Late morbidity and mortality following revascularization surgery for moyamoya disease in the pediatric population

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OBJECTIVE There are limited reports on long-term morbidity in pediatric patients who have undergone surgical revascularization for moyamoya disease (MMD). Here, the authors report long-term morbidity and mortality in a population of pediatric patients who underwent pial synangiosis for MMD from 1988 through 2016.

METHODS A single-center retrospective review of the hospital and personal operative databases of the senior authors was carried out to identify all patients who were treated for MMD at Boston Children’s Hospital between 1988 and 2016, and who experienced any episode of late morbidity or mortality, which the authors defined as an event resulting in significant neurological deficit or death occurring more than 1 year after revascularization surgery. Hospital records were reviewed to determine pertinent demographic data, the initial mode of patient presentation, and associated comorbidities. Radiographic studies, when available, were reviewed for documentation of the diagnosis and for confirmation of the late complication, and the literature on this topic was reviewed.

RESULTS In total, 460 patients with MMD underwent surgery between 1988 and 2016 using the pial synangiosis surgical technique; 15 (3.3%) of these patients (9 females and 6 males) experienced documented late death (n = 14) or severe morbidity (n = 1). The median age at revascularization surgery was 8.0 years (range 1–21 years). The causes of these late complications were grouped into three etiologies: intraventricular or intracerebral hemorrhage (n = 8), systemic complications related to associated comorbidities or preoperative disabilities (n = 5), and the development of malignant brain tumors (n = 2). Four patients whose MMD was associated with a history of cranial radiation therapy died. These events occurred from as early as 2 years to as late as 27 years postoperatively.

CONCLUSIONS The risk of late morbidities and mortality following pial synangiosis for MMD in the pediatric patient appeared to be low. Nevertheless, the occurrence of catastrophic cerebrovascular events, particularly intracerebral and intraventricular hemorrhage in the otherwise neurologically stable revascularized patient, was concerning. Although there is value in long-term surveillance of patients who have undergone surgery for MMD, from both a neurological and a general medical standpoint, particularly in patients with the risk factor of prior cranial radiation therapy, it is not clear from the data how the late deaths in this population could have been prevented.

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KEYWORDS moyamoya disease; morbidity; mortality; long-term follow-up; pial synangiosis; vascular disorders
who experienced any episode of late morbidity or mortality, which we defined as an event resulting in significant neurological deficit or death occurring more than 1 year after revascularization surgery. Each record was reviewed to determine all pertinent demographic data, the initial mode of patient presentation, and associated comorbidities. Radiographic reports and images were reviewed for confirmation of the diagnosis and the late complication, and the literature on this topic was reviewed.

Results and Case Histories

During this 28-year period, 15 patients were identified as having experienced a late life-threatening complication or death. The etiologies of the late deaths and serious complications were grouped into categories (Tables 1–3), and representative case histories from each group are presented below. No patient in the operative series experienced a late ischemic stroke leading to significant neurological deficit or death.

Death or Severe Neurological Disability Due to Intraventricular and/or Intracerebral Hemorrhage

Patient 1

A 6-year-old male presented with bilateral strokes. The patient had a history of acute T-cell lymphoblastic leukemia, diagnosed at 2 years of age, that had been treated with systemic and intrathecal chemotherapy and cranial irradiation. The patient’s imaging studies demonstrated bilateral MMD, right greater than left, and he underwent bilateral pial synangioses. The follow-up angiogram obtained 2 years later showed only minimal collateral flow resulting from the revascularization procedures. The MMD had progressed, and there were abundant pial-pial collaterals anterior to the middle cerebral artery territory from the posterior circulation. The patient experienced an intraventricular hemorrhage (IVH) at 10 years of age, and an angiogram showed an intraparenchymal aneurysm on a right lenticulostriate vessel that was deemed inoperable and untreatable with neurointerventional techniques. On repeat angiography 1 year later, the aneurysm could no longer be visualized; cerebral collaterals through the synangioses remained poor. Six years after surgery, at 12 years of age, the patient experienced a second, fatal IVH, which appeared to originate from the right thalamus, in the same area of the previously visualized lenticulostriate aneurysm.

Patient 2

A 16-year-old female presented 1 year earlier with transient ischemia attacks (TIAs). Bilateral MMD was diagnosed based on angiography findings, and the patient underwent pial synangioses. A postoperative angiogram obtained 1 year later showed good results on the left side but only moderate surgically induced collaterals on the right side. At 21 years of age, she experienced syncopal spells and psychological problems, but both symptoms gradually disappeared, and her imaging studies every 2 years remained stable, with no evidence of new ischemic lesions. The studies documented continued progression of her MMD and increased surgical site collaterals. At 39

