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Review Article

Childhood Moyamoya: Looking Back to the Future

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ABSTRACT

Moyamoya is a chronic, progressive steno-occlusive arteriopathy that typically affects the anterior circulation arteries of the circle of Willis. A network of deep thalamoperforating and lenticulostriate collaterals develop to by-pass the occlusion giving rise to the characteristic angiographic "puff of smoke" appearance. Moyamoya confers a lifelong risk of stroke and neurological demise, with peak age of presentation in childhood ranging between five and 10 years. Moyamoya disease refers to patients who do not have a comorbid condition, whereas moyamoya syndrome refers to patients in whom moyamoya occurs in association with an acquired or inherited disorder such as sickle cell disease, neurofibromatosis type-1 or trisomy 21. The incidence of moyamoya disease and moyamoya syndrome demonstrates geographic and ethnic variation, with a predominance of moyamoya disease in East-Asian populations. Antiplatelet therapy and surgical revascularization procedures are the mainstay of management, as there are no available treatments to slow the progression of the arteriopathy. Future research is required to address the major gaps that remain in our understanding of the pathologic basis, optimal timing for surgery, and determinants of outcome in this high-stroke risk condition of childhood.

Background

Moyamoya is a progressive steno-occlusive large vessel cerebral arteriopathy which results in both ischemic stroke, often presenting in childhood, as well as hemorrhagic stroke, especially in adults. Moyamoya is a Japanese term for "puff of smoke" and describes the classic angiographic appearance of a bilateral progressive intracranial arteriopathy which typically involves the distal internal carotid, proximal middle cerebral arteries (MCA) and proximal anterior cerebral arteries of the circle of Willis.[1] In a Japanese population, Suzuki defined 6 stages, from initial narrowing of the distal internal carotid arteries to the "puff of smoke" appearance of the lenticulostriate (moyamoya) collaterals and finally to the disappearance of this network of collaterals (Fig 1)[1]:

1. Bilateral internal carotid arteries (ICA) or MCA narrowing;
2. Formation of early moyamoya collaterals;
3. Progression of stages 1 and 2 with prominence of collaterals;
4. Severe stenosis or occlusion of ICA's with involvement of the Circle of Willis;
5. Progressive reduction of moyamoya collaterals with an increase in extracranial collaterals;
6. Disappearance of moyamoya collaterals and complete ICA occlusion.

Revised guidelines for the diagnosis of moyamoya require the presence of moyamoya collaterals,[2] but these

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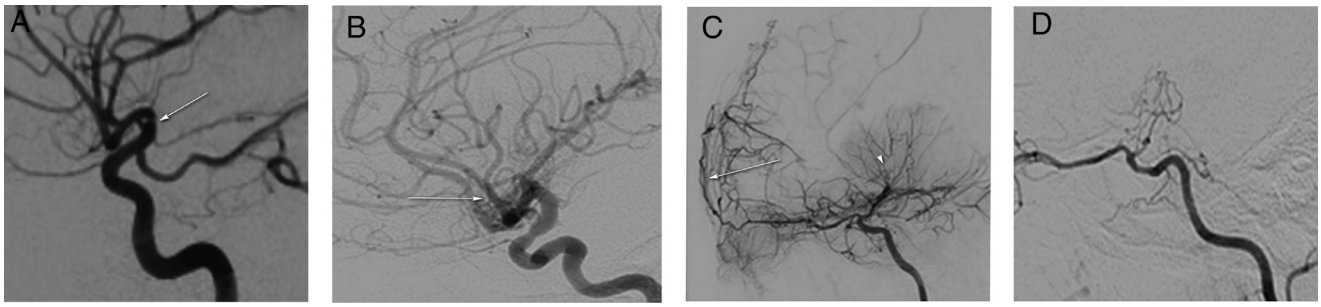

Figure 1. Angiographic findings in Moyamoya (A) Lateral view of internal carotid artery (ICA) injection showing mild, nonflow limiting luminal narrowing of the terminal ICA—Suzuki stage 1. (B) Early moyamoya collaterals seen in the form of an increased density of lenticulostriate arteries—Suzuki stage 2. (C) Near-total occlusion of the terminal ICA with increased prominence of collaterals and extracranial arterial caliber —Suzuki stages 4 and 5. (D) Complete ICA occlusion, disappearance of moyamoya collaterals—Suzuki stage 6.

