Moyamoya: Epidemiology, Presentation, and Diagnosis

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KEYWORDS

• Moyamoya • Epidemiology • Stroke
• Natural history • Diagnosis

DEFINITION AND HISTORY

Moyamoya syndrome is an increasingly recognized arteriopathy associated with cerebral ischemia and has been associated with approximately 6% of childhood strokes.[1–3] It is characterized by chronic progressive stenosis at the apices of the intracranial internal carotid arteries (ICA), including the proximal anterior cerebral arteries and middle cerebral arteries. Occurring in tandem with reduction in flow in the major vessels of the anterior circulation of the brain, there is compensatory development of collateral vasculature by small vessels near the carotid apices, on the cortical surface, leptomeninges, and branches of the external carotid artery supplying the dura and skull base.

These collateral vessels, when visualized on angiography, have been likened to the appearance of a puff of smoke, which translates to moyamoya in Japanese. First described in 1957 as "hypoplasia of the bilateral internal carotid arteries,"[4] the descriptive title of moyamoya was applied more than a decade later by Suzuki and Takaku in 1969 (**Fig. 1**).[5] The use of the term moyamoya has subsequently been adopted by the International Classification of Diseases as the specific name for this disorder.[6]

NOMENCLATURE (DISEASE VS SYNDROME)

Patients with the characteristic moyamoya vasculopathy who also have well-recognized associated conditions (see later discussion) are categorized as having moyamoya syndrome, whereas those patients with no known associated risk factors are said to have moyamoya disease. By definition, the pathognomic arteriographic findings are bilateral in moyamoya disease (although severity can vary between sides).[5] Patients with unilateral findings have moyamoya syndrome, even if they have no other associated risk factors.[6] However, up to nearly 40% of patients who initially present with unilateral findings later progress to develop disease on the unaffected side.[7,8] When used alone, without the distinguishing modifier of disease or syndrome, the term moyamoya refers solely to the distinctive findings on cerebral arteriography, independent of cause.

It is important to recognize that the angiographic changes in patients with moyamoya represent a final common pathway shared by a diverse collection of genetic and acquired conditions.[1] Investigations into the pathogenesis of moyamoya suggest that the clinical presentation of affected patients may be the result of disparate underlying genetic and environmental cues. The heterogeneity of pathophysiologic processes underlying the radiographic findings that define moyamoya predicts distinct moyamoya populations, with individual clinical presentations and responses to therapeutic interventions.

EPIDEMIOLOGY

First described in Japan and originally considered a disease that predominantly affected individuals

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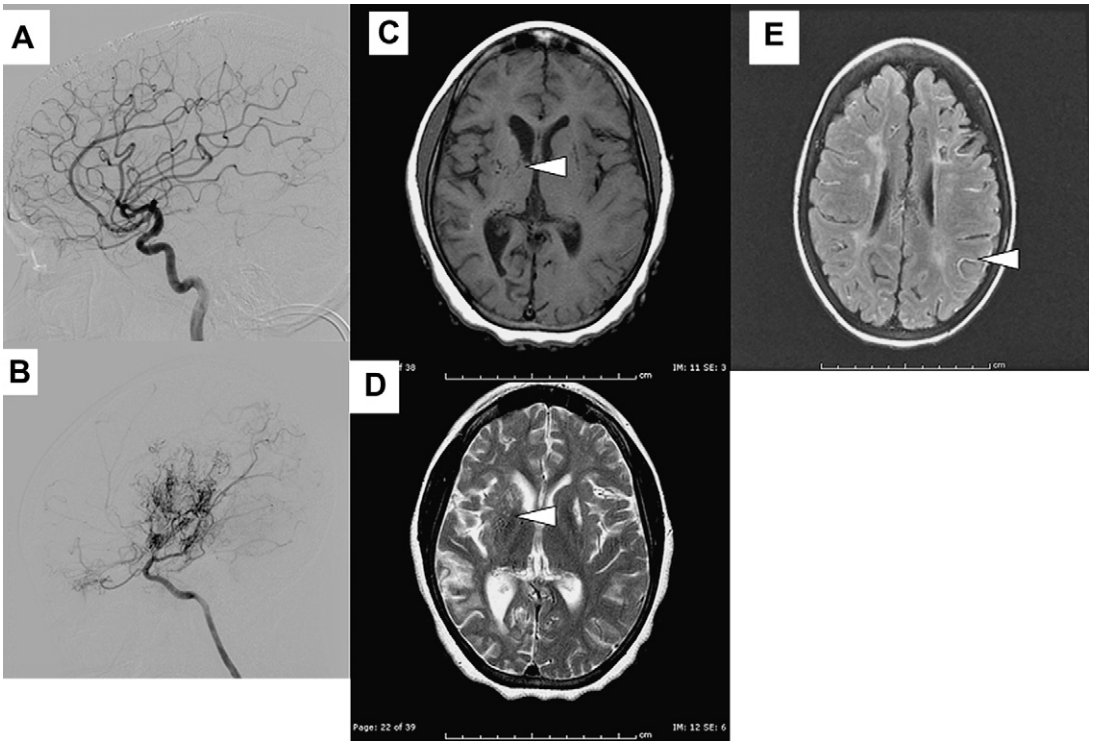

