Clinical Features, Surgical Treatment, and Long-Term Outcome in Pediatric Patients with Moyamoya Disease in China

Xiang-Yang Bao  Lian Duan  Wei-Zhong Yang  De-Sheng Li  Wei-Jian Sun  Zheng-Shan Zhang  Rui Zong  Cong Han

Department of Neurosurgery, 307 Hospital, PLA, The Center for Cerebral Vascular Disease, PLA, Beijing, China

Key Words
Indirect · Encephaloduroarteriosynangiosis · Moyamoya disease · Pediatric · Outcome · China

Abstract
Background: There was few detailed demographic and clinical data about Chinese patients with moyamoya disease. Here we describe the clinical features, surgical treatment, and long-term outcome of pediatric patients with moyamoya disease at a single institution in China. Methods: Our cohort included 288 pediatric patients with moyamoya disease. The demographic and clinical characteristics were obtained by retrospective chart review and long-term outcome was evaluated using the stroke status. Univariate and multivariate logistic regression analyses were performed to determine the risk factors for clinical outcome. The risk of subsequent stroke was determined using the Kaplan-Meier method. Results: The median age for the onset of symptoms was 8.0 years. The ratio of female to male patients was 1:1. Familial occurrence of moyamoya disease was 9.4%. The incidence of postoperative complications was 4.2%. Postoperative ischemic events were identified as predictors of unfavorable clinical outcome, while older age of symptom onset was associated with a favorable clinical outcome. The Kaplan-Meier estimate stroke risk was 5% in the first 2 years, and the 5-year-Kaplan-Meier risk of stroke was 9% after surgery for all patients treated with surgical revascularization. Overall, 86% of patients had an independent life with no significant disability. Conclusion: This long-term survey demonstrated that most surgically treated pediatric patients with MMD maintain good outcomes. Our results indicate that an early diagnosis and active intervention before the establishment of irreversible hemodynamic change are essential to achieve a favorable clinical outcome.

Introduction

Moyamoya disease (MMD) is a progressive occlusive cerebrovascular disease of the internal carotid arteries or their branches with compensatory development of a fine collateral vascular network at the base of the brain (moyamoya vessels) [1, 2].

MMD is the most common pediatric cerebrovascular disease in far eastern countries. In children, MMD frequently manifests as ischemic symptoms. The benefits of revascularization surgery, whether direct or indirect, have been well established in MMD patients with isch-
emic symptoms. In adults, the increase in cerebral blood flow achieved with indirect revascularization is often unsatisfactory, and direct revascularization is usually feasible. In children, however, direct revascularization is frequently technically not feasible, whereas the response to indirect revascularization is excellent. Recently, surgical revascularization is recommended for MMD manifesting as cerebral ischemic symptoms according to Japanese guidelines about the treatment of MMD [3].

MMD occurs worldwide [1, 4]; however, the greatest incidence continues to be in East Asia including Japan, Korea, Mainland China, and Taiwan [5]. The prevalence, clinical features, treatment, and long-term outcome of MMD in Japan and South Korea have been well-documented. However, clinical features, surgical treatment, and long-term outcome about Chinese patients with MMD are largely unknown [6, 7]. Recently, we have done some clinical studies about the outline of MMD Korea, Mainland China, and Taiwan incidence continues to be in East Asia including Japan, perothyroidism, neurofibromatosis, leptospiral infection, or prior erosion sclerosis, meningitis, Down syndrome, systemic vasculitis, hy-

The presence of secondary moyamoya phenomenon caused by atherosclerosis, meningitis, Down syndrome, systemic vasculitis, hyperthyroidism, neurofibromatosis, leptospiral infection, or prior skull-base radiation therapy.

Retrospective Chart Review
Clinical records, including hospital charts, clinic notes, and radiological studies were reviewed. All data were collected through January 2010. The preoperative angiographic stage was evaluated according to Suzuki’s classification [2]; the higher Suzuki grade was used when it was different on each side. The research ethics board at 307 Hospital approved the study design.

