Progression of disease in unilateral moyamoya syndrome

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Object. Progression of vasculopathy associated with moyamoya syndrome is extremely variable. The authors review their experience in patients with unilateral moyamoya syndrome to identify factors predictive of contralateral clinical and imaging-documented disease progression.

Methods. The authors reviewed the clinical and imaging records of all patients with moyamoya syndrome and unilateral disease who underwent cerebral revascularization surgery between January 1985 and June 2006 by using a standardized surgical procedure, pial synangiosis.

Results. Of 235 surgically treated patients with moyamoya syndrome, 33 (14%) presented with unilateral disease (4 adults and 29 children). There were 16 female and 17 male patients, with an average age of 10.4 years (26.8 years for adults and 8.1 years for children; range 1.5–39 years). Twenty patients presented with left-sided disease and 13 with right-sided disease.

The average follow-up after surgery was 5.3 years (3.1 years for adults and 5.6 years for children; range 1–16 years). During this period, 10 (30%) of 33 patients progressed to bilateral disease. The mean time until disease progression was 2.2 years (range 0.5–8.5 years). Factors associated with progression in this series included contralateral abnormalities on initial angiography, previous history of congenital cardiac anomaly, cranial irradiation, Asian ancestry, and familial moyamoya syndrome. Young age at diagnosis was associated with a more rapid rate of progression (age < 7 years, 0.9 years to progression; age ≥ 7 years, 3.1 years to progression).

Conclusions. Of patients with unilateral moyamoya syndrome, 30% will have progression of arteriopathy during long-term follow-up. In this series, the average time of progression from unilateral to bilateral angiographic disease was 2.2 years. Several factors, including contralateral abnormalities on initial imaging, congenital cardiac anomaly, previous cranial irradiation, Asian ancestry, and familial moyamoya syndrome, were associated with an increased risk of progression. Patients with known unilateral angiographic disease should undergo continued monitoring by using MR imaging and MR angiography at regular intervals. Treatment with pial synangiosis is safe and confers durable protection against stroke in patients with both bilateral and unilateral moyamoya syndrome.

Key Words • moyamoya disease • moyamoya syndrome • pial synangiosis • progression • unilateral stroke

Moyamoya syndrome is a chronic occlusive cerebrovascular disorder of unknown etiology characterized by progressive stenosis of the bilateral supraclinoid ICAs, with concomitant formation of tortuous collateral arteries at the base of the brain that reconstitute distal branches of the cerebral circulation. Current nomenclature distinguishes between moyamoya disease (the idiopathic presentation of angiographic moyamoya changes in both ICAs) and moyamoya syndrome (the presentation of angiographic moyamoya changes found in association with a known pathological state [neurofibromatosis, Down syndrome, cranial irradiation, and so on] or found only to be affecting 1 side of the brain). Although the majority of patients present with disease affecting both ICAs, a substantial minority of individuals presents with only 1 side affected. Reports have indicated that up to 18% of patients with moyamoya may present with unilateral angiography-documented disease. Nevertheless, despite knowledge of this association, there are few series of patients with unilateral moyamoya syndrome reported in the literature. The natural history of progression and response to treatment of this group is not well known. We review our experience in patients with unilateral moyamoya syndrome to identify factors predictive of contralateral disease progression and to report long-term outcome of a standardized surgical treatment, pial synangiosis.

Clinical Materials and Methods

We reviewed a consecutive surgical series of patients with moyamoya syndrome who underwent pial synangiosis between January 1, 1985, and June 30, 2006, to identi-
fy all patients who presented with moyamoya syndrome and unilateral disease. All patients within this time period were included. In accordance with an institutional review board–approved protocol, the charts of these patients were retrospectively reviewed to determine age and sex at presentation, comorbid conditions, symptoms, imaging findings (including CT scanning, MR imaging, and MR angiography, and cerebral arteriography), perioperative and late complications, duration of follow-up, and long-term clinical and imaging outcomes.

