Moyamoya disease: a summary

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Moyamoya, meaning a “hazy puff of smoke” in Japanese, is a chronic, occlusive cerebrovascular disease involving bilateral stenosis or occlusion of the terminal portion of the internal carotid arteries (ICAs) and/or the proximal portions of the anterior cerebral arteries and middle cerebral arteries (MCAs). The Ministry of Health and Welfare of Japan has defined 4 types of moyamoya disease (MMD): ischemic, hemorrhagic, epileptic, and “other.” The ischemic type has been shown to predominate in childhood, while the hemorrhagic type is more often observed in the adult population. The highest prevalence of MMD is found in Japan, with a higher female to male ratio. Studies have shown a possible genetic association of MMD linked to chromosome 17 in Japanese cases as well as in cases found in other demographics. During autopsy, intracerebral hematoma is found and most commonly serves as the major cause of death in patients with MMD. Moyamoya vessels at the base of the brain are composed of medium-sized or small muscular arteries emanating from the circle of Willis, mainly the intracranial portions of ICAs, anterior choroidal arteries, and posterior cerebral arteries, forming complex channels that connect with distal positions of the MCAs. Off of these channels are small tortuous and dilated vessels that penetrate into the base of the brain at the site of the thalamoperforate and lenticulostriate arteries. On angiography, there is the characteristic stenosis or occlusion bilaterally at the terminal portion of the ICAs as well as the moyamoya vessels at the base of the brain. Six angiographic stages have been described, from Stage 1, which reveals a narrowing of the carotid forks, to Stage 6, in which the moyamoya vessels disappear and collateral circulation is produced solely from the external carotid arteries. Cases with milder symptoms are usually treated conservatively; however, more severe symptomatic cases are treated using revascularization procedures. Surgical treatments are divided into 3 types: direct, indirect, and combined/other methods. Direct bypass includes superficial temporal artery-MCA bypass or use of other graft types. Indirect procedures bring in circulation to the intracranial regions by introducing newly developed vasculature from newly approximated tissues. These procedures may not be enough to prevent further ischemia; therefore, a combination of direct and indirect procedures is more suitable. This article will give a review of the epidemiology, natural history, pathology, pathophysiology, and diagnostic criteria, including imaging, and briefly describe the surgical treatment of MMD. (DOI: 10.3171.2009.1.FOCUS08310)

KEY WORDS • moyamoya disease • progressive intracranial occlusive arteriopathy • extracranial-intracranial bypass • cerebral angiography

MOYAMOYA disease is a chronic, occlusive cerebrovascular disease involving bilateral stenosis or occlusion of the terminal portion of the ICAs and/or the proximal portions of the ACAs and MCAs.⁶⁰ Moyamoya disease is also characterized by irregular perforating vascular networks, called moyamoya vessels, near the occluded or stenotic regions corresponding to the lenticulostriate and thalamoperforate arteries. It is this outgrowth of small vessels that produces the radiological image of a hazy “puff of smoke” giving the disease its

name, “moyamoya” in Japanese.⁶⁰ Moyamoya disease has also been termed “bilateral hypoplasia of the ICAs,” “cerebral juxta-basal telangiectasia,” “cerebral arterial rete,” “rete mirabile,” “cerebral basal rete mirabile,” and, more commonly, “spontaneous occlusion of the circle of Willis.”⁴²

Clinically, children with MMD present with ischemic attacks, and adults present with either ischemic or hemorrhagic events. However, this point has recently undergone debate, depending on the patient’s geographical location.⁴³ Moyamoya disease has been reported to be higher in the Japanese population in the past, but this point has also recently undergone debate, depending on the patient’s ethnicity and current demographics.¹⁹

Moyamoya disease creates hemodynamic abnormalities that have inspired unique treatments. We present an overview and update on this disease focusing on epidemiology, pathology, pathophysiology, imaging, diagnosis, and treatment.

Abbreviations used in this paper: ACA = anterior cerebral artery; bFGF = basic fibroblast growth factor; CBF = cerebral blood flow; CBV = cerebral blood volume; FMD = fibromuscular dysplasia; HIF = hypoxia inducible factor; ICA = internal carotid artery; MCA = middle cerebral artery; MMD = moyamoya disease; OEF = O₂ extraction fraction; PCA = posterior cerebral artery; rCBF = regional CBF; rCBV = regional CBV; rOEF = regional OEF; STA = superficial temporal artery; TGF = transforming growth factor; TIA = transient ischemic attack; VEGF = vascular endothelial growth factor.

