Results of more than 20 years of follow-up in pediatric patients with moyamoya disease undergoing pial synangiosis

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OBJECTIVE There are limited data on the long-term outcomes for children undergoing surgical revascularization for moyamoya disease (MMD) in North America. The authors present a series of pediatric MMD patients who underwent a standard revascularization procedure, pial synangiosis, more than 20 years previously at a single institution by a single surgical team.

METHODS This study is a retrospective review of all patients aged 21 years or younger treated for MMD at Boston Children's Hospital who were operated on more than 20 years previously by the senior author (R.M.S.). Radiographic and operative reports, outpatient clinical records, and communications with patients and families were reviewed to document current clinical status, ability to perform daily activities, and concurrent or new medical conditions.

RESULTS A total of 59 patients (38 female [64.4%], 21 male [35.6%]; median age at surgery 6.2 years [IQR 0.5–21 years]) were identified who were diagnosed with MMD and underwent surgical revascularization procedures more than 20 years previously. Clinically, all but 2 patients (96.6%) presented with the following symptoms alone or in combination: 43 (73%) presented with stroke, 22 (37%) with transient ischemic attack, 12 (20%) with seizures, 7 (12%) with headache, 3 (5%) with choreiform movements, and 2 (3%) with hemorrhage; MMD was incidentally detected in 2 patients (3%). Five patients had unilateral MMD at presentation, but 3 of these ultimately progressed to develop bilateral MMD after an average of 16 months; therefore, pial synangiosis was ultimately performed in a total of 116 hemispheres during the study period. Clinical follow-up was available at a median interval of 20.6 years (IQR 16.1–23.2 years). Modified Rankin Scale scores were stable or improved in 43 of 50 patients with evaluable data; 45 of 55 are currently independent. There were 6 patient deaths (10.2%; 3 due to intracranial hemorrhage, 2 due to tumor-related complications, and 1 due to pulmonary artery stenosis), 4 of whom had a history of previous cranial radiation. One patient (1.7%) experienced a late stroke. Synangiosis vessels remained patent on all available late MRI and MRA studies. Four patients reported uneventful pregnancies and vaginal deliveries years following their revascularization procedures.

CONCLUSIONS Revascularization for MMD by pial synangiosis appears to confer protection from stroke for pediatric patients over long-term follow-up. A history of cranial radiation was present in 4 of the 6 patients who died and in the lone patient with late stroke. Most patients can expect productive, independent lives following revascularization surgery in the absence of significant preoperative neurological deficits and comorbidities.

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KEYWORDS moyamoya; revascularization; stroke; outcomes; pediatric; cerebrovascular; vascular disorders

SURGICAL revascularization is a relatively recent development in the management of pediatric moyamoya.^{9,12,19,21,23,24} Many procedures, including encephaloduroarteriosynangiosis (EDAS),^{12,13,19,31} pial synangiosis,^{1,7,27} superficial temporal artery-to-middle cerebral artery

anastomosis, and encephalomyosynangiosis,⁹ have been employed for treatment of this condition, but relatively few studies have examined extended long-term outcomes in these patients.¹⁵ Of particular interest to patients and treating physicians alike are the long-term functional and so-

ABBREVIATIONS EDAS = encephaloduroarteriosynangiosis; MMD = moyamoya disease; mRS = modified Rankin Scale; NF1 = neurofibromatosis type 1; TIA = transient ischemic attack.

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cial outcomes in the group of patients treated by revascularization procedures.^{20,25,28,29} This is especially important in patients who are treated as children, given questions about the durability of engraftment, the long-term effects of the inevitable progression of the moyamoya arteriopathy, and the disease's effects on the function of the developing brain.

The goal of this study was to review the long-term clinical outcomes of a consecutive series of pediatric patients treated by pial synangiosis for moyamoya disease (MMD) more than 20 years ago, in hopes that this information could inform patients and caregivers of the long-term prognosis of patients undergoing revascularization surgery for this condition, as well as providing benchmark data regarding surgical outcomes.

