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Moyamoya Arteriopathy

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Opinion statement

The arteriopathy of moyamoya is progressive and results in severe disability from cerebral ischemia. Once the diagnosis is confirmed with magnetic resonance imaging (MRI) and catheter angiography, initial measures should consist of administration of low dose aspirin (usually 81 mg daily, barring pre-existing contraindications), maintenance of good hydration and avoidance of hyperventilation (to reduce the risk of reflex cerebral vasoconstriction). Definitive treatment is predicated on surgical revascularization of the affected cerebral hemispheres. Operative treatment should be undertaken at a high-volume center with experienced surgeons and anesthesia staff. The specific technique employed depends on the individual presentation and surgeon preference, although most centers will offer indirect approaches such as pial synangiosis to children and young adults, with direct bypass often reserved for older patients or those presenting with crescendo symptoms. Follow-up is important, with postoperative imaging (either MRI or catheter angiogram) and office visits to confirm surgical efficacy and resolution of symptoms.

Introduction

Moyamoya is an arteriopathy of the internal carotid arteries and their branches that results in progressive occlusion of the intracranial lumen and concomitant development of brain ischemia. Reduction of flow is associated with a response in which the remaining small vessels maximally dilate and spur the growth of a network of new collateral vessels—the so-called "puff of smoke" seen on angiography. Typically these changes only occur in the distribution of the internal carotids, but rare cases may also involve the posterior circulation.

It can sometimes be difficult to confirm the diagnosis of moyamoya, given the heterogeneous nature of its presentation. The classic findings of bilateral narrowing and concomitant collateral development—as seen on angiogram—is defined as moyamoya *disease* when found in the absence of other medical conditions. It is common to see evidence of ischemia, with slow flow or strokes, on other modalities such as magnetic resonance imaging (MRI) (Fig. 1) When the narrowing is only seen unilaterally, or when unilateral or bilateral narrowing is found in association with certain defined clinical conditions, then the moniker of moyamoya *syndrome* is applied (Table 1)[1].

Females are affected at nearly twice the frequency seen in males, and there are two peaks of presentation,

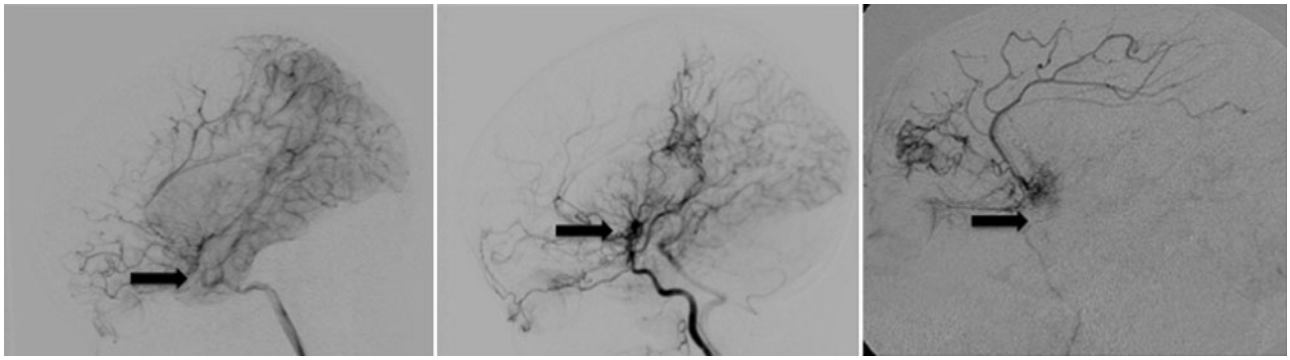

Figure 1. Representative lateral projection angiograms with injections of the internal carotid artery (ICA) illustrating the progressive stages of moyamoya. **a** Suzuki stage I–II with ICA narrowing (*arrow*), but prior to development of extensive collateral vessels. **b** Suzuki stage III–IV with significant ICA narrowing and characteristic "puff-of-smoke" (*arrow*). **c** Suzuki stage V–VI with obliteration of ICA flow (*arrow*) (n.b. some filling of the anterior cerebral artery from spontaneous external collaterals). This occlusion of the ICA results in concomitant diminution of the "puff-of-smoke" collaterals, as they are supplied by the ICA.

at 5 and 40 years old, although the condition can affect all ages.