are not always present at the onset of disease[3] and may not occur in every patient.[4] In addition, the diagnostic criteria for moyamoya do not address the involvement of the posterior circulation, despite steno-occlusive disease of the posterior cerebral arteries being present in approximately one-quarter of cases.[5]

Moyamoya disease (MMD) refers to patients, most commonly of Japanese or other Asian origin, who have no previously diagnosed condition, have a family history in approximately 10%, and have autosomal dominant or recessive genes as the etiology of their cerebrovascular disease.[1,6,7] Moyamoya syndrome (MMS) is the occurrence of angiographic moyamoya in association with an acquired or inherited disorder such as sickle cell disease, neurofibromatosis type 1, or trisomy 21.[7-19] (Table) Patients with unilateral disease are classified as probable moyamoya, and 30% to 40% of these individuals will progress to bilateral disease (Fig 2).[20]

The incidence of moyamoya demonstrates ethnic variation. Prevalence is highest among the Japanese, estimated at 6/100,000, with a female to male ratio of almost 2:1 and positive family history in 14.9%. The prevalence in China is approximately 4/100,000 persons, with no female predominance and a positive family history in approximately 1.5%.[21] In one North American study the incidence of moyamoya was 0.086/100,000, with the rate among US Asians noted to be similar to rates in Asia.[22] Age at presentation is bimodal, with peaks occurring at five and 40 years of age.[21,23] However, the childhood age peak and female predominance seen in the Japanese population are not replicated in comparative European or American populations.[22,24]

Table. Conditions Associated With Moyamoya

Sickle cell disease
Trisomy 21 (Down syndrome)
Neurofibromatosis type 1
Congenital heart disease
Coarctation of aorta
Renal artery stenosis
History of cranial radiation therapy
Autoimmune disease
Hyperthyroidism
PHACES
Congenital dwarfism

MMS represents a heterogeneous group of disorders. The prevalence and incidence of MMS is most likely related to the epidemiology and frequency of the underlying disease or risk factors.[7-18] MMS is proportionally more common than MMD in European and North American communities. Conversely, in East Asian populations where this has been studied, the prevalence and incidence of MMS is up to ten times lower than that of MMD.[22,25-28]

Hemodynamics of moyamoya

Distal stenosis of the arteries of the circle of Willis results in reduction of localized cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) distal to the stenosis. Collateral networks from the deep thalamoperforating and lenticulostriate perforating arteries, pial collateral arteries from the posterior circulation and transdural collateral arteries from the external carotid arteries supply the compromised brain in an

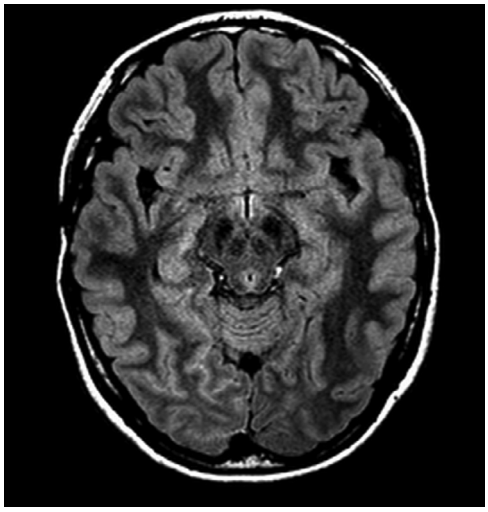

Figure 2. A 16-year old girl with moyamoya disease who underwent bilateral pial synangiosis. Axial section of FLAIR MRI showing increased T2-signal in the sulcal spaces in both occipital regions, more predominantly right-sided, consequent to progressive disease involving the posterior cerebral arteries.

attempt to maintain adequate CPP. Reduction in CPP may ensue with or without a compensatory rise in systemic blood pressure. Subsequent failure of CPP may result in cortical and subcortical ischemia, with the clinical consequence of covert or overt arterial ischemic stroke.[29-31]

