J Neurosurg (Pediatrics 2) 100:142–149, 2004

Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis

R. Michael Scott, M.D., Jodi L. Smith, M.D., Richard L. Robertson, M.D., Joseph R. Madsen, M.D., Sulpicio G. Soriano, M.D., and Mark A. Rockoff, M.D.

Departments of Neurosurgery, Radiology (Neuroradiology), and Anesthesiology, The Children's Hospital, Harvard Medical School, Boston, Massachusetts; and Department of Neurosurgery, Indiana University School of Medicine, Indianapolis, Indiana

Object. Moyamoya syndrome, a narrowing of the basal intracranial vessels accompanied by the development of a cloud of collateral "moyamoya" vasculature, causes cerebral ischemia and stroke. This study was undertaken to determine if a standardized neurosurgical revascularization procedure, pial synangiosis, conferred long-term benefit in pediatric patients.

Methods. The authors reviewed the clinical and radiographic records obtained in a consecutive series of patients with moyamoya syndrome. Patients were 21 years of age or younger and underwent surgery performed by a single neurosurgeon during a 17-year period.

There were 143 patients (89 females and 54 males). Sixteen patients were Asian. Neurofibromatosis was present in 16 patients, 13 had undergone therapeutic cranial irradiation, and Down syndrome was present in 10. In 66 there was no known predisposing condition. Stroke had occurred in 67.8% of the population and transient ischemic attacks (TIAs) in 43.4% prior to surgery. Within the first 30 days following 271 craniotomies for pial synangiosis, there were 11 episodes of stroke (7.7% per patient; 4% per surgically treated hemisphere) and three severe TIAs.

Follow-up evaluation was performed in all but one patient (mean period 5.1 years). In 126 patients followed for more than 1 year, four suffered a late-onset stroke, one suffered a severe reversible TIA without magnetic resonance imaging–documented evidence of stroke, and two experienced persistent TIAs. In 46 patients followed for more than 5 years in whom the major initial presentation was stroke alone, only two late-onset strokes have occurred. Functional status at the time of surgery determined long-term functional status.

Conclusions. Following pial synangiosis, the majority of pediatric patients with moyamoya syndrome stop having strokes and TIAs, and they appear to experience an excellent long-term prognosis.

Key Words • moyamoya disease • pial synangiosis • stroke • cerebral revascularization • cerebral arteriopathy • intracranial stenosis • pediatric neurosurgery

Moyamoya disease, a cerebrovascular arteriopathy of unknown origin, leads to progressive narrowing of the intracranial ICAs. It is a cause of stroke and TIAs in pediatric and adult patients. A unique feature is its associated concomitant enlargement of intracranial carotid artery tributaries, which ordinarily supply the optic nerves, pituitary gland, anterior perforated substance, dura mater, and other skull base structures. These dilated vessels, which form a striking cloudlike rete on cerebral arteriograms (Fig. 1), provide collateral blood flow to the brain distal to the narrowed vessels. Because this disease process was described originally in Japanese patients, the Japanese term "moyamoya," which means something hazy or ill defined, like a cloud of smoke, has been used both to describe and define the illness. Surgery to revascularize the ischemic brain is a frequently recommended treatment option in this patient population.[3,5–8,15,23]

In this study, we describe the moyamoya disease in a consecutive series of patients 21 years of age or younger treated during a 17-year period by a single neurosurgeon. We reviewed the common clinical associations and modes of presentation, and determined whether surgery prevented stroke and disability during long-term follow-up review. We use the term "moyamoya disease" throughout this report to describe patients with idiopathic arteriopathy as well as those with associated medical conditions.

Abbreviations used in this paper: CBF = cerebral blood flow; CSF = cerebrospinal fluid; ECA = external carotid artery; EEG = electroencephalography; ICA = internal carotid artery; MCA = middle cerebral artery; MR = magnetic resonance; mRS = modified Rankin Scale; STA = superficial temporal artery; TIA = transient ischemic attack.

Clinical Material and Methods

We reviewed hospital, office, and radiographic/imaging records obtained in all patients with moyamoya disease treated by the senior author (R.M.S.) between January 1985 and December 2001. During this period, we conducted a standardized surgical procedure, pial synangio-

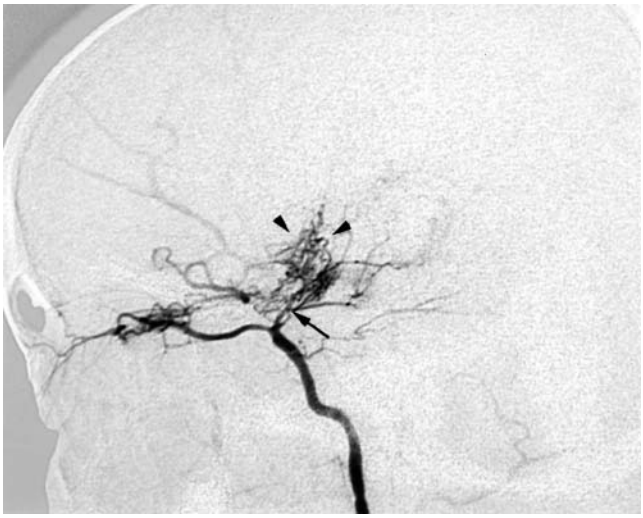

FIG. 1. Left ICA arteriogram (lateral view), obtained in an 8-year-old girl with moyamoya disease. The *single arrow* points to the stenosis and occlusion of the supraclinoid ICA. *Arrowheads* indicate the apex of the cloud of moyamoya vessels, which pass through the deep white matter and superficial basal ganglia of the hemisphere to reconstitute the distal cerebral vessels. The ophthalmic artery, seen below the arrow and running anterior (to the left), is supplying a few vessels in the frontal lobe through transdural–cribriform plate collateral structures.