Moyamoya produces symptoms by reducing the flow of blood to the brain. These symptoms can be direct—such as stroke or transient ischemic attacks (TIAs)—or secondary to the responses induced by ischemia—such as hemorrhage (caused by rupture of delicate collateral vessels or flow-related aneurysms), headache (possibly due to dilated transdural vessels) or seizure. The onset and rate of disease can be difficult to predict, with some patients remaining stable for years and others rapidly progressing to death [2]. It is important to note, however, that moyamoya is an unrelenting, progressive disease in the vast majority of individuals [3, 4].

While the cause remains unknown, the treatment is focused on maximizing the efficacy of existing vasculature and supplementing supply with surgical revascularization. Overall prognosis of patients with moyamoya syndrome depends on the rapidity and extent of vascular occlusion, the patient's ability to develop effective collateral circulation, the age at onset of symptoms, the severity of presenting neurological deficits and degree of disability, and the extent of infarction seen on imaging studies at the time of initial presentation. In general, neurologic status at time of treatment, more so than age of the patient, predicts long-term outcome. Initial measures to minimize stroke risk include avoiding hypovolemia/hypotension, maintaining good oxygenation and minimizing

Table 1. Associated conditions, risk factors, or syndromes

There is a range of medical disorders that can be associated with moyamoya (moyamoya syndrome). These include:
Prior radiotherapy to the head or neck
Optic gliomas, craniopharyngiomas, and pituitary tumors
Genetic disorders, such as Down syndrome, neurofibromatosis type I (NF1) (with or without hypothalamic-optic pathway tumors)
Fanconi's anemia, and sickle cell anemia and other hemoglobinopathies
Collagen vascular disorders
Congenital cardiac disease
Renal artery stenosis
Infections, such as tuberculous meningitis
Atherosclerosis
Fibromuscular dysplasia

hyperventilation (to reduce reflex cerebral vasoconstriction). Aspirin is often used to decrease thrombotic complications of narrowed vessels and small collateral circulation.

Definitive treatment involves surgical revascularization of the brain, which ultimately reduces the 5-year stroke rate from 60–90 % to <5 % [5]. **[GRADE IV]** Importantly, if surgical revascularization is performed prior to disabling infarction in moyamoya syndrome, even if severe angiographic changes are present, the prognosis tends to be excellent [6•]. **[GRADE IV]** It is important to recognize that moyamoya will invariably worsen—both radiographically and clinically—with progressive deficits in the majority of cases if untreated [1]. It is therefore extremely important to accurately diagnose and rapidly treat moyamoya to minimize the risk of permanent neurologic deficit.

Treatment

Diet and lifestyle

- There is no substantive data on the role of diet exerting a specific effect on the onset or course of moyamoya. However, it is critical to maintain proper hydration to avoid hypotension. In a similar fashion, little is known about lifestyle habits impacting this arteriopathy. A single report with five patients suggested a possible link with high dose oral contraceptives, smoking and accelerated arteriopathy [7].

Pharmacologic treatment

- There are no medications that are proven to arrest or reverse the course of moyamoya.
- The goals of medical therapy include: (1) reducing the risk of thrombosis, (2) reducing the impact of related symptoms (seizure and headache), and (3) sustaining normotension through blood pressure control and maintaining intravascular volume.
- One of the most commonly employed medications is aspirin, used to prevent thrombotic occlusion of the vessels at the areas of narrowing. Dosing is done by weight for smaller children, with most grade-school patients treated with 81 mg daily [2, 8]. In some centers, low-molecular weight heparin is used as an alternative or in combination with aspirin [9, 10].
- Sustaining normotension is primarily achieved by maintaining intravascular volume. In children, particular attention must be given during periods of illness, such as diarrhea, fever or vomiting. For all patients, perioperative fluid management is critical. Outside the hospital, the focus does not have to be on over-hydration as much as avoiding dehydration—for example, during exercise or in hot weather [6•].
- Management of related symptoms is predicated on relieving the underlying ischemia and also treating the problem directly. Seizures can be treated with anti-epileptic medication. Headaches can be troublesome, although they will frequently diminish with time after revascularization. Numerous approaches have been tried, including the use of calcium channel blockers. While this class of medication can be useful, it should be used with caution, given

the risk of hypotension, which can lead to stroke in this susceptible population [11].

