Moyamoya: An Update for the Practicing Neurologist

By Timothy G. White, MD; Julia R. Schneider, BS; Kay O. Kulason, BA; Ralph Rahme, MD; Kevin Kwan, MD; Rafael A. Ortiz, MD; and David J. Langer, MD

Moyamoya disease (MMD) is a rare idiopathic disorder characterized by progressive narrowing of the bilateral suprachiasmatic internal carotid arteries (ICAs) and/or proximal anterior and middle cerebral arteries (ACAs, MCAs). The term “moyamoya,” Japanese for “something hazy, like a puff of smoke,” serves to describe the abnormal network of fine collateral vessels that develops at the base of the brain and is often seen angiographically in patients with MMD. Over time, additional collaterals may develop, including leptomeningeal collaterals on the surface of the brain from the posterior cerebral artery and transdural collaterals from the external carotid artery.

Similar angiographic findings resembling MMD have also been observed in a variety of pathologic conditions, including atherosclerosis, radiation toxicity, traumatic brain injury, meningitis, Down syndrome, neurofibromatosis type 1, microcephalic primordial dwarfism, sickle cell disease, thyroid disease, autoimmune diseases, and brain tumors. Those cases, which can involve a single or both ICAs, are generally referred to as moyamoya syndrome (MMS).

Although the diagnosis of “definite” MMD requires bilateral presentation, patients with unilateral ICA involvement and no associated predisposing pathology are considered to have “probable” MMD, given that many such patients (i.e., up to 70%) will ultimately develop contralateral disease over time. Similarly, in some cases, MMD may start in the proximal MCA (M1 segment) before spreading to the ICA terminus. MMD is more common in Asia, whereas MMS tends to be more prevalent in North America and Europe. However, given that clinical features, pathophysiology, and treatment are essentially the same for both entities, distinguishing between definite MMD, probable MMD, and MMS may not have significant practical implications. Thus, the term moyamoya phenomenon or simply moyamoya can be used to refer to either of these pathologic entities.

Epidemiology and Pathogenesis

Although it has been reported worldwide, MMD is most commonly seen in Asian countries and among people of Asian descent. In Japan and Korea, the annual incidence of MMD varies from 0.4 to two per 100,000, and its prevalence varies from three to 10 per 100,000. In contrast, the incidence in the US is less than 0.1 per 100,000 and is highest among Asian Americans. Likewise, the incidence in Europe has been estimated at one-tenth of that in Japan. Interestingly, in recent years, there has been a dramatic increase in hospital admissions for moyamoya in the US, as well as a rising trend in surgical revascularization for moyamoya, despite an overall decline in cerebrovascular bypass surgery.

When it comes to age, moyamoya has a bimodal distribution, with a first peak in the first decade of life and a second peak in the fifth decade. There is also clear female predominance, with a female-to-male ratio close to 2:1. A family history of MMD increases the risk of developing the disease 30- to 40-fold. Roughly 10-15% of patients with MMD have a positive family history, the mode of inheritance appearing to be either polygenic or autosomal dominant with incomplete penetrance.

Pathologic examination of stenotic vessels in MMD reveals hyperplasia of smooth muscle cells causing eccentric fibrocellular thickening of the intima with intraluminal thrombosis. In contrast, there is attenuation of the media with an irregular...
There are multiple genetic associations between MMD and specific chromosomal loci, the most promising of which (RNF 213 and TIMP-2) are located on chromosome 17. Specifically, the TIMP-2 gene (tissue inhibitor of matrix metalloproteinase type 2) on chromosome 17q25 is a known regulator of vascular remodeling and angiogenesis.

In fact, MMD is characterized by a heavily proangiogenic environment that contains high levels of growth factors and extracellular matrix peptides, including hypoxia-inducing factor \( \alpha \), vascular endothelial growth factor, basic fibroblast growth factor (bFGF), transforming growth factor-\( \beta \), hepatocyte growth factor, and matrix metalloproteinases (MMPs).

**Clinical Features**

The two classic modes of moyamoya presentation are cerebral ischemia and intracranial hemorrhage (ICH). As stenosis progresses in the distal ICA, cerebral perfusion pressure (CPP) drops, ultimately reaching values below the physiologic limits of cerebrovascular autoregulation. This results in reduced cerebral blood flow (CBF) and increased hemodynamic stress on circle of Willis and leptomeningeal collaterals. The ensuing cerebral ischemia induces a proangiogenic environment promoting the development of fragile moyamoya collaterals, which are prone to hemorrhage and hemodynamic failure.

Ischemic stroke and TIA are the most common mode of presentation in both children and adults, representing 50-75% of cases.