sis, in all patients. We determined patient age and sex, symptoms at presentation, the presence of associated medical conditions, the arteriographic stage of the illness at presentation, and the clinical and neuroimaging-based outcomes of patients after surgery and during late follow-up examination. We obtained information regarding the functional status by performing late follow-up examinations as well as by reviewing reports from referring physicians, patients, and their families.

We treated 149 patients during the study period. Six of these patients were excluded from further review because atypical preoperative arteriographic findings were documented in four and initial revascularization surgery was performed in two at outside institutions. Of the 143 patients remaining, 89 were female and 54 were male (female/male ratio 1.6:1). The mean age at onset of symptoms was 6.5 years (range 0.3–21 years); the mean age at surgery was 7.1 years (range 0.5–21 years).

Functional status was graded using a mRS for disability scoring (Table 1); for patients under 6 years of age, we estimated a score based on degree of neurological deficit and age-appropriate functional levels.

Results

Mode of Presentation

Most patients presented with a combination of symptoms (Table 2) and many with associated medical conditions or syndromes (Table 3). Some conditions overlapped, as might be expected. For example, six children with hypothalamic–optic system gliomas also suffered neurofibromatosis Type 1, and in three children who had undergone surgery for congenital cardiac defects, Down syndrome was also present. There were eight patients with familial disease from four families (two siblings with the same mother and different fathers, and mother–son, sister–sister, and brother–sister combinations). There were two pairs of identical twins, but MR imaging/angiography results in the sibling of each twin with moyamoya syndrome were normal and the patients were asymptomatic.

TABLE 1

Summary of functional grades in a mRS

Grade	Description
0	no symptoms, neurologically intact
1	some neurological symptoms or headache, but no significant disability & performing at age level & all usual activities
2	mild neurological deficit; some difficulty performing at age level on all previous activities; independent
3	moderate neurological deficit, requiring some help with activities of daily living; delay in developmental milestones; walking unassisted
4	moderate-to-severe neurological deficit; requires help in self-care; unable to walk unassisted
5	severe neurological disability or vegetative
6	dead

Surgical Treatment

Each patient in this series underwent as an initial operation (pial synangiosis) to promote the development of increased blood flow to the involved hemisphere.[1] In this procedure, we transpose and affix the intact STA to the brain surface by using No. 10-0 sutures after the dura mater and arachnoid have been opened widely, maintaining continuity of blood flow in the STA from scalp over the brain surface and back to scalp. The operative technique remained essentially unchanged throughout the 17-year study period, except for minor modifications, specifically in the extent of dural and arachnoid opening. We documented the development of new vasculature supplying the brain from the repositioned STA and from meningeal arteries at the craniotomy site by using routine arteriography 1-year postoperatively (Fig. 2).

We performed 271 craniotomies for pial synangiosis in 143 patients, in 96 of whom both hemispheres were treated in the same anesthetic session. In 164 of these craniotomies, we placed a single additional frontal or parietal burr hole, opening dura, arachnoid, and pia to provide a possible additional route of collateral supply to the under-

TABLE 2

*Symptoms at presentation in 143 patients with moyamoya syndrome**

Sign or Symptom	No. of Cases (%)
stroke	97 (67.8)
TIA (including drop attacks)	62 (43.4)
seizure	9 (6.3)
headache	9 (6.3)
choreiform movement	6 (4.2)
incidental finding	6 (4.2)
intraventricular or intracerebral bleeding	4 (2.8)

* The total number of symptoms exceeds that of cases because some patients suffered multiple symptoms at presentation.

TABLE 3

*Summary of associated conditions, risk factors, and syndromes**

Syndrome/Variable	No. of Cases
no associated conditions (idiopathic)	66
neurofibromatosis Type 1	16
no. of Asian patients	16
cranial therapeutic radiation	15
hypothalamic–optic system glioma	8
craniopharyngioma	4
medulloblastoma (w/ Gorlin syndrome)	1
acute lymphocytic leukemia, intrathecal chemotherapy	2
Down syndrome	10
previous op for congenital cardiac anomaly	7
renal artery stenosis	4
hemoglobinopathy (2 sickle cell, 1 "Bryn Mawr")	3
other hematological	2
giant cervicofacial hemangioma	3
shunt-treated hydrocephalus	3
idiopathic hypertension requiring medication	3
hyperthyroidism (one w/ Graves syndrome)	2

* Other syndromes (one patient each) included the following: Reyes (remote), Williams, Alagille, cloacal extrophy, renal artery fibromuscular dysplasia, and congenital cytomegalic inclusion virus infection (remote). Two patients exhibited unclassified syndromic presentations. There were four African-American patients, two of whom had sickle cell disease.

lying brain. We used a previously described anesthetic protocol designed to enhance cerebral perfusion; this involves the liberal administration of intravenous fluids and maintenance of normocarbia and normotension.[20] Since late 1994, detection and treatment of cerebral ischemia has been performed in most patients by continuous intraoperative EEG monitoring involving the 10 to 20 international electrode placement system modified to accommodate the surgical incision(s). All patients receive aspirin beginning 24 hours postoperatively, usually at doses of 81 mg/day.