Epidemiology

The highest known prevalence of MMD is in Japan. A survey from 2003 reports 7700 Japanese treated for the disease, an almost 100% increase over the 3900 reported in 1994.³⁵ This prevalence corresponds to a rate of newly diagnosed cases in Japan of 0.54 per 100,000 people in 2003.³⁵ A study from 2002 to 2006 states the incidence rate is now up to 0.94 patients per 100,000 people, with a prevalence of 10.5 patients per 100,000.⁵ Moyamoya disease in this survey was more prevalent in women than men, with a female to male ratio of 1.8:1.³⁵ The survey showed the highest prevalence for males at ages 10–14 and smaller peaks at 35–39 and 55–59. For females, the biggest peak was at ages 20–24 and a smaller peak at 50–54.³⁵ In one-third of these reported cases, onset of the disease was more than 10 years prior to the survey and in another third was within the 5 years prior.³⁵ These data correspond to a prevalence of 6.03 per 100,000 people in 2003, up from 0.35 in 1993.³⁵ However, the surveyors of the data, Kuriyama et al.,³⁵ do acknowledge that improved diagnostic measures as well as improved prognosis for these patients may have contributed to the increase in the incidence and prevalence of the disease. In a recent study by Baba et al.⁴ from 2002 to 2006, the female to male ratio was up to 2.18:1, with similar bimodal age distributions.

The strong prevalence of MMD in Japan suggests a genetic trait associated with the disease. There was a family history of MMD in 12.4% and 11.9% of cases for men and women, respectively, from the 2003 survey.³⁵ In a recent study by Mineharu et al.,⁴⁴ MMD was noted to follow an autosomal dominant inheritance pattern with the gene found in the telomeric region of 17q25.3.⁴ Although this study was limited to 15 extended Japanese families, other researches have found associations between MMD and chromosome 17q25.⁷⁵

Recent studies in the US have highlighted a difference between MMD presentation in Japanese and American cases.⁴³ In these studies, MMD cases in the US have shown a lack of bimodal age of onset, a prevalence of the ischemic type at all ages, more benign symptoms at presentation, and better response to surgical treatment. However, still evident in all the studies is a higher prevalence among women. Studies in which the MMD profile more closely matches that in Japan are found in the states of Hawaii, California, and Washington.⁶⁶ These studies attribute their aberrations from the other US studies to high Japanese immigrant populations, while also noting that the disease continues after Japanese move to the US.⁶⁶ The incidence of MMD in California was only 0.087 per 100,000 from 1987 to 1998, even with a higher Asian population. The adjusted incidence rates by ethnicity were Caucasian 0.06, Asian American 0.28, African American 0.13, and Hispanic 0.03.⁶⁶ Although the data suggest a higher incidence, predominantly genetic, in Asian subpopulations, the incidence of MMD in the US may change with improved imaging technology and increased awareness of the disease in the differential diagnosis of patients with intracranial cerebrovascular disease.

Presentation and Natural History

Moyamoya disease cases typically present acutely with various cerebrovascular events including intracranial hemorrhage, TIAs, brain infarction, and sometimes epileptic seizures. The Ministry of Health and Welfare of Japan has defined 4 types of MMD with the following presentation percentages: ischemic 63.4%, hemorrhagic 21.6%, epileptic 7.6%, and “other” 7.5%.¹⁵ There are also asymptomatic cases in which MMD is found incidentally on angiography.³⁶ As stated before, the ischemic type of MMD predominates in childhood, making up 69% of cases in patients under 10 years old. Some cases involve ≥ 1 one symptom, including 40% of patients with TIAs and 29% with infarction resulting in motor paresis and disturbances of consciousness, speech, and sensation.^{36,42} Ischemic symptoms are often instigated by hyperventilation. The symptoms may present repetitively and can result in motor aphasia, cortical blindness, or, within several years of onset, even a vegetative state. The course of the disease often leads to mental retardation and low IQ over the long term, especially in children.⁷²

Also, as stated before, the hemorrhagic type of MMD is more characteristic of adult onset. Sixty-six percent of adult cases exhibit hemorrhages with a higher occurrence in females. Symptoms often include disturbance of consciousness, motor paresis, and headache. Hemorrhages are often recurrent with intervals of days to 10 years. Large hemorrhages are often fatal. The epileptic type is noted more often in children younger than 10 years of age.

Progression of occlusion is more common in children than adults. In a study of 120 Japanese adult cases, progression over a 15-year period (1990–2004) was noted in 15 of 120 patients.³⁶ Even though a low percentage of cases progressed, this contradicts the previous notion that the disease was progressive in childhood but stable in adults.⁵⁹ Three of these cases showed occlusion of the PCA.³⁶ Four of 11 unilateral cases showed progression of the contralateral carotid fork leading to a bilateral case. Progression of MMD started, on average, more than 1.5 years from onset for all types, although significantly sooner in bilateral cases. From the Kuroda et al.³⁶ study, none of the following were considered to be predictors for progression: age of onset, disease type, symptoms at onset, or previous bypass surgery. However, 13 (32.5%) of 40 female cases and 2 (8.7%) of 23 males exhibited disease progression, which was statistically significant. Overall, about 20% of all adult MMD cases progressed.³⁶

At diagnosis, adults are usually at a more advanced stage than children.^{24,25} Pediatric cases appear to progress into adult cases although the process is still unclear. Children progress much more rapidly than adults. This is especially true in patients younger than 2 years of age, accounting for their poor prognosis.²⁴ According to the study by Ishii et al.,²⁵ childhood patients with MMD progressed within 5–10 years to more severe stages angiographically, while some of the cases progressed after adolescence. Some of the pediatric patients exhibited slow progression, proving to be adult cases with pediatric onset. All of these cases had an MMD onset after the patient was 5 years old. Although most adult cases were