| TABLE 1. Death or severe neurological disability due to IVH and/or ICH |
|--------------------------|------------------|-----------------|-----------------|------------------|
| Patient No. | Age at Synangiosis (yrs) | Age at Death/Complication (yrs) | Cause of Death/Complication | Comorbidity/Relevant History |
| 1 | 6 | 12 | IVH, fatal | T-cell acute lymphoblastic leukemia |
| 2 | 16 | 40 | ICH & IVH, fatal | None |
| 3 | 13 | 40 | ICH & IVH, fatal | Hypothalamic-optic system glioma treated w/ radiation therapy, age 3 yrs |
| 4 | 1 | 19 | IVH, fatal | PHACES syndrome |
| 5 | 8 | 28 | ICH, fatal | Korean ancestry |
| 6 | 9 | 32 | Pontine hemorrhage, fatal | Hypothalamic-optic system glioma treated w/ radiation therapy at age 5 yrs |
| 7 | 8 | 27 (alive at age 30 yrs) | ICH, devastating, nonfatal | None |
| 8 | 7 | 9 | IVH, fatal | None |

PHACES = posterior fossa, hemangioma, arterial lesions, congenital defects, and eye or endocrine abnormalities.

| TABLE 2. Death due to associated comorbidity or severe preoperative neurological disability |
|--------------------------|------------------|-----------------|-----------------|
| Patient No. | Age at Synangiosis (yrs) | Age at Death (yrs) | Cause of Death | Comorbidity |
| 9 | 16 | 20 | Self-mutilation–induced late wound infection & cerebritis | Down syndrome, debilitating bilateral strokes preop |
| 10 | 18 | 29 | Cardiac failure | Congenital peripheral pulmonary artery stenosis & pulmonary hypertension |
| 11 | 1 | 12 | Unknown, died in sleep | Bilateral strokes preop, severe developmental delay |
| 12 | 15 | 19 | Bone marrow failure | Aplastic anemia |
| 13 | 8 | 20 | Complications after renal transplant | Chromosome 1 inversion |
years of age, the patient was noted to have polycystic kidney disease but no evidence of hypertension. At 40 years of age, she experienced a fatal intracerebral hemorrhage (ICH) and IVH, apparently originating in the right basal ganglion (Fig. 1), 24 years after her initial revascularization surgery. Postmortem examination revealed no definite etiology of the hemorrhage. Her most recent stable MRI and MRA studies had been performed 6 months prior to the fatal event; MRA demonstrated complete occlusion of both the middle and anterior cerebral arteries, severe occlusive disease of both posterior cerebral arteries, and florid flow at the surgical sites (Fig. 2). No deep moyamoya vessels or aneurysms could be identified. The patient had been taking 81 mg of aspirin daily since her original surgery.

Patient 3

A 13-year-old female presented with a small right basal ganglion hemorrhage, and arteriography demonstrated bilateral MMD. The patient had previously been diagnosed at an outside institution with a hypothalamic-optic system glioma and treated with conventional external-beam radiation therapy at 3 years of age. Two days after undergoing bilateral pial synangioses, the patient experienced a deep left frontal and basal ganglion infarct that produced pseudobulbar affect and bilateral spasticity. She subsequently remained neurologically stable, living in an assisted-living facility, taking 81 mg of aspirin per day as well as replacement hormonal medication. At 40 years of age, she experienced a fatal IVH from an ICH apparently originating from the right basal ganglion (Fig. 3). Findings on MRI and MRA obtained only 5 months earlier were unchanged from prior studies, showing Suzuki stage 5–6 MMD, worse on the left side, persistent transcerebral moyamoya collaterals emanating from the right middle cerebral artery and around the midbrain, steno-occlusive disease in both posterior cerebral arteries, florid vasculature in the areas of both pial synangioses, and no evidence of tumor regrowth. All findings had been stable over decades (Fig. 4).

Death Due to Associated Comorbidity or Severe Preoperative Neurological Disability

Patient 13

An 8-year-old male presented with multiple TIAs at 8 years of age. The patient was born with a chromosome 1 inversion that is associated with progressive renal failure. An arteriogram demonstrated bilateral MMD, and the patient underwent bilateral pial synangioses. He had no further neurological events but developed progressive...
renal failure and died of complications following a renal transplant at 20 years of age.

Patient 10

An 18-year-old female presented with right hemisphere TIAs and imaging evidence of a prior right hemispheric stroke. The patient had a history of congenital peripheral pulmonary artery stenosis and pulmonary hypertension. After arteriography demonstrated bilateral MMD, she underwent bilateral pial synangioses. She remained neurologically stable but died at 29 years of age of complications of pulmonary hypertension after multiple failed cardiac interventions.

Radiation-Induced Malignant Brain Tumors

Patient 14

A 6-year-old female presented with TIAs. Two years previously, she had been diagnosed with neurofibromatosis (NF) and a hypothalamic optic system glioma, and, at 5 years of age, she underwent treatment with conventional external-beam radiation therapy. After angiography demonstrated bilateral MMD 1 year later, she underwent bilateral pial synangioses, and a 1-year postoperative angiogram demonstrated excellent surgically induced collaterals. She developed a malignant brainstem glioma at 25 years of age (19 years after her revascularization surgery), presumably radiation induced, and she died from widespread tumor infiltration of the brain.