Intraoperative EEG

We recorded EEG data during 98 procedures in 52 patients. Transient EEG slowing suggestive of cerebral ischemia was demonstrated during 60 procedures (66%) and was not associated with anesthetic depth or end-tidal carbon dioxide levels. The slowing generally occurred in both hemispheres simultaneously when the STA was sutured to the brain surface and/or when the bone flap was replaced, suggesting abnormal cerebral reactivity. When we replaced the thrombin-soaked Gelfoam—used to cover the open dura and exposed brain prior to securing the bone flap—with saline-soaked Gelfoam, the incidence of EEG slowing at this intraoperative stage markedly diminished, suggesting that thrombin may induce vasospasm or perhaps enhance the abnormal cerebral reactivity in many of these patients. This observation merits additional laboratory and clinical study, because topical thrombin–soaked Gelfoam and patties are commonly applied in many neurovascular procedures.

Surgical Complications

Eleven strokes (7.7% per patient; 4% per surgically treated hemisphere) and three severe TIAs occurred within the first 30 days after surgery. Neurological instability, defined as the occurrence of a major stroke within 1 month of surgery or multiple strokes within 3 months prior to surgery, was thought to be the major predisposing risk factor in four of these patients. Eleven other patients in whom preoperative status was also deemed unstable, however, did not suffer neurological morbidity during the postoperative period, and therefore this clinical presentation did not automatically convey an increased risk of perioperative stroke. In additional patients, postoperative strokes occurred after episodes of prolonged crying (one patient), after prolonged hypotension following aggressive pharmacological control of postoperative hypertension (two patients, one of whom was also neurologically unstable, as defined previously), and when antiplatelet medication was not begun on the 1st day postoperatively (one patient). The latter patient is the only one in the entire series who did not receive aspirin therapy on postoperative Day 1. Three patients suffered strokes within 30 days of surgery for no obvious reason, despite careful attention

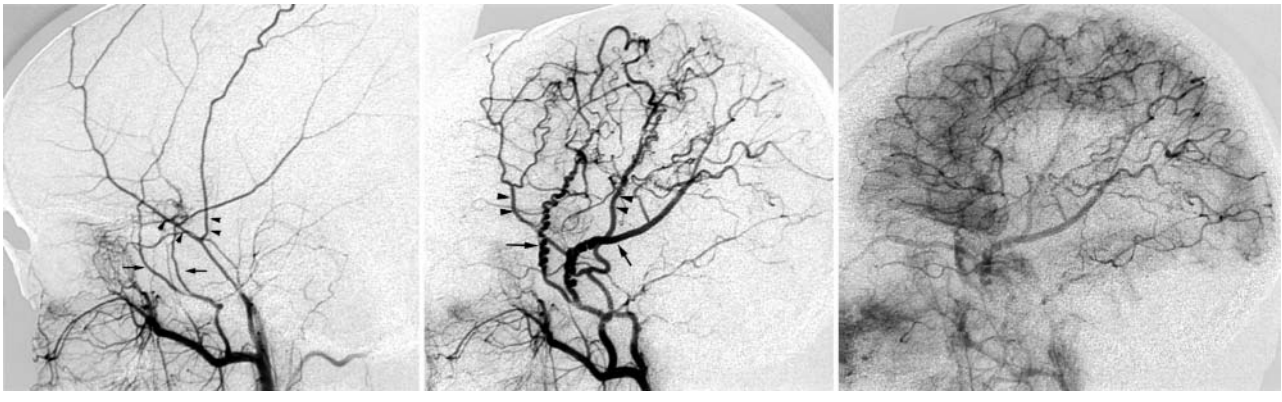

FIG. 2. Left ECA arteriograms obtained in a 7-year-old girl with multiple strokes and moyamoya syndrome. *Left:* Preoperative study. *Arrows* identify the anterior and posterior branches of the middle meningeal artery; *arrowheads* indicate the anterior and posterior branches of the STA. The posterior branch of the temporal artery was used for pial synangiosis. *Center:* One-year postoperative study (early arterial phase). Both middle meningeal artery branches and STA branches have dilated threefold and are collateralizing the middle cerebral circulation. *Right:* Late arterial–capillary phase demonstrating CBF to the entire hemisphere supplied through the craniotomy site.

