Clinical features, surgical treatment, and long-term outcome in adult patients with moyamoya disease

Clinical article

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Object. The object of this study was to report the clinical features, surgical treatment, and long-term outcomes in adults with moyamoya phenomenon treated at a single institution in the US.

Methods. Forty-three adult patients with moyamoya disease (mean age 40 ± 11 years [SD], range 18–69 years) were treated with encephaloduroarteriosynangiosis (EDAS). Neurologists examined patients pre- and postoperatively. Follow-up was obtained in person or by structured telephone interviews (median 41 months, range 4–126 months). The following outcomes were collected: transient ischemic attack (TIA), infarction, graft collateralization, change in cerebral perfusion, and functional level according to the modified Rankin scale (mRS). Kaplan-Meier estimates of infarction risk were calculated for comparison of surgically treated and contralateral hemispheres.

Results. The majority of patients were women (65%), were Caucasian (65%), presented with ischemic symptoms (98%), and had bilateral disease (86%). Nineteen patients underwent unilateral and 24 patients bilateral EDAS (67 treated hemispheres). Collateral vessels developed in 50 (98%) of 52 hemispheres for which imaging was available and there was evidence of increased perfusion on SPECT scans in 41 (82%) of the 50 hemispheres evaluated. Periprocedural infarction (< 48 hours) occurred in 3% of the hemispheres treated. In the follow-up period patients experienced 10 TIs, 6 infarctions, and 1 intracranial hemorrhage. Although the hemisphere selected for surgery was based upon patients’ symptoms and severity of pathology, the 5-year infarction-free survival rate was 94% in the surgically treated hemispheres versus < 36% in the untreated hemispheres (p = 0.007). After controlling for age and sex, infarction was 89% less likely to occur in the surgically treated hemispheres than in the contralateral hemispheres (hazard ratio 0.11, 95% CI 0.02–0.56). Thirty-eight (88%) of 43 patients had preserved or improved mRS scores, relative to baseline status.

Conclusions. In this mixed-race population of North American patients, indirect bypass promoted adequate pial collateral development and increased perfusion in the majority of adult patients with moyamoya disease. Patients had low rates of postoperative TIs, infarction, and hemorrhage, and the majority of patients had preserved or improved functional status. (DOI: 10.3171/2009.3.JNS08837)

Key Words • indirect bypass • encephaloduroarteriosynangiosis • moyamoya disease • outcome • stroke

MOYAMOYA disease is a chronic cerebrovascular disorder defined by progressive occlusion of the intracranial vessels. The stenosis begins with the intracranial carotid arteries and may progress to involve the anterior, middle, and posterior cerebral arteries. As these arteries gradually stenose, a collateral network of capillaries develops at the base of the brain, giving rise to the characteristic reticulate (“puff of smoke”) appearance on angiography.

Abbreviations used in this paper: CBF = cerebral blood flow; EDAS = encephaloduroarteriosynangiosis; MCA = middle cerebral artery; mRS = modified Rankin Scale; PCA = posterior cerebral artery; STA = superficial temporal artery; TCD = transcranial Doppler; TIA = transient ischemic attack.

In Asian populations, moyamoya disease has a well-defined phenotype. The disease has a bimodal age of presentation, with children developing ischemia secondary to inadequate collateral vessels and adults presenting with intracranial hemorrhage due to rupture of fragile collateral vessels.25,27 A number of studies have provided evidence that moyamoya disease in the US may represent a different phenomenon:2,4 Patient ethnicities are in proportion to the ethnicities of people in the region of diagnosis, and adult patients present with ischemic symptoms rather than intracranial hemorrhage.