Presentation

Although often preceded by a history of transient ischemic attacks, moyamoya in childhood is usually diagnosed in the setting of acute ischemic stroke.[32] In addition, children may present with headache, cognitive decline, or other signs of anterior circulation ischemia including aphasia, dysarthria, hemiparesis, and seizures.[24,33,34] Headache with associated hemiparesis can mimic complicated migraine. Less common presentations such as syncope, visual changes, and chorea can occur. Symptoms are often provoked by hyperventilation, for example with crying or physical exertion, due to hypocarbia-induced vasoconstriction. Moyamoya can have an aggressive course in young children who are likely to have more infarcts at baseline, have recurrent stroke while awaiting revascularization surgery and have poor clinical outcomes including neurocognitive impairment in childhood which persists into adulthood, even in the absence of stroke.[35,36] Whether idiopathic or syndromic, unilateral moyamoya often progresses to bilateral disease, with young children being the most likely to progress.[20,37] Some children are diagnosed following disease-specific screening protocols and are asymptomatic on diagnosis.[17,38] However, vascular progression and ischemia often occur in childhood even if initially asymptomatic.[1,39-42] Moyamoya in childhood can rarely present with intracranial hemorrhage, in contrast to adults, in whom hemorrhagic rather than ischemic stroke dominates the clinical presentation.[43]

Genetics of moyamoya

MMD is likely a genetic disease, most probably polygenic, based on the high prevalence of moyamoya in Asia as well as familial aggregation in 10% to 15% of patients.[23,44] The most common mode of inheritance appears to be autosomal dominant with incomplete penetrance.

Liu et al.[45,46] demonstrated a major founder susceptibility gene for familial moyamoya at p. R4810K on the ring finger protein 213 gene *(RNF 213)* which has been confirmed in Japanese,[47,48] Korean[49] and Chinese populations.[50] However, mutations at 17q25 have also been found in nonfamilial moyamoya in the Chinese population.[50] The female to male ratio in familial moyamoya is 5 to 1, and there is a suggestion of anticipation among parent-offspring pairs.[51] Additional studies have shown linkage of familial moyamoya in Japanese populations to 12p12,[52] 3p24.2-p26,[53] 6q25,[54] and 8q23.[52] No major cofounder susceptibility genes including mutations in *RNF213* have been identified in a Caucasian idiopathic moyamoya population. However, candidate genes of interest include *MYRIP* which is highly expressed in the brain, located around the suggestive association region for cerebral infarction and has its C-terminal domain directly bound to actin which is encoded by *ACTA2*.[55,56] This could be responsible for the progression of vascular disease in Caucasian idiopathic moyamoya. Other novel genes of interest include the *BRCC3* and *MTCP1* genes. *BRCC3* encodes for a nuclear DNA repair complex and a cytoplasmic complex that might have a role in cardiomyocyte protection. Knockdown studies in zebrafish suggest that *BRCC3* plays an important role in angiogenesis. The function of *MTCP1* is yet unknown.[57,58]

Neuroimaging techniques in moyamoya

Conventional anatomic imaging techniques focus on accurate neuroradiological identification of acute or chronic ischemic parenchymal disease, the presence and extent of moyamoya arteriopathy and post-treatment appearances. Brain MRI and MR angiography (MRA) are the imaging tools of choice for long-term follow-up, avoiding ionizing radiation and typically not requiring contrast administration. MRI is able to demonstrate areas of acute or chronic parenchymal ischemia recognized as areas of diffusion restriction on diffusion-weighted imaging, gliosis, or encephalomalacia on T2-FLAIR imaging, within vascular territories or in the border-zones created by deep and cortical penetrating collaterals of the MCA, anterior cerebral arteries, and/or PCA. The mechanism of ischemia is likely hemodynamic and can be inferred by involvement of watershed regions on imaging.[59] Magnetic resonance angiography is most often performed using a three-dimensional time-of-flight technique, which tends to overestimate stenosis of major arteries, and underestimate the number and extent of pial and dural collaterals.[60,61] In this regard, the sensitivity and specificity of MRI for ischemia and time-of-flight-MRA for vessel stenosis increases with magnet strength. Similar to MR angiography, CT angiography[62] provides information about the anatomic state of the vessels but is not routinely used due to radiation and contrast exposure. Conventional angiography, still the gold standard for lumenography, allows for a more dynamic and hence functional assessment than MRA or CTA by examination of the temporal arterial-venous cycle. Additionally, it allows for selective evaluation of arterial supply to brain parenchyma, either of native arteries or postsurgical anastomoses. However, given the risks from invasiveness and radiation, requirement for a dedicated neuroangiographic service, and limited understanding of the implications of these findings with respect to stroke risk, catheter angiography is being performed very selectively in some centers, e.g. for presurgical planning, or replaced entirely by MRA.