### Results

#### Demographic Data

Of 235 surgically treated patients with moyamoya syndrome during the period of the study, 33 presented with unilateral disease. We defined an adult as an individual >18 years of age. Using this definition, the series included 4 adults and 29 children.

There were 16 female and 17 male patients. There were 3 female and 1 male adult patients and 15 female and 14 male pediatric patients. The mean age at presentation was 10.4 years (range 1.5–39 years). The mean age for adults was 26.8 years and that for children was 8.1 years (Table 1).

#### Findings at Presentation

##### Side of Disease

Of the 33 patients, 20 presented with left-sided disease and 13 presented with right-sided disease. When stratified by age, 2 adults presented with left-sided disease and 2 with right-sided disease. Eighteen children presented initially with left-sided moyamoya and the remaining 11 presented with disease on the right (Table 1).

##### Presenting Symptoms

The majority of patients (27 [82%] of 33) presented with symptoms consistent with chronic cerebral ischemia. These 27 patients presented with a history of transient ischemic attacks, of which completed strokes were clinically evident in 11 (40.1%). Additionally, a history of seizures was present in 2 of these 27 patients with ischemic symptoms.

Of the 6 patients without a preexisting history of chronic ischemia symptoms, 2 presented acutely, 1 with a new completed ischemic stroke and the other with an intracranial hemorrhage. The 4 remaining asymptomatic patients all had NF1; their moyamoya was detected incidentally on NF1-related cranial MR imaging studies.

##### Associated Conditions

Of the 33 patients, 4 had first-degree relatives with known diagnoses of moyamoya, 2 patients were of Asian ancestry, 3 had previously been treated with cranial irradiation for tumors, 3 had congenital cardiac abnormalities, and 3 had sickle cell disease. One of these patients had both Asian ancestry and a cardiac anomaly.

#### Preoperative Imaging and Angiographic Features

Of the 33 patients with unilateral findings, preoperative CT scans and/or MR images demonstrated the presence of previous infarction in 21 (63%). Of those without imaging evidence of stroke at presentation (12 patients), 5 had NF1 and 2 had a known family history of moyamoya.

The mean Suzuki grade[12] (a severity of arteriographic disease scale ranging from Grade 1 to 6, with 6 being the most severe) at presentation on the affected side was 3.5, with a range of 2–5. Twelve angiograms (36%) were read as normal on the contralateral side at the time of presentation, with no note of any abnormality of the nonaffected anterior or posterior intracranial vasculature. Twenty-one (64%) of the angiograms showed some abnormality present in the anterior or posterior intracranial vasculature on the nonmoyamoya side, defined as any degree of focal stenosis or vessel wall irregularity in the intracranial ICA, middle cerebral artery, anterior cerebral artery, or PCA. Normal developmental variants, such as fetal PCAs, were not categorized as abnormalities in this study.

#### Factors Associated With Progression

##### Clinical Factors

Risk factors for progression in this series included previous history of congenital cardiac anomaly (3 of 3 progressed), previous cranial irradiation (3 of 3 progressed), Asian ancestry (2 of 2 progressed) and, less notably, familial moyamoya syndrome (2 of 4 progressed). Sickle cell disease did not appear to be associated with progression (3 of 3 did not progress).

Age and sex did not predict progression, although in those patients who did develop contralateral disease, a young age at diagnosis was associated with a more rapid rate of progression (age <7 years, 0.9 years to progression and age ≥7 years, 3.1 years to progression) (Fig. 1).

##### Imaging Factors

All 10 patients who eventually developed moyamoya on the previously nonaffected side had an identified angiographic abnormality present on the asymptomatic side at the time of initial presentation. In contrast,
48% (11 of 23) who did not experience progression had an identified angiography-documented abnormality on the contralateral side at initial presentation. If a patient had an angiogram with an abnormality on the contralateral (non-moyamoya) side, there was an ~ 50% (10 of 21) likelihood that the previously unaffected side would progress to a stenosis critical enough to require surgery. None of the 12 patients who had angiograms that were read as normal on the contralateral (nonmoyamoya) side experienced progression during the follow-up period of the study.