Fig. 1. Radiographic findings in moyamoya. Representative angiograms illustrating a normal study compared with moyamoya. (*A*) Normal lateral projection angiogram with injection of the internal carotid artery (ICA). (*B*) Suzuki grade III to IV with significant ICA narrowing and characteristic puff-of-smoke collaterals; note diminished cortical perfusion compared with (*A*). (*C–E*) Typical MRI images of moyamoya. (*C*) T1- and (*D*) T2-weighted studies reveal cortical atrophy, old infarcts, and flow void signals resulting from basal collaterals (*white arrowheads*). (*E*) FLAIR images demonstrating ivy sign consistent with bilateral ischemia (*white arrowhead*).

of Asian heritage, moyamoya syndrome has now been observed throughout the world and affects individuals of many ethnic backgrounds, with increasing detection of this disease in American and European populations.[9,10] There are 2 peak age groups: children at 5 years of age and adults in their mid-40s.[11–14] There is a gender predominance with females affected nearly twice as often as males.[11,12,15] Moyamoya is the most common pediatric cerebrovascular disease in Japan with a prevalence of approximately 3/100,000.[3,11,12] A recent European study cited an incidence about 1/10th of that in Japan.[16] Studies in the United States suggest an incidence of 0.086/100,000 persons (about 1 in a million).[17] Studies of individual ethnic groups suggest that moyamoya is more common in Americans of Asian or African American descent compared with whites or Hispanics. Ethnicity-specific incidence rate ratios compared with whites were 4.6 for Asian Americans, 2.2 for African Americans, and 0.5 for Hispanics.[17]

Although the cause and pathogenesis of moyamoya disease are poorly understood, genetic factors play a major role. The familial incidence of affected first-degree relatives in Japan is 10%, with a rate of 6% reported in a recent series in the United States.[15,18] Associations with loci on chromosomes 3, 6, 8, and 17 (MYMY1, MYMY2, MYMY3) as well as specific human leukocyte antigen haplotypes have been described.[19–24] However, despite evidence supporting a genetic basis of moyamoya, important caveats remain. Reports exist of identical twins with only 1 affected sibling.[15,25] These data support the premise that environmental factors precipitate the syndrome's clinical emergence in susceptible patients. Ultimately, the pathogenesis of moyamoya will likely involve genetic and environmental factors.