In addition, inferences regarding cortical perfusion can be made from the linear hyperintensities in a sulcal pattern seen on FLAIR sequences and called the “ivy sign.”[63,64] Diffuse leptomeningeal enhancement was first reported in contrast-enhanced T1-weighted image in patients with MMD by Ohta et al.[60] Fujiwara et al, demonstrated an association between the prominence of moyamoya vessels on T1-and T2-weighted images, poor visualization of middle cerebral artery branches on MR angiography, and the presence of the ivy sign.[65] In

addition, the presence of the ivy sign may be a useful indicator of moyamoya in the absence of (lenticulostriate) moyamoya collaterals. Fronto-parietal predominance is reported and the presence of the ivy sign has been shown to be positively correlated with ischemic symptoms and negatively correlated with CBF and cerebrovascular reactivity (CVR).[66]

Treatment of moyamoya

There are currently no known treatments to prevent the vascular progression, which occurs in the majority of children with moyamoya, even if asymptomatic.[1,39,40] Medical treatment strategies for the prevention of stroke including acetazolamide, aspirin, and anticoagulants such as warfarin or heparin are of unproven benefit.[67-70] Blood transfusion may decrease the risk of recurrent stroke in children with moyamoya associated with sickle cell disease, however, the risk of stroke recurrence is still high, reported as 22% at a mean follow-up of 10.1 years despite the use of blood transfusion in one study.[71] In addition, steno-occlusive arteriopathy often progresses despite treatment with red blood cell transfusion or hydroxyurea resulting in further ischemic and hemorrhagic strokes.[69,70] Bone marrow transplantation offers another therapeutic approach to the management of moyamoya in sickle cell disease. Transient stabilization of vascular disease has been reported following bone marrow transplantation, however later progression often still occurs.[72-75]

Moyamoya typically spares the external carotid arteries (ECA) and its branches. Surgical treatment aims to improve CBF in the impaired region either by bypassing the area of occlusion (direct anastomosis) or encouraging neovascularization from the ECA (indirect anastomosis).[76]

Current indicators for revascularization surgery include arterial ischemic stroke, transient ischemic attacks, cognitive decline, and evidence of vascular or parenchymal progression of disease.[77] Younger children with moyamoya have a greater risk of a poor outcome, including a greater risk of infarction, which can occur while awaiting revascularization surgery.[78-80] Hence, revascularization surgery is also recommended in asymptomatic moyamoya as these patients will often progress to radiographic evidence of ischemia and overt stroke.[42] Given that medical options are limited in number and efficacy, revascularization surgery is usually the intervention of choice. Although the underlying steno-occlusive disease progresses, there appears to be a reduction in symptomatic progression from 66% in those receiving no treatment to 2.6% following surgery and there is a 96% probability of remaining stroke free five years following surgery.[81,82] Revascularization not only reduces the incidence of ischemic stroke in childhood, but appears to decrease the risk of hemorrhagic stroke in adulthood.[83,84] Revascularization also often improves the frequently seen severe headaches associated with moyamoya.[85,86] However, revascularization surgery is not without risk as demonstrated by an estimated surgical morbidity rate of 3.5% to 4% and a mortality rate of 0.7% per treated hemisphere in one study.[87]