TABLE 4

Functional status in 126 surgically treated patients followed for more than 1 year

Status (mRS score)	No. of Cases
independent, w/ no significant disability (0 & 1)	90
mild neurological deficit, independent (2)	13
mod disability, requires some help walking (3)	14
mod-to-severe neurological deficit, unable to walk, requires help w/ all activities of daily living (4 & 5)	6
dead (invasive meningioma; intracerebral hemorrhage) (6)	2
lost to follow up	1

to hydration, blood pressure control, and antiplatelet (aspirin) administration. In an additional patient an acute subdural hematoma developed after a fall 20 days postoperatively, and chronic subdural hematomas developed in three patients (45, 53, and 72 days postoperatively, respectively). Two of the chronic subdural hematomas required evacuation via a burr hole, but there was no permanent hematoma-related morbidity in any of these cases.

Long-Term Follow-Up Data

We followed the patients in this series for between 3 months and 17 years after surgery (mean follow-up period 5.1 years, median 4.7 years). Only one patient has been lost to follow up. In 126 patients followed for more than 1 year, there were the following seven late-onset neurological complications: four strokes, one severe reversible ischemic neurological deficit, and two severe persisting TIAs. In these seven patients, symptoms were in the anterior circulation in four, posterior circulation in two, and of unclear distribution in one. Subsequent angiography in the two patients with posterior circulation symptoms demonstrated development of progressive narrowing of the posterior cerebral arteries. We made multiple occipital burr holes in one of these patients because the first follow-up arteriogram revealed impressive collateral structures to the brain through the frontal burr holes made at the time of the initial synangioses. In the other patient, we performed bilateral occipital artery–occipital lobe synangioses. Status in both patients has been stable since reoperation at 2.5 and 3 years, respectively. The three patients with late-onset frontal lobe strokes or ischemia underwent either repeated synangiosis (one patient) or wide frontal craniotomy with onlay of a vascularized periosteal flap ("periosteal synangiosis"). One patient in whom a periosteal synangiosis was performed underwent angiography 1 year after the procedure, but unfortunately no significant new collateral circulation had been created by the procedure.

In two patients subsequent reoperation was undertaken by another neurosurgeon. One patient suffered debilitating headaches and intermittent episodes of visual loss and extremity weakness 7 years after initial synangiosis. Results of CBF studies were interpreted as indicating reduced hemodynamic reserve in both hemispheres despite flow demonstrated through the synangioses. The patient underwent a right STA–MCA anastomosis and a left omental transposition. At follow-up examination 3 years later, the patient still suffered headaches but was otherwise well. Another patient in whom postoperative arteriography demonstrated an excellent result sustained intermittent leg weakness and aphasia aggravated by hyperventilation. This patient underwent bilateral STA–MCA bypass surgery for presumed anterior cerebral artery and anterior cerebral artery–MCA watershed territory ischemia 2 years after initial synangiosis. At 6-month follow-up after the last reoperation, TIAs and hyperventilation have persisted but are less intense and less frequent. The TIAs similar to those at presentation persisted only in one other patient, and six others still experience TIAs of lesser intensity and severity than at presentation.

Headache of varying intensity also has been a common problem in patients postoperatively. The headaches frequently are accompanied by clinical phenomena resembling typical migraine syndromes and have usually responded to antimigraine medication regimens. Finally, because stroke is the most clearly defined symptom in patients with moyamoya disease, both clinically and radiographically, we evaluated the long-term ($>$ 5-year) surgery-related outcome in the 46 patients in whom stroke alone was the primary symptom at presentation. Only two strokes developed in this group during the long-term follow-up period, a result that indicates the effectiveness of pial synangiosis for reducing stroke in this population, and one made more dramatic by its contrast with the greater number of strokes suffered by each patient before surgery (Fig. 3).

Long-term functional results were clearly related to functional status at the time of surgery (Tables 4 and 5). Young age at onset of symptoms did not always herald a poor late outcome. For example, of the 19 patients treated at 2 years of age or younger, 10 have exhibited no deficits on late follow-up examination and another four have only

TABLE 5

*Functional status at initial operation and minimum follow up of 1 year**

		Score at Late FU							
Initial Score	No. of Cases	0	1	2	3	4	5	6	Lost to FU
0	32	32							
1	41	23	17	1					
2	23	4	10	7	0	1	0	1	
3	19	2	2	5	9	0	0	1	
4	11				5	5			1
5	0								
total	126	61	29	13	14	6	0	2	1

* FU = follow up.

sustained mild deficits while remaining totally independent. These results are particularly gratifying because all but one of these very young patients presented after a significant stroke.

There were two deaths in this series. A 21-year-old woman in whom moyamoya syndrome was found after radiotherapy for a craniopharyngioma died of a radiation-induced invasive meningioma 5 years after synangiosis. A 12-year-old boy in whom moyamoya syndrome was demonstrated following cranial irradiation and intrathecal chemotherapy for acute lymphoblastic leukemia died 6 years after synangiosis of recurrent hemorrhage secondary to a deep basal ganglia/third ventricular aneurysm on a moyamoya collateral vessel. This case must be considered a surgery-related failure, because his initial 1-year follow-up angiogram demonstrated only modest new operation-induced collateral vessels. The moyamoya vessels continued to supply considerable blood flow to the brain distal to the severe stenoses in the circle of Willis, perhaps leading to the formation and sequential bleeding from the aneurysm on the deep collateral vessel. There were no deaths due to ischemic stroke in this series.

