Moyamoya disease is a cerebrovascular condition characterized by idiopathic chronic progressive steno-occlusive changes of the terminal portions and proximal branches of the internal carotid arteries (ICAs). These changes reduce blood flow through the anterior circulation of the brain causing progressive cerebral ischemia. To compensate for the ischemia, a collateral vascular network of small vessels arising from the carotid artery, leptomeninges, and transdural branches of the external carotid artery (ECA) may form. In the final stages of the disease, the brain’s blood supply is provided almost exclusively by the ECA and the vertebrobasilar systems.1,2

Although moyamoya disease was first described in 1957 by Takeuchi and Shimizu3 as “hypoplasia of the bilateral internal carotid artery”, the term moyamoya (a Japanese word that means puff of smoke) was coined 12 years later (1969) by Suzuki and Takaku.4 The puff of smoke is a description of the hazy appearance of the collateral vasculature on angiography. Recently, it has become increasingly apparent that the term moyamoya encompasses many different arteriopathies with distinct genetic and environmental drivers that share a common end-stage radiographic appearance.

Moyamoya Terminology

Disease Vs Syndrome

By definition, people with moyamoya disease typically have the pathognomonic arteriographic findings bilaterally with no associated risk factors. In contrast, people with the characteristic moyamoya vasculopathy who also have certain associated conditions (Box 1) are categorized as having moyamoya syndrome. Those with unilateral arteriographic findings are also said to have moyamoya syndrome, even if they have no other associated risk factor. However, approximately 40% of people who initially present with unilateral moyamoya syndrome eventually develop contralateral vasculopathy, such that they will meet the definition of moyamoya disease if they do not have associated conditions.5 When the term moyamoya is used alone without the distinguishing modifiers syndrome or disease, it refers merely to the findings on cerebral arteriography, regardless of the etiology and/or the laterality.

Atypical Moyamoya

This term is used by some to describe the pathognomonic moyamoya arteriography findings in the setting of associated aneurysms or pseudoaneurysms; or in the rare occasion of noncarotid steno-occlusive disease, namely the basilar artery and posterior cerebral arteries.1

Demographic Characteristics

Incidence

The incidence of moyamoya disease varies geographically, with the highest incidence in eastern Asia. In Japan, the incidence is highest in Japanese students.

Box 1. Conditions Associated With Moyamoya Syndrome

- Asian ancestry
- Down syndrome
- Sickle cell disease
- Autoimmune disease (DM I, thyroid disease)
- Neurofibromatosis type I (NF1)
- Cranial radiation
- Congenital structural cardiac disease
- Microcephalic osteodysplastic primordial dwarfism (MOPD)
- Posterior fossa malformations–hemangiomas–arterial anomalies–cardiac (PHACE) syndrome defects–eye abnormalities–sternal cleft and supraumbilical raphe syndrome
- Robinow syndrome
- Alagille syndrome
- Seckel syndrome
idence of moyamoya is 0.35 per 100,000 people. Moyamoya disease is the most common cerebrovascular disease in children in Japan, with a prevalence of approximately 3 cases per 100,000 children. Many cases in children are considered secondary to a common genetic driver, mutations in the RNF213 gene. Moyamoya disease is uncommon in the non-Asian population with an incidence of 0.086 per 100,000 people in the US, although that number may underrepresent the total cases of arteriopathy, including people with sickle cell disease and other cohorts outside of those with Asian ancestry. The incidence in European populations is estimated to be about 10% of that observed in Japan.1

Age and Sex
Moyamoya disease can occur at any age, however, the age of presentation follows a bimodal distribution. There is a peak in the first decade of childhood, especially around age 5 years; the second peak is in adulthood around the middle of the fifth decade. Moyamoya disease is more common in women with a 2:1 ratio of women to men in most populations.1

Ethnicity
Although moyamoya was originally described as predominantly affecting populations with Asian ancestry, it has been identified worldwide, in people of varied ethnic backgrounds, including American and European populations. The reported ethnicity-specific incidence rate ratio compared with Caucasian US populations was 4.6 (95% CI, 3.4-6.3) for Asian Americans, 2.2 (95% CI, 1.3-2.4) for African Americans, and 0.5 (95% CI, 0.3-0.8) for Hispanics.6 A family history was present in 10% to 15% of people from Japan with moyamoya and in 3% to 6% of people from western countries.2 In a large North American series, familial moyamoya was reported to account for 3.4% of cases.7 Indeed, the ethnicity pattern and familial penetration suggest that genetic predisposition plays a major role in moyamoya disease.

Natural History and Prognosis
The natural history of moyamoya is variable; however, moyamoya progresses in the majority of cases. Progression may have a slow indolent course, an intermittent pattern with rare events, or be fulminating with steep neurologic decline.

