Neurosurgical Advances in the Treatment of Moyamoya Disease

Paritosh Pandey, MD; Gary K. Steinberg, MD, PhD

Background and Purpose—Moyamoya disease is characterized by chronic stenoocclusive vasculopathy involving the distal supraclinoid internal carotid arteries and presents with ischemic or hemorrhagic symptoms. We review advances in the understanding and management of moyamoya disease.

Summary of Review—Cerebral revascularization, either direct or indirect, is the cornerstone of treatment for moyamoya disease. Recent advances have been made in understanding the molecular biology and pathophysiology of moyamoya disease, and new genetic mutations and deletions have been identified. Imaging for moyamoya disease is also rapidly improving with new sequences of MRI and better methods of assessing ischemia and cerebrovascular reserve. Positron emission tomography has emerged as an important tool to measure cerebrovascular reserve. Novel surgical techniques assess patency and ischemia during superficial temporal to middle cerebral artery bypass, including indocyanine green videoangiography to evaluate anastomosis patency, and various methods to monitor intraoperative blood flow. Newer methods of indirect revascularization have been described with placement of more tissues supplied by the external carotid artery on the brain surface. Postoperative hyperperfusion to the chronically ischemic brain tissue is a recently identified causative factor of complications. Interestingly, complications from hyperperfusion mimic those caused by ischemia, although they have different treatments, making the role of postoperative blood flow assessment important in distinguishing between the two. Awareness has also increased that even asymptomatic patients can experience significant cognitive decline attributable to chronic ischemia. Whether this reverts after successful revascularization requires investigation.

Conclusions—Surgical revascularization with direct, indirect, and combined methods remains the preferred procedure for patients with moyamoya disease. (Stroke. 2011;42:3304-3310.)

Key Words: moyamoya disease ■ revascularization ■ STA-MCA bypass

Moyamoya disease (MMD) is a chronic, progressive disease characterized by stenosis or occlusion of the bilateral supraclinoid internal carotid arteries along with development of leptomeningeal collaterals at the base of the brain. The classical presentation of MMD is transient ischemic attacks (TIAs), ischemic strokes, and intracranial hemorrhages. Its natural history is often progressive and includes recurrent ischemic episodes with neurological and cognitive deterioration. Unfortunately, the disease is unresponsive to any medical treatment. Surgery aimed at revascularization of the hemispheres either by direct or indirect bypass techniques is the treatment of choice. Over the past years, there has been major progress in understanding MMD, including its molecular biology, genetics, pathophysiology, radiology and blood flow, and surgical management. This article reviews the major neurosurgical advances in the treatment of MMD.

Genetics and Pathophysiology

The pathophysiology of MMD is poorly understood but genetic, acquired, and environmental factors have been implicated. Recent studies have focused on genetic factors in the pathogenesis of MMD. It is most prevalent in Japanese and Asian populations, and there is a 7% to 12% familial occurrence in the Japanese population as well. The disease is also associated with many genetically transmitted disorders, including neurofibromatosis, Down syndrome, sickle cell anemia, Fanconi anemia and other hemoglobinopathies, and collagen vascular diseases including Marfan syndrome, Ehler-Danlos syndrome, Algille syndrome, and Majewski osteodysplastic primordial dwarfism Type II.

Chromosomal analysis and genomewide sequencing have been performed to identify genes associated with MMD. Both 3p24-26 and 8q23 in genomewide analyses, in addition to both 6q24 and 17q25 in chromosomal level analyses, have
been identified in familial MMD. A recent genomewide association study of 785,720 single nucleotide polymorphisms comparing 72 Japanese patients with MMD with 45 control subjects revealed a strong association of chromosome 17q25-ter with MMD. Mutations in smooth muscle alpha actin (ACTA2) can predispose to developing MMD as well as premature coronary artery disease and thoracic aortic disease. A single haplotype consisting of 7 single nucleotide polymorphisms at the RNF213 locus was tightly associated with MMD. Mutational analysis of RNF213 revealed a founder mutation, p.R4859K, in 95% of MMD families, 73% of nonfamilial MMD cases, and 1.4% of the control subjects. Hence, RNF213 is identified as a susceptibility gene for MMD. Recently Xq28 deletions removing MTC1P1/MTPC1NB and BRCC3 have been shown to cause a type of X-linked familial moyamoya syndrome.

A number of growth factors are thought to be associated with MMD. Because of the extensive collateral formation defining MMD, research has focused on vascular and angiogenic factors. Investigations regarding the role of vascular endothelial growth factor have been inconclusive. Other growth factors identified in cerebrospinal fluid, intracranial or temporal arteries associated with MMD are transforming growth factor-β, basic fibroblast growth factor, hepatocyte growth factor, and platelet-derived growth factor. Basic fibroblast growth factor was found to be specific to MMD and not to other forms of ischemia and hence may serve as a potential marker for MMD. Various adhesion molecules such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 have been shown to increase in the cerebrospinal fluid of patients with MMD. Other markers like lupus anticoagulant, prostaglandin E2, and interleukin-1β are also being investigated for their roles in smooth muscle proliferation and the pathogenesis of the disease and further studies are focusing on inflammation or infectious origin. Additional research is identifying novel biomarker candidates using proteomic analysis of cerebrospinal fluid from patients with MMD. A recent report recognized 2 important biomarkers in cerebrospinal fluid of patients with MMD. This was done using the surface-enhanced laser desorption/ionization–time of flight–mass spectroscopy technique, and although the exact target protein could not be identified, 6 proteins of the corresponding molecular weight (oxygenmodulin, urocortin-2, β-defensin 133, antibacterial protein LL-37, liver-expressed antimicrobial peptide-2, and proenkephalin-A) were inferred to be the exact protein. Smith et al reported in an abstract at the December 5, 2008, American Association of Neurological Surgeons Scientific meeting the identification of a panel of urinary biomarkers predicting MMD. There was significant elevation in the levels of matrix metalloproteinase-9, matrix metalloproteinase-2, matrix metalloproteinase-9/NGAL, and vascular endothelial growth factor in the urinary samples of patients with MMD as compared with normal subjects with sensitivity of 87.5%, specificity of 100%, and accuracy of 91.3% (www.aans.org/Media/Article.aspx?ArticleId=53823).

