CI, 9.9%–10.3%) in the first 2 years for all patients treated with surgical revascularization. The 5-year-Kaplan-Meier risk of recurrent stroke was 12.7% (95% CI, 12.5%–12.9%) after surgery for all patients treated with surgical revascularization (Figure 3). Pediatric and adult patients were analyzed separately (Supplemental Figures S1 and S2). There was a significant difference between frequency
of strokes in the first 2 years after surgery and thereafter (P<0.01).

**Functional Outcome**

Actual follow-up information on disability and functional status was available for 743 of 799 surviving patients (93%). The outcome of the other 56 surviving patients was determined at the point of the final clinical visit.

Eleven of the patients died during follow-up: 9 adults and 2 children. Their initial clinical manifestations were hemorrhage in 4 cases, cerebral infarction in 3 cases, transient ischemic attack in 3 cases, and headache in 1 case. The causes of death were recurrent hemorrhage in 7 cases, ischemic stroke in 1 case, cerebral trauma in 1 case, accident in 1 case, and unknown cause in 1 case. Of the 788 surviving patients, 623 patients (79.1%) had no disability (modified Rankin Scale 0 and 1), 131 patients (16.6%) had mild or moderate disability and were able to walk (modified Rankin Scale 2 or 3), 34 patients (4.3%) were severely disabled or unable to walk (modified Rankin Scale 4 or 5).

**Discussion**

MMD is a chronic cerebrovascular disorder mainly found in Asia, especially in Japan and South Korea. Although MMD has now been observed throughout the world in people of many ethnic backgrounds, including American and European populations, the disease is extremely uncommon in non-Asian populations.3,7,11–15 Epidemiological features of MMD in China are largely unknown. Recently, an epidemiological study in the area of Nanjing, the capital city of Jiangsu province, with a total population of approximately 6.2 million, showed the prevalence at 3.92/100,000,9 which was lower than the prevalence of 6.03/100,000 found in Japan; however, it was similar to the report from Taiwan.8 This study was limited to a small area of China and there was no clinical data on treatment and outcomes for this area. Reviewing the literature, one realizes that the knowledge about clinical features, surgical treatment, and long-term outcome of MMD in mainland China is minimal.

We present data from a cohort of 802 patients with MMD from all geographic areas of mainland China, with details about clinical manifestation and outcome. Several differences between MMD in our cohort and patients from other published series are notable.3,5,12,14,16–19 In the present study, a geographical distribution of our patients with MMD in mainland China was shown. The distribution consisted of 29 provinces with a particularly high prevalence in Henan, Shandong, and Hebei province. One explanation is that the 3 provinces have larger population than do other provinces. Another explanation is the relatively closer locations of the 3 provinces to our institute in Beijing. Given that some other provinces with a larger population and closer proximity to our hospital are represented by much fewer patients, other factors such as inheritance or environment may be involved.20 China has 55 minority groups spread all over the country. Although the amount of patients from minority was minimal, considering proportionally minor population of the minorities, we thought that there was no difference in the prevalence of MMD among Han and minorities.

Asian epidemiological surveys have shown women-to-men predominance ranging from 1.8:1 to 2.2:1 of MMD in Japan.3,18 In the American ethnic heterogeneous analysis, there are women-to-men ratios of 2.5:1 and 1:8:1.12,14 In the European white cohort, female predominance is more pronounced, with a women-to-men ratio of 4.25:1.11 In our Chinese cohort, the ratio of women to men was 1:1 by chance. This ratio is similar to the report from Taiwan8 and the Nanjing area.9 The results suggest that there is no difference in sex distribution of MMD in China, whereas reports from Japan, South Korea, the United States, and Europe showed women predominance.