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stable, some showed progression even after long periods of angiographic stability.²⁵

Recent research into asymptomatic cases of MMD has shown that its classification is likely a misnomer. Patients are usually considered asymptomatic if they have MMD angiographically but have not suffered ischemic or hemorrhagic episodes.³⁶ In 1 study, about 20% of “asymptomatic” MMD hemispheres had a silent cerebral infarction and 40% showed disturbed cerebral hemodynamics during an average 43.7-month follow-up period.³⁶ These disturbed hemodynamics included increased O₂ extraction and decreased performance with acetazolamide challenge. Seven of 34 patients who did not undergo surgery suffered a TIA, stroke, or intracranial hemorrhage during follow-up, projecting to a 3.2% annual risk of infarction in asymptomatic MMD. Also, 5 cases (20%) showed disease progression, 4 of which involved an ischemic event or silent infarction. Interestingly, in other case series, none of the patients who underwent surgical revascularization showed any MMD symptoms on follow-up.^{36,72} Recent research on asymptomatic MMD suggests that it is not truly asymptomatic but rather an early stage or less severe form of MMD. The prevalence of asymptomatic MMD favors females in a ratio of 2:1, about the same as in symptomatic cases.³⁶

Further investigation into progression of unilateral to bilateral MMD has shown that neither unilateral cases nor their progression to bilateral cases is rare. Three separate studies reviewed a total of 512 patients with MMD, 14% of whom had unilateral disease at diagnosis. Thirty-two (44%) of the original 72 unilateral cases progressed to bilateral cases. The 3 studies all showed an average time of progression between 1.5 and 2.2 years.^{31,36,56} The researchers suggest predictors of progression as follows: abnormalities on the initial angiogram of the contralateral ACA, ICA, or MCA; previous history of cardiac anomalies; cranial irradiation; Asian heritage; or a family history of MMD. A younger age of onset (younger than 7 years old) corresponded to faster progression in the study by Smith and Scott.⁵⁶ The only factor noted to predict no progression was a normal angiogram of the contralateral side at diagnosis.

Pathophysiology

Despite the genetic features of the disease, sporadically occurring MMD is still the most common form. Although the pathogenesis of MMD is still not completely clear, the general findings of thickened intima of the major branches of the circle of Willis, moyamoya vessels, and associated clinical symptoms are usually present.

Due to the collaterals formed in MMD, angiogenic factors are currently undergoing study to examine their potential role in the disease. Recent research to determine the role of VEGF in MMD has been inconclusive. Vascular endothelial growth factor has been shown to be a factor in vascular permeability and vasculogenesis. However, VEGF has been shown to lead to cerebral angiogenesis during ischemia, but not in MMD.^{54,63} Research has shown that meningeal cellularity and VEGF-positive cells are significantly higher in the dura mater of patients

with MMD, but are not responsible for moyamoya vessels.⁵⁴ Basic fibroblast growth factor, another angiogenic agent, was found to be 64.0 pg/ml in the CSF on average for MMD cases and 6.5 pg/ml on average for non-MMD cases.⁷⁷ Yoshimoto and colleagues⁷⁷ in the bFGF study argue that bFGF is specific to MMD and not to other types of cerebral ischemia. Therefore, bFGF may serve as a potential marker for MMD. Hepatocyte growth factor has been suggested in the angiogenesis of moyamoya vessels. The level of hepatocyte growth factor in patients with MMD has been found to be elevated to 820.3 ± 319.0 pg/ml compared with 408.2 ± 201.6 pg/ml and 443.2 ± 193.5 pg/ml in patients with cervical spondylosis and ICA occlusion, respectively.⁴⁷ Platelet-derived growth factor has also been indicated in MMD pathology.³

Another factor associated with MMD is TGF- β . Transforming growth factor- β has been shown to be elevated in CSF and in expression in the STA of MMD cases. Transforming growth factor- β was shown to increase elastin synthesis, offering a potential mechanism for intimal thickening.^{21,73} Furthermore, HIF-1 α and endoglin have been found to be significantly higher in patients with MMD. Endoglin modulates cellular response to TGF- β and is involved in vascular morphogenesis. Endoglin is upregulated in arteriovenous malformations and cavernous hemangiomas. Hypoxia inducible factor-1 α regulates TGF- β transcription. Also, HIF-1 α in the presence of bFGF or hepatocyte growth factor, both of which are elevated in the CSF, promotes the proliferation of smooth muscle cells.⁶² These substances are believed to have a significant role in vascular development, and their abnormal levels in patients with MMD may be a factor in its pathogenesis.