Given their frail cerebrovascular reserve (CVR), patients with moyamoya have very low tolerance for any sort of physiologic stress. Thus, cerebral ischemia can often be precipitated by such events, including dehydration, blood pressure fluctuations (e.g., general anesthesia for minor procedures), and excessive crying in children, which may lead to hyperventilation and hypocapnia. ICH is a common presentation in adults, representing 20-50% of cases, but it only rarely affects children (2-3% of cases). Intraparenchymal, intraventricular, and subarachnoid hemorrhage have all been reported. They are thought to result from rupture of the fragile moyamoya vessels, although hemodynamic stress-induced aneurysms may also develop in circle of Willis collaterals and eventually rupture. In addition to ischemia and hemorrhage, individuals
with moyamoya may also present with seizures (probably ischemia-related) and headaches. The latter are thought to result from stimulation of dural nociceptors by pathologic transdural collaterals. Finally, movement disorders (chorea) and cognitive decline have been reported in children. Rather than ischemia, direct pressure on the basal ganglia by moyamoya vessels is believed to underlie choreiform movements in children.

Radiologic Features
Although cerebral catheter angiography is considered the gold standard imaging modality for moyamoya, diagnosis can often be made solely on noninvasive imaging, such as magnetic resonance imaging and angiography (MRI and MRA) and computerized tomography angiography. To avoid radiation exposure, MRI and MRA are generally preferred in children. Cerebrovascular imaging, particularly catheter angiography, also provides an assessment of disease severity, associated intracranial aneurysms, and external carotid artery anatomy (transdural collaterals, surgical planning).

While required for the diagnosis of “definite” MMD, moyamoya collaterals are not always angiographically visible. In fact, angiographic findings in moyamoya progress through six stages (I–VI) described by Suzuki and Takaku (Table 1). Moyamoya vessels are not visible in stage I, start developing in stage II, become prominent in stages III and IV, then start regressing in stage V, before disappearing completely in stage VI. In addition to vascular imaging, CBF assessment is another essential component of moyamoya workup. Some of the available hemodynamic imaging modalities include single-photon emission computed tomography, positron emission tomography, CT perfusion, MR perfusion, and noninvasive optimal vessel analysis quantitative MRA (NOVA qMRA).

Hemodynamic imaging can also be performed after acetazolamide or carbon dioxide (CO₂) challenge. In patients with poor or no CVR, this will result in a steal phenomenon, given that cerebral arteries are already maximally dilated on the affected side. Patients with impaired CVR are generally those most likely to benefit from surgical revascularization. In our practice, the standard workup for individuals with moyamoya includes cerebral angiography (or MRI/A in children), SPECT without and with acetazolamide challenge, and NOVA qMRA.

Treatment
Medical therapy has been used with some success in patients with mild and asymptomatic forms of moyamoya. In the absence of ICH, antiplatelet therapy, particularly aspirin, is typically used for secondary stroke prevention. Likewise, factors that can precipitate cerebral infarction, such as hypotension, dehydration, hyperthermia, hypoxia, hypercapnia, hypocapnia, or anemia, should be strictly avoided in patients with impaired CVR. This becomes particularly important in the setting of physiologic stress, such as after acute stroke or during and after surgery. Perioperative cerebral ischemia may complicate moyamoya-unrelated elective procedures and has been reported in up to 12% (mean, 4-5%) of patients after revascularization surgery. In young children, it is essential to ensure excellent postoperative pain control, so that excessive crying, hyperventilation, and hypocapnia are avoided. Hypocapnia can induce cerebral vasoconstriction and precipitate infarction in patients with moyamoya. Finally, calcium channel blockers (e.g., verapamil) can be used to relieve intractable headaches and reduce the frequency and severity of TIAs in well-selected individuals with moyamoya.

However, in more advanced forms of the disease, medical therapy becomes less effective. In one study, patients with symptomatic moyamoya had a 65% ipsilateral stroke risk at five years when treated medically, compared with only 17% in the surgically revascularized group. Although a less aggressive natural history has been suggested by others, and despite the lack of a conclusive randomized controlled trial it is generally well accepted that, for patients with ischemic symptoms, surgical revascularization is more beneficial than conservative management in terms of secondary stroke prevention.

Conversely, in adult patients with hemorrhagic moyamoya, the role of surgical revascularization has long remained a matter of controversy. Recently, however, the effectiveness of surgery in this patient population was established by the Japan Adult Moyamoya Trial. In fact, in this multicenter RCT, an
8.2% per year recurrent hemorrhage rate was observed in the medical arm, compared with only 3.2% per year in the surgical arm, a statistically significant difference.\textsuperscript{35} In terms of surgical technique, there are three types of revascularization procedures: direct bypass, indirect revascularization, and combined techniques.

