Transition to Adulthood for Pediatric Moyamoya Patients

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J Pediatr Neurol 2020;18:273–278.

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Abstract

Moyamoya is a progressive arteriopathy of the intracranial vasculature, predominantly affecting the terminal branches of the internal carotid artery. Treatment is predicated on surgical revascularization to reduce the risk of stroke. For patients diagnosed and treated as children, it is important to recognize the long-term implications of the disease, for example, that moyamoya is treatable, but not curable. Pediatric moyamoya patients face unique challenges as they transition to adulthood as a consequence of the chronic nature of this disorder. Successful long-term care requires a strategy that incorporates ongoing longitudinal disease monitoring, coordination of care between physician teams, and anticipation of socioeconomic factors that change over time. This article provides an approach to transition care to adult caregivers for pediatric moyamoya patients with a specific focus on the three key stakeholders in the process: the neurosurgeon, the primary care physician, and the individual patient.

Keywords

- moyamoya
- pediatric
- adult
- transition
- cerebrovascular
- stroke

Introduction

Moyamoya disease is characterized by progressive narrowing of the terminal branches of the internal carotid arteries, including the middle and anterior cerebral arteries.[1] The arteriopathy is an end-stage process resulting from a diverse mix of genetic and/or environmental drivers.[1,2] There is often a compensatory development of collateral vessels from both the intra- and extracranial (transdural) circulation, but this is typically incapable of meeting the ischemic demand of the brain and therefore stroke will ensue if the patient is left without treatment.[3,4] Surgical revascularization is the primary treatment for moyamoya disease and is considered both safe (particularly when done at high-volume centers) and very successful in providing significant and durable reductions in stroke rates.[3,5,6] However, surgery does not cure the disease and pediatric patients require lifetime monitoring and management of their condition.

The rarity of moyamoya disease means that there is limited information available to patients and caregivers to guide long-term follow-up. In particular, there is a need to improve the process of transitioning from pediatric to adult care.[7] The three key stakeholders involved in this transition are the neurosurgeon, the primary care physician, and the patient. This article provides a summary outlining the strategy employed for managing this transition at Boston Children's Hospital, with data to answer some of the more common questions relevant to this process.

Role of the Neurosurgeon

The pediatric neurosurgeon has a critical role in identifying key issues relevant to moyamoya-disease-related care and helping the patient, family, and primary care physician navigate the transition to adulthood. The responsibilities of the neurosurgeon can broadly be divided into two categories. The first category involves outlining health-care areas specific to moyamoya disease that require neurosurgical involvement. These topics include timing of clinical and radiographic monitoring, justification of the need for these visits, and guidance on the medical management of

received
December 20, 2018
accepted
March 29, 2019
published online
August 20, 2020

Issue Theme Problems in the Transition from Child Neurosurgery to Adult Neurosurgery; Guest Editors: Ekkehard M. Kasper, MD, DPhil, FAANS, and Hüseyin Çaksen, MD

DOI https://doi.org/10.1055/s-0040-1715500.
ISSN 1304-2580.

moyamoya disease (medications, fluid balance, and comorbidity risks).

A second category of responsibility for the pediatric neurosurgeon is to formulate a strategy to smoothly transition care to an adult medical team. In many (but not all) cases, this will primarily include shifting neurosurgical care from a pediatric to an adult neurosurgeon and also transitioning the patient from a pediatrician to a family practitioner or internist. Depending on the individual, there may also be a move from a pediatric to an adult neurologist, epileptologist, or neuropsychologist. It is important to identify all of the physicians participating in the care of the patient early on to provide continuity of care in each of the subspecialties involved.

Clinical and Radiographic Follow-Up

Appropriate clinical and radiographic follow-up is critical to the long-term success of stroke prevention in moyamoya patients. While surgical revascularization is very successful at reducing stroke rates, the risk of stroke persists over the life of the patient. Recent data suggests that the risk of stroke after surgery levels out over time, but remains slightly higher than patients without moyamoya disease, with rates quoted at ~5% over 5 years, 7.5% at 10 years, and less than 1% per year thereafter.[1,3,5] In a series of 147 patients with 10 years of clinical and radiographic follow-up, there was a 3.4% need for reoperation, a 13% rate of transient ischemic attack (which is reflected in at least one transient ischemic attack within 5 years), and a 5.4% stroke rate over 10 years (unpublished data, Boston Children's Hospital). New strokes can result from a wide range of etiologies (►**Table 1**). While not all strokes are preventable, careful follow-up may help the astute clinician identify modifiable risks at an early stage, offering potential opportunities to intervene and mitigate risk.