Additionally, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 have been shown to be increased in the CSF of patients with MMD.⁵⁷ Protein S deficiency, lupus anticoagulant, and anticardiolipin antibodies have been found in other cases.⁵ Anticardiolipin antibody binds to phosphatidyl-glycerol, a component of the plasma membrane. Its higher concentration in MMD patients suggests a possible autoimmune mechanism in MMD as the antibody could contribute to thrombus formation in strokes.³⁷ The role of prostaglandin E₂ and interleukin-1 β is also under investigation in relation to intimal smooth muscle cell proliferation.⁷³

Development of MMD is often noted with microthrombi in the stenotic vasculature. Microthrombi could cause endothelial injury leading to a thickened intima and smooth muscle cell proliferation as observed in the vessels of MMD cases.⁴² However, a microthrombus is not unique to MMD and thus does not offer the sole explanation for its pathogenesis. Macrophages and T cells have also been found in moyamoya vessels, but they may be a response to and not a cause of MMD. One novel hypothesis is a possible infectious pathogen preceding the development of MMD,⁷⁰ but no infectious pathogen has been implicated. Epidemiological studies have indicated though that infection in the head and neck might be implicated in the development of MMD.⁷⁰

Pathology

Most autopsy specimens are obtained from adults who died of intracranial hemorrhage. Intracerebral hemorrhage is often the major cause of death in patients with MMD.¹⁷ There are two main causes of intracranial bleeding: the rupture of dilated and fragile moyamoya vessels or rupture of saccular aneurysms in the circle of Willis, or on dilated perforators.³⁷ A third cause has been identified—rupture of dilated collateral arteries on the brain surface—although this is rare.⁵⁰

The moyamoya vessels at the base of the brain are made up of medium-sized or small muscular arteries. These vessels branch from the circle of Willis, mainly at the intracranial portions of the ICAs, anterior choroidal arteries, and PCAs, forming complex channels that connect with the distal portions of the MCAs.⁵² Vessels from these channels enter into the base of the brain, corresponding to lenticulostriate and thalamoperforate arteries. Yamashita et al.⁷⁴ performed autopsies on 22 cadavers and described 2 types of these perforating arteries: the first a dilated artery with a relatively thin wall, and the second a thick-walled artery showing luminal stenosis. The dilated type was found to be more prominent in children compared with adults. The majority of dilated vessels are fibrotic, have attenuated media, and often have segmentation of the elastic lamina.^{30,42,46} In the stenotic type, vessels show concentric thickening of the intima with duplication of the elastic lamina and fibrosis of the tunica media.^{9,30,34,46,63,74} Fibrocellular intimal thickening is responsible for luminal stenosis in both large and perforating arteries.^{42,61,63}

Histopathologically, the intima of the major arteries shows eccentrically laminated thickening. This thickness is 2 or 3 times that of normal corresponding vessels and has a wavy appearance representing the discontinuity of the elastica lamina.⁷⁴ Data from Takagi et al.⁶² showed that 20% of patients under 30 years old, 40% of patients between 30 and 40 years old, and 11% of patients over 40 years old had abnormal internal elastic laminae. In the data of this study, the thickness of the intima of the MCAs of patients with MMD was shown to be $19.4 \pm 9.7 \mu\text{m}$, whereas that of the patients without MMD was $8.0 \pm 4.7 \mu\text{m}$. The thickened intima contains an increased number of smooth muscle cells, which are considered to be synthetic-type smooth muscle cells migrating from the media.¹⁷ The outermost diameter of the vessel is smaller than usual, although the intima was thickened. The data of Takagi et al.⁶² revealed that the average thickness in the MCA of patients with MMD was $23.0 \pm 7.7 \mu\text{m}$, whereas in those without MMD the mean was $61.8 \pm 30.4 \mu\text{m}$.⁶² Lipid-containing macrophages (foam cells) and lipid deposits have been found at autopsy but are considered more likely a result of atherosclerosis.

These changes in the vessel may predispose to microaneurysmal formation. The frequency of aneurysms in the vertebrobasilar system in MMD is much higher than that of the general population.⁴⁰ Three types of aneurysms have been described in patients with MMD.³⁹ Major artery aneurysms are those that develop from the circle of Willis. These aneurysms are commonly found in the arte-

rial complex of the anterior communicating artery-ACA in patients with unilateral MMD and in the basilar artery in patients with bilateral MMD.²⁰ Histopathologically, the aneurysmal wall consists of endothelium with adventitial layers and a disappearance of internal elastic lamina and media, which is the same as those found in saccular aneurysms. Peripheral artery aneurysms, the second type, are responsible for parenchymatous hemorrhage. Two types of aneurysms have been reported—saccular aneurysms and pseudoaneurysms, which consist of fibrin and erythrocytes. The third type, as previously mentioned, is rupture of dilated moyamoya vessels or dilated collateral arteries on the brain surface.^{29,37}

The fibrocellular intimal thickening noted in the intracranial arteries is also observed in other arteries of patients with MMD. These arteries include extracranial arteries, pulmonary arteries, renal arteries, and coronary arteries.⁵¹ Case reports with histological examinations show extracranial arteries with features similar to FMD intimal hyperplasia type. This type of FMD shows concentric fibrocellular intimal thickening made up of elastic fibers and smooth muscle cells in arteries in various locations throughout the body.⁵¹ Moyamoya disease with associated renovascular hypertension has been reported, which often shows angiographic or pathological evidence of FMD.¹⁸ This finding suggests that FMD or FMD-like vascular lesions may be present in MMD, and that hypertension may result from these lesions. Intimal thickness of extracranial arteries at autopsy in advanced MMD has been found to be greater compared with this thickness in controls. Mural thrombi formation and its organization are also observed in extracranial arteries of patients with MMD.³⁷