Aspirin

Standard dosage	81–325 mg po qd
Contraindications	Bleeding, ulcers, Reye syndrome (in children)
Main drug interactions	Ketorolac, mifepristone.
Main side effects	Stomach irritation / ulcers, easy bruising (allergy: rare)
Special points	Often lifelong therapy
Cost / cost effectiveness	3–5 cents / dose

Interventional procedures

- The advent of endovascular stenting of intracranial vessels has led to attempts to treat moyamoya with this technique. Unfortunately, the results have been uniformly unsuccessful at maintaining durable patency of the vessels [12, 13].
- It has been hypothesized that moyamoya is not amenable to this approach because of its progressive nature (unlike focal atherosclerotic disease), in which narrowing occurs on either side of the stent.
- One area of potential interest is the use of endovascular management of acute ischemic events in moyamoya, such as emergent angioplasty or delivery of intra-arterial therapies (vasodilators or thrombolytics) [14].

Surgery

Surgical treatment of moyamoya is designed to revascularize the ischemic cortex through the creation of alternative vascular pathways. There is no way to reverse the primary arteriopathy—rather, the focus is on minimizing the possibility of stroke or hemorrhage through improving blood flow to the brain.

Indications for surgery

Class I–III data does not exist to guide indications for surgery, with most information derived from a meta-analysis of 1,448 patients [5]. Noted problems included:

- Few measures to determine efficacy of surgery
- Limited natural history data
- Lack of comparative trials
- Marked variations in surgical techniques
- Subjective outcome measures
- Limited long-term follow-up

Acknowledging these limitations, the overall consensus was that "the data from the medical literature suggest that surgical revascularization is a safe intervention for pediatric moyamoya syndrome and most treated patients derive some symptomatic benefit [5]."

A summary of surgical indications included:

- Neurological symptoms suggestive of ischemia coupled with radiographic evidence of moyamoya
- Transient ischemic attacks (TIAs) or loss of cognitive function
- Radiographic evidence of diminished cerebral blood flow (stroke, decreased reserve on cerebral blood flow testing) [5].

Japan's Ministry of Health and Welfare uses the following guidelines to justify surgery in moyamoya:

- Clinically evident symptoms referable to brain ischemia

- OR -

- Imaging studies demonstrating decreased focal cerebral blood flow or perfusion [15] **[GRADE IV]**

Recommendations from the American Heart Association are equally supportive of surgery, stating "progressive ischemic symptoms or evidence of inadequate blood flow or cerebral perfusion reserve in an individual without a contraindication to surgery" should be used as indications to operate [8].

It should be noted that recent evidence supports the treatment of asymptomatic patients in select cases, even when moyamoya is incidentally found [16].

The timing of surgery is less clear, although most centers offer revascularization once the diagnosis of moyamoya is made. While a delay may be appropriate in some situations (for example, if the diagnosis is unclear, if the patient needs to recover from a stroke to reduce swelling or if there are other acute medical issues), the overall goal is to provide treatment as soon as possible. However, this desire to move expeditiously should be balanced with the ability to maximize safety of the operation by electively scheduling cases with experienced staff and availability of all the resources needed to perform the operation.

Specific surgical procedures

- There are numerous types of operative approaches for moyamoya, with no accepted standard.
- Most operations employ branches of the external carotid artery (ECA) or tissue supplied by the ECA as the source of new blood for the ischemic cortex, as the external circulation is characteristically not affected by the arteriopathy.
- Generally, approaches can be divided into **direct** or **indirect** techniques.
- **Direct** revascularization involves some sort of end-to-side anastomosis of a branch of the ECA (such as the superficial temporal artery, STA) to superficial branches of the middle cerebral artery (MCA), such as a STA-MCA bypass.
- **Indirect** approaches employ the strategy of putting vascularized tissue in contact with the ischemic brain, facilitating the growth of a new vascular network.
- Both techniques have been reported to offer similar rates of success

in reducing the risk of stroke, particularly when performed in high-volume centers by experienced surgeons [2, 5].

Standard procedure

There is no standard procedure for moyamoya in the United States. Most children are treated with variations of indirect approaches, including pial synangiosis (Fig. 2), encephaloduroarteriosynangiosis (EDAS) or—much less commonly—multiple burr holes. Many adults (and some older children) are treated with direct approaches, most commonly a STA-MCA bypass. However, marked variability—even within a subset of an approach—coupled with the ability to potentially combine aspects of different techniques makes the identification of a single standard procedure impossible.

Contraindications

Surgery is relatively contraindicated in patients who are a poor operative risk (severe cardiac disease, advanced debilitation from stroke burden or other severe comorbidities).