Our institution has adopted a standardized protocol for immediate and long-term follow-up of moyamoya patients after surgery (►**Table 2**). Imaging, office visits, and telemedicine are used in combination to ensure successful surgical engraftment, monitor for new areas of arteriopathy, and aid with recovery from any moyamoya-related strokes. Justification for imaging on an annual basis centers on confirmation of engraftment, evidence of improved flow, and absence of new infarction (assessed by magnetic resonance angiography (MRA) or catheter angiogram to verify surgical collateral patency and axial fluid-attenuated inversion-recovery imaging to track improvements in blood flow via loss of ivy sign)[8–11] (►**Fig. 1**). In addition, we monitor for areas of new arteriopathy and the potential development of aneurysms. Studies suggest that up to ~30% of pediatric moyamoya patients with unilateral disease will progress to involvement on the opposite side, and development of aneurysms can occur even in a delayed fashion (equally important, the disappearance of aneurysms following revascularization has also been reported).[12–18] Given that these findings might prompt surgical or endovascular intervention, ongoing sequential monitoring with imaging is typically approved by insurance companies.

The neurosurgeon can also help with follow-up of comorbid conditions that may affect the care of patients with moyamoya. For children that develop moyamoya after radiation treatment for brain tumors, there should be an awareness of the risk of secondary tumors, endocrinologic disease (especially diabetes insipidus, given the risk of fluid status on intracranial circulation), and the higher risk of stroke in this population.[1,3,19] Patients who have ventricular shunts may need catheter revision in the future, and there is a risk of interrupting important transdural collaterals that may involve the shunt site.[4,20] Consideration of this possibility prior to shunt revision may allow for alternative approaches to minimize the risk of stroke. Lastly, patients with syndromic moyamoya disease associated with systemic disorders that have independent stroke risk factors (sickle cell disease, Down syndrome, structural cardiac defects, etc.) can benefit from routine communication between neurosurgeons and other subspecialists to provide effective multidisciplinary care.

Strategies to Transition Care to Adult Providers

Transitioning care to other health care providers is common as children age. Pediatricians are not trained to treat adults, patients may move with the onset of employment, and insurance may change, with attendant changes in network physicians. Some pediatric neurosurgeons can continue to care for children for some time into adulthood, while others, either by hospital mandate or by personal preference, cannot. In either case, the neurosurgeon caring for children with moyamoya disease can help to ease this transition by anticipating it and providing the patient with a strategy for the process.

The first step in the strategy for transition is to discuss the topic with the patient and family, with a review of the rationale for changing care and talking about timing. In many cases, transitioning will be a process over a period of

Table 1 Potential etiologies of new stroke in moyamoya patients postrevascularization

1. Arteriopathy progression involving new vascular territory (posterior circulation, opposite side)
2. Physiological stressor (severe illness, dehydration)
3. New medications (antihypertensives, high estrogen oral contraceptives)
4. Excessive alcohol use (vomiting, dehydration)
5. Smoking (nicotine-related vasoconstriction and blood pressure volatility)
6. Illicit drug use (blood pressure volatility, loss of cerebral autoregulation)

Table 2 Postoperative follow-up protocol for pediatric moyamoya patients

1 month postop a. Telemedicine or in-office visit b. Review incision(s), discuss return to activity/school
6 months postop a. MRI/A with axial FLAIR; assess surgical sites and early engraftment. Determine new baseline for stroke burden b. Phone review of results and check-in with patient
1 year postop a. MRI/A with axial FLAIR b. If unilateral disease, consider digital subtraction angiogram to formally assess opposite (nonaffected) side c. Telemedicine or in-office visit
Annually for 5 years a. MRI/A with axial FLAIR b. Telemedicine or in-office visit
Every 3 years thereafter a. MRI/A with axial FLAIR b. Telemedicine or in-office visit
Patients maintained on aspirin, typically 81 mg daily if older than 5 years of age

Abbreviations: FLAIR, fluid-attenuated inversion-recovery; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography.