Due to the size of the patient population, detailed statistical analysis was not possible. All diseases noted on review of systems were included in this analysis, and associations were selected based on multiple patients presenting with the same condition. Particular attention was paid to conditions previously reported to be found in association with moyamoya syndrome. 3,8,10

Treatment Procedure

All patients in this series underwent a standardized indirect cerebral revascularization procedure, pial synangiosis, to treat the affected hemisphere. 10 Patients were maintained on daily aspirin therapy postoperatively.

Surgical Complications

Of 43 operations the overall complication rate was 9.3% and the postoperative stroke rate was 4.6% (1 case each of the following: CSF leak in a patient who had undergone a previous craniotomy for craniosynostosis, superficial wound infection, stroke resulting in slurred speech, and stroke with transient expressive aphasia and weakness). Only one of these complications occurred at the time of the initial surgery (the CSF leak). Both of the strokes and the 1 superficial wound infection occurred in 3 different patients following operations on the second side for progressive moyamoya. No patient suffered a new stroke on the revascularized side at long-term follow-up. There were no cases of hematoma, perioperative seizure, or death in this series.

Follow-Up Course

The average follow-up after surgery on the initial affected side was 5.3 years (3.1 years for adults and 5.6 years for children; range 1–16 years). During this period, 10 (30%) of 33 patients experienced progression of bilateral disease (adults 50% [2 of 4] of adults and 28% [8 of 29] of children). The mean time to disease progression was 2.2 years (range 0.5–8.5 years).

The mean follow-up after surgery on the second side (for those patients who experienced progression and were treated on the contralateral side) was 4.3 years (2 years for adults and 4.6 years for children; range 11 months–12 years).

Patient Outcome

Outcomes were reviewed with an average follow-up of 5.3 years (first operation) and 4.3 years (second operation).

Clinical Outcome. Patients were evaluated clinically for deterioration of their conditions by a modified Rankin Scale score (0, no symptoms; 1, minor symptoms not affecting lifestyle; 2, minor handicap but independent in ADLs; 3, requiring some help with ADLs; 4, requiring substantial help with ADLs; and 5, totally dependent). Using this scale, 32 (97%) of 33 patients had stable or improved neurological function.

Imaging Outcome. All patients underwent postoperative CT scanning and/or MR imaging studies for review performed ≥ 1 year after the most recent surgery. Postoperative angiograms (performed ≥ 1 year after the most recent surgery) were available in 26 of 33 patients. No patient had new strokes in treated hemispheres (following hospital discharge), despite evidence of progression of moyamoya in 55% of 43 operated hemispheres.

In all patients in whom postoperative arteriography could be evaluated using the Matshushima scale 6 (Grade A indicating > two thirds of the middle cerebral artery circulation filled by the new collateral vessel), a Matshushima Grade A or B collateral vessel was seen in 75% of studies (Fig. 2). A more severe Suzuki grade at time of surgery correlated with better Matshushima grade at long-term follow-up (Table 2).
Discussion

In moyamoya syndrome, neurological status at time of treatment predicts long-term outcome, suggesting that early diagnosis and treatment are important to avoid irreversible neurological deficits.\(^6\) Children suffering from multiple strokes, particularly if they affect both hemispheres, can be severely developmentally delayed. However, patients with a low stroke burden, or strokes limited to 1 hemisphere, may have a satisfactory long-term prognosis if further infarcts can be prevented. The ability to identify factors predictive of the development of moyamoya in an at-risk population (that is, those previously treated for unilateral moyamoya at risk of developing contralateral angiographic disease) coupled with data supporting an effective treatment (surgical revascularization) could lead to better outcomes for these patients through earlier diagnosis and treatment.