Direct superficial temporal artery (STA) to middle cerebral artery (MCA) bypass surgery has been used successfully to augment collateral blood flow in patients with moyamoya disease for over 30 years.10,12,14,18,19 Direct STA-MCA bypass, however, can be difficult in children.
Indirect bypass for adult moyamoya disease

because of both the size and progressive occlusion of the MCAs. In contrast, encephaloduroarteriosynangiosis (EDAS) is a method of indirect bypass and cerebral revascularization that has been shown to be beneficial in this patient population. This operative technique is also considered easier, safer in patients with serious medical comorbidities, and feasible in patients with inadequate recipient or donor artery grafts. There have only been a few small case series case, however, in which authors have reported on this operative technique in an adult population (> 18 years of age). \(^4,5,8,21,24\)

To this end, we present our institutional experience using EDAS for the treatment of adult patients with moyamoya disease. The primary goals of our study were: 1) to elucidate the demographic characteristics, presentation, and natural history of our patients to determine if they differed from the Asian disease phenotype; 2) to determine the rates of postoperative and long-term deficits; 3) to evaluate the growth of collateral vessels and alterations in perfusion after surgery; 4) to calculate the follow-up rates of TIA, stroke, intracranial hemorrhage, and seizures; and 5) to determine how surgery and disease progression affect functional independence.

### Methods

**Patient Population and Management Protocol**

From November 1997 to September 2007, 43 patients with symptomatic moyamoya disease were treated with 67 indirect bypass operations at Columbia University Medical Center. All patients provided consent in this institutional review board–approved study. All patients were examined by a neurologist immediately prior to and after surgery. Patient evaluation included assessment of neurological status, CT, MR imaging, digital subtraction angiography, and TCD ultrasonography with CO, reactivity or SPECT with acetazolamide challenge. The patients were classified according to the Suzuki and Takaku staging (Table 1).

Baseline epidemiological information about moyamoya syndrome risk factors was obtained, including history of vasculitis, neurofibromatosis, tuberous sclerosis, retinitis pigmentosa, fibromuscular dysplasia, pseudoxanthoma elasticum, Fanconi anemia, antiphospholipid syndrome, Down syndrome, rheumatoid arthritis, other collagen vascular disease, head trauma, meningitis, sickle cell disease, head, neck or skull radiation, and family history of moyamoya disease. Baseline stroke risk factors were assessed, and patients with a diagnosis of arteriosclerosis determined through patient history, presence of athero-sclerosis in extracranial areas, and angiographic changes were excluded. \(^13\) Patients were also excluded if they had any disease other than moyamoya disease that might be responsible for the observed vasculopathy.

Patients with active TIAs or strokes were followed up until they had gone without new ischemic events for at least 5 weeks before receiving operative intervention, but all patients were symptomatic within the 3 months prior to surgery. Intractable TIAs were defined as > 5 episodes of reversible focal symptoms. Stroke was defined as a new neurological deficit that persisted for more than 24 hours. Infarction was defined by any new infarction on follow-up radiographic imaging regardless of the presence of new neurological deficit.

After discharge, long-term outcomes were ascertained through either in-person follow-up or a structured telephone interview at a median follow-up of 41 months (range 4–126 months). Neurological outcomes were classified by the mRS. Any postoperative worsening of the patients’ mRS score (relative to the preoperative baseline) was coded as “new neurological deficit” as previously defined. New neurological deficits were classified as “disabling” when mRS scores were 3, 4, or 5.

Cerebral blood flow was evaluated by SPECT scan after intravenous administration of 21 mCi of techne-
tium-99m–HMPAO, and CBF reserve was evaluated with acetazolamide challenge. Patients were followed up with angiography when possible, starting 6 months after EDAS and with SPECT and acetazolamide challenge or TCD ultrasonography and CO2 challenge 3 months after surgery and at 3- to 12-month intervals thereafter.