Surgical Treatment
The revascularization procedure that patients received should meet the following criteria: (1) diagnosed MMD or unilateral MMD based on angiographically or MRA. (2) MMD-manifested cerebral ischemic symptoms or hemorrhagic symptoms, or an im-

EDAS is the preferred surgical revascularization procedure at our institution. Briefly, EDAS involves placement of an external carotid artery branch beneath the dura in ischemic territories. Most commonly, the STA is used. In certain circumstances, depending on the territory at risk, the occipital artery may also be used. Intraoperatively, the donor with the strip of galea (the arterial bridge) is detached from the pericranium or the fascia below. Two burr holes are made beneath the proximal and distal ends of the arterial bridge. Burr holes are connected by mill to make an oval bone flap (in our cases, the average size was 3.0 × 8.0 cm), and the dura opened. The target artery is then sewn to the dura with a 10-0 Prolene suture. The bone flap is replaced after cutting out entry and exit sites for the envisage artery [10]. In select patients, arachnoid dissection was made over the region of infarct.

Clinical Follow-Up
After discharge, the long-term outcome was ascertained through clinical visits, telephone, or letter interview. The overall clinical outcomes were divided into 4 categories: (1) excellent, where the preoperative symptoms (such as TIAs or seizures) had totally disappeared without fixed neurological deficits; (2) good, where the symptoms had totally disappeared but the mild neurological deficits remained; (3) fair, where the symptoms persisted albeit less frequently, and (4) poor, where the symptoms remained unchanged or worsened. Also we evaluated the long-term outcome using the stroke status, and a modified Rankin Scale was used to determine the neurological functional outcome [11]. In patients whom we were not able to contact or from whom we obtained no actual data, features and long-term outcome were determined from the last clinical visit.

Postoperative stroke was defined as new neurological deficits lasting 24 h or longer after revascularization surgery and associated with a new infarct or hemorrhage on MR or CT imaging in the first 30 days after the revascularization procedure.

The development of collateral circulation of the middle cere-

Statistical Analysis
Categorical variables were analyzed using the Chi-square test. The clinical outcome was dichotomized into favorable (excellent and good outcomes) and unfavorable (fair and poor outcomes),

Materials and Methods

Patient Selection
We identified all consecutive patients with MMD treated by EDAS at the neurological department at the Department of Neurosurgery, 307 Hospital PLA, Beijing, China, from 2002 through 2010. Diagnostic criterion of MMD is that cerebral angiography or MRA must show at least the following findings: (1) Stenosis or occlusion of the terminal portion of the intracranial internal carotid artery or proximal portions of the anterior and/or the middle cerebral artery. (2) Abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase. (3) Bilaterality of findings (1) and (2) [3]. 24 patients presenting with unilateral MMD were included in the study. 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.

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We used the logistic regression model to estimate the impact of preoperative and operative clinical factors on the surgical outcome. The risk of subsequent stroke was determined using the Kaplan-Meier method. Differences were considered statistically significant at p < 0.05. All analyses were carried out with the use of SPSS software for Windows (release 13.0).

Results

Demographics and Clinical Presentation

Between January 2002 and January 2010, a total of 288 pediatric patients underwent 512 revascularization procedures. The mean (range) age at symptom onset was 8.0 (0.5 to 17.9) years. There were 142 females and 146 males. The ratio of female to male patients was 1:1. In our cohort, TIA was the most common initial symptom (61.4%, table 1). The others were infarction (14.9%), headache (12.8%), hemorrhage (4.2%), seizure (2%), and syncope (0.7%). The majority of patients presented with Suzuki Angiographic stage 4 or 5 (62.4%) and 91.7% of patients had bilateral disease. The incidence of familial occurrence was 9.4% (27/288).