Epidemiology and Natural History

MMD occurs worldwide; however, it is most common in the Japanese population, in which the incidence is estimated to be 0.35 to 0.54 per 100,000 population. In contrast, the incidence in the European population was estimated to be one-tenth of the incidence in the Japanese population, whereas the incidence in California and Washington states was estimated to be 0.086 per 100,000 population. MMD presents with various cerebrovascular events, including TIAs, ischemic stroke, intracranial hemorrhage, headache, or seizures. In the Japanese literature, the ischemic type predominates in children (<18 years), whereas the hemorrhagic type predominates in adults. However, in our experience, most of the adult patients also present with ischemic symptoms, and only 14.6% adult patients presented with hemorrhage. Hemorrhage was exceedingly uncommon in children.

The natural history of the disease is not well known, and few studies have been conducted on clinically asymptomatic patients. Kuroda et al conducted a nationwide survey of asymptomatic moyamoya patients, defined as patients who did not have ischemic or hemorrhagic symptoms. Of the 40 patients who participated, 34 were not operated and 7 patients developed TIA (3), ischemic stroke (1), or hemorrhage (3) during a follow-up period (mean, 43.7 months). The annual risk for any stroke was 3.2% per year. None of the 6 patients who were surgically treated had any ischemic or hemorrhagic symptoms during their follow-up period. Yamada et al reported that in the 28 patients with asymptomatic MMD who were conservatively treated, 2 patients died of hemorrhage, whereas 4 patients had TIAs. These findings suggest that asymptomatic MMD is not a silent disorder and may progress to cause ischemic or hemorrhagic stroke. However, there is no consensus on offering surgery to all patients with asymptomatic MMD. This is because majority of the poor outcomes in asymptomatic moyamoya patients were secondary to hemorrhage, and there is still no definite evidence that surgical revascularization reduces the risk of intracranial hemorrhage, although a randomized clinical trial is ongoing in Japan to assess the role of revascularization in reduction of subsequent hemorrhage. However, surgical revascularization maybe offered to patients with asymptomatic MMD if there is deranged cerebral hemodynamics and the surgical morbidity is low. However, in symptomatic patients, there is a high incidence of stroke in medically treated patients. Hallemeier et al reported a series of 34 patients with MMD, 22 bilateral and 12 unilateral. In medically treated hemispheres, the 5-year risk of recurrent ipsilateral stroke was 65% after the initial symptom, whereas in surgically treated hemispheres, the 5-year risk of perioperative and subsequent ipsilateral stroke was 17% (P=0.02).

Imaging

For >6 decades, cerebral angiography has been the gold standard in the diagnosis and management of MMD. MRI and MR angiography have also been used for diagnosis of MMD and its sequelae and for follow-up after revascularization. Present research in imaging for MMD focuses on evaluation of cerebrovascular reactivity, predictors of ischemic and hemorrhagic episodes, and predictors of postoperative ischemia and complications. Single-photon emission computed tomography (SPECT) has long been used to measure cerebral blood flow (CBF) and...
cerebrovascular reactivity, and positron emission tomography (PET) is being increasingly used. PET studies for hemodynamic assessment are usually performed with the following tracers: C15O PET for cerebral blood volume measurement, H2 15O for CBF, and 15O2 to measure oxygen extraction fraction and cerebral metabolic rate of oxygen. Nariai et al22 observed that the oxygen extraction fraction in the frontal, temporal, and parietal cortices was higher in patients with MMD compared with healthy patients. However, regional cerebral metabolic rate of oxygen tends to be decreased in most cerebral regions because of reduced regional CBF. These patients also have high cerebral blood volume owing to maximal compensatory vasodilatation. A paradoxical steal phenomenon is observed when the vascular bed is maximally dilated and autoregulation is impaired. Nariai et al22 also showed that the oxygen extraction fraction was high in patients presenting with TIA and ischemic symptoms; however, it was normal in patients presenting with fixed deficits or with hemorrhage. PET is now 1 of the most reliable assessment tools for MMD. In a study of 23 patients with MMD, Kuwabara et al noted that there was marked increase in CBF and TT measured by PET, especially in the striatum.14 The cerebrovascular response to hypercapnia was markedly impaired. All the parameters including CBF, TT, and cerebrovascular response to hypercapnia improved after surgery. Whether PET is more reliable than other methods of measurement of cerebrovascular reactivity remains to be seen. A prospective observational study is underway to test the hypothesis that increased oxygen extraction fraction in the cerebral hemispheres beyond the occlusive lesion is a predictor of subsequent risk for ipsilateral stroke in medically treated patients with MMD.23

Novel MRI techniques have been used for quantitative hemodynamic analyses, including dynamic susceptibility contrast-weighted bolus-tracking MRI, arterial spin labeling MRI, and blood oxygen level-dependent MRI. Arterial spin labeling MRI has been compared with SPECT imaging in MMD, and a strong correlation has been found between arterial spin labeling value and ACZ-IMP value with SPECT, suggesting that perfusion imaging with arterial spin labeling MRI could show potentially dangerous zones for ischemia.24 Cerebrovascular reactivity as measured by blood oxygen level-dependent MRI has also been shown to have a direct correlation with impaired vascular supply as measured by modified Suzuki score on angiography.25 Quantitative MR angiography with NOVA software can show actual blood flow across large intracranial vessels and also flow across the superficial temporal artery after revascularization.26 In our practice, xenon CT (without and with acetazolamide) has provided an excellent quantitative method of assessing CBF and hemodynamic reserve with good spatial resolution; however, it is not currently approved by the Food and Drug Administration and can only be used on an Institutional Review Board-approved protocol. The data regarding xenon CT is currently under analysis.