Familial occurrence of MMD in this cohort (5.2%) was lower than that reported in the Japanese and South Korean series (approximately 10%–15%).3,18,21 but similar to that reported in the United States (5.6%).22 In our cohort, only family members with MMD symptoms were examined and eventually diagnosed by angiography or MRA. Family members without symptoms were not screened. Therefore, some familial MMD may be unaccounted for, which may lower the incidence of familial MMD in our series. These findings support the view that a genetic factor may play a role in the incidence of MMD.23–24

It is well-known that MMD occurs mostly in children in Asia.13 However, the present study showed a preponderance of adults. With the advances in knowledge regarding MMD, more patients once previously ignored can now be diagnosed. As the number of newly diagnosed patients increases, the proportion of adult patients will increase, which may be an explanation for the preponderance of adults. A bimodal age distribution has been demonstrated in Asia, with children primarily suffering from ischemic symptoms and adults experiencing intracranial hemorrhage.8,10,25–26 This study also revealed a 2-peak pattern, the higher peak observed in patients age 5 to 9 years being more prominent than in adults. The result is similar to reports from Japan and South Korea.5,13 In our cohort, the majority of affected adults and children present with ischemic symptom onset, although the rate of hemorrhage among adults is approximately 7 times as high as is the rate among children (18.4% versus 2.3%). Symptom onset of MMD in China is different from that in Japan and South Korea, but similar to the reports from the United States and Europe.11–12,14

The percentage of asymptomatic MMD seems low in this study. The low rate of asymptomatic MMD may involve different factors. Most of these patients are identified accidentally by angiography and/or MRA. Routine Digital Subtraction Arteriography and MRA check-up is impossible for a large population with economic limitations as there are in China. Therefore, more accurate detection of asymptomatic cases is needed, along with improvements in the medical system and financial capability of the patients in China.

The main goal of revascularization surgery in patients with MMD remains preventing future ischemic and hemorrhagic strokes and, potentially, limiting disease progression. Previous studies have described an inevitable disease progression (without surgery) in 23.8%27 and 38.9%28 of patients. The 5-year cumulative stroke risk in patients with medically treated hemispheres varied from 40% to 82% in patients with
bilateral disease and stroke presentation. In the present study, the cumulative 5-year Kaplan-Meier risk of stroke was 12.7% in surgically treated patients. Our surgical study was comparable to the results of the North American study (17%) and the European study (27.3%).

Although MMD has long been regarded as a disease of the anterior circulation, there is evidence that the posterior circulation is also involved in 30% to 58% of patients. We found steno-occlusive changes of the PCA in 31% of the 802 patients. The frequency is generally consistent with the findings of previous studies. No PCA territory infarctions occurred in the 52 hemispheres treated with encephaloduro-arterio-synangiosis using the occipital artery in our study. Based on the progressive nature of ischemia, revascularization of the PCA territory should be considered in patients who have symptoms or radiological evidence of hemodynamic insufficiency in those territories.

In conclusion, this study expands the current base of knowledge on MMD in China. This study on the clinical features of MMD in mainland China indicated bimodal incidence distribution with women-to-men ratios of 1:1 and lower rate of hemorrhages in adults compared with children. Patients had low rates of postoperative ischemic or hemorrhagic strokes, and the majority of patients had preserved functional status after revascularization. It is difficult to compare the Kaplan-Meier risk of medically treated and surgically treated patients because of small sample size of medically treated patients and selection bias in our study. Randomized clinical trials are needed to evaluate the efficacy of revascularization procedures.

Sources of Funding
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Disclosures
None.

References
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SUPPLEMENT MATERIAL

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Supplemental Figures: 2
Supplemental Materials and Methods

Inclusion criteria included unilateral or bilateral angiographic identification of severe stenosis or occlusion of the distal internal carotid, proximal middle cerebral, and anterior cerebral arteries, associated with an abnormal network of collateral vessels. An exclusion criterion was the presence of secondary moyamoya phenomenon caused by atherosclerosis, meningitis, Down syndrome, systemic vasculitis, hyperthyroidism, neurofibromatosis, leptospiral infection, or prior skull-base radiation therapy.

The initial symptoms were divided into four subgroups: (a) ischemia, including transient ischemic attack (TIA) and ischemic stroke; (b) hemorrhage, including subarachnoid (SAH), intraparenchymal (IPH), or intraventricular hemorrhage; (c) headache; (d) other symptoms, including seizure, syncope, and asymptomatic (patients were accidentally identified during their annual check-up).