In the study by Hoshimaru and Kikuchi,²³ 13 of 66 patients with MMD were found to have stenotic branches of the external carotid artery visible on angiography. Of these cases, 8 of the stenoses were found in the middle meningeal branch, 4 in the STA, and 2 in the occipital branch.²³ In pediatric cases as well, the intima of the STA was measured against controls and found to be significantly thicker.³ Histological sections showed fibrocellular intimal thickening with little lipids and stained intensely for multilayered elastic fibers within the intima. Control patients showed mild staining for elastic fibers in the intima.³

Diagnosis

The criteria for a diagnosis of MMD have been set forth by the Research Committee on Spontaneous Occlusions of the Circle of Willis (Moyamoya Disease) of the Ministry of Health and Welfare of Japan (Table 1).^{15,16} Diagnostic criteria for imaging using MR imaging and MR angiography are shown in Table 2.¹⁶

Conventional digital subtraction angiography remains the gold-standard imaging technique and will best demonstrate the characteristic, though not pathognomic, features of a chronic stenooclusive angiopathy localized predominantly at the supraclinoid ICAs and the proximal ACAs/MCAs. Although the stenotic lesions themselves may be indistinguishable from noncalcified atheroma and other cerebrovascular angiopathies (Table 1), MMD is

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TABLE 1: Research Committee on Spontaneous Occlusions of the Circle of Willis of the Ministry of Health and Welfare of Japan: Diagnostic criteria of MMD*

A. Cerebral angiography is indispensable for the diagnosis and should present at least the following findings:

1. Stenosis or occlusion at the terminal portion of the ICA and/or at the proximal portion of the ACAs and/or the MCAs.
2. Abnormal vascular networks in the vicinity of the occlusive or stenotic lesions in the arterial phase.
3. These findings should present bilaterally.

B. When MR imaging and MR angiography clearly demonstrate all the subsequently described findings, conventional cerebral angiography is not mandatory:

1. Stenosis or occlusion at the terminal portion of the ICA and at the proximal portion of the ACAs and MCAs on MR angiography.
2. An abnormal vascular network in the basal ganglia on MR angiography. Note that an abnormal vascular network can be diagnosed when more than 2 apparent flow voids are observed in 1 side of the basal ganglia on MR imaging.
3. (1) and (2) are observed bilaterally.

C. Because the origin of this disease is unknown, cerebrovascular disease with the following basic diseases or conditions should thus be eliminated:

1. Arteriosclerosis
2. Autoimmune disease
3. Meningitis
4. Brain neoplasm
5. Down syndrome
6. Recklinghausen disease
7. Head trauma
8. Irradiation to the head
9. Others (sickle cell disease, tuberous sclerosis, etc.)

D. Instructive pathological findings:

1. Intimal thickening and the resulting stenosis or occlusion of the lumen is observed in and around the terminal portion of the ICA, usually on both sides. Lipid deposits are occasionally noted in the proliferating intima.
2. Arteries constituting the circle of Willis such as the ACAs, MCAs, and posterior communicating arteries often show stenosis of various degrees or occlusion associated with fibrocellular thickening of the intima, a waving of the internal elastic lamina, and an attenuation of the media.
3. Numerous small vascular channels (perforators and anastomotic branches) are observed around the circle of Willis.
4. Reticular conglomerates of small vessels are often noted in the pia mater.

Diagnosis: In reference to A–D mentioned above, the diagnostic criteria are classified as follows: Autopsy cases not undergoing cerebral angiography should be investigated separately while referring to D.

1. Definite case: One which fulfills either criteria A or B, and C. In children, however, a case that fulfills A-1 and A-2 (or B-1 and B-2) on 1 side and with remarkable stenosis at the terminal portion of the ICA on the opposite side is also included.
2. Probable case: One which fulfills criteria A-1 and A-2 (or B-1 and B-2) and C (unilateral involvement).

* Adapted from Fukui, 1997.¹⁶

suggested by the patients' younger age, bilateral/symmetrical lesions, and the pattern of arterial collateralization. The prominent collateral vascular network, representing both the hypertrophy of perforator branches as well as a true neoangiogenesis around the circle of Willis (often referred to as a "rete" or "leash" of vessels), results in the transient dense angiographic blush occurring in the arterial phase, which is responsible for the "puff of smoke" description after which the condition is named. Other collateral pathways may occur via pial-to-pial anastomoses from other less compromised territories, particularly the posterior circulation, or in more advanced cases via dural-pial parasitization, the latter constituting the "vault MMD" pattern.^{37,42} The balance between these collateral routes varies between patients. Suzuki and Takaku⁶⁰ listed 6 angiographic stages of MMD that appear with progression of the disease (Table 3).