Methods

Institutional review board approval was obtained for this research. All cases of MMD treated by the senior author (R.M.S.) at Boston Children's Hospital were reviewed to identify patients who underwent pial synangiosis for MMD 20 or more years ago. Patient data, including demographics, medical histories, operative reports, imaging results, and hospital records, were collected and analyzed. Outcome data were obtained from follow-up clinic notes and communications with patients and families via telephone and mail contacts. In some patients, aspects of data collection were limited or incomplete, and such limitations are noted explicitly in the analyses.

Presenting symptoms were identified from neurosurgical clinic visit notes, hospital records, and the senior author's surgical database. Surgical information, including laterality of disease, procedure type, and intraoperative complications, was collected from similar sources. Information on perioperative complications was collected from inpatient notes and discharge summaries.

Preoperative images and reports were reviewed in order to confirm disease severity and Suzuki grade and to identify evidence of ischemia and/or infarction.³⁰ Postoperative imaging studies were reviewed to determine the presence or absence of new cerebral ischemic changes and degree of cerebral filling from surgically induced collaterals based on the Matsushima grading system.¹³ All available MR and angiographic images were reviewed independently by 2 authors.

Late clinical and quality-of-life data were collected from long-term postoperative clinical notes. Additional information was extracted from the senior author's personal surgical database. The senior author has routinely maintained close contact with patients and families through email, phone calls, and postal mail as standard practice whenever feasible. Important outcomes included presence of new associated conditions, report of any new neurological symptoms, degree of educational and professional achievement, and general independence. Information on pregnancy and delivery was self-reported by 4 patients. Information on quality of life obtained from these data sources was used to evaluate postoperative disability as measured using the modified Rankin Scale (mRS) scores.

TABLE 1. Demographics and surgical management of patients who underwent revascularization for MMD more than 20 years ago

Characteristic	All Patients (n = 59)
Sex, n (%)	
Male	21 (35.6)
Female	38 (64.4)
Median age at op, yrs (IQR)	6.2 (3.0–9.7)
Associated characteristics, %	
Asian ancestry	10.2
NF1	10.2
History of cranial radiation	8.5
Down syndrome	6.8
Structural cardiac disease	5.1
Associated symptoms, %	96.6
Stroke	72.9
TIA	37.3
Seizure	20.3
Headache	11.9
Choreiform movements	5.1
Hemorrhage	3.4
Laterality at initial presentation, n (%)	
Bilateral	54/59 (91.5%)
Unilateral	5/59 (8.5%)
Timing of ops, n	
Same-day or short-staged op or bilateral disease	108 cases (54 patients)
Unilateral at initial presentation	5 cases (5 patients)
Progression in initially asymptomatic hemisphere (bilateral)	3 cases (3 patients)
Op treatment	
Pial synangiosis	116 cases
Additional burr holes	48 cases

Results

Demographics and Clinical Presentation

A review of the senior author's personal database revealed 71 consecutive patients who underwent pial synangiosis for MMD more than 20 years ago—from 1985 through 1998. Twelve of these patients had to be excluded due to lack of available clinical follow-up after surgery. The remaining 59 patients were included for analysis (Table 1). The cohort consisted of 38 female patients (64.4%) and 21 males (35.6%), with a median age at surgery of 6.2 years (IQR 3.0–9.7 years).