For the patients with unilateral lesions, the mean (range) age at symptom onset was 9.0 (2.0 to 16.6) years. There were 9 females and 15 males. The initial symptoms were TIA (50%), infarction (19.2%), headache (30.7%). The Suzuki Angiographic stage was 1 (16.7%), 2 (16.7%), 3 (20.8%), 4 (16.7%), 5 (16.7%), and 6 (12.5%). The incidence of familial occurrence was 16.7% (4/24).

Surgical Treatment

Of the 288 pediatric patients received neurosurgical revascularization procedures, 202 were bilateral. A total of 512 EDAS procedures were performed, including 23 EDAS using the occipital artery as donor vessel. The mean age at the first operation was 10.5 years (range 0.9–18 years). Postoperative TIA or infarctions of variable size were the most clinically relevant complication and occurred in 14 cases (4.8% per patient; 2.7% per operation) after 512 operations (mean, 4.9 days; range, 0–16 days). Notably, 66% of them improved to normal neurological status during follow-up. The other complications were: subdural hematoma (1.3%), epidural hematoma (1.0%), seizure (0.3%), and subcutaneous effusion (0.3%). All patients with TIA made a full recovery when examined 6 months after surgery. Among these patients, no patient died due to ischemic or hemorrhagic complications. Of the 9 patients suffering a new stroke, 4 patients were independent with regard to their functional outcome according to a modified Rankin Scale (independent; grades 0, 1, and 2) at final follow-up.

Table 1. Clinical features of 302 pediatric patients with moyamoya disease

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Number of patients (n = 288)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8.0 (range 0.5 to 17.9)</td>
</tr>
<tr>
<td>Female</td>
<td>142 (49.3%)</td>
</tr>
<tr>
<td>Familial occurrence</td>
<td>27 (9.4%)</td>
</tr>
<tr>
<td>Initial symptoms</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>183 (61.4%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>43 (14.9%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>12 (4.2%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Bilateral lesions</td>
<td>264 (91.7%)</td>
</tr>
<tr>
<td>PCA involvement</td>
<td>117 (40.6%)</td>
</tr>
<tr>
<td>Suzuki angiographic stage</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (2.8%)</td>
</tr>
<tr>
<td>2</td>
<td>25 (8.3%)</td>
</tr>
<tr>
<td>3</td>
<td>69 (23.9%)</td>
</tr>
<tr>
<td>4</td>
<td>86 (29.8%)</td>
</tr>
<tr>
<td>5</td>
<td>65 (22.6%)</td>
</tr>
<tr>
<td>6</td>
<td>35 (12.2%)</td>
</tr>
</tbody>
</table>

The occurrence of postoperative infarction as a complication was associated with unfavorable functional outcome (OR, 6.38; 95% CI, 3.22–18.21; p < 0.001).

Long-Term Clinical Outcome

We followed the patients in this series for between 36 months and 127.8 months after surgery (median follow-up period 52.3 months). The overall clinical outcome was excellent in 67.4%, good in 16.8%, fair in 12.1%, and poor in 3.7% of the total patients, and excellent in 65.4%, good in 15.4%, fair in 19.2%, and poor in 0% of the patients with unilateral lesions. Therefore, 84.2% of the patients had a favorable clinical outcome (excellent and good). Overall, patients experienced a significant clinical improvement. A significant reduction in TIAs was observed after treatment. Of the 177 patients presenting with TIAs, 93.2% (165/177) were TIA free at the last follow-up. A similar effect was observed in patients presenting with headaches. Of the 37 patients presenting with headaches, preoperative headache disappeared in 73% of the patients at the last follow-up.

Univariate logistic regression analyses of the preoperative clinical variables showed that older age of symptom onset (odds ratio [OR], 0.82; 95% confidence interval [CI], 0.74–0.86; p < 0.001) was associated with a favorable
clinical outcome. On the contrary, the fact that patients were male (OR, 1.89; 95% CI, 0.99–3.75; p < 0.05), presence of infarction (OR, 2.20; 95% CI, 1.03–4.43; p < 0.05), and postoperative ischemic events (OR, 6.12; 95% CI, 2.16–19.02; p = 0.001) were identified as predictors of unfavorable clinical outcome (table 2). Multivariate logistic regression analyses of the preoperative clinical variables showed that postoperative ischemic events (OR, 5.07; 95% CI, 1.700–16.12; p = 0.006) was identified as predictors of unfavorable clinical outcome, while older age of symptom onset odds ratio [OR], 0.82; 95% confidence interval [CI], 0.74–0.86; p < 0.001 was associated with a favorable clinical outcome (table 3).