Patients with unilateral moyamoya syndrome can be difficult to treat, particularly regarding predicting the likelihood of subsequent progression involving the contralateral side. The rate of progression of the vasculopathy associated with moyamoya syndrome is extremely variable.\(^1,4,7\) Here we have reviewed our experience in patients with unilateral moyamoya syndrome to identify factors which may predict a predilection for disease progression to the opposite side.

Patient Population

Similar to what has been reported by other groups, we have found that 14% of our patients with moyamoya presented with unilateral angiography–documented disease.\(^1,4,7\) We found no sex or age differences when compared with our population of patients with bilateral disease. Interestingly, we identified an increased number of pediatric patients presenting with dominant hemisphere disease (18 left vs 11 right) compared with no difference in sides in adult patients (2 left and 2 right). It is tempting to speculate that the potential effects on speech and dominant limb function caused by a stroke in the dominant hemisphere may lead to earlier diagnosis in the pediatric population because these effects may be more noticeable. In contrast, adults may be more capable of detecting or expressing concern over more subtle deficits caused by nondonor hemisphere injury than young children.

Presentation and Evidence That Imaging Surveillance Results in Earlier Detection of Moyamoya With Less Disease Burden

The majority of patients (82%) in this series presented with symptoms of chronic ischemia, including transient ischemic attacks and/or clinical evidence of infarction (40%). Other than the unilateral nature of the disease, the angiographic findings in patients with unilateral disease were indistinguishable from those seen in patients with bilateral disease. Compared with a series of patients with bilateral disease, the presence of unilateral disease does not manifest unique clinical or imaging findings beyond the obvious distinction of the one-sided involvement.\(^8\)

Severity of disease at presentation (Suzuki grade) appeared to be an important prognostic factor as we analyzed various patient subgroups. Two subgroups of patients were found to have lower Suzuki grades (less severe arterial narrowing) at time of surgery compared to the group as a whole. The first group included all patients with NF1 and unilateral disease (7 patients), who had an average presenting Suzuki grade of 2.9, in contrast to an average of 3.7 in the patients without NF1. The second group included those patients previously treated for unilateral moyamoya who subsequently progressed to needing treatment on the opposite side (10 patients). In this group, the average Suzuki grade on the second side was 2.6 compared with 3.4 in the group as a whole (and an average grade of 3.5 in the same 10 patients on the first side). The unifying theme in these 2 groups of patients is an increased frequency of radiographic surveillance. As might be expected, increased scrutiny of these groups correlates with earlier detection of disease. In the patients with NF1, who had been subjected to intracranial imaging prior to the diagnosis of moyamoya, the average age at diagnosis (6.5 years) was considerably lower than that of the group as a whole (10.4 years) adding further support to this premise.

Within the clinical subgroups of patients in this series, individuals with brain tumors, NF1, and those with known unilateral moyamoya are unique in that they are subjected to scheduled intracranial imaging. Aside from the patients with NF1, we had 2 patients with brain tumors. The patients with brain tumors but not NF1 had completed their routine imaging follow-up and were no longer undergoing periodic imaging. In these patients, the moyamoya was detected at an advanced stage. In contrast, the patients with NF1 and unilateral moyamoya were actively undergoing scheduled imaging during the time of their diagnoses. The patients with NF1 were diagnosed with moyamoya at younger ages, with lower Suzuki grades, and less than half the incidence of strokes as patients with unilateral moyamoya syndrome but not NF1. Similarly, patients with known unilateral moyamoya who were undergoing routine imaging and who subsequently experienced disease progression on the contralateral side had the second side diagnosed with a lower Suzuki grade and 6-fold lower incidence of strokes when compared with the diagnosis of the first side. Overall, patients undergoing routine surveillance neuroimaging had moyamoya diagnosed at a younger age, with fewer strokes and less severe imaging–documented disease. Taken together, this evidence supports the premise that increased imaging surveillance results in demonstrably earlier detection of moyamoya with decreased stroke risk.