Arteriographic Findings. Cerebral arteriography and MR imaging/angiography were performed 1 year postoperatively to assess the efficacy of the synangiosis and to guide subsequent management. Although we request 1-year follow-up arteriograms in all of our patients, the studies were refused by some families or could not be obtained in others because of geographical or other considerations. We reviewed either the arteriograms themselves or our previous reports of these studies in the 102 patients in whom these studies were performed. We graded the newly developed collateral vessels according to the method of Matsushima, et al.,[14] (Grade A representing synangiosis-induced filling of $>$ two thirds of the MCA circulation, Grade B between one third and two thirds, and Grade C $<$ one third). Sixty-five percent of the 195 hemispheres studied were classified as Grade A collateral circulation, 25% as Grade B, and 10% as Grade C. Of the 102 arteriograms, 82 (80%) had at least one hemisphere demonstrating Grade A circulation. Visible collateral vessels to the brain at the additional burr hole sites could be identified in approximately 69 (57%) of the 120 burr holes that could be assessed, but in only 34 (28%) could these vessels be termed significant (that is, filling more than a small focal area at the burr hole site).

Discussion

In the present study we describe moyamoya disease in a consecutive series of patients 21 years of age or younger treated during a 17-year period by a single neurosurgeon. Despite the varied clinical associations observed in this series, the modes of presentation, age at onset of symptoms, and age at surgery were similar to those reported in the Japanese literature.[5–8,26] We believe that our series, the largest reported in the Western hemisphere, is representative of the wide spectrum of pediatric cases involving moyamoya disease.

Progression Rate and Long-Term Outcome

In the Japanese literature numerous authors have documented the unfavorable natural history of untreated moyamoya disease, with its gradual neurological and cognitive deterioration[2,6,10,11,22] as well as mortality rates of up to 4.3% in certain pediatric series.[17] We noted a variable and unpredictable rate of clinical progression of moyamoya disease in our patients and believe that a long follow-up period is necessary to determine the effectiveness of any treatment. 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. The exceptions to this conclusion are the few patients in whom synangiosis did not effectively perfuse anterior or posterior cerebral artery circulations and in whom required additional revascularization surgeries were directed at these persistently ischemic areas.

Controversy exists regarding the appropriate initial surgical therapy for moyamoya disease in young patients;[3,4,16] however, the present study provides evidence that pial synangiosis, a surgical procedure combining dural and arachnoid opening with the attachment of the donor STA directly to the pial surface by using interrupted No. 10-0 sutures, prevents future associated neurological events in the majority of pediatric patients. The effectiveness of this type of "indirect" surgery likely is enhanced by the increased levels of growth factors in the CSF of children with moyamoya disease;[13,24,27] these growth factors may be responsible for the development of new collateral vessels via the skull and dura to the brain through any corridor provided by the neurosurgeon, including burr holes. The additional arteriography-detected collateral structures seen on 1-year postoperative arteriograms obtained through the burr holes placed at the time of synangiosis were extremely variable, however; in most cases, the newly formed vessels were inconsequential, indicating to us the importance of using some type of donor vessel as part of the surgical procedure. Since 2002, we have abandoned the routine placement of additional burr holes at the time of synangiosis and believe that the neurosurgeon should not rely on burr holes alone as a revascularization technique in most patients with moyamoya disease.

The synangiosis-induced collateral vessels themselves appear long lived, and on an arteriogram obtained in one patient 9 years after the initial operation persistent and even some increase in the florid collateral structures were present compared with the initial postoperative study (Fig. 4). Although concomitant stenosis of the renal arteries was diagnosed in four patients during initial angiography, in all cases the arterial stenosis was otherwise restricted to cerebral vessels around the circle of Willis and did not involve vessels on the brain surface or in the scalp and meninges. Throughout the accrual of this series, selective cerebral arteriography to assess ICA and ECA blood flow was the most useful diagnostic modality by which to assess the cerebral circulation preoperatively and to determine the extent of postoperative CBF through the synangiosis. Magnetic resonance angiography was undertaken as a baseline measure at the time of follow-up arteriography in all patients, but this modality often ineffectively demonstrated the extent of perfusion to the surgically treated hemisphere through the operative site. Because of the constraints implicit in a pediatric population, we were unable to study systematically CBF changes pre- and