There is no definite evidence for the superiority of different surgical modalities as to neurological outcomes. Indirect procedures are more commonly used in children due to lower surgical morbidity, lack of dependence on intact distal MCA arteries, and the ability to revascularize beyond the MCA territory. Indirect synangiosis procedures include encephaloduroarteriosynangiosis or encephalomyosynangiosis, omental synangiosis, and burr-hole surgery. During these procedures, tissues containing ECA branches (dura mater, temporal muscle, galeal tissue, or superficial temporal artery) or omental vessels are placed in direct contact with the ischemic brain. Burr-hole surgery can be conducted in children at higher risk with the more involved revascularization surgery or those without donor arteries.[88] Neovascularization after indirect surgical procedures is gradual, depending on neoangiogenesis and therefore complex interactions between local and systemic hemodynamics and tissue properties.[89] Direct procedures are more commonly used in adults and involve the anastomosis of a branch of the ECA, typically the superficial temporal artery, with a branch of the MCA or anterior cerebral arteries. Hence, improvement in CBF is immediate. There is however an increased risk of postoperative neurological impairment with or without an increased risk for hemorrhage presumed to be secondary to hyperperfusion.[90] Combined (direct and indirect) revascularization procedures are reportedly more effective in improving cerebral circulation than single direct or indirect procedures,[91,92] but the benefit of this approach is not proven[93,94] and response to indirect revascularization in childhood is usually excellent.

There is only one published observational cohort study comparing disease progression and outcome in patients with and without surgical revascularization. This study, in children with sickle cell-associated moyamoya suggests that in this group, revascularization surgery may be effective.[95]

It has been proposed that the stage of cerebrovascular hemodynamic compromise before the operation may be an important determinant of surgical success. Theoretically, patients with no clinical signs of infarction, decreased regional cerebral blood flow increased regional oxygen extraction fraction and regional cerebral blood volume without any change in regional cerebral metabolic rate of oxygen consumption may be good candidates for bypass surgery in MMD. Matsushima et al. suggested that if surgery is performed in a brain with normal blood flow or following an extreme reduction in regional cerebral metabolic rate of oxygen consumption, i.e. too early or too late, collateral vessels may not form.[96] Children may be more likely than adults to self-collateralize, as well as to develop neovascularization from anastomosis, as cerebral circulation and oxygen metabolism tend to decline with age.[97,98] Functional neuroimaging techniques are being more frequently used for selecting surgical candidates. Pre- and postsurgical single photon emission computed tomography (SPECT) and positron emission tomography studies in children with MMD have demonstrated abnormalities in cerebral hemodynamics preoperatively, even in the absence of infarction, with improvement postcombination (direct and indirect)

revascularization surgery,[99] mostly in the area surrounding the bypass.[91] Improvements in CBF have also been documented in children with stroke.[100,101] In a recent large study, Kim et al.[37] found that baseline regional cerebral blood volume from perfusion MRI and regional cerebral blood flow using SPECT predicted surgical outcome in univariable analysis.[102] Magnetic resonance imaging assessment of oxygen extraction has been demonstrated in adults.[103] More recently, arterial spin labeling MRI has shown value in identifying brain regions with poor perfusion[104,105] in moyamoya and other arteriopathies. However, in spite of significant progress, it is not currently clear how to use these studies for clinical decision making.

Ten to fifteen percent of patients with moyamoya disease will have an affected family member, but there are inadequate data to recommend or guide presymptomatic screening. Family members should be educated regarding signs and symptoms suggestive of moyamoya, including transient neurological deficit, seizure, and migrainous headaches. Moyamoya is concordant in approximately 80% of identical twins, and MRI and MRA screening of identical twins of affected patients should be undertaken.[106] The optimal timing for follow-up screening if initial study is negative is unknown.

Future directions

Optimal timing of surgery

Published Japanese and US indications for revascularization surgery include presentation with ischemic symptoms; progressive vasculopathy; decreased regional cerebral blood flow, vascular response and perfusion reserve, retrieved from cerebral circulation and metabolism studies.[67,107,108] A unique challenge in the management of children with moyamoya is the increasing early age of diagnosis due to improved access and use of MRI imaging and disease-specific screening protocols. This has resulted in asymptomatic diagnosis of moyamoya in children of all age groups. Specific indications to guide the timing and type (unilateral or bilateral) of surgery in asymptomatic or incidentally diagnosed moyamoya are not well established. In a study of asymptomatic children with sickle-cell disease or neurofibromatosis type-1 moyamoya, clinical progression heralded by radiographic progression occurred in the majority leading to a recommendation that the majority of children with moyamoya arteriopathy would benefit from revascularization surgery even if asymptomatic at presentation.[42,109]