It is estimated that up to two-thirds of people with moyamoya disease have symptomatic progression that cannot be halted by medical treatment alone. A large meta-analysis of 1,156 people with moyamoya showed 87% who underwent surgical revascularization (see Surgical Management) had symptomatic benefit in the form of reduction or complete disappearance of symptomatic cerebral ischemia.8,9

The initial neurologic status of an individual is the best predictor of the disease course. Early diagnosis coupled with close follow-up and intervention when appropriate are the major determinants of a favorable long-term outcome.10

Clinical Presentation
The clinical presentations of moyamoya are attributed to the changes in intracranial blood flow dynamics and cerebral perfusion. Symptoms can be classified as arising from brain ischemia (eg, strokes, transient ischemic attacks [TIA], and seizures) or as sequelae of the compensatory mechanisms in response to ischemia (eg, hemorrhages from rupture of fragile collateral vessels and headaches from dilated collaterals).

Age-Related and Geographic Differences
In all age groups, ischemia (TIA or stroke) is the most common presentation of moyamoya, but adults are 7 times more likely than children to present with intracranial hemorrhage. Manifestations also vary geographically. In the US, ischemic symptoms are the predominant presentation in adults and children, although adults are still 7 times more likely to have intracranial hemorrhage than children (20% vs 2.8%). In contrast, the rate of adults in Asian populations presenting with hemorrhage (42%) is much higher than among those of Asian descent living in the US.10

Ischemic Symptoms
Symptoms are typically dependent on which brain region is ischemic (eg, frontal, parietal, temporal lobes). Common symptoms include hemiparesis, aphasia, cognitive impairment, seizures, syncope, and visual deficits. Ischemic symptoms may be transient (TIA) or permanent (stroke), and are commonly precipitated in children by hyperventilation (eg, crying, exercise), dehydration, or exertion.

Intracranial Hemorrhage
Clinical symptoms vary according to the location of the hemorrhage, which can be intraventricular, intraparenchymal, or subarachnoid. Hemorrhage has been attributed to rupture of fragile collateral vessels and may also be caused by moyamoya-associated microaneurysms in some cases.1,2

Other Symptoms and Signs
Headache is a frequent presenting symptom and is typically of a migraine-like quality and refractory to medical treatment. Headache is generally believed to be caused by dilatation of the collateral vessels that may stimulate the dural nociceptors. Choreiform movement is another presenting symptom of moyamoya in children, attributed to dilated collateral vessels in the basal ganglia.1 Additionally, the morning glory disk is an ophthalmologic finding occasionally seen in moyamoya. It is highly recommended to obtain cerebrovascular imaging to evaluate for moyamoya if this sign is observed on an ophthalmologic examination.11
Evaluation

In cerebral ischemia, moyamoya should be included in the differential diagnosis, especially in children, because moyamoya is associated with approximately 6% to 10% of nonperinatal pediatric strokes and TIA. Evaluation should consist of clinical assessment, including consideration of specific populations with increased moyamoya risk, and radiographic studies, incorporating MRI and potential digital subtraction angiography (DSA). If moyamoya is identified, careful review of family medical histories is warranted to assess familial moyamoya risk factors, with subsequent referral for genetic counseling if present.

Clinical Evaluation

Moyamoya arteriopathy has been reported in association with a wide range of distinct populations, clinical conditions, and genetic disorders. Awareness of these associations is crucial for the physician to consider moyamoya as a diagnostic possibility during the initial evaluation. This is especially important in those who have confounding diagnoses (eg, children with Down syndrome who have a structural cardiac disease as a potential cause of stroke) or who are at high risk of recurrent stroke if not identified in a timely fashion.

Although most pediatric moyamoya cases are idiopathic, there are population-based patterns. Historically, Asian ancestry is an increased risk factor for moyamoya, with up to 56% of Asian-Americans with moyamoya harboring a specific mutation of RNF213. In contrast, only 3.6% to 29% of non-Asian individuals with moyamoya harbor RNF213 mutations. Additionally, Caucasians with moyamoya in the US have a higher rate of autoimmune disorders, including type I diabetes (8.5% vs 0.4% in the general population) and thyroid disease (17% vs 8%). Down syndrome (with a 26-fold increased likelihood of moyamoya), neurofibromatosis type I (with a 2%-5% prevalence of moyamoya), sickle cell disease, and other associated conditions are summarized in Box 1.

