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Cerebrovascular Disorders (DG Jamieson, Section Editor)

Surgical Treatment of Adult Moyamoya Disease

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Abstract

Purpose of review Moyamoya disease (MMD) is being increasingly diagnosed with the development of radiological surveillance technology and increased accessibility to medical care. Accordingly, there have been several recent reports on treatment outcomes in MMD. In this review, we summarize recent advances in surgical treatment and outcomes of adult MMD, while addressing related controversies.

Recent findings Recent studies suggest that revascularization surgery leads to significantly more favorable outcomes for stroke prevention, angiographic and hemodynamic changes, and clinical outcomes than does conservative treatment for adult patients with ischemic MMD. Moreover, direct revascularization methods should be considered as the first-line treatment over indirect methods, although the latter may be considered if a direct method is not possible. In cases of hemorrhagic MMD, several studies have demonstrated that surgical treatment is more effective than conservative treatment in preventing further hemorrhage. In addition to revascularization surgery, endovascular treatment is emerging as a breakthrough therapy for hemorrhagic MMD.

Summary Accumulating evidence regarding the surgical treatment of adult MMD suggests the benefit of revascularization over conservative management for both

ischemic and hemorrhagic patients. However, the benefit of revascularization in asymptomatic adult MMD remains unclear.

Introduction

Moyamoya disease (MMD) is a cerebrovascular steno-occlusive disease characterized by the bilateral involvement of the internal carotid artery (ICA) bifurcations. It affects both the proximal anterior cerebral artery (ACA) and middle cerebral artery (MCA). Numerous collateral vessels develop in MMD, mainly from choroidal arteries and are termed basal collaterals. Because the angiographic appearance of these vessels resembles a puff of smoke, the condition was named moyamoya (puff of smoke, in Japanese).

One of the well-known epidemiological features of MMD is the presence of regional differences in prevalence and incidence, worldwide. [1•] Generally, both the prevalence and incidence of MMD are reported to be higher in Asian countries, including Korea and Japan, than in Western countries. [2] Furthermore, a predominance of female patients with MMD has consistently been reported. [1•, 2–5] Moreover, a bimodal age distribution of patients is another characteristic feature of MMD. [1•]

Patients with moyamoya-like vasculopathy concomitant with other well-characterized diseases or syndromes are categorized as having moyamoya syndrome (MMS). [6] These diseases or syndromes can include sickle cell disease, neurofibromatosis type 1 (NF1), thyroid disease, cranial therapeutic irradiation, and Down's syndrome. More rarely, MMS may include systemic lupus erythematosus, Turner syndrome, and Noonan syndrome. Although the prevalence of MMS among patients diagnosed with moyamoya-like vasculopathy is less than 20% and most affected patients are children, [6, 7] the prevalence accounts for 34–60% of children with moyamoya-like vasculopathy in the West. [7–9]

As a result of steno-occlusive changes around the ICA bifurcation, the principal pathophysiology of MMD is hypoperfusion of the brain. Unlike single-vessel lesions, such as M1 stenosis, hypoperfusion affects adjacent vascular territories leading to more significant ischemia, particularly in the border zones. Thus, MMD patients are prone to various ischemic symptoms from transient ischemic attack (TIA) to cerebral infarction. [10] This chronic ischemia induces the formation of collateral vessels from arterial branches before the ICA bifurcation. As described earlier, the main source of these collaterals are choroidal arteries, including the anterior, lateral posterior, and medial posterior choroidal artery. Other possible collaterals arise from the ophthalmic and posterior cerebral arteries. Transcranial and transdural collaterals are also commonly observed from the external carotid arteries (ECA). The amount of blood flow through collateral channels increases as the disease progresses. However, flow burden through these collateral channels can lead to excessive hemodynamic stress. Thus, a proportion of MMD patients experience intracranial hemorrhage due to the rupture of collateral vessels. [11]

The clinical features of MMD differ substantially between children and adults. Children most commonly present with arterial ischemic stroke or TIA (73.9–97.5%), with a smaller proportion presenting with hemorrhagic stroke (2.5–8.0%). [7, 8, 12, 13] Meanwhile, more than 50% of adult patients develop TIA or cerebral infarction (57.7–70.0%), while fewer develop intracranial bleeding (19.1–42.3%). [14, 15•, 16, 17]

Given the pathophysiology of MMD, revascularization surgery can be performed to ease hypoperfusion. Revascularization surgery can be divided into direct and indirect types. In the former, various arteries harvested from the ECA system can be used as donors that are anastomosed with cerebral arteries. [18] This can lead to the prompt augmentation of cerebral perfusion where a patient is prone to hyperperfusion syndrome. [19] In contrast, indirect revascularization involves covering the brain's surface with various connective tissues, such as the galea, myofascial tissue, and dura mater, to promote collateral formation by synangiosis. This method is relatively easy to perform technically, but it requires a certain amount of time before hypoperfusion is resolved.