Surgery

Although there has not been any randomized controlled trial comparing surgical and medical treatment in patients with MMD, surgical revascularization has been accepted as the only effective form of treatment. Multiple case series, both retrospective and prospective, have shown the effectiveness of revascularization procedures in preventing future ischemic episodes in patients with MMD. Direct revascularization (superficial temporal to middle cerebral artery bypass [STA-MCA], high-flow bypasses), indirect bypasses (encephaloduroarteriosynangiosis, encephalo-duro-arterio-myo-synangiosis, pial synangiosis), and combined procedures (combination of direct and indirect procedures) have been used for many years. However, significant advances have been made in recent years in the techniques and intraoperative monitoring of blood flow during surgery.

STA-MCA bypass has been used for MMD since 1973, when it was used by Kikuchi and Karasawa. Since then, it has been the mainstay of direct revascularization with many authors showing excellent results. We published our results for 450 revascularization procedures, which included direct revascularization in 95.1% adults and 76.2% pediatric patients, in which the surgical morbidity rate was 3.5% and mortality was 0.7% per treated hemisphere.18 The cumulative 5-year risk of perioperative or subsequent stroke or death was 5.5%. Of the 171 patients presenting with a TIA, 91.8% were free of TIAs at ≥1 year. There was a significant improvement in quality of life in the cohort as measured by modified Rankin Scale. Other authors have also reported excellent results with direct revascularization.27

The technique of STA-MCA bypass is fairly standard and has been described before.28,29 However, a new technique, excimer laser-associated nonocclusive anastomosis, has been developed.30 In this technique, there is no need for temporary vascular occlusion during the anastomosis. The conduit vessel is sewn to the recipient vessel along with the excimer laser-associated nonocclusive anastomosis platinum ring and then the laser catheter is used to make the arteriotomy. After the anastomosis is performed between the excimer laser-associated nonocclusive anastomosis platinum ring and the conduit, the ring/grat complex is sewn to the recipient vessel, and then the laser catheter, composed of a central suction portion and outer circular fiberoptic array, is passed through a side slit in the donor vessel and the arteriotomy is created. The advantage of this technique is that there is no need for temporary vascular occlusion. Unfortunately, at the present time, this technique can only be used for vessels >2.5 mm, so the bypass is applicable to the supraclinoid internal carotid artery or proximal middle cerebral artery vessels and not for STA-MCA anastomoses. However, progress is underway to improve the technology and extend excimer laser-associated nonocclusive anastomosis to smaller intracranial arteries. Newer advances have been made in intraoperative monitoring during direct bypass for MMD. Previously, intraoperative Doppler and visual assessment were used to verify the patency of the anastomosis. Two important developments have allowed evaluation of graft patency and flow during surgery. Indocyanine green (ICG) emits near-infrared fluorescence when excited by near-infrared light. After completion of the anastomosis, ICG is injected, excited by near-infrared light, and visualized. Woitzik et al31 examined the role of ICG videoangiography after extracranial–intracranial bypass in 40 patients, of whom 18 had MMD. After the
anastomosis, ICG (0.3 mg/kg body weight) was given systematically through an intravenous bolus injection. The findings of ICG angiography were compared with those of postoperative digital subtraction angiography or CT angiography. In every case, excellent visualization of the cerebral arteries, bypass graft, and brain perfusion was noted. ICG videomapping was used to identify 4 nonfunctioning STA-MCA bypasses, which could be revised successfully. In every case, the final findings of the ICG angiography could be positively validated by digital subtraction angiography or CT angiography. Awano et al.32 evaluated the bypass blood flow in 13 MMD and 21 non-MMD patients during STA-MCA bypass and monitored hemodynamic changes caused by bypass surgery for postoperative management. ICG perfusion was calculated when the ICG fluorescence reached the maximum. They compared the ICG perfusion area in MMD and non-MMD patients and found that the ICG perfusion area in patients with MMD was significantly larger that in non-MMD patients. Thus, ICG can provide useful information regarding the blood flow after anastomosis and possibly for postoperative management as well. We have used intraoperative ICG in hundreds of MMD direct revascularization anastomoses over the last few years, and we are analyzing our data to determine the value of ICG in assessing patency of direct anastomoses.