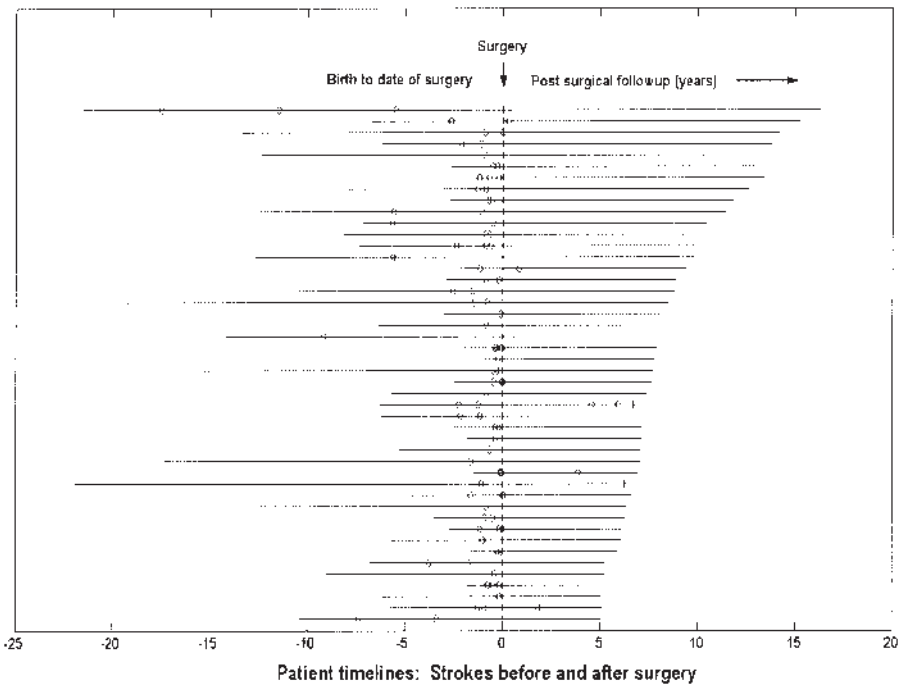

FIG. 3. Graph depicting the life timelines of the 46 patients in this series whose primary presentation was stroke and who were followed for 5 or more years after surgery. *Diamonds* indicate clinically verified strokes. Two patients in this cohort died *(plus sign)* during the follow-up period (see text for details).

postoperatively by using positron emission tomography, single-photon emission computerized tomography, or Xe-based computerized tomography scanning.

We believe that antiplatelet medication, in particular aspirin, also plays an important role in the postoperative treatment of patients with moyamoya disease. In a condition involving multiple intracranial stenoses such as moyamoya disease, symptoms probably result not only from progressive distal ischemia but also from embolization due to thrombi forming at areas of stenosis. Anticoagulation therapy with agents such as warfarin sodium is dangerous in this pediatric population, not only because of the difficulty of preventing head trauma secondary to unanticipated sources but also because of the potential of life-threatening spontaneous intracranial hemorrhage that can occur in some children with moyamoya syndrome. We prescribe life-long aspirin therapy (usually in doses of 81 mg/day) in all of our patients postoperatively. There are no published studies indicating that aspirin therapy alone will prevent stroke in this patient population, however, and several of our patients were receiving aspirin therapy prior to surgery, with symptoms of ischemia developing nonetheless.

Significance of Intraoperative EEG Findings

During surgery, we commonly observed EEG changes suggestive of transient cerebral ischemia not precipitated by hyperventilation or hypotension, and these occurred during direct surgical stimulation of the brain surface by pial sutures or during bone flap replacement. We postulate that this EEG slowing is due to defective cerebral reactivity; it is not known, however, whether these EEG changes are unique to pial synangiosis or to patients with moyamoya syndrome in general, or if the finding has long-term clinical significance. One patient in whom surgery was performed in 2002 after the accrual of this clinical series suffered new bilateral hemisphere strokes evident immediately at the completion of her bilateral synangiosis, despite a totally stable intraoperative EEG, indicating that this monitoring technique will not always prevent an adverse operative outcome. We believe that the study of intraoperative EEG warrants further investigation in this patient population.

Clinical Associations

One of the more interesting aspects of moyamoya syndrome has been its association with other pathological processes (Table 3), some of which (Down syndrome, congenital cardiac anomalies, congenital giant cervicofacial hemangiomas, and Alagille and Williams syndromes) are characterized by the aberrant development of vascular structures throughout the body. Other patients had undergone medical interventions that may potentially cause cerebral vessel injury, including skull base tumor extirpation, cranial radiotherapy, or intrathecal chemotherapy. Three patients suffered hemoglobinopathies, in which thrombosis in cerebral vasa vasorum has been postulated to damage blood vessel walls.[25] We have noted elevated concentrations of soluble endothelial adhesion molecules in the CSF in a cohort of our patients,[19] suggesting that a chronic inflammatory process might play a role in the development of moyamoya syndrome; however, no evidence of inflammation has ever been identified in the CSF of these patients, and steroid agents have never been shown to ameliorate symptoms or reverse arteriographically documented findings. The few postmortem studies