PRESENTATION

Patients with moyamoya present with signs and symptoms resulting from changes in flow to the ICAs. These signs and symptoms can be categorized into 2 groups: (1) ischemic injury, producing transient ischemic attacks (TIAs), seizures, and strokes[1,15,26–28]; (2) deleterious consequences of

compensatory mechanisms responding to this ischemia including hemorrhage from fragile collateral vessels, flow-related aneurysms, or headache from dilated transdural collaterals.[1,13–15,29–31] Individual variation in degrees of arterial involvement, rates of progression, regions of ischemic cortex, and response to the reduction in blood supply helps to explain the wide range of presentations seen in practice.

In the United States, most adults and children present with ischemic symptoms, although the rate of hemorrhage is approximately 7 times greater in adults (20% vs 2.8%).[15,31] Some degree of geographic variability exists; reports from Asian populations indicate adults have much higher rates of hemorrhage as a presenting symptom (42%) compared with US populations (20%).[13–15,29–31] In contrast, it is extremely rare for children to present with hemorrhage (2.8%); they predominantly present with TIAs or ischemic strokes (68%) as shown in the largest current report of pediatric moyamoya patients (**Table 1**).[15] The much higher rate of completed strokes found in children may be related to less developed verbal skills in this age group as young children may not be able to clearly communicate TIA symptoms, thus delaying diagnosis and subsequent treatment and increasing the risk of progressive disease culminating in a stroke.[32]

Headache is a frequent presenting symptom in moyamoya, particularly in children. A recent review has speculated that dilatation of meningeal and leptomeningeal collateral vessels may stimulate dural nociceptors.[33] Typically, headache is migrainelike in quality, refractory to medical therapies, and may persist in up to 63% of patients even after successful surgical revascularization.[33] Headache may improve in patients within 1 year after surgical treatment of moyamoya, possibly concordant with regression of basal collateral vessels. Unfortunately, headache can cause persisting disability even after successful treatment of the syndrome.

Associated Conditions

There are numerous published links between moyamoya and a wide variety of other disorders. The clinical associations identified in a recently reported series are summarized in **Table 2**.[1,15] These include prior radiotherapy to the head or neck for optic gliomas, craniopharyngiomas, and pituitary tumors; genetic disorders such as Down syndrome, neurofibromatosis type 1 (NF1) (with or without hypothalamic-optic pathway tumors), large facial hemangiomas, sickle cell anemia, and other hemoglobinopathies; autoimmune disorders such as Graves disease; congenital cardiac disease; renal artery stenosis; meningeal infections including tuberculous meningitis; and a host of unique syndromes such as Williams, Alagille, and so forth.[1,15,34–36]

Two of these conditions merit particular attention. First, the association between moyamoya and radiotherapy to the head or neck has been well described, but to date the dose of radiation capable of causing this effect is unknown and the time between treatment and disease onset is highly variable, ranging from months to decades. Second, patients with sickle cell disease may represent a population with a markedly underreported prevalence of moyamoya, especially amongst individuals who suffer repeated strokes in the setting of failed transfusion therapy.[1,37] The prevalence of these 2 groups, especially the large number of individuals with sickle cell disease in the United States, suggest that careful observation of these patients for signs or symptoms of cerebral ischemia may be warranted.

Table 1
Symptoms at presentation in 143 patients

	Number of Patients With Symptom	% of Patients With Symptom
Stroke	97	67.8
TIAs (including drop attacks)	62	43.4
Seizures	9	6.3
Headache	9	6.3
Choreiform movements	6	4.2
Incidental	6	4.2
Intraventricular or intracerebral bleed	4	2.8

Symptom totals are greater than patient numbers, because some patients had multiple symptoms at presentation.