The second important advance is the intraoperative monitoring of flow using perivascular probes with various intraoperative blood flow or cerebral oxygenation monitoring methods. A flexible perivascular flowprobe (Charbel Probe; Transonic Systems, Inc) can be positioned over the donor and recipient vessels and the flow monitored.26 The flowmeter uses an ultrasonic transit time principle to measure volumetric flow in mL/min. The direction of flow, whether antegrade or retrograde, can also be determined. This is a very important tool both to measure the patency of the graft and the flow through the graft and to appropriately modify blood pressure and hemodynamics in the postoperative period. We analyzed various hemodynamic factors in 292 patients with MMD using this perivascular flow probe.33 After anastomosis, middle cerebral artery flow increased on average 5-fold. Very high postanastomotic middle cerebral artery flow was associated with postoperative ischemic stroke and hemorrhage and transient neurological deficit. Hence, flow monitoring can be a predictor of complications, and in those patients at risk, a tighter control of blood pressure maybe warranted. Other novel methods for measurement of CBF or cerebral oxygenation have been described in the literature.39,40 The principle behind indirect procedures is the placement of vascularized tissue supplied by the branches of external carotid artery on the brain to stimulate angiogenesis and collateral vessels in the brain. Although indirect revascularization procedures have been found to be very beneficial and safe in children,40 their efficacy in adult moyamoya patients has been more controversial. However, some recent reports suggest they have low perioperative risks and significantly decreased subsequent ischemic events.41,42 Multiple procedures have been described, including encephaloduroarteriosynangiosis, encephalo-duro-arterio-myo-synangiosis, emergency management of stroke, omental transposition, and pial synangiosis. Newer procedures have been developed that use different combinations of tissues placed over the brain to provide additional revascularization. Ishii et al.43 described a STA-MCA bypass with encephalo-duro-myo-synangiosis to augment revascularization in 6 adult patients with effective neovascularization through the grafts in all patients. Kuroda et al described their 11-year experience with a novel bypass procedure, STA-MCA anastomosis with encephalo-duro-myo-arterio-pericranio-synangiosis.44 They performed this surgery in 123 hemispheres in 75 patients. In addition to the STA-MCA bypass and indirect bypass for the middle cerebral artery territory, the medial frontal lobe was revascularized using the frontal pericranial flap through a medial frontal craniotomy. The overall incidence of mortality and morbidity was 0% and 5.7%, respectively, whereas the annual risk of cerebrovascular events was 0% in pediatric patients and 0.4% in adults. SPECT/PET studies revealed that CBF and its reactivity with acetazolamide markedly improved in both the middle cerebral artery and anterior cerebral artery territories. It is still not clear if the combined procedures improve outcome compared with direct or indirect bypasses alone.
There is increased understanding of the predictors for perioperative complications after revascularization surgery. Hyun et al analyzed the incidence and causes of perioperative ischemic complications in 165 patients with adult-onset MMD who underwent 246 revascularization procedures, mostly encephaloduroarteriosynangiosis. There were 19 (7.7%) perioperative ischemic complications, 4 with permanent neurological deficit and 15 with reversible deficits. Interestingly, 17 of the 19 complications occurred in the initially affected hemisphere regardless of the side of the surgery. Multiple ischemic episodes, presence of hypodensity on CT scan, and high signal intensity on diffusion-weighted MRI were significantly associated with perioperative ischemia complications. In our study, high postanastomotic middle cerebral artery flow significantly correlated with hemorrhage, transient neurological deficits, and perioperative ischemia.

An important consideration in the postoperative management of patients with MMD is the concept of hyperperfusion causing transient or permanent neurological deficits. This complication is well known in carotid endarterectomy and high-flow bypasses; however, it has been increasingly described in low-flow STA-MCA bypasses. Pathologically, it occurs due to a rapid increase in blood flow in chronically ischemic regions of the brain. In 1 study, the incidence of symptomatic hyperperfusion was estimated to be as high as 38.2% in patients with adult-onset MMD. In this syndrome, hemorrhage or infarct/diffusion lesions are not present in the MRI scan; however, patients have gross neurological deficits in form of aphasia, dysarthria, orofacial apraxia, or sensorimotor loss. It is important to recognize this syndrome because the treatment for it is the opposite of that of ischemia. A patient with postoperative ischemia despite a patent graft requires an increase in blood pressure and perfusion, whereas a patient with symptomatic hyperperfusion requires tight control and lowering of blood pressure. The diagnosis is usually made with SPECT scan following the STA-MCA bypass or sometimes with other perfusion studies such as CT perfusion and MR perfusion. Fukimura et al. analyzed the incidence of symptomatic hyperperfusion in patients with MMD and performed SPECT 1 and 7 days after the bypass. Of 58 patients (80 hemispheres), 21 (22 sides [27.5%]) had symptomatic hyperperfusion and were subjected to intensive blood pressure control. Postoperative MRI showed patent bypass in every patient without infarct; however, SPECT showed increased perfusion in every patient. There were 17 patients with transient neurological deficits because of localized hyperperfusion mimicking ischemia, whereas 4 patients had severe headache with subarachnoid hemorrhage or intracerebral hemorrhage. The authors reported that tight control of blood pressure and use of a free radical scavenger relieved the symptoms in all patients. Adult-onset disease (P = 0.013) and hemorrhagic-onset patients (P = 0.027) had a significantly higher risk of hyperperfusion. Hayashi et al described their experience with postoperative worsening and the role of hyperperfusion in 22 pediatric patients. Frequent TIAs preoperatively were significantly associated with postoperative hyperperfusion and watershed shift. Hyperperfusion has also been correlated with delayed intracerebral hemorrhage. Kohama et al described the temporal changes of 3-T MRI/MR angiography during symptomatic hyperperfusion after STA-MCA bypass. The time-sequential 3-T MR angiography showed an intense high signal of the donor superficial temporal artery and dilated branches of the middle cerebral artery around the anastomosis during hyperperfusion. Thus, the recognition, diagnosis, and management of this important complication after STA-MCA bypass for MMD is important for achieving good patient outcomes. Although there is no definite proof regarding hyperperfusion causing neurological deficits, there is some Level 3 data supporting this hypothesis. It is important to note that these studies did not have a control arm, and hence additional studies are required to establish the role of hyperperfusion in MMD. Interestingly, some of the patients in our Stanford series who developed postoperative neurological deficits (transient or permanent) actually showed decreased perfusion on MR or xenon CT in some areas (ipsilateral or contralateral to the direct bypass), raising the possibility of competing flows between native collaterals and the bypass.

Angioplasty and/or stenting have been proposed as an alternative treatment for MMD. However, reported failure of these endovascular techniques suggests surgical revascularization is the preferred procedure. In rare cases when initial surgical revascularization is ineffective, repeat revascularization may achieve excellent outcomes.