Fifty-three of the 59 (89.8%) patients presented with ischemic symptoms, including strokes (43/59, 72.9%), transient ischemic attacks (TIAs; 22/59, 37.3%) or a combination of both (12/59, 20.3%). In addition, seizures were noted in 12 patients (20.3%), headache in 7 (11.9%), choreiform movements in 3 (5.1%), and hemorrhage in 2 (3.4%). Of the 2 asymptomatic patients, both underwent revascularization following the development of progressive MMD arteriopathy and worsening cerebral blood flow detected

TABLE 2. Long-term outcomes of patients undergoing revascularization for MMD 20 or more years ago

Characteristic	All Patients (n = 59)
Median follow-up duration, yrs (IQR)	20.6 (16.1–23.2)
Adverse events, n (%)	
Death	6/59 (10.2)
Stroke w/ neurological decline	1/59 (1.7)
mRS score stable/improved, n (%)	43/50 (86.0)
Independent, n (%)	45/55 (81.8)
Social outcomes, n (%)	
Completed high school	43/46 (93.5)
Completed college	19/38 (50.0)
Completed advanced degree	7/33 (21.2)
Employed	27/35 (77.1)
Uncomplicated vaginal delivery	4/4 (100)

Denominators represent the number of patients with available information.

on sequential MRI scans done as part of a follow-up protocol for neurofibromatosis type 1 (NF1).

Review of associated risk factors for MMD in the patient histories revealed several notable clusters. Asian ancestry was reported in 6 (10.2%), NF1 in 6 (10.2%), previous cranial radiation for brain tumors (n = 4) and leukemia (n = 1) in 5 (8.5%), Down syndrome in 4 (6.8%), structural cardiac disease in 3 (5.1%), and PHACES in 1 (1.7%) (Table 1). Some of these patients manifested multiple risk factors, for example, Down syndrome and congenital cardiac disease (1/59; 1.7%), and NF1 and previous cranial radiation (3/59; 5.1%) in an era when radiation was frequently used to treat inoperable brain tumors in this patient population.

Radiographic Presentation

Initial imaging revealed bilateral MMD in 54 (91.5%) of the 59 patients and unilateral disease in 5 (8.5%) patients (2 right and 3 left). Evidence of infarction was present in 43 (72.9%) patients and hemorrhage in 2 (3.4%).

Surgical Indications and Operative Treatment

The indication for surgery was symptomatic focal cerebral ischemia with corresponding arteriopathy in 57 (96.6%) patients. The 2 asymptomatic patients were selected for surgery after evidence of worsening cerebral perfusion based on MRI criteria coupled with progressive arteriopathy on serial imaging.

One hundred sixteen craniotomies for pial synangiosis were carried out during 79 scheduled operations, 57 for bilateral disease and 2 for unilateral disease. In patients with bilateral disease at initial presentation (n = 54), 37 patients (68.5%) had same-day bilateral operations under single anesthesia and 17 (31.5%) had short-term staged operations, typically within 4 weeks and with the symptomatic side done first. Three patients had up to 12-week gaps between surgeries due to scheduling or insurance issues. In 5 of these 17 patients (29.4%), an originally planned same-day bilateral procedure was attempted and aborted due to intraoperative concerns such as brain swelling, hemostasis issues, and/or EEG changes that could not be re-

versed. The remaining 3 patients who underwent bilateral procedures presented initially with unilateral MMD (2 right, 1 left), which showed progression of disease after unilateral pial synangiosis, requiring subsequent surgery on the opposite side. For these patients exhibiting progression, the second surgery was performed 7 to 30 months after the first (average 16.6 months).

In 48 operations, a total of 67 burr holes were added to the synangiosis procedure in an attempt to augment vascularization in vascular territories remote from the synangiosis site. The majority (66/67, 98.5%) were done in the anterior cerebral territory, with 1 burr hole (1.5%) placed in the parietooccipital region.

After the 79 synangiosis operations, there were 2 perioperative strokes (2.5% per operation). Minor complications included 6 perioperative TIAs (7.6% per operation) and 1 seizure (1.3%). No perioperative infections, CSF leaks, or deaths occurred. One patient (1.3%) exhibited unexplained transient cortical blindness that resolved before hospital discharge.