Surgical Treatment

Sixty-seven EDAS surgeries were performed in 43 patients, using either the STA or occipital artery. Briefly, EDAS involves placement of an external carotid artery branch beneath the arachnoid mater in ischemic territories. Most commonly, the STA is used. In certain circumstances, depending on the territory at risk, the occipital artery may be used. Preoperatively, Doppler ultrasound examination is used to map the course of the target artery. Intraoperatively, the target artery is dissected completely free, a craniotomy is performed, and the dura mater is opened. The target artery is then sewn to the pia/arachnoid with a 10-0 Prolene suture under microscopic vision after extensive arachnoid dissection. The bone flap is replaced after cutting out entry and exit sites for the donor artery. In selected patients, multiple bur holes with arachnoid and dural incisions were made over the region of interest without vessel transplantation.

Additionally, 15 of the 43 patients received bur holes with arachnoid and pial dissection to increase blood flow to the regions of the anterior cerebral arteries or posterior circulation not supplied by the EDAS procedure. The EDAS and bur holes were carried out on the symptomatic side and in the distribution of perfusion failure as demonstrated by SPECT or TCD ultrasonography.

Intraoperative Doppler ultrasonography was used to demonstrate graft patency. Patients received outpatient follow-up, and follow-up imaging was performed with SPECT scan, TCD ultrasonography, angiography, CT, or MR imaging as clinically indicated. Postoperatively, medical management was optimized to treat vascular risk factors, and patients were treated with antiplatelet therapy (aspirin or clopidogrel). Blood pressure was managed conservatively to avoid relative hypotension and decreased CBF in hemodynamically challenged patients.11

Statistical Analysis

Analysis was carried out using an unpaired t-test and the chi-square and Fisher exact tests as appropriate. Kaplan-Meier infarction risk was calculated for the incidence of any periprocedural infarction and infarction in EDAS-treated hemispheres during the follow-up period relative to the incidence of infarction in hemispheres that were not treated with EDAS. The log-rank test was used to assess differences in survival curves, and Cox regression was used to assess hazard ratios. Probability values ≤ 0.05 were considered statistically significant.

Results

Forty-three patients underwent indirect bypass with EDAS and/or bur holes for the treatment of symptomatic moyamoya disease. The study cohort included 15 men and 28 women with a mean age of 40 ± 11 years (SD) at the time of surgery (Table 1). Patient ethnicities included Caucasian (65%), African-American (5%), Latino (9%), and Asian (21%). Eight (19%) and 19 patients (44%) had a history of receiving anticoagulation and antiplatelet medications, respectively, to treat moyamoya disease. Three (11%) of 28 women had a history of oral contraception use.

The majority of patients presented with ischemic symptoms. All patients had a history of TIA (58%) or stroke (60%) except for 1 patient who presented with intracranial hemorrhage. No patient was treated with indirect bypass on an emergency basis (< 5 weeks from last event), and in patients undergoing > 1 operation, operations were separated by a minimum of 3 weeks. Prior to 23 (34%) of the 67 procedures, patients had significant disability (mRS > 2, Table 2).

The majority of patients presented with Suzuki and Takaku Angiographic Stage 3 (77%), and 86% of patients had unilateral disease. All patients with unilateral disease demonstrated formation of moyamoya collateral vessels in conjunction with occlusion or stenosis of an intracranial portion of an internal carotid artery. Sixteen percent of patients had aneurysms on diagnostic angiograms, of which 57% were in the posterior circulation. All patients had hypoperfusion on baseline SPECT scans and decreased reserve during CBF challenge.

The median duration of long-term follow-up was 41 months (range 4–126 months). In 67 operations there were a total of 12 complications in 10 patients occurring prior to hospital discharge (Table 3). Five patients experienced new neurological deficits prior to discharge, with 4 of these deficits being transient and 1 persisting on follow-up. There were 2 (3%) infarctions prior to discharge (both < 48 hours from the time of surgery).

Following 50 of the 67 EDAS operations, patients underwent 1 or more SPECT studies starting 3 months after surgery. In 41 (82%) of the hemispheres there was increased perfusion to previously hypoperfused areas, in 5 (10%) there was no change in perfusion, and in 4 (8%) demonstration of moyamoya collateral vessels.