Most of the outcome assessments after revascularization procedures have focused on cerebrovascular events, especially TIAs or strokes. However, there is increasing awareness about cognitive impairment related to MMD in both adult and pediatric patients. We analyzed the effect of MMD on neuropsychological functioning in 36 patients with MMD who were given presurgical neuropsychological assessments. Mean group performance was within normal limits for all measures assessed; however, executive functioning was highly impaired. Of the 36 patients, cognitive impairment was present in 11 (31%) and was moderate to severe in 4 (11%). Calviere et al. analyzed the relationship between cognitive impairment and cerebral hemodynamic disturbances on perfusion MRI in 10 adults with MMD. Dysexecutive cognitive syndrome was found in 6 of the 10 patients and was related to impairment of blood flow in the frontal region as seen on perfusion imaging. Intellectual decline has also been seen in pediatric patients. Few studies have compared the neuropsychological outcomes before and after revascularization. Jefferson et al reported a case of adult-onset MMD in which the patient had normalization of dysexecutive functions after revascularization surgery. Larger studies will be required to determine if an STA-MCA or indirect bypass is able to improve the global CBF and the cognitive impairment due to chronic cerebrovascular ischemia.

Conclusions

Recent advances have been made in elucidating the genetics and pathophysiology, applying novel imaging modalities, innovative CBF measurements, surgical techniques, and outcome assessments of MMD. Further advances understanding the molecular pathways underlying development of the disease will likely lead to novel therapies. For now, surgical revascularization with direct, indirect, and combined methods remains the procedure of choice in patients with MMD.
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References


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안(평균 43.7개월) 34명은 수술을 받지 않았고 7명에서 증상이 발생하였는데, 3명은 TIA, 1명은 혈혈뇌출혈, 3명은 뇌출혈이었다. 뇌출혈의 위험률은 연간 3.2%였다. 수술적 치료를 받은 환자 6명에서는 주기적 기간 동안 혈혈이나 출혈증 증상이 발생하지 않았다. Yamada 등은Brunton 치료를 받은 무증상 MMD 환자 28명을 보고하였는데, 이 중 2명은 출혈로 사망하였고 4명의 환자는 TIA를 경험하였다. 이러한 결과들에서, 무증상 MMD 환자도 여전히 허혈이나 출혈증을 일으키는 것으로 보인다. 그러나, 무증상 MMD 환자 모두 수술을 받아야 한다는 데 대해 합의된 바는 없다. 무증상 MMD 환자가 아닌 애待의 주된 원인은 출혈에 의한 것인데, 지금 일본에서 수술적 혈관재건성이 출혈 위험을 감소시키는지에 대한 무작위 임상시험은 진행 중이다. 또한, 수술적 혈관재건성이 두대뇌출혈의 위험을 낮춘다는 직접적인 증거가 없기 때문이다. 그러나, 만약 적절한 혈관재건이 있거나 수술적 위험이 낮다면 수술적 혈관재건성을 무증상 MMD 환자에게 시행할 수 있을 것이다. 그러나, 증상이 있는 환자는 내과적 치료를 받는 것이 적절한 위험이 높다. Hallemeyer 등은MMD 환자 34명에 대해 보고한 바에 따르면, 22명이 양측성, 12명이 일측성이었다. 내과학적으로 치료를 받은 환자들에게서 중추 신경계변화 이후 동반된 뇌출혈 재발 위험률이 5년간 65%였는데, 수술적 치료를 받은 반수에서는 수술 전후와 그 이후의 동측 뇌출혈 발생 위험률이 5년간 17%였다(P=0.02). 26

영상
60년 이상의 기간 동안, 뇌혈관조영술은 MMD의 진단 및 치료에 있어서 최고의 방법인데, MRI와 MR 혈관조영술 또한 MMD와 그 후유증의 진단 및 혈관재건이후 주요 관찰과 관련하여 사용된다. MMD의 연령, 병사의 경우에 대한 연구들은 혈관 재건성, 허혈 및 출혈성 질환 발생에 대한 예측 인자로 수술 후 혈관 및 뇌혈관의 예후 인자와 평가에 중점을 두고 있다.

단일광자방출강조관단층촬영(single-photon emission computed tomography, SPECT)은 오랫동안 뇌혈류(cerebral blood flow, CBF), 뇌혈관 반응성의 측정에 사용되어 왔으며, 양자방출단층촬영(positron emission tomography, PET)의 사용이 점차 증가하고 있다. PET는 다음과 같은 추적자(tracer)를 이용하여 혈류역학을 측정하는데, C-O 15PET는 뇌 혈액량의 측정에 사용하고, H 2 15O는 CBF, 15O 2는 산소추출(oxygen extraction fraction)과 대뇌의 산소 대사량의 측정에 사용된다. Nariai 등은 전두엽과 측두엽, 두정엽 피질의 산소추출률이 MMD 환자에서 급격한 대조군에 비해 높다 는 것을 관찰하였다. 그러나 국소CBF의 감소 때문에 대부분의 뇌영역에서 국소적 대뇌 산소 대사량은 줄어드는 경향을 보였다. 이들 환자에서의 포도 알작용으로 인하여 최대한으로 혈관이 확장되어 있어서 높은 뇌혈액량을 보였다. 혈관망이 최대한 확장되어 있고 자동 조절능이 소실되어 있을 때 재질의 도류 현상(stenal phenomenon)이 관찰된다. Nariai 등은 TIA와 혈혈 증상을 보인 환자에서 산소추출량이 높았다고 보고하였는데, 영구적인 손상을 보이거나 출혈이 있는 환자에서의 정상이었다. PET는 TIA에서 가장 신뢰할 만한 평가 도구 중 하나이다. MMD 환자 23명을 대상으로 한 연구에서Kuwabarad 등은 PET 환자시 CBF와 혈류 동파 시간(transit time, TT)이 현저하게 증가함을 보고하였으며, 이는 특히 선조예시(strium)에서 관찰되었다. 고관현상형(hyper-capnia)에 대한 신경학은 현재까지 수술되어 있다. CBF, TT, 고관현상증에 대한 괴혈관 반응을 포함한 모든 매개 변수가 수술 후에 환전되었다. PET가 괴혈관 반응성을 측정하는 다른 방법들보다 더 신뢰할 만한지는 조건을 더 확인해 보야 한다. 내과학적으로 치료받은 MMD 환자에서는, 질병진단의 대략진단에서의 산소추출률의 증가가 동측의 뇌출혈 발생 위험의 예측 인자인지에 대한 연구적 관찰 연구가 진행 중이다. 27