Clinical Follow-Up and Outcomes

The standard follow-up regimen for pediatric MMD patients at Boston Children's Hospital during the study period was MRI and MRA at 6 months postoperation and an arteriogram 1 year postoperation, followed by yearly MRI and MRA for the first 5 years after surgery, transitioning to every 2 years thereafter until 10 years postoperation, and finally every 3 years subsequently.

Varying extents of long-term clinical follow-up data were available in all 59 patients with a median period of 20.6 years (IQR 16.1–23.2 years). There were no late clinically detected or patient-reported strokes in 58 patients (98.3%). The single patient with late stroke presented clinically with deteriorating neurological status and speech and balance problems 12 years after pial synangiosis. This patient had a history of NF1 and radiation for a hypothalamic-optic astrocytoma; the stroke was thought to be due to postradiation vasculopathy, as there were no visible changes on either arteriography or MRA. This patient was alive at last contact 20 years postoperatively and was wheelchair-bound, living in a residential facility with an aide.

There were 6 patient deaths (10.2%) (Table 2). These deaths occurred on average 15.9 years after pial synangiosis (range 5.5–27.4 years). The first deceased patient had a complicated medical history, with a diagnosis of NF1 and an optic glioma treated with cranial radiation 11 years prior to her MMD surgery. She ultimately died of a massive thalamic and intraventricular hemorrhage at 40 years of age. Her family had refused postoperative arteriography, but MRI and MRA performed 6 months prior to her death revealed Suzuki grade VI MMD and no other obvious vascular pathology such as aneurysm, proliferative basal collateral, or new stroke. Another patient with a history of NF1 and an optic glioma treated with cranial radiation died of complications related to a progressive brainstem glioma 19 years after pial synangiosis. One death occurred in a 27-year-old woman who died of a malignant meningioma 6 years after revascularization surgery; her MMD had developed after radiation therapy for a craniopharyngioma.

A fourth patient died 17 years after surgery due to a sudden massive intraventricular hemorrhage; CT images did not reveal a clear source of the hemorrhage, and, due to the emergency nature and rapid deterioration of the patient's clinical status, MRI was not performed. The fifth patient died of rupture of a previously diagnosed, untreatable lentulostriate aneurysm 6 years after synangiosis surgery; this patient had undergone intrathecal chemotherapy and cranial radiation therapy as part of a treatment protocol for acute lymphocytic leukemia. His postoperative arteriogram had demonstrated only marginal filling from the pial synangioses. The final death was in a patient with bilateral peripheral pulmonary artery stenoses who died of cardiac and pulmonary complications 21 years after pial synangiosis.

Information regarding degree of disability was available for 50 patients at a median interval of 19.7 years postoperatively (IQR 17.1–23.4 years). In 9 patients, although clinical follow-up was available at a median interval of 17.6 years (IQR 11.5–21.9 years), the data were insufficient to determine the degree of functional disability. The mRS scores were stable ($n = 19$) or improved ($n = 24$) in 43 of these patients at most recent contact; 7 patients exhibited a worsening mRS score postoperatively. However, 6 of these 7 patients were those who had complex comorbidities leading to death. The single living patient whose status worsened following pial synangiosis was the same patient who experienced late stroke as described above.

Long-term follow-up for the 4 patients with Down syndrome was available at a mean ($\pm$ SD) length of 23.5 ± 0.4 years postoperatively. None of these patients experienced any late stroke or neurological decline from preoperative baseline.

Radiographic Outcomes

Long-term MRI data were available for 38 of the 59 patients (64.4%) at a median interval of 19.3 years following treatment (IQR 12.7–22.1 years). Imaging revealed 1 late radiographic stroke (2.6%) in the same patient discussed previously. Of the 5 patients who presented with unilateral disease, 3 (60.0%) experienced progression to bilateral disease requiring surgery with an average time to progression of 1.4 years (range 0.6–2.5 years).