TABLE 2: Baseline and postoperative mRS scores in 43 patients undergoing 67 hemispheric procedures

<table>
<thead>
<tr>
<th>Score</th>
<th>Baseline</th>
<th>Postop Discharge</th>
<th>Long-Term FU</th>
</tr>
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<tbody>
<tr>
<td>0–1</td>
<td>14 (20)</td>
<td>30 (45)</td>
<td>39 (58)</td>
</tr>
<tr>
<td>2</td>
<td>30 (45)</td>
<td>20 (30)</td>
<td>16 (24)</td>
</tr>
<tr>
<td>3</td>
<td>16 (25)</td>
<td>12 (18)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>4</td>
<td>7 (10)</td>
<td>5 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>death</td>
<td>0</td>
<td>0</td>
<td>2 (3)†</td>
</tr>
</tbody>
</table>

* Values represent numbers of procedures (%). Abbreviation: FU = follow-up.
† One patient had decline in mRS score due to comorbidities unrelated to moyamoya disease progression.
there was decreased perfusion. Follow-up images were available for 52 of the 67 procedures. In 50 (96%) of these 52 hemispheres for which imaging studies were available, the images showed collateral formation in the surgical territory.

Seven patients experienced seizures after surgery. One patient experienced a seizure after a meningeal wound infection, and 3 patients with a prior history of seizures had a single seizure during the follow-up period. In the follow-up period (hospital discharge to time of event or censor), there was 1 intracranial hemorrhage and there were 10 TIA and 6 infarctions. There were no new infarcts from the time of discharge to the end of the first year of follow-up. Two infarctions occurred ipsilateral to EDAS operations and 4 infarctions occurred in the contralateral hemisphere. The 5-year infarction-free survival rate, including all perioperative infarcts, was 70% (Fig. 1).

There was a significant difference between cumulative infarction curves when comparing operative and contralateral hemispheres (p = 0.007, Fig. 2). The 5-year infarction-free survival rate was 94% (95% CI 0.84–0.98) in the surgically treated hemispheres (including all perioperative infarcts) versus < 36% (95% CI 0.15–0.78) in the contralateral hemispheres. After controlling for age and sex, we found that infarction was 89% less likely to occur in one of the surgically treated hemispheres than in a contralateral hemisphere (hazard ratio 0.11, 95% CI 0.02–0.56).

Patients had significant disability (mRS > 2) at discharge after 17 (25%) of the 67 surgical procedures and at long-term follow-up after 13 (18%, Table 2). From the time of admission to follow-up, 4 (9%) of 43 patients had a decline in their functional independence according to the mRS due to moyamoya disease progression. One died as a result of a stroke and 1 patient died due to unrelated comorbidities. Thirty-eight (88%) of 43 patients had improvement or no change in functional independence.

**Discussion**

Moyamoya disease is rare outside Asia, but increased awareness regarding this condition has led to its characterization in many other countries. In this study we have found that: 1) indirect bypass promotes adequate development of pial collateral vessels and increased perfusion in adult patients, and 2) patients undergoing indirect bypass have acceptably low rates of neurological deficits, TIAs, stroke, infarction, and hemorrhage, with functional independence being preserved or improved in the majority of cases.

The racial demographics of our cohort were roughly representative of the northeastern US, with 65% of patients being Caucasian, 5% African-American, 9% Latino, and 21% Asian. The majority of patients in our cohort were women between the ages of 30 and 50, which is consistent with prior studies. Although a bimodal age distribution has been demonstrated in Asia, with children primarily suffering from ischemic symptoms and adults experiencing intracranial hemorrhage, the majority of our adult cohort of surgically treated patients presented with ischemic symptoms (98%), and only a small num-