Table 2
Associated conditions, risk factors, or syndromes

Syndrome	Number
No associated conditions (idiopathic)	66
Neurofibromatosis type 1 (NF1)	16
Asian	16
Cranial therapeutic radiation	15
Hypothalamic-optic system glioma	8
Craniopharyngioma	4
Medulloblastoma, with Gorlin syndrome	1
Acute lymphocytic leukemia, intrathecal chemotherapy	2
Down syndrome	10
Congenital cardiac anomaly, previously operated	7
Renal artery stenosis	4
Hemoglobinopathy (2 sickle cell, 1 Bryn Mawr)	3
Other hematologic (1 spherocytosis, 1 ITP)	2
Giant cervicofacial hemangiomas	3
Shunted hydrocephalus	3
Idiopathic hypertension requiring medication	3
Hyperthyroidism (1 with Graves syndrome)	2

Other syndromes, 1 patient each: Reyes (remote), Williams, Alagille, cloacal extrophy, renal artery fibromuscular dysplasia, and congenital cytomegalic inclusion virus infection (remote). Two patients had unclassified syndromic presentations. There were 4 African Americans, 2 of whom had sickle cell disease.

NATURAL HISTORY AND PROGNOSIS

The prognosis of moyamoya syndrome is difficult to predict because the natural history of this disorder is not well known. The progression of disease can be slow with rare intermittent events, or can be fulminant with rapid neurologic decline.[15,38] However, regardless of the course, it seems clear that moyamoya syndrome, in terms of arteriopathy and clinical symptoms, inevitably progresses in untreated patients.[5,39] A 2005 study revealed that the rate of disease progression is high even in asymptomatic patients and that medical therapy alone does not halt disease progression.[40] It has been estimated that up to 66% of patients with moyamoya have symptomatic progression in a 5-year period with poor outcomes if left untreated.[41–43] This number contrasts strikingly to an estimated rate of only 2.6% of symptomatic progression following surgical treatment in a recent meta-analysis of 1156 patients.[44]

The single greatest predictor of overall outcome for patients with moyamoya is the neurologic status at time of treatment.[15,45]

Other factors that influence outcome include the speed and degree of arterial narrowing, the patient's ability to develop functional collateral vessels, the age at diagnosis, and the extent of infarction as demonstrated radiographically at the time of initial presentation.[46] Because neurologic status at the time of treatment is of paramount importance to outcome, early diagnosis is imperative and needs to be coupled with the timely delivery of therapy. If surgical revascularization is performed before disabling infarction in moyamoya syndrome, even if severe angiographic changes are present, the prognosis tends to be excellent.[15]

DIAGNOSIS

The diagnosis of moyamoya is made based on characteristic radiographic findings involving narrowing of the terminal segments of the ICA, often with the associated development of collateral vessels. Consideration of moyamoya syndrome should be given to any patient, particularly those in the pediatric age group who present with clinical findings suggestive of stroke or TIA. An important aspect of the diagnostic evaluation hinges on accurate recognition of the condition, which can be greatly increased with rapid referral to centers experienced in the care of these patients. Any child with unexplained symptoms suggestive of cerebral ischemia should be considered as possibly at-risk for moyamoya. Although the differential diagnosis for these symptoms is broad, the presence of moyamoya can be readily confirmed radiographically. Radiographic evaluation of a patient suspected of having moyamoya usually proceeds through several studies.

The workup of a patient in whom the diagnosis of moyamoya syndrome is suspected typically begins with a either a magnetic resonance imaging (MRI) study or computerized tomography (CT) of the brain. On CT, small areas of hypodensity suggestive of stroke are commonly observed in cortical watershed zones, basal ganglia, deep white matter, or periventricular regions.[47,48] Although rare in children, hemorrhage from

moyamoya vessels can be readily diagnosed on head CT with the most common sites of hemorrhage being the basal ganglia, ventricular system, medial temporal lobes, and thalamus.