Association Between Suzuki and Matsushima Grades

Interestingly, more severe Suzuki grade at time of surgery seemed to correlate with better Matsushima grade at long-term follow-up, supporting the hypothesis that increasing degrees of ischemia of the brain results in increased expression of factors conducive to angiogenesis.
(the “fertile soil” phenomenon). In this series, Matsushima Grade C collateral vessels had an average Suzuki grade of 2.8, Grade B collateral vessels had a Suzuki grade of 3.1, and Grade A collateral vessels had an average Suzuki grade of 4. As current work from our laboratory (and others) has demonstrated, patients with moyamoya have elevated levels of soluble growth factors in the CSF that may be involved in facilitating the ingrowth of collateral vessels.\textsuperscript{2,5,11}

The data from this series adds to the growing body of evidence supporting this hypothesis.

Factors Associated With Progression

One of the major concerns facing patients with unilateral moyamoya is how to address the nonaffected side. The data from this study corroborate previous reports from our group and others that many patients with unilateral moyamoya may develop disease on the nonaffected side in a very delayed fashion or not at all.\textsuperscript{1,4,7,8} Although surgical revascularization provides a clear benefit in the setting of active moyamoya, it has been our experience that it is of limited or no use in unaffected hemispheres. As such, it has not been our practice to prophylactically operate on the unaffected side in patients with unilateral moyamoya.

The ability to accurately identify patients with unilateral moyamoya who are at greater risk for developing contralateral disease would be of substantial clinical benefit. An appreciation of the expected time course for progression, coupled with knowledge of specific risk factors associated with the development of contralateral disease, would enable clinicians to more accurately design individualized follow-up strategies. Ultimately, this knowledge would enable increased numbers of patients to receive a diagnosis and be treated prior to experiencing significant strokes.

As reviewed in Results, the clinical factors that we found in association with the development of moyamoya in the nonaffected hemisphere included a history of congenital cardiac anomaly, previous cranial irradiation, Asian ancestry, and familial moyamoya syndrome. The finding of any abnormal vessels on the nonaffected side on initial imaging had a correlation with subsequent progression (10 of 10 patients who experienced progression had some type of abnormality on the contralateral side initially, vs only 11 of 23 patients who did not). In those patients with progression, a young age at diagnosis was associated with a more rapid rate of progression (age < 7 years, 0.9 years to progression and age ≥ 7 years, 3.1 years to progression).

This information would support the strategy of shorter follow-up interval (including increased frequency of imaging studies) in patients with unilateral disease presenting at a younger age (especially < 7 years) or with any of the risk factors noted earlier (particularly any abnormal findings on the vasculature of the nonaffected side). Conversely, patients without the aforementioned risk factors, patients of older age (especially adults) or patients with angiographically normal intracranial vasculature on the nonaffected side can be reassured that the likelihood of disease progression is low, although they should be cautioned that follow-up is still warranted. This finding has been suggested in other series as well, although not with the number of cases reported here.\textsuperscript{1,4}

Follow-up of patients with unilateral moyamoya with sequential imaging studies is indicated. Varying methods of follow-up have been reported at different institutions, including MR imaging, transcranial Doppler ultrasonography, perfusion studies (such as single photon emission computed tomography) or conventional angiography. It has been our practice at Children’s Hospital Boston to monitor these patients noninvasively with annual MR imaging and MR angiography studies and clinical visits as needed, with a conventional angiogram (including selective ICA and ECA injections) and a formal follow-up visit at 1 year postoperatively.