역동학자율대조개당 여러 주기 MRI (dynamic susceptibility contrast-weighted bolus-tracking MRI), 동맥 스팬 표시MRI(arterial spin labeling MRI), 혈장 산소 수치 의존 MRI (blood oxygen level-dependent MRI) 등 최근 MRI 기법이 혈류역학의 정량 분석을 위해 사용되고 있다. 동맥 스팬 표시MRI는 MMD에서 SPECT 영상과 비교하였을 때 동맥 스팬 표시와 SPECT의 ACZ-IMP 수치가 강한 연관성을 보였고, 동맥 스팬 표시MRI를 이용한 관류영상이 혈류 발생시의 임의적 복합과를 보여 줄 수 있을 것이라 생각된다. 혈장 산소 수치의 의존 MRI를 이용하여 혈관 반응성을 측정한 것 또한 혈관조영술에서 수술(Suzuki 점수(modified Suzuki score)로 혈관 공급의 장애 정도를 측정한 것과 직접적인 관계가 없다. NOVA sofware를 이용한 정량적 MR 혈관조영술은 두개 내혈관을 통과하는 실제 혈류를 보여 주며, 혈관재건후 이후 맥측동맥(super-ficial temporal artery)을 통과하는 혈류 또한 보여 줄 수 있다. 본 연구자의 임상 결과, xenon CT (acetaolamide 사용 또는 미사용)가 CBF와 혈류학적 예기능성을 평가하는 데 이르는 간간 해상도가 좋은 대조적 실형 분석방법이었다. 그러나, 이는 FDA의 허가를 받지 못하였고, 임상시험 심사 위원회의 승인을 받은 프로토콜에서만 사용 가능하다. Xenon CT는 결과는 현재 분석 중이다.

수술
MMD 환자에서 내과적 치료와 외과적 치료를 비교한 무작위 임상시험은 있지만, 외과적 혈관재건성이 유일한 효과적 치료법으로 받아들여지고 있다. 여러 전향적, 후향적 환자군 연구에서, MMD 환자에서 혈관재건성형술이 그 이후의 혈혈증
상 발전을 예방할 수 있음을 보고하였다. 직접적 혈관내형성 (만순두근맥-대뇌동맥 용혈로조영술(STA-MCA 우회로 조영술), 고혈압 용혈로조영술) 및 간접적 용혈로조영술(뇌경혈 막동맥간접협동술(encephaloduoarteriosynangiosis), 뇌 경혈막동맥간격간접협동술(encephalo-duro-arterio-myov-synangiosis), 유연막간접협동술(pial synangiosis), 혈관 시각(혈관과 간접 혈관 시각을 혈관 표면)이 수년간 사용 되어 왔다. 그러나 최근 몇 년간, 기존적인 구축 및 수술 후 혈류 모니터 방법에서 의미 있는 발전이 이루어져 왔다.

STA-MCA 용혈로조영술은 Kikuchi와 Karasawa에 의해 시행된 1973년 이후 MMD 환자에서 시행되어 왔고, 그 이후로 STA-MCA 용혈로조영술은 직접 혈관내형성의 주축이었으며, 훗날로 발전한 결과를 보였다. 본 연구자들은 450례의 혈관내형 성술을 발표하였는데, 직접 혈관내형성술은 성인의 95.1%, 소아의 76.2%에서 시행하였고, 치료반응 대비판구당 수술에 따른 합병증율은 3.5%, 사망률은 0.7%였다. 수정 관련 또는 이후 뇌출혈이나 사망의 5년 누적 합병증율은 5.5%였다. TIA가 발생한 환자 171명 중 91.8%는 1년 이상 TIA를 겪지 않았으며, mRS로 측정한 삶의 질도 우수한 호전을 보였다. 다른 자료들의 직접 혈관내형성의 탈함정 결과를 보고하였다.[9]