The treatment was based on patient symptoms, cerebral blood flow studies, and angiographic findings. Neurosurgical revascularization was performed in patients with ischemic or hemorrhagic symptoms and impaired haemodynamics defined by perfusion CT or positron-emission-tomography. In bilateral MMD, we first revascularized the side of more symptomatic, such as frequent TIAs. If no lateralizing signs or symptoms were present, we preferred to revascularize the dominant side first. The second side was usually revascularized 3 months after the first surgery, as tolerated by the patient. The medically treated patients consisted of two groups: one group includes asymptomatic or atypical patients without impaired hemodynamics; the other group includes patients who were not able to afford surgery because of the critical strokes occurred in the hospital.
### Supplemental Table 1

**Table S1. Initial symptoms of moyamoya disease**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>&lt; 10 years old</th>
<th>≥10 years old</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=216 (%)</td>
<td>n=586 (%)</td>
<td>n=802 (%)</td>
</tr>
<tr>
<td>Headache</td>
<td>35 (4.4%)</td>
<td>64 (8%)</td>
<td>99 (12.4%)</td>
</tr>
<tr>
<td>Syncope</td>
<td>5 (0.6%)</td>
<td>5 (0.6%)</td>
<td>5 (0.6%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>5 (0.6%)</td>
<td>7 (0.9%)</td>
<td>12 (1.5%)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>170 (78.7%)</td>
<td>394 (67.2%)</td>
<td>564 (70.3%)</td>
</tr>
<tr>
<td>TIA</td>
<td>140</td>
<td>248</td>
<td>388</td>
</tr>
<tr>
<td>Infarction</td>
<td>30</td>
<td>146</td>
<td>176</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>5 (2.3%)</td>
<td>108 (18.4%)</td>
<td>113 (14.1%)</td>
</tr>
<tr>
<td>SAH</td>
<td>1</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>IPH</td>
<td>1</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>Intraventricular</td>
<td>3</td>
<td>42</td>
<td>45</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>1 (0.1%)</td>
<td>8 (1%)</td>
<td>9 (1.1%)</td>
</tr>
</tbody>
</table>

### Supplemental Table 2

**Table S2. Comparison of moyamoya disease between the present study, Japan, South Korea, United States and Taiwan.**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>The present study</th>
<th>Japan1</th>
<th>South Korea2</th>
<th>United States3</th>
<th>Taiwan4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female-to-male ratio</td>
<td>1:1</td>
<td>1.75:1</td>
<td>1.5:1</td>
<td>2.5:1</td>
<td>1.3:1</td>
</tr>
<tr>
<td>Pattern of age distribution</td>
<td>Two-peak</td>
<td>Two-peak</td>
<td>Two-peak</td>
<td>One-peak</td>
<td>One-peak</td>
</tr>
<tr>
<td>patients &lt; 10 years old</td>
<td>26.9%</td>
<td>55%</td>
<td>24.3%</td>
<td>5.7%</td>
<td>18.4</td>
</tr>
<tr>
<td>Adult patients (%)</td>
<td>61.6%</td>
<td>33%</td>
<td>64%</td>
<td>80%</td>
<td>73.9%</td>
</tr>
<tr>
<td>Adult patients presented with hemorrhage (%)</td>
<td>18.4%</td>
<td>51%</td>
<td>53%</td>
<td>13%</td>
<td>65%</td>
</tr>
<tr>
<td>Familial occurrence (%)</td>
<td>5.2%</td>
<td>6%</td>
<td>1.5%</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Unilateral lesions (%)</td>
<td>10.8%</td>
<td>Not mentioned</td>
<td>15.2%</td>
<td>9.4%</td>
<td>Not mentioned</td>
</tr>
</tbody>
</table>
Supplemental Figures

Figure 1

Supplemental Figure 1: The Kaplan–Meier estimate of postoperative or subsequent stroke was 13% with a 95% confidence interval ranging from 12.6% to 13.4% in the first 2 years for adult patients treated with surgical revascularization. The 5-year-Kaplan–Meier risk of recurrent stroke was 16% with a 95% confidence interval ranging from 15.6% to 16.4% after surgery for adult patients treated with surgical revascularization.

Figure 2

Supplemental Figure 2: The Kaplan–Meier estimate of postoperative or subsequent stroke was 5% with a 95% confidence interval ranging from 4.8% to 5.2% in the first 2 years for pediatric patients treated with surgical revascularization. The 5-year-Kaplan–Meier risk of recurrent stroke was 9% with a 95% confidence interval ranging from 8.8% to 9.2% after surgery for pediatric patients treated with surgical revascularization.
Supplemental References