Radiographic Studies

MRI is the current standard for evaluation of cerebral ischemia (Figure 1). Although protocols may be institution specific, commonly available MRI sequences are generally used, including axial T1-/T2-weighted images to assess structural anatomy and chronic stroke, diffusion-weighted imaging (DWI) and apparent diffusion coefficient values (ADC map) to assess acute stroke, fluid-attenuated inversion recovery (FLAIR) images to assess chronic stroke burden and areas of slow flow (ie, the ivy sign, present in nearly 80% of cases) and MR angiography (MRA) to visualize the circle of Willis. Advances in vessel wall imaging may help to differentiate between vasculitis and moyamoya.

If moyamoya is identified on MRI, DSA should be considered, as this modality has increased diagnostic sensitivity for Figure 1. Radiographic imaging modalities for diagnosis and follow-up the internal carotid artery (ICA) terminus, M1 segment of middle cerebral (red arrows), Axial brain MRI T2WI, at level of basal cisterns (B) and basal arrows). Anteroposterior (E) and lateral (F) digital subtraction angiogram ACA candelabra by lenticulostriate collaterals; most consistent with Suzuki meningeal and superficial temporal artery. Atypical moyamoya with pos pial synangiosis (white arrows). Preoperative lateral DSA of left ECA (K) and collaterals from the occipital artery. Notice the increased size of the donor
of moyamoya include magnetic resonance angiogram (MRA) coronal view (A) demonstrating bilateral stenosis and occlusion (white arrows) of artery (MCA), and A1 segment of anterior cerebral artery (ACA). Notice extensive proliferative changes of the lenticulostriate arteries bilaterally ganglia (C) demonstrate void signals (red arrows) of moyamoya collaterals. Axial brain MRI FLAIR sequence (D), showing ivy sign bilaterally (yellow (DSA) of the left ICA show stenosis of the terminal ICA and thread-like appearance of the M1 and A1 segments, with reconstitution of MCA and stage III. Anteroposterior (G) and lateral (H) DSA of the left external carotid artery (ECA) shows intrinsic ECA to ICA transdural collaterals from middle posterior cerebral disease (I-L): preoperative (I) and postoperative (J) FLAIR sequence showing preoperative ivy sign and its disappearance following postoperative lateral DSA of left occipital artery (L) following pial synagniosis using the occipital artery as a donor, demonstrating ingrowth of artery (green arrows) compared to the preoperative DSA.
moyamoya compared with MRI (including the ability to better differentiate vasculitis) and offers valuable data pertinent to preoperative planning. Transdural collaterals visualized on DSA are critical biomarkers of disease that can assess angiogenetic potential, predict 1-year postoperative radiographic outcomes and, when incorporated into surgical planning, have been demonstrated to reduce perioperative stroke complications by more than 40%, especially in the setting of previous cranial surgery or shunting.\textsuperscript{3,16,17} The risk of angiogram is generally low, with an approximately 1% complication rate at high volume centers.\textsuperscript{18} Contraindications include contrast allergies, aortic stenosis, and unstable general medical conditions that preclude sedation or anesthesia.

**Screening and Genetic Testing**

When moyamoya is diagnosed in a child, families are frequently concerned about the need to screen other siblings and relatives. Initial screening commonly includes an MRI and MRA, looking for the defining radiographic characteristics of moyamoya.\textsuperscript{15} Indications for radiographic screening are still to be defined, but because the rate of familial involvement is low (3.4% in a large North American series), initial screening of unaffected family members is generally reserved for first-degree relatives of those who have other first- or second-degree relatives with 1) established moyamoya diagnosis, 2) clinical histories strongly suggestive of moyamoya (eg, TIA, stroke, severe headaches or seizures without identified cause), or 3) identical twins.\textsuperscript{7} If an initial screening MRI is normal, it remains unclear what, if any, interval for follow-up imaging is appropriate. There is data, however, to indicate that previously normal scans can later evidence clear (and clinically symptomatic) moyamoya, suggesting that follow up may have utility.\textsuperscript{19}

Genetic testing and counseling are also relevant to children and families diagnosed with moyamoya. There is generally high penetrance of the phenotype with most mutations and there is a potential surgical treatment if identified. In North America, only a small minority of pediatric moyamoya cases (<5%) appear to have clear associations with specific mutations, unless the children have Asian heritage (for whom RNF213 mutations exist in 30%-50%). When present, RNF213 mutation with moyamoya has marked significance for familial screening, as data suggest that familial penetrance is approximately 23%. If an individual carries the mutation, there is a near 50% likelihood of manifesting arteriopathy. Other mutations are rarer, but may be detected by specific clinical or radiographic phenotypes (ACTA2 carriers with distinctive stellate arteries branching from a dilated proximal internal carotid, GUCYA3 mutations with achalasia, etc.).\textsuperscript{2,13} Current moyamoya-associated mutations are noted in Box 2.\textsuperscript{2,13,20}