While the standard for definitive operative follow-up in patients with MMD is a catheter arteriogram, for many patients these postoperative images were not available in the electronic medical records, since many of the studies were performed prior to the transition to digitized images and had been discarded. Late arteriograms were available for only 6 patients (12 hemispheres) at a median interval of 13.0 years postoperatively (IQR 10.7–13.4 years). Matsushima grade A collaterals were present in 7 of these 12 hemispheres (58.3%), Grade B in 4 (33.3%), and Grade C in 1 (8.3%). Due to the scarcity of available angiography, no conclusions could be drawn about the population as a whole.

In 74 hemispheres (36 bilateral, 2 unilateral) for which long-term MRA data were available, surgically induced collaterals persisted and were easily visualized at a median interval of 17.7 years postoperatively (IQR 12.7–22.1 years). The degree of cerebral filling from surgical collat-

erals on the MRA studies was defined using a subjective approximation of the Matsushima grading scale used on postoperative arteriography to grade the degree of middle cerebral artery (MCA) opacification.¹³ Images were reviewed and evaluated by 2 authors. Of the 74 hemispheres, filling was considered “excellent” (Matsushima grade A; > two-thirds of the MCA territory filled) in 66 (89.2%), “good” (Matsushima grade B; two-thirds to one-third filled) in 3 (4.0%), and “moderate” (Matsushima grade C; < one-third filled) in 5 (6.8%). It is important to note that MRA studies do not offer the degree of detail required to truly evaluate filling of the MCA territory as graded by the Matsushima system. This MRA-based evaluation instead characterized the relative number of middle cerebral vessels visible on the scans.

Long-Term Quality-of-Life and Societal Outcomes

In those patients for whom this specific long-term information was available, 43 of 46 have completed high school, 45 of 55 were independent in adulthood, 27 of 35 were employed, 19 of 38 have completed college, and 7 of 33 have completed advanced degree programs (including medicine and law). Four female patients reported becoming pregnant and having one or more uncomplicated vaginal deliveries; no familial MMD has yet been reported in these children.

It is important when evaluating quality-of-life outcomes for this patient population to consider not only preoperative neurological disability, but also comorbid diagnoses, particularly in patients with syndromic MMD. This patient cohort included 6 patients with NF1, 4 patients with Down syndrome, 1 with spastic cerebral palsy and quadriplegia secondary to preoperative strokes, and 1 with sickle cell disease, among others described in Table 1. All of these conditions carry significant morbidity that in isolation would have profound effects on a patient's ability to perform daily activities. For example, the patient with cerebral palsy completed 12 years of special education and ultimately received a high school diploma as his highest level of education; he is severely cognitively impaired at baseline and lives with full-time supervision and care.

Discussion

Background

Many studies in the neurosurgical literature have evaluated immediate postoperative outcomes and optimal management schemes for patients undergoing surgical intervention for MMD.^{1,8,9,19–23,25,27,31} These reports have demonstrated that revascularization procedures like EDAS and pial synangiosis are relatively safe and effective in appropriately selected pediatric patients, with careful perioperative protocols; these authors have reported low rates of operative mortality and stable or improved functional outcomes postoperatively. It is known that the natural history of MMD in untreated patients, particularly in children, is poor, with reported stroke rates of 66%–90% over 5 years,^{5,30} and thus surgical intervention has become the standard of care in patients with symptomatic or radiographically confirmed MMD.^{22,24}

As pediatric patients who underwent surgical inter-

vention for MMD in the earliest years of these procedures grow older, recent reports have evaluated surgical outcomes with mean follow-up ranging from 5 to 14 years.^{2-4,6,10,15,18,25,29} Many of these studies have demonstrated that surgical intervention for MMD provides protection from cerebral ischemia and hemorrhage and patients often go on to live independent and productive lives.^{5,6} However, the overall number of reported patients is—understandably—relatively small, and the data are typically focused on specific metrics, such as angiographic outcome or stroke rate.