Patients with these findings on CT are often subsequently evaluated with MRI/magnetic resonance angiography (MRA). Acute infarcts are well seen using diffusion-weighted imaging (DWI), chronic infarcts are better delineated with T1 and T2 imaging and cortical ischemia may be inferred from fluid attenuated inversion recovery (FLAIR) sequences, which demonstrate linear high signal following a sulcal pattern, felt to represent slow flow in poorly perfused cortical circulation (the so-called ivy sign).[49,50] Most suggestive of moyamoya on MRI is the finding of diminished flow voids in the internal carotid and middle and anterior cerebral arteries coupled with prominent collateral flow voids in the basal ganglia and thalamus. These imaging findings are virtually diagnostic of moyamoya syndrome (see **Fig. 1**).[48,51–55]

Because of the excellent diagnostic yield and noninvasive nature of MRI, it has been proposed that MRA be used as the primary diagnostic imaging modality for moyamoya syndrome instead of conventional cerebral angiography.[51,56–60] Although MRA can detect stenosis of the major intracranial vessels, visualization of basal moyamoya collateral vessels and smaller vessel occlusions is frequently subject to artifact. Therefore, to confirm the diagnosis of moyamoya syndrome and to visualize the anatomy of the vessels involved and the patterns of flow through the hemispheres, conventional cerebral angiography is typically required.

Definitive diagnosis is based on a distinct arteriographic appearance characterized by bilateral stenosis of the distal intracranial ICA extending to the proximal anterior (ACA) and middle (MCA) arteries (see **Fig. 1**). Disease severity is frequently classified into 1 of 6 progressive stages originally defined by Suzuki and Takaku[5] (**Table 3**). Development of an extensive collateral network at the base of the brain along with the classic puff of smoke appearance on angiography is seen during the intermediate stages of the Suzuki grading system.

Angiography should consist of a full 6-vessel series, including selective injection of the external carotid systems (both internal carotid arteries, external carotid arteries, and vertebral arteries). External carotid imaging is essential to identify preexisting collateral vessels so that surgery, if performed, will not disrupt them. Aneurysms or AVMs, known to be associated with some cases of moyamoya, can also be best detected by conventional angiography. In a study of 190 angiograms of pediatric patients, the risk of complications from performing angiography in children with moyamoya syndrome has been demonstrated to be no higher than the risk of performing angiography in nonmoyamoya populations being evaluated for cerebrovascular disease, with a rate of serious complications of less than 1%.[61]

Table 3
Suzuki stages of moyamoya disease

Stage	Appearance
1	Bilateral ICA stenosis
2	Collateral vessels begin to form
3	Prominence of collateral vessels
4	Severe stenosis/complete occlusion of circle of Willis, moyamoya vessels narrow, extracranial collaterals begin to form
5	Prominence of extracranial collaterals
6	Complete carotid occlusion

Periprocedural hydration for these patients is useful along with aggressive measures to control pain and anxiety. Crying can lower P_{CO_2} with resultant cerebral vasoconstriction and a subsequent increased risk of stroke. Class III data support the use of these measures, with studies demonstrating decreased frequency of TIAs and strokes when patients are treated with these techniques.[62] In addition, the risk of angiography is increased in patients with sickle cell disease because of the contrast load on the kidneys. It is recommended that these patients undergo preangiography exchange transfusion and preprocedural hydration when feasible.

Cerebral blood flow studies, using techniques such as transcranial Doppler ultrasonography (TCD), xenon-enhanced CT, positron emission tomography (PET), and single photon emission computed tomography (SPECT) with acetazolamide challenge, can also be helpful in the diagnostic evaluation of patients with moyamoya syndrome as well as assisting in treatment decisions. For example, transcranial Doppler examination provides a noninvasive way to follow changes in blood flow patterns with time in larger cerebral vessels; xenon CT, PET, and SPECT can be used to detect regional perfusion instability before treatment and to determine the extent of improvement of functional perfusion after therapy.[63–70]

There is compelling class I data to support the use of TCD as an initial screening study for stroke in the sickle cell population. In a recent randomized trial, the stroke prevention trial in sickle cell

anemia (STOP) evaluated more than 2000 children with sickle cell disease and validated the use of TCD as a screening study for stroke in this patient group.[71] Use of the information gained from these TCD studies resulted in a more than 90% decreased risk of strokes through the use of transfusions.[71] Although this trial was not primarily focused on moyamoya disease, the anticipated widespread use of TCDs will likely increase the number of MRI/MRA studies in this population, with a corresponding increase in the number of diagnosed cases of sickle cell–related moyamoya.