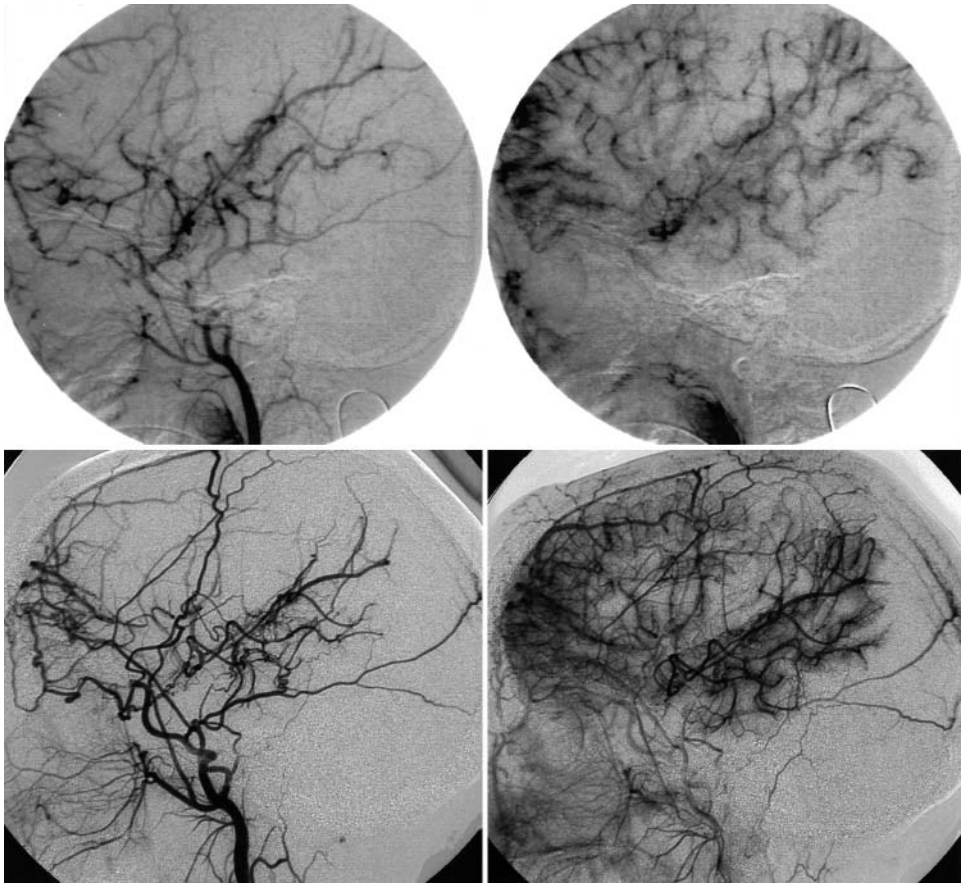

FIG. 4. *Upper Left* and *Right:* Left ECA arteriograms, early arterial phase *(left)*, and late arterial phase *right*, obtained in 1989, 1 year after pial synangiosis in a 31-month-old child presenting with a major stroke. The studies demonstrate filling of most of the middle cerebral circulation via collateral vessels induced by the synangiosis. *Lower Left* and *Right:* Left ECA arteriograms, early arterial phase *(left)* and late arterial phase *(right)* obtained 8 years later, prior to surgery for a newly developed left posterior frontal ganglioglioma. The images demonstrate continued robust filling of the hemisphere via the surgery-induced collateral vessels.

in patients with moyamoya disease have demonstrated only a nonspecific thickening of the intima and endothelial hyperplasia, without evidence of inflammation,[12] and the elevated levels of soluble adhesion molecules in the CSF obtained in patients with moyamoya disease may be the result, rather than cause, of chronic ischemia.

A hereditary or familial syndrome was observed in eight of four patients (5.6%), with either mother–child (two families) or sibling–sibling involvement. In Japan the familial incidence is reported to be as high as 7 to 12%,[9,18] but in two pairs of identical twins in this series, the second twin was unaffected, indicating that an additional environmental factor must be necessary in certain patients to initiate the arteriopathic process. One adult patient treated by the senior author, not in this series, is also an identical twin whose sibling is unaffected. We found a definite female preponderance similar to that previously demonstrated in the Japanese literature,[21] suggesting that a sex-specific factor as yet unidentified must also play a role in certain forms of the disease.

Six patients exhibited choreiform movements on their initial evaluation. In many patients with moyamoya disease, MR imaging demonstrates accentuated flow voids through the basal ganglia secondary to the dilated moyamoya collateral vessels, and it is possible that in patients with chorea, these vessels have either compressed the basal ganglia or created local ischemia, leading to this symptom complex. After surgery, the abnormal movements have virtually disappeared in each patient by late follow-up examination. Headache resembling the classic migraine has been a frequent symptom both at presentation and follow up and has occasionally been difficult to treat, requiring trials of multiple pharmacological agents for control. We have attributed the development of migraines after synangiosis to enlargement of meningeal vessels newly collateralizing the brain, but the application of this finding to the understanding of classic migraine remains unclear.

Conclusions

In this study our evidence indicates that following a specific revascularization surgery—pial synangiosis—the majority of pediatric patients with moyamoya syndrome cease to experience symptoms of cerebral ischemia and stroke. The surgery halts what is normally a relentless

clinical deterioration in the untreated patient. Such surgery is not without risk, especially in the neurologically unstable patient, but nearly 75% of children in our series followed for more than 1 year are leading independent and normal lives.

Acknowledgments

We wish to thank Dr. Leslie Hellbusch and Dr. Gary Steinberg for providing important follow-up information on several patients in this series.