Unique Aspects of This Study

The aim of this study was to add a very-long-term pediatric MMD series to the literature, which is unique in several ways. First, this patient population was treated by a single neurosurgeon using a standardized operative approach (pial synangiosis) and perioperative protocol. Second, this report adds functional and social outcomes to available long-term follow-up data of real importance to patients and families. That these children with treated MMD will be able to attend secondary schools and college, even postgraduate programs, and find gainful employment, as well as being able to start families and undergo successful pregnancy and delivery has not been apparent from data reviews of currently published series. This review therefore focused on these outcomes. Third, this series has a lengthy duration of postoperative follow-up of over 20 years. While some patients are lost to follow-up due to initial referral from remote areas of the world or family mobility, the overall length of available follow-up of this study is the longest of which we are aware for this specific population.

Notable Patient Findings

Our work supports the premise that surgical revascularization in the pediatric patient with MMD confers long-term protection from stroke, in marked contrast to the natural history of the untreated disease. The length of the follow-up reported here, including both clinical and radiographic data, should provide substantial reassurance to parents, patients, and caregivers regarding the efficacy and durability of pial synangiosis for the treatment of pediatric MMD.

There were 6 late deaths in this series; 4 of these patients had medical histories notable for preoperative cranial radiation for treatment of tumors of the hypothalamic-optic system, craniopharyngioma, and leukemia. Two of these patients postoperatively developed radiation-induced malignant tumors that led directly to their deaths and were unrelated to their MMD. The other 2 patients with a history of cranial radiation died of intracranial hemorrhage, likely as a result of their MMD. One patient who presented initially with ischemic symptoms died 17 years after surgery of massive intraventricular hemorrhage, likely due to her MMD. The final death was due to complications of pulmonary artery stenosis. These late deaths indicate the importance of continued monitoring of patients who undergo revascularization for pediatric MMD.

In addition to the customary reporting of stroke out-

comes shared by other similar studies, we are fortunate to be able to demonstrate that patients in this series fared remarkably well in both functional and social outcomes. Despite a high proportion of patients who had preoperative strokes, 82% of patients for whom we have follow-up data were living independently at most recent contact, and the majority of patients were high school graduates. Fifty percent of patients with available data had completed college, and the majority of patients were employed. Importantly, 4 of the female patients treated in this series subsequently had children via uncomplicated vaginal deliveries, demonstrating that normal childbearing is possible after MMD treatment and that cesarean section may not be necessary as a default method of delivery in these patients.

Additionally, we believe that the long-term follow-up on the 4 patients with Down syndrome represents the longest such series in the literature on pediatric MMD and indicated a favorable neurological prognosis in these patients following revascularization.

Evolution of Moyamoya Practice Over Time

In addition to patient outcomes, analysis of the clinical presentation and surgical management of the patients in this series illustrates the changing landscape of the diagnosis and treatment of pediatric MMD, which are of particular interest to pediatric neurosurgeons.

Patients treated for MMD over 20 years ago were almost exclusively diagnosed after the onset of clinical symptoms such as stroke, in marked contrast to a clear trend of increasing numbers of patients whose MMD was incidentally detected (97% of patients in this series presented with ischemic symptoms including stroke and TIA vs 81% in a more recent report).¹¹ The higher rate of asymptomatic MMD patients being recognized and referred for treatment is likely due to improvements in neuroimaging and effective screening protocols for at-risk populations, such as patients with NF1 and sickle cell anemia. Additionally, improved understanding of the poor natural history of untreated MMD may have led over the past 2 decades to more aggressive surgical management in diagnosed but as yet asymptomatic patients.¹¹

In addition to diagnostic changes, there has been concomitant evolution in surgical technique. Patients in this series were more likely than those in today's practice to undergo additional burr hole placement at the time of pial synangiosis. Analysis of the benefit of this additional procedure, however, demonstrated that the development of additional collateral through the burr hole site on follow-up angiography was negligible, and consequently burr holes are no longer employed in current practice except in rare situations.^{14,16,17,32} Patients in this early series were also more likely to undergo staged procedures for bilateral disease. In marked contrast, nearly all bilateral contemporary cases undergo a same-day, single anesthesia bilateral craniotomy procedure.²⁶