Computed tomography is rapid, easily available, and usually the first-line assessment of a patient suffering an

acute ictus. Computed tomography is relatively insensitive for acute infarction in the first 24 hours but can effectively exclude neurosurgical emergencies such as hemorrhage and large mass lesions. Infarcts, typically distributed in a watershed distribution between major territories, initially appear as a loss of gray-white matter differentiation, becoming progressively better defined with lower attenuation over several days and demonstrating volume loss over several weeks. Subcortical and deep white matter infarcts are also related to regional hypoperfusion and are underestimated on CT compared with MR imaging, as are lacunar infarcts of the basal ganglia and thalamus; the latter tending to occur in adult MMD but are rare in children. Postcontrast CT demonstrates poorly defined enhancement related to the basal perforator neovascularity,⁴² whereas CT angiography may better define some of the larger perforator collaterals. The latter could provide a substitute for MR imaging/angiography, but is not currently included in the research committee guidelines

TABLE 2: Ministry of Health and Welfare of Japan diagnostic criteria utilizing MR imaging and angiography*

A. When MR imaging and MR angiography clearly demonstrate all the findings described below, conventional cerebral angiography is not mandatory:

1. Stenosis or occlusion at the terminal portion of the intracranial ICA and at the proximal portion of the ACAs and CAs.
2. An abnormal vascular network in the basal ganglia.
3. 1) and 2) are seen bilaterally.

B. Imaging methods and judgment:

1. More than a 1.0-T magnetic field strength is recommended.
2. There are no restrictions regarding MR angiography imaging methods.
3. The imaging parameters, such as the magnetic field strength, the imaging methods, and the use of contrast medium, should be clearly documented.
4. An abnormal vascular network can be diagnosed when more than two apparent flow voids are observed on 1 side of the basal ganglia on MR imaging.
5. Either an over- or underestimation of the lesion could be made according to the imaging conditions. To avoid a false-positive diagnosis, only definite cases should thus be diagnosed on the MR imaging and MR angiography findings.

C. Because similar vascular lesions secondary to other disorders are sometimes indistinguishable from this disease in adults, a diagnosis based on MR imaging and MR angiography without conventional angiography is thus only recommended in pediatric cases.

* Adapted from Fukui, 1997.¹⁶

(Table 1). Computed tomography perfusion can be performed with or without an acetazolamide challenge, and the mean transit time has been shown to correlate significantly with the angiographic stage of the disease.²⁷

Single-photon emission computed tomography is a long-established, whole-brain radioisotope axial perfusion study that provides relative perfusion compared with the opposite side. Its main limitation is very poor spatial resolution.⁵⁵ Single-photon emission computed tomography involves injection of a radioactive radioisotope bound to a lipophilic pharmaceutical that can cross the blood-brain barrier such as ^{99m}Tc-hexamethyl propyleneamine oxime, ^{99m}Tc-bicisate ethyl cysteinyl dimer, and ¹²³I-iodoamphetamine, and can be performed with or without acetazolamide challenge. The acetazolamide challenge helps determine the CBF reserve and therefore helps monitor the progressive stages of the disease.²² Use of SPECT in MMD shows low perfusion in the upper and lower frontal, parietal, and temporal regions, especially in cases at Stages 2 and 3. Single-photon emission computed tomography helps to measure rCBF especially in vessels that cannot be visualized angiographically.

In recent years the technetium-based agents have become more widely available than ¹²³I-iodoamphetamine. The two agents can be used in a single sitting, one for baseline and the other for postacetazolamide blood flow measurement with 3-headed scanners, using separate windowing for the keV values of ^{99m}Tc and ¹²³I to furnish accurate data with fewer injections and eliminate the need for subtraction techniques.¹¹ Although extremely unlikely, caution must be exercised when using acetazolamide to avoid provoking an ischemic injury in patients with MMD, who have marginal cerebrovascular reserve.³⁸

Positron emission tomography scans in MMD show significantly reduced rCBF, but not significantly lower absolute CBF compared with controls. Positron emission tomography scans may demonstrate an elevation of rOEF, implying "misery perfusion" in MCA regions and elevation of rCBV consistent with neovascularity in the

striatum.^{26,48} Despite the increased rOEF, the regional cerebral metabolic rate of O₂ tends to be decreased due to the greater influence of the reduced rCBF. Patients with ischemic MMD showed significantly higher CBV than controls in most cerebral regions, suggesting compensatory territorial vasodilatation.⁴⁸ There are no variations in rCBF, regional cerebral metabolic rate of O₂, or rOEF in the MCA region between hemorrhagic and ischemic types in adult cases. However, rCBV in the striatum was higher in ischemic adult cases. Adult patients of both bleeding and ischemic types had significantly lower rOEF and rCBV in the MCA territories and rCBV in the striatum than did children with ischemic presentation. All adult cases showed a cerebral hemodynamic deficit.²⁶ Oxygen extraction fractions in the frontal, parietal, and temporal cortices were significantly higher in the ischemic cases than in controls. The hemorrhagic type showed decreased metabolism with normal OEF.⁴⁸ Occlusion of the ICA and high OEF increased the risk for cerebral infarction compared with occlusion of the ICA and normal OEF. These data formed the basis of a second study to assess the efficacy of extracranial-intracranial bypass requiring the presence of a high OEF for entry.¹² Earlier PET studies suggest a similar importance of OEF in patients with MMD.^{1,64}