However, operative technical constraints, higher complication rate, and anesthetic risk in the very young and those with comorbid diagnosis, countered by the risk of cognitive decline and stroke over time highlights the need for a clinically usable biomarker of ischemic risk to inform the decision to proceed to surgery, operative procedure choice—including whether to operate on one or both hemispheres—and optimal timing of surgery.[42,79,80,110,111]

Nuclear medicine techniques such as 133Xenon clearance, positron emission tomography, and SPECT are all associated with a risk of radiation exposure, are technically challenging, have poor spatial resolution and incur high capital costs.[112,113] In addition, MR perfusion imaging using dynamic susceptibility contrast remains challenging to apply in children with steno-occlusive arteriopathy such as moyamoya. Measures from conventional or digital subtraction angiography such as arterial circulation time may be used to calculate hemodynamic status. However, there is reluctance to perform conventional angiography in children due to safety concerns compounded by an increase in early diagnosis of moyamoya in asymptomatic children in whom the risk of an invasive angiographic procedure may be even less acceptable. Despite attempts to demonstrate parity in findings between conventional catheter angiographic modalities and MRI and/or MRA, the latter's ability to inform on hemodynamic status is confined to demonstration of parenchymal ischemic injury, presence of the ivy sign, signal attenuation on MRA, and presence of collaterals.[114] MRA has been shown to overcall the degree of parent artery stenosis and under-call collateralization again limiting its utility in determining hemodynamic status. Newer and faster MRA techniques at higher field strength could offer adequate spatial and temporal resolution to accurately assess luminal narrowing, collaterals, and circulation times. However, whether these techniques will allow MRA to replace catheter angiography as a preoperative tool will need to be assessed.

CVR is an important marker of cerebrovascular reserve and a biomarker of cerebrovascular health. CVR in adult arterial stenotic diseases has been shown to predict ischemic risk and impaired CVR is associated with conditions of cognitive decline.[115-119] Hence impaired CVR is an indicator of tissue at risk of ischemia. Hypercapnic challenge blood oxygen level dependent-MRI CVR studies are technically feasible in children and can provide information on tissue level hemodynamic compromise and existing or at-risk regions beyond that demonstrated on standard conventional angiography, MRI, or MRA.[120-122] Further exploration of this technique is required in the pediatric population.[123]

Inflammation as a therapeutic target in moyamoya

An understanding of the pathogenesis of moyamoya and the role of inflammation in moyamoya remain elusive. Histopathologically, despite the absence of specific cellular inflammatory markers in the vessel wall, the presence of macrophages and T cells in nonstenosed vessels is suggestive of chronic inflammation potentially amenable to treatment with anti-inflammatory agents.[124,125] Linkage analysis has demonstrated a number of inflammatory genes in moyamoya including chromosome 3p—a principle site of proteins involved in multiple signaling pathways—which control and regulate angiogenic and inflammatory pathways[53] and chromosome 6q25 associated with human leukocyte antigens.[54,126,127] In addition, the aberrant expression of growth factors including vascular endothelial growth factor, basic fibroblast growth factor and transforming growth factor-β1 in patients with moyamoya disease[128-131] provide additional

support for an inflammatory role in the pathogenesis of moyamoya and therefore potential therapeutic targets.

Conclusion

The natural history of moyamoya in childhood is increasingly understood, but significant gaps in our understanding of the pathogenesis remain. Children are being diagnosed before symptomatic presentation and at a younger age due to advances in imaging and syndrome-specific screening protocols. Yet our therapeutic approaches remain limited. Embracing novel applied MRI technologies such as hypercapnic challenge blood oxygen level dependent CVR, arterial spin labeling perfusion, and novel approaches to genomic and proteomic studies has the potential to yield important advances in the management of children with moyamoya in the near future, but these new technologies will only be meaningful if they can be used to inform clinical care. Effective strategies are needed to prevent, arrest, or possibly even reverse the progressive steno-occlusive arteriopathy which is the hallmark and primary pathology of moyamoya.

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It may be that the race is not always to the swift, nor the battle to the strong; but that is the way to bet.

Damon Runyon