In this review, we summarize recent reports regarding the surgical treatment of MMD, particularly in terms of their effectiveness in preventing further stroke.

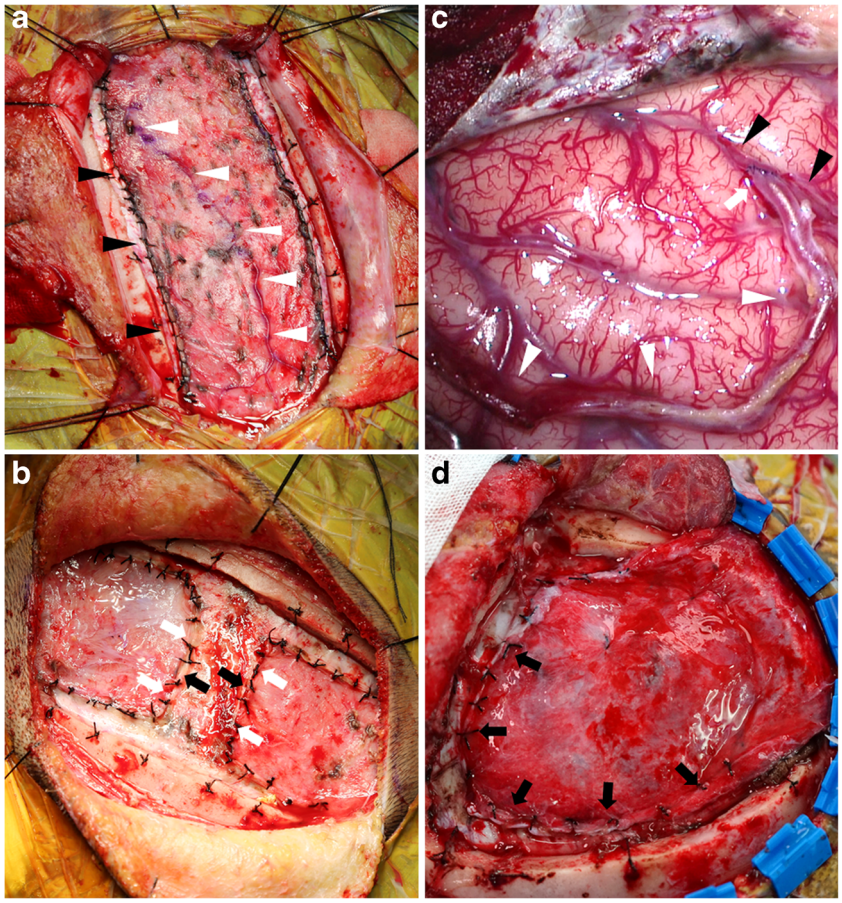

Fig. 1. Intraoperative photos show encephalo-duro-arterio-synangiosis (EDAS) (**a**), bifrontal encephalo-galeo-periosteal synangiosis (EGPS) (**b**), direct revascularization (**c**), and combined revascularization (**d**). **a** For EDAS, the superficial temporal artery (STA, white arrow heads) and accompanying galea connective tissue were overlaid and sutured (black arrow heads) onto the brain surface. **b** Bifrontal EGPS used an approximately 4 × 8-cm midline craniotomy, anterior to the coronal suture. The incised dura was folded into the interhemispheric fissure (black arrows) and the galeo-periosteal flap was sutured to the margin of the folded in dura (white arrows). **c** The STA (white arrow heads) was used as a donor artery. The cortical branch of the middle cerebral artery (MCA), such as the angular artery (black arrow head), was usually selected as the recipient artery, and end-to-side anastomosis was performed (white arrow). **d** After anastomosis, harvested galea was placed on the brain surface and sutured with the dura margin (black arrow) as part of the indirect revascularization combined with direct revascularization.