Complications

- *Stroke* occurs in approximately 4–10 % of cases of surgical revascularization for moyamoya [6•]. Surgical series suggest that judicious perioperative hydration, careful blood pressure control and maintenance of oxygenation may minimize this risk. Intraoperative physiologic monitoring, including arterial blood pres-

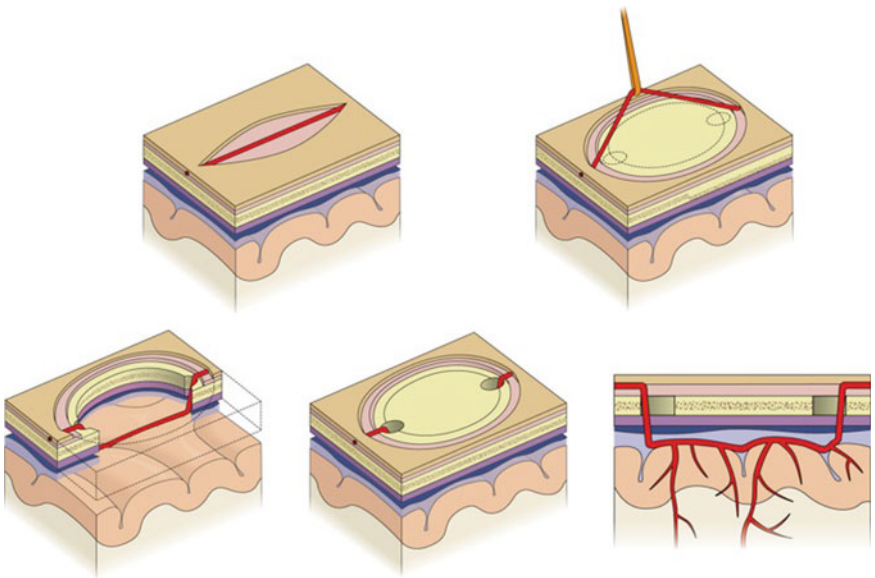

Figure 2. Representative schematic depicting the steps of a commonly used indirect approach, pial synangiosis. In this approach, a branch of the external carotid artery (ECA) is dissected free but left patent, without cutting it. A bone flap is removed, the dura and arachnoid opened and the vessel stitched to the surface of the brain. The bone flap is replaced, but with the vessel now in contact with the brain, new collaterals grow to supply blood to the hemisphere.

sure and electroencephalography (EEG), coupled with the use of neuroprotective agents and careful anesthetic management has also been reported to be beneficial [17, 18]. Postoperatively, careful and repeated neurologic examinations are important for detecting signs of ischemia so that interventions can be made in a timely fashion [8, 18].

- *Infection, cerebrospinal fluid leak, subdural hematoma and intraparenchymal hemorrhage* have all been reported, usually in the 1–2 % range.

Special points

- Anesthetic management is critical to the success of the operation.
- Hypotension, hyperthermia and hypocarbia are to be avoided at all times, especially during induction.
- EEG technicians must communicate changes in the EEG to allow the team to respond immediately, with appropriate changes in blood pressure, pCO2 and anesthetic agents.

Cost/cost effectiveness

There is no substantive data on cost or cost effectiveness of surgical treatment of moyamoya.

Emerging therapies

While laboratory investigations are ongoing, most therapies focus on modifications of existing surgical techniques and improvements in perioperative care.

Work has been done to attempt to codify surgical indications, care and follow-up in pursuit of the goal of providing evidence-based care of moyamoya patients [19•]. **[*GRADE IV].**

Pediatric considerations

Use of coordinated care teams, involving anesthesia, intensive care staff, nursing and relevant non-surgical specialists (hematology for sickle cell patients, oncologists for tumor patients, etc.) can streamline care of this population.

Crying is common in children, which can result in reflexive cerebral vasoconstriction from hypocarbia. Steps to minimize crying, such as resorbable sutures, aggressive pain management and reduction of psychosocial stressors may help to reduce the risk of stroke [8]. Younger children, patients with previous tolerances to pain medications (such as sickle cell) or individuals with cognitive delays (Down syndrome, etc.) may especially benefit from these sort of efforts [18, 20, 21].

Particular note needs to be made of children with sickle cell. These individuals may be medically complex, with pain issues, increased risk of anesthetic complications (such as acute chest syndrome), reduced renal function (relevant to dye loads in angiograms other than radiographic studies), and may have complex fluid management concerns (with exchange transfusions, limited intravenous access, renal impairment, etc.). Awareness of these potential problems may reduce the risk of complications, especially if managed by an experienced hematologist [18].

Disclosure

No potential conflicts of interest relevant to this article were reported.

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[Grade IV - A more detailed recent review of the literature summarizing Moyamoya.]

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