STA-MCA 용혈로조영술의 기법은 상당히 표준화되어 있으며, 이전에 기술된 바 있다.[10,11] 그러나 excimer laser-associa ted nonocclusive anastomosis의 새로운 기법이 개발되었다.[12] 이 기법에서는 통합술 동안 일시적으로 혈관 폐쇄를 유도할 필요가 없다. 연결 혈관을 이식함으로 혈관에 펼치며, excimer laser-associa ted nonocclusive anastomosis platinum ring과 함께 펼친 다음 laser catheter로 혈관벽에 구멍을 만든다. Excimer laser-associa ted nonocclusive anastomosis platinum ring과 혈관 사이를 연결시킨 후, ring graft 복합재료를 이식한 혈관 부위에 폐쇄하고, 중심의 흡 입 부분과 주변의 원형과 평행으로 구성된 있는 laser catheter를 이식한 혈관의 측면 구멍을 통과시켜 혈관 구멍을 만든다. 이 방법을 쓰면 일시적인 혈관 폐쇄를 유도할 필요가 없다는 장점이 있다. 그러나 현장에서는 적정 2.5 mm 이상인 혈관에서는 사용할 수 있어서 상상및 성부의 내 경동맥이나 근위부 중매내동맥에만 적용 가능하며, STA-MCA 혈관술에는 적용할 수 없다. 그러나 기술이 계속 발전하고 excimer laser-associa ted nonocclusive anastomosis를 조금 더 작은 두개내 혈관에 적용시킬 수 있도록 하는 데에 MMD의 직접 혈관내형성술 중의 모니터링에서도 새로운 발전이 이루어져 왔다. 이것은 수술 중 도플러(Doppler)이나 육안으로 평가하는 것이 단순하므로 확장 도달성을 확인하는 방법이었다. 수술 중 이식하의 개통 정도와 혈류를 평가하는 데 두 가지 중요한 발전이 있었다. 안토시아닌그린(indocyanine green, ICG)은 근적외선에 의해 침음되며 근적외선 형광을 낼다. 문헌이 완료되어 ICG를 주입하고 근적외선으로 자극을 주어 시각화시킨다. Woitzik 등은 18명의 MMD 환자가 포함된 40명에서 두개내 두개내 혈관조영술을 시행한 후 ICG 비디오 혈관조영술의 역할을 시험하였다. 혈관조영술 시 시행된 ICG (0.3 mg/kg body weight)를 정맥내 급속 주입(bolus injection)을 통해 혈관으로 투여하였다. ICG 혈관조영술은 수술 후 피질혈관과, 대뇌 경맥의 시각화가 탁월하게 이루어져서 것이 확인되었다. ICG 비디오 혈관조영술은 혈관내 형성술을 제대로 기능하지 못하는 STA-MCA 우회로 4대를 찾아내었으며, 이는 성공적으로 제시되었다. 모든 증례에서 ICG 비디오 혈관조영술의 최종 결과는 디지털혈관조영술이나 CT 혈관조영술에 의해 입증될 수 있었다. Awano 등은 13명의 MMD 환자와 21명의 비MMD 환자에서 STA-MCA 용혈로조영술을 통해 동족과 혈관내 혈류를 평가하고 수술 후 치료를 위해 용혈로조영술에 의해 야기되는 혈류학적 변화를 모니터링하였다. ICG 관류는 혈관 내성이 최저레인지 낮은 때 계산되었다. MMD 환 자에게는 ICG 관류 영역과 비MMD 환자의 ICG 관류 영역을 비교하였는데, MMD 환자에서 ICG 관류 영역은 우수하게 낮았다. 즉, ICG는 관류율이 높아져야 할 때 계산되었다. 연구자들은 이 실험을 이용하여 혈관내 형성술 유용성을 측정할 수 있으며 또한 수술 후 치료를 위해서도 측정한 정보를 제공할 것이다. 본 연구자들은 또한 최근 수술건 수백 명의 MMD 환자에서 직접적 혈관내형성 문헌을 중에 ICG를 사용해 왔는데, 직접적 문헌의 개통 정도를 평가하는 데 있어서의 ICG 가시성을 분석하는 중요하다.

두 번째 중요한 발견은 다양한 수술 중 혈류 또는 대뇌 산소화, 혈관내 막유막환과 혈관 주위 막혈상을 사용한 수술 중 혈류 모니터링이다. 신층성은 있는 혈관 주변 혈류 막막자(Charbel Probe: Transonic Systems, Inc)를 이용한 혈관과 이식운 혈관과 혈관에 의해 혈류를 모니터링할 수 있다.[13] 유량계는 100ml/min으로 혈류 양을 측정하는 데 초음파 시간관측(ultrasonic transit time) 원리를 이용한다. 혈류의 방향이 전방향성인 관 련방향성은 측정할 수 있다. 이는 이식 혈관의 개통 정도와 이식혈관의 혈류를 평가하고 수술 후의 혈압과 혈류학적 자극도를 체크하기 위한 매우 중요한 방법이다. 본 연구자들은 이 실험은 혈관 주변 혈류 막막장을 사용하여 MMD 환자 992명을 대상으로 다양한 혈류학적 인자를 분석하였다.[14] 혈관판막 이후의 측정내 혈류가 평균 5배 가량 증가하였다. 본 연구자들은 이 연구를 개선하고 혈관의 막막혈량의 문헌에 기술되었다. ICG 혈관조영술이 VT 혈관 조영술로서 혈관 내정맥 혈류가 높아진 경우 수술 후 혈관내혈점이나 뇌출혈, 일시적인 신경학적 이상 증상과 연관되어 있다. 그러므로, 혈류와 혈관내 막막조영은 혈관내 혈액 순환 방법을 정합할 수 있으며, 혈관내 막막이 있는 환자에서는 혈관의 혈관내 막막조영이 나타난다. 그 외 CBF나 뇌내 산소화를 측정하는 새로운 방법들을 문헌에 기술하였다. Takeuchi 등은 애로 확산 유량 막막자.
(thermal diffusion flow probe)를 이용하여 12명의 젊은 MMD 환자에서 우회로조영상 전후로 14개소의 대뇌피질 영역의 국소적 CBF를 측정하였다. 인식적으로 혼란을 배제하였을 때, 대뇌피질의 관리자는 한 환자에서도 볼어지지 않았다. 우회로 시행 직후 국소적 CBF가 증가하였고 6개 비교 후 4개소에서 증가할 상태가 유지되었다. 평균적으로 문맥술 후 1~2분과 5~10분에 유의하게 증가하였다. 혼란 문맥 부위의 개방 정도의 대비표지로 직접적 우회로조영상 중에 사용할 수 있다. Nakagawa 등15은 위장수 전 표본 혈류 모니터링 방법을 이용하여 혈관내성혈 통시 식별적 조사를 직접한 결과를 접목하였고, 증상과 과관류의 발생을 탐지하였다. Hoshino 등은 STA-MCA 우회로조영상 중의 혈류 상황을 모니터링을 이용하여 혈관내성혈 통시 지역적 표본의 혈류학적 변화를 감지하고 증상과 과관류의 발생을 탐지하였다.16