Surgical treatments

Indirect revascularization

The basic concept of indirect revascularization is to cover the surface of the brain with connective tissues, which subsequently leads to the development of numerous vascular channels toward the cortices. This phenomenon is called synangiosis. To establish synangiosis, various connective tissues can be used, including galea (encephalo-galeo-synangiosis), muscle (encephalo-myo-synangiosis), dura (encephalo-duro-synangiosis), and their combinations.

The branches of the superficial temporal artery (STA) can also be harvested to use as a covering tissue alone (encephalo-arterio-synangiosis) or in combinations (e.g., encephalo-duro-arterio-synangiosis) (Fig. 1a, b). [20–23] The fundamental limitation of revascularization surgery is that it takes at least a few months for synangiosis to develop sufficiently. Nevertheless, this method is relatively easy to perform and requires a shorter surgery than does direct revascularization.

Direct revascularization

A significant feature of direct revascularization surgery for MMD is the anastomosis that forms between donor and cortical recipient arteries. In most direct revascularization surgery, the STA is used as a donor artery. Alternatively, other arteries can be used, such as the deep temporal and occipital arteries. Cortical branches of the MCA are favored as the recipient due to the ease of exposure and manipulation.

In STA-MCA anastomosis, the course of the STA is determined with an ultrasonic probe or manual palpation before the skin incision. Through a delicate dissection of the STA parietal branch, a scalp flap can be produced to expose the surgical field. Following muscle layer splitting, adequate craniotomy is made around Chater's point (6 cm above the external auditory meatus), which provides a good landmark to find robust cortical MCA branches. Subsequently, anastomosis between the donor and recipient is made using 10-0 or 11-0 nylon. Various indirect revascularization methods can also be combined with direct methods (combined surgery) (Fig. 1c, d).

Prompt augmentation of blood flow is the most advantageous feature of direct revascularization. [24] Delayed synangiosis can be developed, also. (Fig. 2) However, direct revascularization is a more complicated procedure than is indirect revascularization, and it requires a longer learning curve. The higher incidence of post-operative cerebral hyperperfusion syndrome should also be considered.

Treatment outcomes

Surgery compared with conservative treatment for preventing ischemic stroke

Previous studies have reported positive surgical outcomes for ischemic MMD, supporting surgery as an effective treatment. [25, 26, 27•, 28••, 29] A recent meta-analysis reported that 35 of 404 people (8.7%) presented with stroke events in a bypass group compared with 24 out of 149 people (16.1%) in the conservative group. This indicates that bypass surgery reduces stroke events significantly compared with conservative treatment in ischemic MMD (odds ratio [OR], 0.24; 95% confidence interval [CI], 0.06–0.99; $p < 0.05$). [28••] Most studies define conservative treatment as careful observation or symptomatic care (e.g., for hyperthyroidism and seizures). Aging patients with MMD are vulnerable to additional atherosclerosis as is the general elderly population, and therefore vascular risk factor management can be considered, such as antiplatelet therapy. [14, 27•, 30–32] Our affiliated group reported that the annual risks of symptomatic hemorrhage and infarction in adult patients with ischemic MMD were 0.4 and 0.2%, respectively. Patients had undergone combined revascularization surgery and showed improvements in clinical, angiographic,