Another diagnostic evaluation that has been used in the workup of patients with moyamoya syndrome includes electroencephalography (EEG). Specific alterations of EEG recordings are usually observed only in pediatric patients and include posterior or centrotemporal slowing, a hyperventilation-induced diffuse pattern of monophasic slow waves (ie, buildup), and a characteristic re-buildup phenomenon.[72] The re-buildup phenomenon looks identical to the buildup slow waves seen in nonmoyamoya patients, but differs from buildup in timing of presentation; buildup occurs during hyperventilation and re-buildup occurs after the hyperventilation is completed and indicates diminished cerebral perfusion reserve.

Although each of these studies has the potential to add information in the diagnosis and management of moyamoya, not all are routinely used in the United States. MRI/MRA and conventional angiography are the standard diagnostic tools used for most patients with moyamoya. Following surgical treatment, an angiogram and/or MRI/MRA are often obtained 1 year after operation and, depending on the age of the patient, subsequent yearly MRI. The role of SPECT and PET scans in the evaluation and management of moyamoya syndrome has been increasing in the past decade.[69,70] Further studies are needed to optimize screening and follow-up imaging protocols for patients with moyamoya.

SCREENING

Although there are neither broad-based initiatives nor any class I data supporting screening protocols for moyamoya syndrome, particular note should be made of the association of moyamoya with NF1, Down syndrome, and sickle cell disease. These diseases are relatively common in pediatric practice and class III data support the premise of prospective noninvasive screening for moyamoya syndrome in these selected populations.[36,73–75] Recent literature reviewing the treatment of patients with sickle cell disease and moyamoya may provide additional evidence favoring screening of patients with sickle cell disease who fail transfusion therapy for moyamoya.[37]

There is less compelling evidence to suggest some usefulness to screening first-degree relatives of patients with moyamoya. The familial incidence of affected first-degree relatives in Japan is 7% to 12% and a similar rate of approximately 6% was found in the Children's Hospital Boston series.[15,76–78] Despite these relatively small percentages, the compelling association between neurologic status at presentation and long-term outcome after treatment may support a more aggressive posture toward screening in this population.[15]

TREATMENT

Once the diagnosis of moyamoya is made, rapid referral of the patient to a center experienced with moyamoya should be made to develop a plan for treatment. Current therapies are designed to prevent strokes by improving blood flow to the affected cerebral hemisphere, not to reverse the primary disease process for which there is no known treatment. Improvement in cerebral blood flow can protect against future strokes, effect a concurrent reduction in collaterals, and reduce symptom frequency.

Most of the data available supports the use of surgical revascularization as a first-line therapy for the treatment of moyamoya syndrome, particularly for patients with recurrent or progressive symptoms.[1,44,79] Many different operative techniques have been described; all with the main goal of preventing further ischemic injury by increasing collateral blood flow to hypoperfused areas of cortex, commonly using the external carotid circulation as a donor supply.[15,38] Abundant type III data including 2 relatively large studies with long-term follow-up have demonstrated a good safety profile for surgical treatment of moyamoya (4% risk of stroke within 30 days of surgery per hemisphere) with a 96% probability of remaining stroke-free in a 5-year follow-up period.[15,41] These type III data suggest that surgical therapy for moyamoya is an effective durable treatment of the disease. Recent guidelines published by the American Heart Association support the use of surgery to treat moyamoya.[79]

SUMMARY

Moyamoya is an increasingly recognized entity associated with cerebral ischemia. Diagnosis is made from clinical and radiographic findings, including a characteristic stenosis of the internal

carotid arteries in conjunction with abundant collateral vessel development. Surgical revascularization is recommended for definitive treatment of children with moyamoya syndrome.

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