Surgical Effectiveness

In addition to identifying risk factors predictive of disease progression, this study was undertaken to evaluate the effectiveness of a specific therapeutic intervention (pial synangiosis) in this patient population. This method of indirect surgical revascularization has been the treatment of choice for patients with moyamoya by other authors, with recent publications from our group documenting the effectiveness of its use and describing the surgical technique.\textsuperscript{8,10}

In this series of patients with unilateral moyamoya, pial synangiosis was used exclusively as the method of surgical revascularization. The complication rate was low, with only 2 perioperative strokes, and both occurred in children with rapid disease progression in the unoperated hemisphere. One child had a transient CSF leak in the setting of a previous complex craniofacial surgical repair, and another had a superficial wound cellulitis that resolved with antibiotic therapy. There were no hematomas, perioperative seizures, or deaths in this series.

With an average follow up of > 5 years for the initial surgery (and > 4 years for patients undergoing a second side surgery), we observed that 96% of patients had stable or improved neurological function on long-term follow-up, despite imaging evidence of continued worsening of moyamoya arteriopathy in 55% of operated hemispheres. Other than the 2 previously described perioperative strokes, no other strokes were identified either clinically or on images in any patient. These good clinical results were concordant with the development of new collateral vessels at the pial synangiosis site, as demonstrated by postoperative imaging. In all patients in whom postoperative imaging was available, synangiosis collateral vessels were identified, with 75% of the hemispheres reported as Matsushima Grade A or B. The revascularization surgery in these patients seemed to be the major factor in preventing cerebral infarcts in the presence of worsening stenosis of major cerebral arteries.

Previous data from our institution support the practice of treating patients with moyamoya syndrome as soon as possible. Timelines of stroke in patients document that moyamoya arteriopathy is a progressive disease with cumulative morbidity and that this progression can be arrested using surgery.\textsuperscript{8} The clinical course and imaging features of the moyamoya syndrome seen in these unilateral patients appears to mirror that of idiopathic moyamoya disease, and the patients with unilateral moyamoya respond well to cerebral revascularization procedures such as pial synangiosis, just as the general moyamoya population does. Following surgery, further strokes do not occur, and good functional outcome can be anticipated in the vast majority of surgically treated patients.
To our knowledge, this is the largest series of patients with unilateral moyamoya with the longest average follow-up outside of Japan. The series further validates observations reported in smaller series, as well as providing a number of novel findings in this important moyamoya population. In particular, the importance of identifying abnormalities on the nonaffected side on the initial angiogram is a finding recognized by both our group and others. Age-dependent rates of progression (younger being faster), is also a previously reported characteristic in this population that we appreciated in our patients. Novel to our series are the data confirming the premise that increased frequency of imaging studies actually results in earlier diagnosis of moyamoya progression with decreased stroke burden. This finding has important implications not only for unilateral patients, but for all patients affected by diseases known to have an association with moyamoya, such as sickle cell disease, Down syndrome, and others. The results reported in our series lend support to the usefulness of screening for moyamoya in at-risk populations by providing evidence that increased frequency of imaging results can result in better neurological status at time of diagnosis.

Conclusions

Thirty percent of patients with unilateral moyamoya syndrome will have progression of arteriopathy during long-term follow-up. In this series, the average time of progression from unilateral to bilateral angiography-documented disease was 2.2 years. Several factors, including contralateral angiographic abnormalities on initial imaging, congenital cardiac anomalies, previous cranial irradiation, Asian ancestry, and familial moyamoya syndrome were associated with an increased risk of progression. Given that neurological status at time of treatment is predictive of long-term outcome and that patients in this series who were subjected to routine surveillance imaging studies had detection of moyamoya disease at younger ages and at earlier Suzuki grades, our data support the use of sustained imaging monitoring of patients with known unilateral moyamoya syndrome. Treatment of moyamoya syndrome by using pial synangiosis appears to be safe and confers durable protection against stroke in patients with both bilateral and unilateral disease.

References

10. Smith ER, Scott RM: Surgical management of moyamoya syndrome. Skull Base 15:15–26, 2005

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