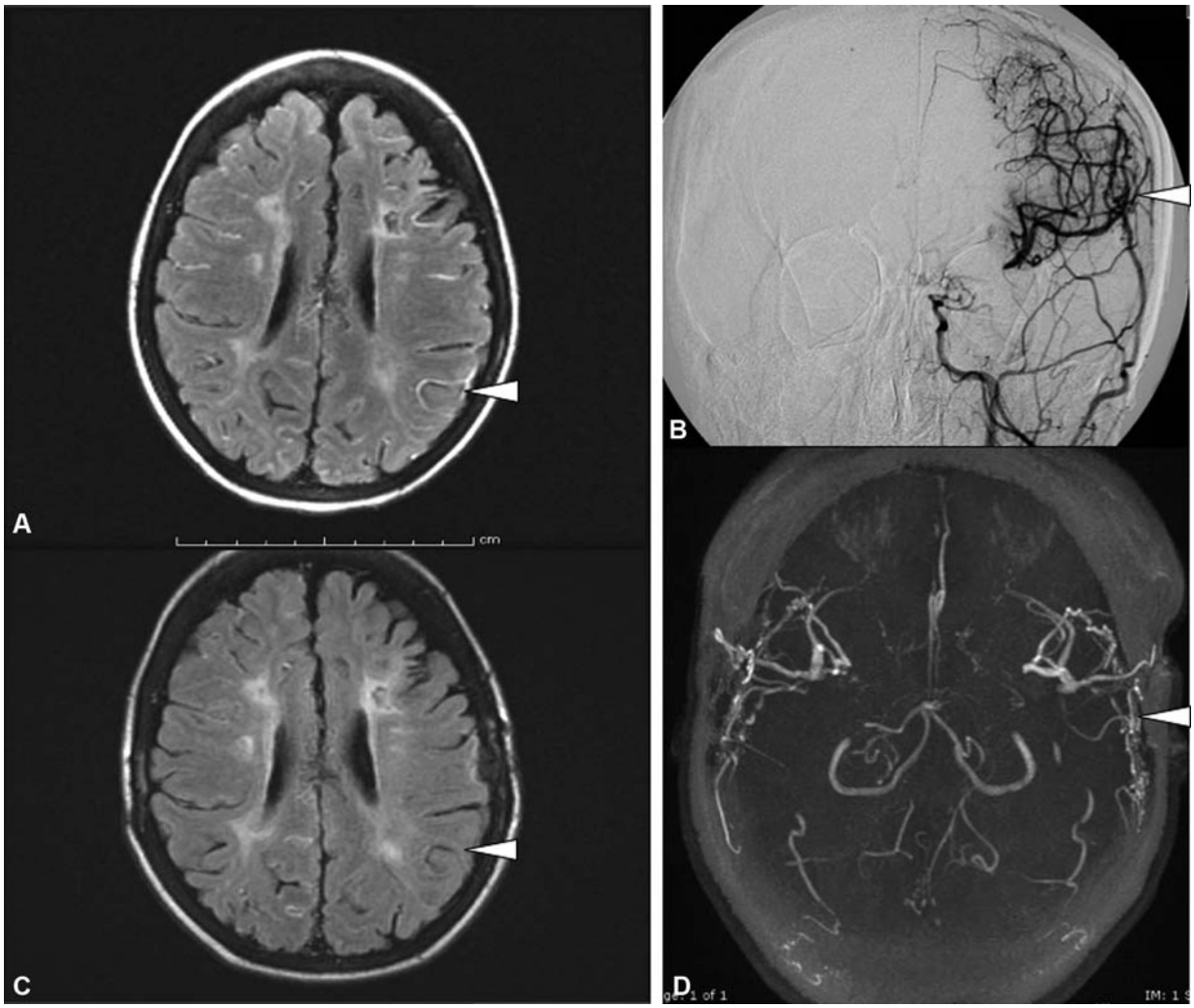

Fig. 1 Axial fluid-attenuated inversion-recovery magnetic resonance imaging studies pre (**A**) and (**B**) postrevascularization, demonstrating ivy sign preop (white sulcal hyperintensity, arrowhead) and marked resolution of ivy sign postop (arrowhead). (**C**) Postoperative anteroposterior projection image of an angiogram with injection of the external carotid artery, demonstrating robust surgical collaterals (Matsushima A) filling the right hemisphere. (**D**) Axial magnetic resonance angiography image demonstrating postoperative surgical collaterals from pial synangiosis (arrowhead).

time, but having a specific age targeted can be helpful. At our institution, we follow patients into their 30s, but try to initiate a transition to a future health care team in the early 20s. Age 21 (as a legal adult), age 22 (for college students, the typical age of graduation), and age 26 (often the time children are mandated to come off of parental insurance policies) are common "break points" that are used.