**TABLE 3: Patient outcomes after 67 operations**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Ops (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>postop complications†</td>
<td></td>
</tr>
<tr>
<td>new focal deficit due to op</td>
<td>5 (7)</td>
</tr>
<tr>
<td>persistent focal deficit due to op on FU</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>postop infarction‡</td>
<td>2 (3)</td>
</tr>
<tr>
<td>wound infection/granuloma</td>
<td>2 (3)</td>
</tr>
<tr>
<td>hygroma§</td>
<td>3 (4)</td>
</tr>
<tr>
<td>CSF leak</td>
<td>2 (3)</td>
</tr>
<tr>
<td>FU events†</td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>10 (7)</td>
</tr>
<tr>
<td>infarction</td>
<td>6 (9)</td>
</tr>
<tr>
<td>infarction ipsilateral to op</td>
<td>2 (3)</td>
</tr>
<tr>
<td>infarction within 1 yr after op</td>
<td>0</td>
</tr>
<tr>
<td>intracranial hemorrhage</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>seizure</td>
<td>7 (10)</td>
</tr>
<tr>
<td>perfusion</td>
<td></td>
</tr>
<tr>
<td>increased</td>
<td>41 of 50 (82)</td>
</tr>
<tr>
<td>decreased</td>
<td>4 (8)</td>
</tr>
<tr>
<td>no change</td>
<td>5 (10)</td>
</tr>
<tr>
<td>collateral formation</td>
<td>50 of 52 (96)</td>
</tr>
<tr>
<td>function**</td>
<td></td>
</tr>
<tr>
<td>improved independence or no change</td>
<td>38 of 43 (88)</td>
</tr>
<tr>
<td>decreased independence</td>
<td>5 (12)††</td>
</tr>
</tbody>
</table>

* Median follow-up duration 41 months (range 4–126 months).
† Less than 48 hours after surgery.
‡ Postoperative infarctions account for 2 of 5 of the new focal deficits due to surgery. Only 1 patient had persistent deficit on long-term follow-up.
§ One of 2 hygromas account for 1 of the 5 new focal deficits due to surgery.
¶ More than 48 hours after surgery.
** Functional outcome according to the mRS.
†† One patient had decline in independence due to unrelated comorbidities.
ber of patients had a history of intracranial hemorrhage (12%). Other studies have reported similar discrepancies, with only 13–20% of adult moyamoya patients in the US presenting with intracranial hemorrhage\textsuperscript{2,9} versus more than 60% in Asian populations.\textsuperscript{9,29} This may be the result of delayed arterial narrowing and collateral circulation formation in patients outside of the Eastern hemisphere. Although possibly due to referral and/or selection bias, our patient demographic data support the hypothesis of a separate disease phenotype in North American moyamoya disease patients.\textsuperscript{2,4}

Although revascularization procedures are frequently performed in patients with moyamoya disease, the safety and efficacy of these techniques remain largely unproven. While the authors of many studies recommend direct bypass or a combination of indirect and direct bypass in adult moyamoya patients,\textsuperscript{4,8,22,24} EDAS is the preferred surgical revascularization procedure at our institution. Currently, there is no evidence to support the notion that there is a superior method of bypass in adult moyamoya disease patients.\textsuperscript{30}

Despite the fact that our patients often had relatively severe presentations (Table 2), the incidence rates for new neurological deficit and persistent deficit on long-term follow-up were 7 and 1.5%, respectively. These results compare favorably with other studies in which the rates of periprocedural infarction range from 4 to 31%, although follow-up was limited in some of the previously published studies.\textsuperscript{2,4,5,8,10,18,20,24} Some authors have noticed an increased incidence of early ischemic injury in patients treated with indirect bypass procedures relative to those treated with direct bypass surgery, possibly the result of delayed revascularization and collateral growth. We did not observe any such increase in our study; further, we believe that reversal of flow in critical perforating vessel segments due to direct or a combination of direct and indirect bypass procedures may result in ischemia, poor collateral growth, and worse outcome.