Magnetic resonance imaging and MR angiography can demonstrate small subcortical lesions that are often undetectable on CT. Magnetic resonance imaging/angiography have proven useful because MMD frequently involves infarcts that are small and multiple. These imaging modalities allow visualization of the occluded distal portions of the ICA. Moyamoya vessels appear as fine unusual vessels on MR angiography or as a signal void on MR imaging. However, both MR imaging and MR angiography poorly visualize smaller moyamoya vessels. Magnetic resonance imaging may be used as a surrogate for conventional angiography in children according to the MMD diagnostic criteria (Tables 1 and 2) if occlusion is clearly observed bilaterally.^{24,42,71} Magnetic reso-

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TABLE 3: Six angiographic stages of MMD*

Stage	Angiographic Findings
1	stenosis of suprasellar ICA, usually bilateral
2	development of moyamoya vessels at base of brain
3	increasing ICA stenosis and prominence of moyamoya vessels (most cases diagnosed at this stage)
4	entire circle of Willis and PCAs occluded, extracranial collaterals start to appear, moyamoya vessels begin to diminish
5	further progression of Stage 4
6	complete absence of moyamoya vessels and major cerebral arteries

* Adapted from Suzuki and Takaku, 1969.

nance angiography can detect some lesions not noted on MR imaging, but often overestimates the extent of the lesion. The increased signal gained with stronger 3-T magnets provides significantly greater angiographic detail.⁷⁸ Also, MR angiography can be used postoperatively to determine the state of collateral flow and patency of extracranial-intracranial bypass grafts. Magnetic resonance angiography is limited in spatial resolution and flow direction evaluation; although the latter can be assessed on time-resolved MR angiography, this technique still suffers from very poor spatial resolution.⁸ Overall, MR imaging and MR angiography are good methods to detect MMD, especially when it is in Stage 3 or 4, but they are not very effective as a means of staging the disease.²

The higher signal and resolution of 3-T MR systems has been used for the better selection of bypass arteries by clearer visualization of donor and recipient artery candidates for revascularization surgery.³² The images provided by the 3-T magnet allow for better postoperative patient care. In one case study following extracranial-intracranial bypass, MR imaging and MR angiography with a 3-T magnet showed dilation of the bypass and local collaterals not evident using a 1.5-T magnet. This finding indicated potential hyperperfusion of the area, which was confirmed using SPECT. The patient had corresponding neurological deficits, and immediate and aggressive treatment of blood pressure alleviated the symptoms until the patient's condition returned to normal.³³

Blood oxygen level-dependent MR imaging can be used to map cerebrovascular reactivity in cases with arterial stenooclusive disease. Blood oxygen level-dependent MR imaging is based on the decrease in T2 signal changes that occurs with an increased concentration of intravoxel deoxyhemoglobin, which is related to either reduced perfusion or increased metabolic activity.⁴¹ Arterial spin labeling is an alternative noncontrast perfusion technique utilizing an inversion pulse to magnetically label intravascular water protons upstream to the region of interest and has been extensively studied due to its noninvasive nature.¹⁰ Both arterial spin labeling and contrast-enhanced dynamic susceptibility imaging, the latter exploiting the T2-shortening effect of concentrated Gd, are limited by the markedly prolonged transit times (often > 5 seconds) in MMD, which stretches the sensitivity of these techniques to their limits, resulting in greater

artifact.⁷ Perfusion-weighted MR imaging allows for the analysis of 3 parameters of OEF: CBF ratio, CBV ratio, and mean transit time. Perfusion-weighted MR imaging also generates parametric maps at a higher resolution than PET maps, thereby revealing focal perfusion failure on the level of each individual gyrus.⁶⁵

Proton MR spectroscopy can be used to noninvasively examine cerebral metabolism, but it is currently still limited to use as a research tool. One study showed that 3 cerebral metabolites (choline, creatine, and *N*-acetylaspartate) of patients with MMD were in the normal range and showed no difference between more and less affected hemispheres. After revascularization surgeries, all 3 metabolites were shown to have increased significantly in all hemispheres.⁵⁵

Treatment

Treatment of MMD often depends on the aggressiveness of its course. Cases with milder symptoms are usually treated more conservatively. More severe symptomatic cases are usually treated using revascularization procedures. Most cases (77%) are treated surgically because this has been shown to be more effective than nonsurgical treatment.^{15,42,67}

Medical treatments that have been proposed include vasodilators, antiplatelet agents, antifibrotic agents, and fibrinolytic agents.⁶⁸ However, the efficacy of medical treatments has yet to be proven in clinical trials. Epileptic cases have been managed using anticonvulsants. Ischemic episodes and thrombosis can be managed using antiplatelets, thus possibly preventing the progression of MMD as well.⁴²

Surgical treatments are divided into 3 groups: direct, indirect, and combined/other methods. Direct bypass includes vein grafts and extracranial-intracranial anastomosis of the STA to the MCA (STA-MCA anastomosis). Extracranial-intracranial bypass was first performed in 1972 by Yasargil. Indirect bypass can involve any of several procedures including encephaloduroarteriosynangiosis, encephalomyosynangiosis, encephalomyoarteriosynangiosis, encephaloarteriosynangiosis, durapexy, multiple cranial bur holes, and transplantation of omentum.^{15,53} The indirect procedures bring in circulation to the intracranial regions by introducing newly developed vasculature from sutured tissue. Indirect surgeries are better for patients without good candidate cortical branches for anastomosis. These procedures may not be enough to prevent further ischemia, therefore a combination of direct and indirect procedures is generally preferred.