Discussion

In our series of 460 pediatric patients with MMD who underwent pial synangiosis revascularization surgery, 15 patients (3.3%) experienced late serious morbidity or mortality. The incidence of late ischemic or hemorrhagic stroke after revascularization surgery in patients with MMD has been reported to occur in 0% to 6.3% and 0% to 5.2% of pediatric patients, respectively. Funaki et al. reported 1.8%, 7.3%, and 13.1% incidences of late cerebrovascular events in a cohort of 58 pediatric patients with MMD at 10, 20, and 30 years, respectively. In reviewing the literature on late complications in pediatric patients after cerebral revascularization surgery, Funaki et al. found that hemorrhages are observed more often in patients with more than 10 years of follow-up compared with patients with less than 10 years of follow-up. These results were replicated in the study of their own patients, which demonstrated that all postoperative hemorrhages similarly occurred more than 10 years after surgery. These studies suggest that late cerebral hemorrhages will occur in this patient population with increasing frequency as the postoperative interval increases.

In patients with intraventricular and/or intracerebral hemorrhage, we do not have information on every patient regarding associated medical conditions that might otherwise contribute to this specific complication, such as hypertension, a known late association with MMD. In a long-term follow-up of more than 100 patients with MMD, Hara et al. identified 3 patients who developed renal artery stenosis more than 10 years after
surgery. For this reason, it may be important to continue neurological and medical surveillance of patients with MMD who have undergone surgery and who, with the development of otherwise treatable systemic illnesses such as hypertension, may be at greater risk of cerebral hemorrhage due to the presumed fragility of moyamoya vessels and altered collateral pressure and flow patterns in the brain. Other modifiable risk factors include smoking, hyperlipidemia, and obesity, which potentially could further contribute to a greater risk of hemorrhagic stroke in this population. In addition, we are unable to determine the efficacy of revascularization surgery in preventing late hemorrhages. It might be postulated that the collaterals induced by surgery might cause regression of fragile deep moyamoya vasculature, accelerating a normal evolution of moyamoya vasculopathy and reducing the risk of bleeding from these vessels. The postoperative arteriograms obtained in patient 1 never demonstrated good collaterals through the synangioses; yet in patient 2, premortem MRA studies demonstrated robust collaterals through both operative sites. Thus, we are unable to draw any conclusions regarding the role of the induced surgical collaterals in the etiology of these intracerebral bleeds. It has not been our practice to reoperate on patients with poor results from an initial pial synangiosis, having observed that the surgically induced collaterals will typically improve over time, and we reserve reoperation for those patients in whom there are persisting symptoms or new strokes.

It has been our practice to prescribe lifelong, low-dose aspirin therapy in our patients with MMD who have undergone surgery on the theory that the steno-occlusive vessels are a potential source for cerebral emboli. However, an idiosyncratic reaction to the medication, with altered platelet function, could also lead to an increased risk of bleeding, although none of our patients or families altered platelet function, could also lead to an increased risk of bleeding, although none of our patients or families reported a history of easy bruising or prolonged bleeding following minor trauma. We were unable to determine how many of these patients with cerebral hemorrhage were actually taking their aspirin at the time of death, but it had been universally prescribed. We have recorded only one significant thromboembolic event in a patient on long-term aspirin therapy—a 37-year-old female who, while taking 81 mg of aspirin per day, experienced an occlusion of the cervical internal carotid artery and blindness from central retinal artery occlusion 30 years after bilateral synangiosis surgery. Although we have recommended surveillance MRI and MRA in our patients every 2 years, lifelong, none of the patients in this series—some of whom had MRI studies within 6 months of their fatal event—had any new abnormal basal or periventricular vascular changes that were visible. The resolution of MRI and MRA studies has continued to improve over time, and we will continue to recommend that follow-up imaging be obtained in our patients every 2 years once 10-year follow-up has been attained. It is also hoped that the radiation therapy–related deaths will become less common, since this modality is being used less frequently in young patients and in those with conditions such as NF that are prone to the development of secondary neoplasms.

Conclusions

Late deaths and severe neurological morbidity occur in a small percentage of patients with MMD who have undergone pial synangiosis. Such complications, particularly ICH, appear to cluster in patients in whom MMD has developed after cranial radiation. Comorbidities associated with moyamoya will continue to require active management and may likewise lead to late mortality. This study provides physicians and patients with new, quantifiable data about the long-term risk of severe adverse events in this population, along with identification of some modifiable risk factors that may have the potential to reduce risk. Long-term surveillance of patients who have undergone surgery for MMD, from both a general medical and an imaging standpoint, may be beneficial, but more data regarding these patients over the long term might be helpful in reducing these late events.

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References


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