After agreeing upon a time, the next step involves working to find a suitable team of caregivers. In particular, a neurosurgeon with an adult practice should be identified, ideally with some expertise in moyamoya disease. Contacting the neurosurgeon directly can often expedite the process, and the referring pediatric neurosurgeon might consider drafting a note summarizing care and active issues. Copies of office notes, operative reports, and physical copies of imaging studies (on compact disk or thumb drive) should be collected by the patient directly, in addition to sending a second set of records to the new team. This should include any neurologists or therapists that may be involved in stroke recovery or managing moyamoya-related issues. Encouraging the patient to take control of his or her own medical care is an additional goal of transitioning care. Lastly, we will often try to coordinate one or two closely overlapping office visits between the current and incumbent medical teams to ensure the handoff goes smoothly. If the patient has not had a recent scan, we will typically arrange for a "graduation" magnetic resonance imaging (MRI)/A around the time of the final visit so that any issues can be addressed together.

Role of the Primary Care Physician

Partnership between the neurosurgeon and primary care physician is critical, as many areas of routine medical care can be impacted by the diagnosis of moyamoya. In particular, three subjects merit specific attention. These include guidance on (1) medications, (2) surgical/dental procedures (including pregnancy), and (3) genetic counseling.

Medications

As patients transition to adulthood, numerous questions about medication use are common. Existing medications may need to have dosing adjusted as patients gain weight or add new agents that might affect drug metabolism. In particular, if patients are on antiepileptic agents, dosing can become complicated. It is our practice to refer patients to a neurologist to help with this area of their care. In addition to adjusting dosing, different agents might be advised in some cases—and in others, there may be an opportunity to wean the medications altogether. We keep patients on lifelong aspirin (prophylactic dose 81 mg per os once daily, barring specific contraindications) and sometimes the dose may need to be increased with weight gain. However, for most patients who remain asymptomatic and with stable scans after surgery we continue 81 mg daily.[3,21]

Other common medication questions include oral contraceptives, antihypertensives, and vaccinations. Prescribing oral contraceptives as birth control is generally well-tolerated in moyamoya patients. There remain concerns about high-estrogen formulations and the risk of stroke, and therefore this specific approach is avoided when possible, with substitution of estrogen-free prescriptions.[22] Several moyamoya patients may have pre-existing hypertension or may develop it later in life, leading to questions about the use of antihypertensive medication. In general, there needs to be a balance between maintaining cerebral perfusion and reducing cardiovascular stress on systemic organs. The risk of stroke is greatest with sudden changes in blood pressure, and while a complete review of blood pressure management is outside the scope of this review, it is prudent to introduce new medications gradually, with dosing spread out over multiple time points whenever possible. Lastly, vaccinations are encouraged when medically indicated, with a particular note to obtain annual influenza boosters, as added protection from the flu is especially helpful for moyamoya patients, given the risk of dehydration and stroke with illness.

Surgical/Dental Procedures/Pregnancy

The majority of moyamoya patients will undergo at times some type of medical or dental procedure in adulthood. General principles of management include avoiding hypotension and hyperventilation to reduce the risk of decreased cerebral perfusion. This often means providing hydration in advance of any prolonged procedure (generally more than 3 hours) and —importantly—managing anxiety and pain effectively (as fear or discomfort may lead to hyperventilation). Discussion of methods to alleviate these concerns (premedications, support networks, etc.) can be helpful. We generally encourage the continuation of aspirin through nearly all procedures, as the small risk of increased bleeding from low-dose aspirin is usually offset by the benefit of stroke protection conferred by continued aspirin use.

Any type of minor treatment performed with local anesthetic (dental work, removal of skin lesions or warts, eye surgery, etc.) generally is safe. More complex procedures, involving general anesthesia, risk of significant blood loss, or hemodynamic shifts should be managed with discussions between the neurosurgeon and the referring team whenever possible. Perioperative hydration, avoidance of hyperventilation, and careful control of blood pressure are all measures that can reduce the risk of periprocedural stroke. In addition, care in positioning to avoid kinking or compression of the scalp graft sites can be important.