References

1. Adelson PD, Scott RM: Pial synangiosis for moyamoya syndrome in children. **Pediatr Neurosurg 23:**26–33, 1995
2. Choi JU, Kim DS, Kim EY, et al: Natural history of moyamoya disease: comparison of activity of daily living in surgery and non surgery groups. **Clin Neurol Neurosurg 99:**S11–S18, 1997
3. Golby AJ, Marks MP, Thompson RC, et al: Direct and combined revascularization in pediatric moyamoya disease. **Neurosurgery 45:**50–60, 1999
4. Houkin K, Kuroda S, Ishikawa T, et al: Neovascularization (angiogenesis) after revascularization in moyamoya disease. Which technique is most useful for moyamoya disease? **Acta Neurochir 142:**269–276, 2000
5. Houkin K, Kuroda S, Nakayama N: Cerebral revascularization for moyamoya disease in children. **Neurosurg Clin N Am 12:** 575–584, 2001
6. Imaizumi T, Hayashi K, Saito K, et al: Long-term outcomes of pediatric moyamoya disease monitored to adulthood. **Pediatr Neurol 18:**321–325, 1998
7. Ishikawa T, Houkin K, Kamiyama H, et al: Effects of surgical revascularization on outcome of patients with pediatric moyamoya disease. **Stroke 28:**1170–1173, 1997
8. Isono M, Ishii K, Kamida T, et al: Long-term outcomes of pediatric moyamoya disease treated by encephalo-duro-arterio-synangiosis. **Pediatr Neurosurg 36:**14–21, 2002
9. Kitahara T, Ariga N, Yamaura A, et al: Familial occurrence of moya-moya disease: report of 3 Japanese families. **J Neurol Neurosurg Psychiatry 42:**208–214, 1979
10. Kurokawa T, Tomita S, Ueda K, et al: Prognosis of occlusive disease of the circle of Willis (moyamoya disease) in children. **Pediatr Neurol 1:**274–277, 1985
11. Maki Y, Enomoto T: Moyamoya disease. **Childs Nerv Syst 4:** 204–212, 1988
12. Maki Y, Nakada Y: Autopsy case with angiomatous anomaly of basal internal carotid arteries. **Brain Nerve 17:**764–766, 1965
13. Malek AM, Connors S, Robertson RL, et al: Elevation of cerebrospinal fluid levels of basic fibroblast growth factor in moyamoya and central nervous system disorders. **Pediatr Neurosurg 27:**182–189, 1997
14. Matsushima T, Inoue T, Suziki SO, et al: Surgical treatment of moyamoya disease in pediatric patients—comparison between the results of the indirect and direct revascularization procedures. **Neurosurgery 31:**401–405, 1992
15. Matsushima Y, Aoyagi M, Nariai T, et al: Long-term intelligence outcome of post-encephalo-duro-arterio-synangiosis childhood moyamoya patients. **Clin Neurol Neurosurg 99:** S147–S150, 1997
16. Nakashima H, Meguro T, Kawada S, et al: Long-term results of surgically treated moyamoya disease. **Clin Neurol Neurosurg 99:**S156–S161, 1997
17. Nishimoto A: [Moyamoya disease (author's translation).] **Neurol Med Chir (Tokyo) 19:**221–228, 1979 (Jpn)
18. Sogaard I, Jorgenson J: Familial occurrence of bilateral intracranial occlusion of the internal carotid arteries (Moya Moya). **Acta Neurochir 31:**245–252, 1975
19. Soriano SG, Cowan DB, Proctor MR, et al: Levels of soluble adhesion molecules are elevated in the cerebrospinal fluid of children with moyamoya syndrome. **Neurosurgery 50:** 544–549, 2002
20. Soriano SG, Sethna NF, Scott RM: Anesthetic management of children with moyamoya syndrome. **Anesth Analg 77:** 1066–1070, 1993
21. Suzuki J: **Moyamoya Disease.** Berlin: Springer-Verlag, 1986, p 8
22. Suzuki J, Takaku A: Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. **Arch Neurol 20:**288–299, 1969
23. Suzuki Y, Negoro M, Shibuya M, et al: Surgical treatment for pediatric moyamoya disease: use of the superficial temporal artery for both areas supplied by the anterior and middle cerebral arteries. **Neurosurgery 40:**324–330, 1997
24. Takahashi A, Sawamura Y, Houkin K, et al: The cerebrospinal fluid in patients with moyamoya disease (spontaneous occlusion of the circle of Willis) contains high level of basic fibroblast growth factor. **Neurosci Lett 160:**214–216, 1993
25. Vernant JC, Delaporte JM, Buisson G, et al: [Cerebrovascular complications of sickle-cell anemia.] **Rev Neurol (Paris) 144:** 465–473, 1988 (Fr)
26. Wakai K, Tamakoshi A, Ikezaki K, et al: Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. **Clin Neurol Neurosurg 99:**S1–S5, 1997
27. Yoshimoto T, Houkin K, Takahashi A, et al: Angiogenic factors in moyamoya disease. **Stroke 27:**2160–2165, 1996

Manuscript received March 12, 2003.
Accepted in final form July 7, 2003.
Support from the Christopher Fellows Educational and Technology Fund was awarded to Dr. Scott.

Address reprint requests to: R. Michael Scott, M.D., Department of Neurosurgery, The Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115. email: michael.scott@tch.harvard.edu.