A total of 20 strokes occurred in 17 patients during follow-up, one (n = 13) or a second (n = 2) ischemic stroke in 15, hemorrhage stroke in 1, ischemic stroke and a second hemorrhage stroke in 1. No stroke occurred in patients with unilateral lesions. In the first 2 years after surgery, the patients experienced 17 ischemic and 1 hemorrhage strokes, including 10 postoperative strokes; later than 2 years after surgery, they experienced 1 ischemic and 1 hemorrhage strokes. There was a significant difference between the frequency of strokes in the first 2 years after surgery and thereafter (p < 0.01).

The Kaplan-Meier estimate of postoperative or subsequent strokes was 5% in the first 2 years for all patients treated with surgical revascularization. The 5-year-Kaplan-Meier risk of recurrent stroke was 9% after surgery for all patients treated with surgical revascularization (fig. 1).

Actual follow-up information on disability and functional status was available for 259 of 288 pediatric patients (89.9%). The outcome of the other 29 surviving patients was determined at the point of the final clinical visit.

Two patients died during follow-up. The causes of death were hemorrhage in one case, unknown causes in another. Of the 286 surviving patients, 249 (86%) had no disability (modified Rankin Scale of 0 and 1), 31 (11%) had mild or moderate disability but were able to walk (modified Rankin Scale of 2 or 3), and 6 (2%) were severely disabled or unable to walk (modified Rankin Scale of 4 or 5).

![Fig. 1. KM plot for stroke-free survival after surgery for pediatric patients treated with surgical revascularization.](image-url)
Follow-Up Arteriographic Findings

Cerebral arteriography was performed six months postoperatively to assess the efficacy of the synangiosis and to guide subsequent management. Although we request six-months follow-up arteriograms in all of our patients, the studies were refused by some families or could not be obtained in others because of economic or other considerations. The follow-up angiogram was done after the EDAS operation in 182 hemispheres (mean, 7.2 months; range, 1.5–39 months). Forty-three percent of the 182 hemispheres studied were classified as Grade A collateral circulation, 34% as Grade B, and 17% as Grade C.

Discussion

MMD is a chronic cerebrovascular disorder mainly found in Asia, especially in Japan, South Korea, and China. 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 [6, 13–17]. Genetic background may explain the high prevalence of MMD among East Asians and its low prevalence among Caucasians [18]. One of the well-known specific features of MMD is its pattern of age distribution, in adults and children, with a higher incidence in childhood [6, 17, 19, 20]. In children, MMD frequently manifests itself as ischemic symptomatology, especially transient ischemic attack (TIA) that is provoked by hyperventilation. Cerebral perfusion gradually decreases as the disease progresses, often leading to cerebral infarction. The benefits of revascularization surgery, whether direct or indirect, have been well established in MMD patients with ischemic symptoms.

In the present study, we describe pediatric MMD in a consecutive series of patients treated from 2002 through 2010 at a single institute. Despite the varied clinical associations observed in this series, the modes of presentation, age at onset of symptoms, familial occurrence were similar to those reported in the Japanese and South Korean literature [17, 19, 21–23]. However, the ratio of female to male patients was 1:1 by chance in our Chinese cohort. This ratio is similar to the report form Nanjing area [6] and Taiwan [24]. The results suggest that there is no difference in gender distribution of MMD in China, while reports from Japan, South Korea, the United States, and Europe showed female predominance. The result may be due to racial difference between Chinese Han and other races. We believe that our series, the largest reported in Chinese hemisphere, is representative of the wide spectrum of pediatric cases involving MMD.