In our cohort there were low rates of new focal neurological deficits, TIAs, strokes, infarction, intracranial hemorrhages, and seizures. Moreover, these conditions resolved in the majority of patients. The 5-year infarction-free rate was >94% in surgically treated hemispheres versus <50% in contralateral hemispheres. This translates into an 89% infarction risk reduction following surgical intervention (hazard ratio 0.11, 95% CI 0.02–0.56). It is important to note that the surgically treated side is determined on the basis of patient symptoms, CBF studies, and angiographic findings. Thus, patients underwent surgery on the side associated with more severe symptoms and in which there was a higher risk of future cerebrovascular accidents. Despite the increased number of patients with bilateral disease (86%) and worse clinical grades of patients on presentation, demonstrated outcomes are more favorable than those reported in the literature. For comparison, a previous study involving medical management of moyamoya disease demonstrated 5-year stroke-free survival rates of only 35 and 18% in patients with unilateral and bilateral disease, respectively. Only randomized clinical trials can determine whether surgery or medical therapy is optimal, but such trials are likely to be difficult to perform in patients with a rare condition like moyamoya disease.

In our study, increased perfusion was seen after 82% percent of the procedures for which follow-up imaging studies were available, and augmented collateral circulation was seen after 96% of the procedures for which follow-up imaging was available. These favorable results may be attributable to a large craniotomy planned according to preoperative CBF pattern, as well as wide and extensive opening of the dura and arachnoid mater. We also believe that a CBF pattern indicating misery perfusion is a prerequisite for excellent revascularization with indirect bypass. Authors of other small case series involving adult patients have reported similar results.\textsuperscript{3} It has been noted in previous studies that EDAS is limited in comparison with direct or combination direct and indirect bypass in its ability to reperfuse the anterior or posterior circulation.\textsuperscript{24} In treating patients with moyamoya disease, we placed additional bur holes with extensive dural and arachnoid dissection to increase collateral blood flow, a maneuver that has been supported by prior investigations.\textsuperscript{3}

It appears that collateral formation and augmentation of perfusion occur readily in patients with moyamoya disease following indirect bypass. In contrast, we have found that EDAS is not beneficial in inducing collateral vascular growth in patients with symptomatic intracranial atherosclerotic disease without moyamoya disease.\textsuperscript{13} Patients with atherosclerotic disease may have impaired angiogenesis secondary to reduced endothelial repair capacity. It is known, for example, that endothelial progenitor cells, which have been characterized as (KDR+)/CD133+ cells,\textsuperscript{1} are reduced in patients with atherosclerotic risk factors and cardiovascular disease. For these reasons, patients should receive a thorough workup to exclude alternative diagnoses of intracranial vascular occlusion.

A number of researchers have noted that it is particularly difficult to judge outcome following surgery in patients with moyamoya disease, as surgery is a form of palliative care in a disease with poor natural history.\textsuperscript{29} Furthermore, studies have not used standardized outcome measures to assess patients’ condition on presentation and
on long-term follow-up. Despite the poor clinical state of patients in this study, only 4 patients had a decline in their functional state (mRS score) due to disease progression over a median follow-up period of 41 months. This provides further evidence regarding the benefits of surgery in this patient population.

It is important to note inherent limitations of our outcome data. The mRS does not measure higher cortical function and postoperative cognitive decline. This must be taken into account when considering operative morbidity. Some authors have noted a subtle decline in neurocognitive function in moyamoya disease patients even in the absence of obvious ischemic or hemorrhagic events. Neuropsychological testing following surgery in moyamoya disease is critical to accurate outcome assessment and should be integrated into future clinical trials. Importantly, referral and selection bias cannot be excluded in this single-institution, single-surgeon case series.

Conclusions

This study provides evidence for a different moyamoya disease phenotype in North American adults. Patients are primarily middle-aged women presenting with ischemic symptoms, and ethnicities reflect those of the regional referral base. In this population, indirect bypass promotes adequate development of pial collateral vasculature and increased perfusion. Surgery leads to a decreased incidence of TIAs, infarction, and hemorrhage, with functional independence being preserved or improved in the majority of patients.

Disclosure

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