**Box 2. Genetic Mutations Associated with Moyamoya**

- **ACTA2 R179**
- **BRCC3/MTCPI**
- **GUCYA3**
- **RNF213**
- **SAMHD1**

**Surgical Management**

There is no known treatment modality that will reverse the primary steno-occlusive process, and current treatments are designed to improve cerebral blood flow to reduce future stroke risk, reduce moyamoya-associated collaterals, and decrease the frequency of symptoms. Surgical revascularization is the fundamental treatment modality for moyamoya.\textsuperscript{1,15}

Key points of surgical management focus on indications for surgery, timing of the operation, selection of specific technique, and expectations of outcome following revascularization. Potential complications of surgery include stroke, infection, and hemorrhage. Tenets of perioperative care to minimize the perioperative stroke risk include careful hydration, often with intravenous fluids at 1 to 1.25 times maintenance levels; avoidance of hyperventilation-related cerebral vasoconstriction, which often occurs because of crying, pain, or emesis; effective pain control, strict blood pressure control to maintain cerebral perfusion; and preoperative use of antiplatelet agents (withheld only on the day of surgery then resumed from the first postoperative day).

**Indications**

Indications include radiographic evidence of moyamoya, including ongoing ischemic symptoms and/or evidence of compromised blood flow or cerebral perfusion reserve. Data also suggest that clinically asymptomatic children who have radiographic or functional evidence of impaired cerebral perfusion should be considered as operative candidates; this position is supported by the American Heart/Stroke Association recommendations. Relative contraindications include very early stage arteriopathy with normal perfusion and/or children with profound medical or neurologic compromise. Of note, the rare data focused on surgical revascularization in individuals with ACTA2 moyamoya suggest that this is a very high-risk population.\textsuperscript{21,22}

**Timing**

Timing of surgery ideally minimizes the duration between diagnosis and revascularization; however, delays of several
weeks may be appropriate to coordinate skilled anesthetic and operating room staffing, or to allow recovery from an acute stroke. If possible, the ability to perform bilateral surgery (if indicated) under a single anesthetic may help to reduce complications and speed up the growth of surgical collaterals, particularly in very young patients.

**Surgical Approaches and Outcomes**

Because moyamoya arteriopathy affects the ICAs and spares the ECAs, surgical treatment utilizes ECA branches as a donor source to supply blood flow to the ischemic brain. There are 2 main categories of surgical revascularization. The first is direct, which involves harvesting a donor vessel (usually superficial temporal artery) and anastomosing it directly to a single recipient cortical vessel. The second is indirect (Figure 2), which uses vascularized tissue (eg, an artery, pericranium, or muscle) to stimulate the growth of a new vascular network when placed in contact with the brain. Although there is considerable debate about the merits and drawbacks of the 2 approaches, both are effective in reducing the stroke rate in individuals with moyamoya. In some children, however, direct procedures may not be technically feasible because of the delicacy and small caliber of vessels. Recent analyses support the premise that indirect operations may be more durable, with better long-term results in the pediatric population.

There is abundant evidence that surgical revascularization improves a wide range of outcome metrics in children with moyamoya. Radiographically, revascularization reverses white matter changes, improves measures of cerebral oxygenation, and increases cerebral blood flow, stabilizing stroke burden, despite progressive arteriopathy. Clinically, surgery decreases ischemic symptoms, headache, and risk of hemorrhage and markedly reduces stroke rates. Surgery reduces stroke risk at years 1 and 5 from 32% and 66% to 90%, respectively, to less than 5% for most populations at both years 1 and 5. Surgery also improves functional and cognitive outcomes. These good outcomes are durable, with recent long-term outcomes (>20 years) demonstrating persistence of the surgical collaterals over decades and the continued protection from stroke while participating in all forms of activity (eg, exercise, advanced educational degrees, and childbirth).

It is increasingly clear that treatment at a high-volume center with a dedicated pediatric cerebrovascular team is among the most important predictors of surgical outcome. A recent national database analysis revealed that high-volume centers (averaging >30 procedures annually) had shorter lengths of stay (32%), lower costs (57%), 8-fold more likely discharge to home (versus rehabilitation), and a 15-fold lower rate of death. These data support the regionalization of care with centers of excellence for subspecialized care.

**Conclusions**

Moyamoya represents a constellation of arteriopathies that vary in genetic and environmental drivers but share a common end-pathway of progressive internal carotid artery narrowing and collateral development that leads to stroke if untreated. Diagnosis is predicated on characteristic radiographic findings observed on MRI and catheter angiogram, with treatment centered on surgical revascularization to reduce the risk of stroke. Surgical treatment is very successful at providing durable substantial reductions in stroke risk particularly when performed at high-volume centers with experienced teams.

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