 많은 저자들은 안정적이고, 그리고 치료를 최적화하여 STA-MCA 우회로조영상 시행하기 위해 가장 수술 계획 시스템(virtual surgical planning system)을 사용해 왔다. Nakagawa 등은 안면주두뇌혈관의 이상적 위치와 증 대뇌동맥의 이상적 위치를 측정하고, 미세개두술 (microcraniotomy)을 계획하기 위해 시각적 디지털관혈관 조영술을 사용하였다. 이 방법을 이용하여 MMD 환자에 대한 28명의 환자를 수술을 시행하였다. 모든 환자에서 수술 전 계획 및 미세개두술을 통해 수술이 시행되었다. 비슷한 방법으로 CT 혈관조영술과 MR 혈관조영술을 시행하였으며, 이 방법이 조금 더 낮은 임상 결과를 보장하지는 않아야 한다.

 문헌분석에 다양한 간접적 혈관내성혈 방법이 기술되어 있다.17 간접적 술기의 원리는 뇌내의 신경혈관 형성과 결손활을 자극하기 위해, 외래도의 위치에 의해 공급되는 혈관포도 조직을 뇌에 이식시키는 것이다. 간접적 혈관내성혈은 소아에서 매우 효과적이고 안전한 방법으로 알려져 있으나, 성인에서의 효과는 논란이 조금 더 많다. 그러나 최근 연구에서 수술 전후의 위치를 높고 수술 후의 혈관내성혈 발생을 유의하게 감소시킨다는 것을 보고하였다.18 다양한 수술 방법이 기술되어 있으며, 여기에는 뇌경막마약단연결술, 뇌경막마약유관간접합술, 뇌질막연 결합술, 대뇌질막연결술 등을 포함한다. 추가적인 혈관내성혈을 위해 뇌내 위치 위치시키는 조질들의 여러 다른 조합을 사용하는 새로운 술기를 개발되어 왔다. Ishii 등19은 혈관내성혈을 증가시키기 위해 6명의 성인 환자에 서 뇌경막간연결합술(encephalo-duro-myo-synangiosis)을 사용한 STA-MCA 우회로조상을 기술하였고, 이 혈관을 통해 효과적으로 신경혈관 형성이 이루어지는 것을 모든 환자에서 확인하였다. Kuroda 등은 뇌경막마약 유관간결합수술을(encephalo-duro-myo-artério-pericranio-synangiosis) 방법으로 STA-MCA 문맥술을 시행한 새로운 운화로조영상은 11년간의 경향을 발표하였고,20 그들은 환자 75명의 123개 발판에서 이 수술을 시행하였다. 증대뇌동맥 영역에 대한 STA-MCA 운화로와 간접적 우회로에 대하여, 내측 두개골두술(medial frontal craniotomy)을 통해 두개골두막 피막을 사용하여 내측 두개골 두혈관 내성혈을 시행하였다. 소아 환자에서 뇌경막간연결합술의 연간 위험률은 0%, 성인은 0.4%였던 반면, 전반적인 사망률과 위험률은 0%와 5.7%였다. SPEC/PET 검사는 CBF와 aceta-zolamide에 대한 반응과 증대뇌동맥 및 증대뇌동맥 영역에 대해 물질을 회복되었다. 혈관내성혈 직접적 또는 간접적 방법 각각에 비해 예후를 향상시키는지는 아직 확실하지 않다.

혈관내성혈 이후 수술기(perioperative) 혈관중증의 예측 인자에 대한 이해가 점차 증가하고 있다. Hyun 등은 성인 MMD 환자 165례에 246례의 혈관내성혈증(대부분 뇌경막마약간결합술)을 시행하고 수술기 혈관내성혈증의 발생률과 원인을 분석하였다.21 17례(7.7%)의 수술기 혈관내성혈 증이 발생하였는데, 4례는 영구적인 신경학적 이상이 남았고 15례는 임상적 손상도 보였다. 흔히들고, 17례의 혈관중증 중 17례에서 수술의 방법과 관계 없이 처음 증상을 보인 반구에서 발생하였다. 다발성 혈관 증상 발열, CT 스탠 verified 있는 보고도 있는 경우 수술기 혈관내성혈증의 유발되며 현관을 보였다. 본 연구에서도, 문 합술 이후 증대뇌동맥 영역의 혈류가 높은 경우, 출혈, 임상적 신경학적 이상, 수술기 혈관 증상으로 유의하게 관련되어 있었다.22

MMD 환자의 수술 후 치료에서 중요하게 고려할 점은 일시적이나 영구적인 신경학적 이상을 유발하는 과관류이다. 이 혈관중증은 경막막내막절체술(carotid endarterectomy)이나 고혈류(high-flow) 우회로조영상에서 잘 알리지 않는다. 그러나 미쇠판 우회로조영상에서는 보고도 점차 늘어나고 있다. 병리학적으로, 이는 뇌내의 만성적 혈류 부족으로 혈류가 급격히 증가함에 의해 발생한다. 한 연구에서, 증상을 유발하는 과관류의 발생은 성인 MMD 환자에서 38.2%까지 높게 측정되었다.23 이 증후군에서, 출혈이나 경색/뇌사망증상 변별 MR영상에서 관찰되지 않으나, 환자들은 심야증, 구개증, 입안 섬유증(ocofacial apraxia), 감각운동 결손(sensorimotor loss)과 같은 형태의 육안으로 확인 가능한 신경학적 손상 을 보인다. 이 증후군은 감지하는 것이 중요하다. 치료가 혈 확의 치료와 반대이기 때문이다. 이식 혈관을 통한 혈류 공급이
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