Currently, there is no definitive medical treatment to halt the progression or stabilize the course of MMD. The main goal of surgical treatment in MMD is reversal of cerebral ischemia and protection of the brain from infarction. The main surgical treatment in MMD is revascularization through the cerebral cortical vessels. A direct (direct anastomosis of scalp arteries and cerebral cortical arteries) or indirect (insertion of a scalp or muscle layer onto the surface of the brain to promote ingrowth of blood vessels into the ischemic brain) revascularization method, or a combination of both is performed to increase the cerebral blood flow (CBF). In children, direct revascularization is frequently technically not feasible, whereas the response to indirect revascularization is excellent, although 1 or 2 weeks are required for stabilization of symptoms. Although objective evidence from randomized controlled clinical trials suggesting improved function following these procedures is still lacking, several studies examining the long-term outcome in children with MMD following revascularization surgery strongly suggest that surgical revascularization improves cerebral hemodynamics and reduces the incidence of subsequent ischemic events [21–23, 25–28]. Similar to previous studies, TIAs rapidly decrease or disappear and strokes rarely recur after surgery in pediatric patients of our cohort.

The indirect revascularization technique that is most commonly used to treat MMD in children is the EDAS procedure. The incidence of postoperative complications was 4.2% (6.8% of patients). Our results are comparable to most large studies, with perioperative complications between 3.5 and 7.7% per surgical hemisphere [25, 27, 29–31].

Previous studies have identified some prognostic factors for pediatric MMD outcome after revascularization operation including preoperative multiple cerebral infarctions, early onset at a young age, high Suzuki stages on cerebral angiography, decreased vascular reserve, the surgical procedure itself, and perioperative ischemic events [10, 13, 21, 25, 27, 29–31]. Our study showed that the younger age of symptom onset and postoperative ischemic events were identified as predictors of unfavorable clinical outcome. Kim et al. found 39% of patients less than 3 years of age with MMD experienced additional infarctions while awaiting surgery and preoperative clinical status deteriorated rapidly among these patients [32]. Furthermore, the subsequent preoperative infarction could have been avoided with early surgical treatment. Therefore, the clinical course for those younger patients was aggressive, and early diagnosis and active sur-
gical treatment are essential for the treatment of younger patients with MMD. Surgery-related ischemic events were the most common perioperative complications. They were closely related to an unfavorable clinical or functional outcome. Therefore, careful attention should be paid to maintaining adequate hemodynamic status during the perioperative period [21, 33–35].

The main goal of revascularization surgery in patients with MMD remains the prevention of future ischemic and hemorrhagic strokes and, potentially, limitation of disease progression. Previous studies have described an inevitable disease progression (without surgery) in 23.8% [36] and 38.9% [37] of patients. Equivocal or mild contralateral disease was the strongest predictor of disease progression [36]. If left untreated, the angiographic process and clinical symptoms invariably progress, leading to clinical deterioration and possible irreversible neurological deficits. In the present study, the cumulative 5-year Kaplan-Meier risk of perioperative or subsequent stroke was 9%. Our surgical study was comparable to the results of recent studies from the United States and Europe [13, 15, 27, 38].

Overall, 86% of patients had an independent life with no significant disability (modified Rankin Scale 0 or 1). The patients also reported increased energy level and an increased ability to concentrate. The long follow-up period and complete follow-up data in this series allow us to conclude that effective revascularization surgery plays a significant role in halting neurological deterioration in a majority of patients.

There are certain limitations to this study that should be noted. First, the present study is a nonrandomized historical cohort study. However, it is ethically undesirable to perform randomized clinical trials to confirm the beneficial effects of surgical revascularization on subsequent ischemic stroke in MMD, because a benefit of surgery for the ischemic type of MMD has been established [3, 17, 23, 28, 39–43]. Second, because of the insufficient postoperative neuropsychological assessment, we have no definite data on those topics in our patients. Future studies using standardized postoperative neuropsychological testing will be necessary to clarify these issues.

Disclosure Statement

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