For female moyamoya patients, questions about the safety of pregnancy are common. Numerous reports have reviewed institutional experiences with moyamoya and pregnancy. If possible, cerebral revascularization prior to becoming pregnant (if surgery is warranted) confers some degree of protection from stroke.[23] A major risk factor for stroke—particularly hemorrhagic stroke—during pregnancy is uncontrolled hypertension, suggesting that careful obstetrical monitoring and early steps to control blood pressure may be important.[24] While many centers choose cesarean section as the default method of delivery, healthy vaginal births are certainly possible, with the caveat that pain management (often with an epidural catheter) and avoidance of hyperventilation are

crucial.[25] Overall, for moyamoya patients already revascularized, > 95% of mothers with moyamoya disease have good neurological outcomes after pregnancies, with all delivered children reported healthy.[23] In contrast, those females who were newly diagnosed with moyamoya during pregnancy (typically with a new stroke or hemorrhage) typically presented after 24 weeks of gestation, with >10% maternal mortality and >20% fetal death.[23] In aggregate, these data suggest that pregnancy can lead to a safe delivery of a healthy child in the vast majority of cases, but with the important caveat that moyamoya is recognized and treated with successful revascularization prior to becoming pregnant.

Genetic Counseling

Increasingly, genetic drivers of moyamoya disease are being identified.[1,2] Of particular importance are mutations associated with RNF213, commonly present in Asian populations.[26,27] A host of other genetic mutations and heritable conditions are also linked to this arteriopathy, including ACTA2 R179, NF1, GUCY, NF-1, and sickle cell disease.[2,28,29] The incidence of familial moyamoya disease is much lower in the United States (3.4%) as compared with Japan, Korea, and China, but the question of familial genetic and radiographic screening is a common question in neurosurgical practice.[28] If first-degree family members provide a medical history or manifest worrisome findings on physical examination that might suggest moyamoya disease, a reasonable first step for screening might include a MRI/A. It is also reasonable to refer identical twins to screening.[28] However, absent specific "red flags" referral to a neurovascular genetic counselor is an appropriate step for families or patients with questions about genetic screening and the evolving technologies of genome sequencing.[28]

Role of the Patient

As a pediatric moyamoya patient transitions to adulthood, there are socioeconomic factors that are important to address. These include use of restricted and illicit substances (alcohol, nicotine and other drugs), changes in diet, sexual activity, exercise, and travel. There is limited data on the effects of smoking and diet on stroke risk in moyamoya disease, although the vasoconstrictive effects of nicotine (in smoking and vaping) may contribute to an increased risk of stroke and development of diabetes has also been shown to increase the risk of stroke in young adults with moyamoya.[30,31] Vasoactive illicit drug use has been reported in association with severe stroke in moyamoya patients, particularly cocaine.[32] There is a paucity of literature on alcohol use and moyamoya stroke risk, but we counsel our patients that it is reasonable to assume that there is a higher risk of stroke with excessive alcohol intake, given the possibility of volume shifts and hyperventilation with nausea and dehydration.[33] However, we do generally permit responsible drinking if the patient is otherwise asymptomatic and more than a year out from surgery.

Questions about sexual activity are common, but other than reviewing the previously noted advice on birth control and pregnancy, we do not suggest any specific restrictions. Similarly, the exertion associated with regular exercise is a similar source of concern, and there are rare reports of exercise-induced neurological deficits in moyamoya patients.[34] Given data linking head trauma with intracranial hemorrhage in patients with cerebrovascular disease, it is reasonable to suggest restrictions of high-risk head-impact activities, such as tackle football and boxing.[35] However, as long as patients avoid these specific high-risk activities and take proper precautions (gradually working up to higher levels of activity, maintaining adequate hydration and knowing to reduce effort if any unusual sensations occur), we encourage physical fitness. We generally do not limit travel, other than discussions of risk in situations of extreme changes of air pressure (such as hiking at elevations over 10,000 feet or scuba diving in excess of 33 feet underwater). Overall, we try to encourage patients to adopt a full and active lifestyle while avoiding a select cohort of higher-risk activities.

Conclusion

The process of transitioning from dependent pediatric moyamoya patient to adulthood requires strategic planning over a period of years with significant investments of time and effort from neurosurgeons, primary care physicians, and the patients themselves. Clear articulation of goals of care coupled with open lines of communication between all parties offers the best chance for successful long-term reductions in stroke risk while simultaneously maximizing the quality of life.

Conflict of Interest
None declared.

Acknowledgments
The authors would like to acknowledge Kids @ Heart Moyamoya Fund and Marcus Chae Research Fund, for their help in this article.

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