Limitations of the Study

Limitations of this study include its retrospective nature, which precludes a comparison of surgical manage-

ment of MMD with other treatment options, including medical management—although all patients in this series were treated with long-term aspirin therapy. Additionally, several patients were lost to prolonged clinical follow-up, and existing clinical records often had incomplete information on patient quality of life. Many of these patients had been referred from remote geographic areas and were impossible to locate, but others could have been lost because of adverse medical events such as stroke or death. This bias could contribute to the inflation of favorable outcomes reported in this series.

Conclusions

Despite the limitations of this retrospective study, this series provides useful data for pediatric specialists in counseling patients and their families on the role of initial treatment and long-term outcomes for MMD. It underscores the changing presentation and management of MMD over the past 4 decades and emphasizes the role of long-term outcome studies in providing benchmarks to evaluate the efficacy of surgical treatment. Revascularization surgery for MMD appears to confer long-term, durable protection from stroke and other symptoms of cerebral ischemia to pediatric patients over decades of follow-up. Many patients with surgically treated MMD can be expected to live active, normal lives.

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References

- Adelson PD, Scott RM: Pial synangiosis for moyamoya syndrome in children. **Pediatr Neurosurg** 23:26–33, 1995
- Cho WS, Kim JE, Kim CH, Ban SP, Kang HS, Son YJ, et al: Long-term outcomes after combined revascularization surgery in adult moyamoya disease. **Stroke** 45:3025–3031, 2014
- Darwish B, Besser M: Long term outcome in children with Moyamoya disease: experience with 16 patients. **J Clin Neurosci** 12:873–877, 2005
- Hishikawa T, Tokunaga K, Sugi K, Date I: Long-term outcomes in adult patients with ischemic-type moyamoya disease involving posterior circulation. **Acta Neurochir (Wien)** 156:1745–1751, 2014
- Imaizumi T, Hayashi K, Saito K, Osawa M, Fukuyama Y: Long-term outcomes of pediatric moyamoya disease monitored to adulthood. **Pediatr Neurol** 18:321–325, 1998
- Isono M, Ishii K, Kamida T, Inoue R, Fujiki M, Kobayashi H: Long-term outcomes of pediatric moyamoya disease treated by encephalo-duro-arterio-synangiosis. **Pediatr Neurosurg** 36:14–21, 2002
- Jackson EM, Lin N, Manjila S, Scott RM, Smith ER: Pial synangiosis in patients with moyamoya younger than 2 years of age. **J Neurosurg Pediatr** 13:420–425, 2014
- Jea A, Smith ER, Robertson R, Scott RM: Moyamoya syndrome associated with Down syndrome: outcome after surgical revascularization. **Pediatrics** 116:e694–e701, 2005
- Karasawa J, Kikuchi H, Furuse S, Sakaki T, Yoshida Y: A surgical treatment of “moyamoya” disease “encephalo-myosynangiosis.” **Neurol Med Chir (Tokyo)** 17:29–37, 1977
- Lee SB, Kim DS, Huh PW, Yoo DS, Lee TG, Cho KS: Long-term follow-up results in 142 adult patients with moyamoya disease according to management modality. **Acta Neurochir (Wien)** 154:1179–1187, 2012
- Lin N, Baird L, Koss M, Kopecky KE, Gone E, Ullrich NJ, et al: Discovery of asymptomatic moyamoya arteriopathy in pediatric syndromic populations: radiographic and clinical progression. **Neurosurg Focus** 31(6):E6, 2011
- Matsushima Y, Fukai N, Tanaka K, Tsuruoka S, Inaba Y, Aoyagi M, et al: A new surgical treatment of moyamoya disease in children: a preliminary report. **Surg Neurol** 15:313–320, 1981