In the direct bypass, a donor vessel, most typically the superficial temporal artery (STA), is harvested, brought into direct contact, and anastomosed with a distal branch of the MCA (M3 or M4 segment), via a small frontotemporal craniotomy. In indirect revascularization, a vascularized extracranial or extradural tissue is brought into direct contact with the cerebral cortex and allowed to slowly form collaterals to the ischemic brain, over a period of weeks to months, driven by the proangiogenic moyamoya environment.\textsuperscript{50,52}

Multiple variations of this procedure exist, depending on which exact tissue is being laid onto the brain. For instance, encephalo-duro-synangiosis, encephalo-myo-synangiosis, and encephalo-duro-arterio-synangiosis (EDAS) involve using the dura, temporalis muscle, and both dura and STA, respectively.\textsuperscript{50} EDAS is probably the most commonly performed indirect procedure today.\textsuperscript{50,52} Another technical variation, multiple burr hole placement, is also being increasingly used, given its versatility and high efficacy.\textsuperscript{50,53-55} Indirect revascularization techniques are generally less technically challenging and less time-consuming than direct bypass, because they often do not involve temporary occlusion of a cerebral artery or direct microanastomosis.\textsuperscript{45,50,52} In combined techniques, both direct bypass and indirect revascularization are performed concomitantly.

The main advantage of direct bypass is that it provides immediate flow augmentation and, thus, may provide protection against perioperative cerebral ischemia.\textsuperscript{38,52,54,60,62} In contrast, indirect revascularization can be particularly valuable in patients with tiny cerebral arteries who are unsuitable for a direct anastomosis, particularly young children, and those without adequate donor vessels.\textsuperscript{225,152,58}

Additionally, indirect revascularization is not associated with a postoperative risk of cerebral hyperperfusion, which has been reported in as many as 45% of patients undergoing direct bypass.\textsuperscript{59,61} Combined techniques tend to offer the best of both worlds and, compared with STA-MCA bypass alone, provide improved ACA territory coverage.\textsuperscript{38,57,59,62,63} Both direct and indirect techniques have been associated with excellent angiographic and clinical outcomes and minimal morbidity.\textsuperscript{22,38,50-52,54,56,63}

In general, it is well accepted that both techniques are equally effective in children, possibly as a result of their high angiogenic activity after indirect revascularization.\textsuperscript{50,64} For this reason, indirect procedures are often preferred in the pediatric population.\textsuperscript{33,50,52} In contrast, direct or combined procedures usually lead to earlier and more robust angiographic collateralization and overall better clinical outcomes in adults.\textsuperscript{33,50,52,60,66} In a recent meta-analysis, adults with moyamoya undergoing direct bypass had significantly higher rates of good angiographic outcome (89.6% vs. 52.8%) and lower rates of future stroke events (7.7% vs. 16.5%) compared with indirect revascularization, despite a trend toward more complications in this group (30.2% vs. 18.8%).\textsuperscript{55}

In our practice, we favor the use of combined revascularization for all patients with moyamoya, whenever possible. We generally use both frontal and parietal branches of the STA to perform direct STA-MCA bypass and EDAS, respectively.\textsuperscript{37} If a direct bypass is not feasible (e.g., young children, inadequately small vessels), we then perform an indirect EDAS procedure. We frequently add medial frontal and parietal burr holes whenever ACA territory coverage is a concern.

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**TABLE 1. THE SUZUKI STAGING SYSTEM\textsuperscript{1,36}**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Angiographic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Narrowing of the carotid fork (i.e., ICA bifurcation)</td>
</tr>
<tr>
<td>II</td>
<td>Initiation of the moyamoya: continued narrowing of the ICA; dilation of the ACA and MCA; initial moyamoya blush</td>
</tr>
<tr>
<td>III</td>
<td>Intensification of the moyamoya: loss of proximal ACA and MCA; leptomeningeal collateralization from the PCA; increase in moyamoya blush</td>
</tr>
<tr>
<td>IV</td>
<td>Minimization of the moyamoya: progressive occlusion of ICA reaching origin of PCA; reduction in moyamoya blush</td>
</tr>
<tr>
<td>V</td>
<td>Reduction of the moyamoya: complete loss of ICA, ACA, and MCA; increased collateral supply from ECA; further reduction in moyamoya blush</td>
</tr>
<tr>
<td>VI</td>
<td>Disappearance of the moyamoya: disappearance of blood supply from ICA; blood supply exclusively from ECA; disappearance of moyamoya vessels</td>
</tr>
</tbody>
</table>

Abbreviations: ACA, anterior cerebral artery; ECA, external carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.
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