Direct revascularization has been shown to drastically improve CBF and thus potentially prevent brain infarction.⁴⁵ Bypass also offloads stressed moyamoya vessels, thus potentially decreasing the risk of hemorrhage. Direct bypass is generally limited to adults or older children due to the small caliber of the STA in younger children. Younger children are thus better candidates for combined indirect bypass methods such as encephaloduroarteriosynangiosis with encephalomyosynangiosis and/or encephalomyoarteriosynangiosis.¹⁷ However, recent research by Fujimura et al.¹⁴ has suggested that direct STA-MCA anastomosis is safe and effective in children of all

ages, and these authors have reported good and excellent outcomes in patients with a mean age of 6.2 years.

Extracranial-intracranial bypass procedures have come under scrutiny since the extracranial-intracranial study group in 1985 reported failure of such surgery to reduce the risk of stroke.¹² However, physiological PET imaging (rCBF and OEF) did not constitute a requirement for entry. More recent Japanese and US studies have shown that those patients who underwent surgical revascularization had no ischemic episodes following surgery in the Japanese study, and fewer ischemic episodes than preoperatively in the US study.^{43,49} In children with MMD, direct and indirect extracranial-intracranial bypass has been shown to improve symptoms, reverse neurological deficits, prevent further ischemic episodes, allow normal intelligence development, decrease seizure activity, and result in the disappearance of involuntary movements.⁶⁷ In adults, these procedures have resulted in the prevention of ischemic episodes and improvement in symptoms and cerebral hemodynamics.

Effectiveness of these procedures in hemorrhagic cases is not as well studied for ischemia. It has been suggested that bypass procedures may offload the “stress” onto perforating vessels and hence decrease subsequent risk of hemorrhage. Some data do exist, however, to justify revascularization for hemorrhage prevention. A 1997 study of patients with hemorrhagic MMD showed that 28.3% of patients without surgery had recurrent hemorrhage during follow-up compared with 19.1% of those who received surgery.¹³ Yoshida et al.⁷⁶ conducted a survey of 28 patients with hemorrhagic MMD with a mean follow-up period of 14.2 years. Rebleeding was observed in 1 of 8 patients who underwent bypass surgery and in 5 of 13 who did not.⁷⁶ This finding suggests that rebleeding was less likely to occur in patients who had undergone bypass surgery. However, there was no significant difference in the rebleeding ratio or death rate between patients with and those without revascularization surgery.⁷⁶ The role of extracranial-intracranial bypass surgery in hemorrhagic MMD does appear promising. In 1 study, 11 of 22 patients were surgically treated, with 6 undergoing STA-MCA bypass and the other 5 undergoing encephaloduroarteriosynangiosis.²⁸ The patients were followed up between 0.8 and 15.1 years. The incidence of hemorrhagic and ischemic stroke was significantly lower in patients who underwent STA-MCA bypass when compared with patients who underwent encephaloduroarteriosynangiosis or conservative therapy.²⁸ In the pediatric population, there may be also a benefit of revascularization; Suyama et al.⁵⁸ reported on 3 patients with hemorrhagic MMD, 2 of whom underwent STA-MCA anastomoses with encephalomyosynangiosis. No subsequent evidence of ischemic episodes or hemorrhage was noted at follow-up in these 2 patients. There are more studies currently underway examining extracranial-intracranial procedures in MMD.⁴⁵

Among 1 of the most recent studies from Japan, Byval'tsev and Suzuki⁶ reported findings on direct and indirect treatments in 140 patients with MMD. Their findings show good and excellent clinical results in 92.9% of cases and cerebral circulation normalization in 97.1%

of patients. These results from 2007 suggest the benefit of surgical treatment tailored to the individual case of MMD.

Better outcomes in revascularization surgery may now be feasible due to improvements in operative methods. Intraoperatively, there have been several developments to assess bypass graft patency. One promising method is using intraoperative video fluorescence angiography, which involves using a fluorescent tracer (indocyanine green) and specially equipped surgical microscopes that are able to view light in the near-infrared spectra. Woitzik et al.⁶⁹ demonstrated that intraoperative angiography was useful in identifying both nonfunctioning and stenotic bypass grafts. Postoperatively, improvements in imaging techniques allow for diagnosis of hyperperfusion and other possible side effects from surgery, enabling prompt treatment.

Conclusions

With advances in imaging and other diagnostic tools, the incidence and prevalence of MMD is increasing. Further molecular analysis of the moyamoya vessels will improve the understanding of MMD and lead to earlier diagnosis with subsequent treatment. It is anticipated that bypass procedures for MMD will be increasingly required at main treatment centers.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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