- Matsushima Y, Inaba Y: Moyamoya disease in children and its surgical treatment. Introduction of a new surgical procedure and its follow-up angiograms. **Childs Brain** 11:155–170, 1984
- McLaughlin N, Martin NA: Effectiveness of burr holes for indirect revascularization in patients with moyamoya disease—a review of the literature. **World Neurosurg** 81:91–98, 2014
- Mukawa M, Nariai T, Matsushima Y, Tanaka Y, Inaji M, Maehara T, et al: Long-term follow-up of surgically treated juvenile patients with Moyamoya disease. **J Neurosurg Pediatr** 10:451–456, 2012
- Mukerji N, Steinberg GK: Burr holes for moyamoya. **World Neurosurg** 81:29–31, 2014
- Nam TK, Park SW, Park YS, Kwon JT, Min BK, Hwang SN: Role of a burr hole and calvarial bone marrow-derived stem cells in the ischemic rat brain: a possible mechanism for the efficacy of multiple burr hole surgery in moyamoya disease. **J Korean Neurosurg Soc** 58:167–174, 2015
- Phi JH, Wang KC, Cho BK, Lee MS, Lee JH, Yu KS, et al: Long-term social outcome in children with moyamoya disease who have reached adulthood. **J Neurosurg Pediatr** 8:303–309, 2011
- Ross IB, Shevell MI, Montes JL, Rosenblatt B, Watters GV, Farmer JP, et al: Encephaloduroarteriosynangiosis (EDAS) for the treatment of childhood moyamoya disease. **Pediatr Neurol** 10:199–204, 1994
- Scott RM: Moyamoya. **J Neurosurg Pediatr** 2:158, 2008
- Scott RM: Moyamoya syndrome: a surgically treatable cause of stroke in the pediatric patient. **Clin Neurosurg** 47:378–384, 2000
- Scott RM: Surgery for moyamoya syndrome? Yes. **Arch Neurol** 58:128–129, 2001
- Scott RM: Surgical treatment of moyamoya syndrome in children. 1985. **Pediatr Neurosurg** 22:39–48, 1995
- Scott RM, Smith ER: Moyamoya disease and moyamoya syndrome. **N Engl J Med** 360:1226–1237, 2009
- Scott RM, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA: Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. **J Neurosurg** 100 (2 Suppl Pediatrics):142–149, 2004
- Smith ER, Scott RM: Progression of disease in unilateral moyamoya syndrome. **Neurosurg Focus** 24(2):E17, 2008
- Smith ER, Scott RM: Surgical management of moyamoya syndrome. **Skull Base** 15:15–26, 2005
- Starke RM, Komotar RJ, Hickman ZL, Paz YE, Pugliese AG, Otten ML, et al: Clinical features, surgical treatment, and long-term outcome in adult patients with moyamoya disease. Clinical article. **J Neurosurg** 111:936–942, 2009
- Sundaram S, Sylaja PN, Menon G, Sudhir J, Jayadevan ER, Sukumaran S, et al: Moyamoya disease: a comparison of long term outcome of conservative and surgical treatment in India. **J Neurol Sci** 336:99–102, 2014
- Suzuki J, Takaku A: Cerebrovascular “moyamoya” disease. Disease showing abnormal net-like vessels in base of brain. **Arch Neurol** 20:288–299, 1969
- Zhang Y, Bao XY, Duan L, Yang WZ, Li DS, Zhang ZS, et al: Encephaloduroarteriosynangiosis for pediatric moyamoya disease: long-term follow-up of 100 cases at a single center. **J Neurosurg Pediatr** 22:173–180, 2018

32. Zhao X, Wang C, Ji Y, Han C, Wang M: Therapeutic effect of multiple burr hole operation combined with dural inversion and periosteal synangiosis for moyamoya disease. **Br J Neurosurg** **29**:811–817, 2015

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Scott. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the

article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Smith.

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