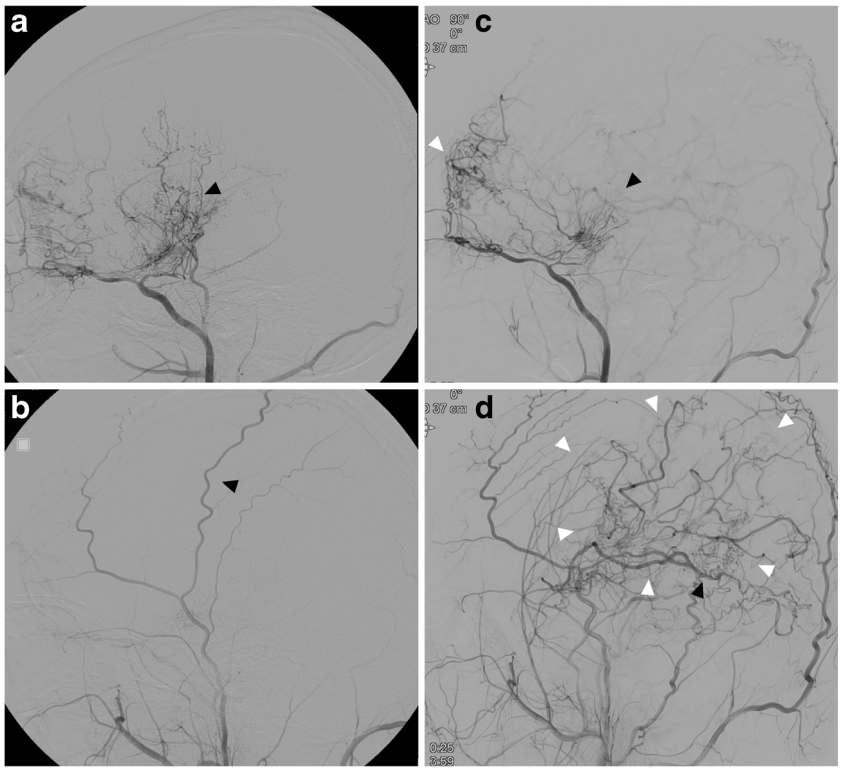

Fig. 2. Digital subtraction angiography shows pre- and post-operative ICA and ECA angiograms. **a** Pre-operative ICA angiogram shows severe stenosis above the ophthalmic artery. Prominent basal moyamoya vessels are noted (black arrowhead). **b** Pre-operative ECA angiogram reveals that there are no developed collateral channels from ECA. The parietal branch of the STA is harvested for direct revascularization (black arrowhead). **c** ICA angiogram performed at 6 months follow-up after revascularization shows decreased extent of basal moyamoya vessels (black arrowhead) while ethmoidal collateral vessels remain robust (white arrowhead). **d** Post-operative ECA angiogram shows robust bypass flow through anastomosis site (black arrowhead). Also, numerous synangiosis channels are developed by indirect revascularization (white arrowhead).

and hemodynamic factors 6 months after the surgery. Moreover, their condition remained stable for 5 years, with a reported 5-year infarction- and hemorrhage-free survival rate of 98.7%. [26] Comparable results were reported in another study that demonstrated that annual risks for hemorrhagic and ischemic stroke in conservatively managed adults were 2.3 and 2.2%, respectively. These rates were higher than that for the surgical group, despite patients being hemodynamically stable. [32].

However, there have been contradictory reports regarding stroke following MMD treatment. Jang et al. reported that there were no preventive effects of surgery against stroke in ischemic-type MMD throughout the post-operative period in their retrospective study, in which there was a 6-year stroke rate of 19.2% in the surgical group ($n = 109$) compared with 10.2% in the non-surgical group ($n = 44$). [14] Another study reported a 5-year ischemic stroke recurrence rate in adult patients with ischemic MMD of 24.4% in the surgical group ($n = 45$) and 11.8% in the non-surgical group ($n = 50$). [33] However, these studies were limited by the fact that the perioperative stroke rates (13.3–17.1%) were

significantly higher than those in other studies, [14, 33] and only indirect revascularization was performed. [33]

Recently, we have reported the stroke prevention effect of combined/direct revascularization for patients with adult-onset MMD presenting with ischemia. We showed that the 10-year cumulative incidence rate for any kind of stroke was significantly lower in the revascularization group (9.4%) than in the control group (19.6%, $p = 0.04$), although 1- and 5-year ischemic stroke rates did not differ. Controlling post-operative stroke seems to be essential to ensure early and mid-term (5-year) benefits of revascularization because most stroke events in the revascularization group occurred within the early post-operative period. [27•] Surgery for patients with MMD should be decided on based on the experience and complication rates for revascularization surgery at each institution, as well as other appropriate surgical indications.

The most effective treatment for adult patients with MMD remains a matter of debate because there have only been a few small case series reporting indirect bypass in an adult population, although indirect revascularization has been widely accepted as the treatment of choice in pediatric patients. According to comparative studies, combined indirect and direct revascularization is more effective at preventing recurrent ischemic stroke [15•, 25, 34] and provides a higher rate of a broad positive angiographic outcomes than does indirect revascularization alone. [29, 35, 36] Two recent meta-analyses have reported stroke events in 7.7–8.6% of patients receiving direct revascularization and 15.0–16.5% in those receiving indirect revascularization. This indicates a significantly lower risk of future stroke events associated with direct revascularization. [28••, 37••] Accordingly, direct revascularization may be considered as the first-line treatment over indirect methods for adult patients with MMD. However, indirect revascularization may be an alternative to direct methods in adult MMD when the latter is not available.

Surgery compared with conservative treatment for preventing hemorrhagic stroke

Rebleeding events in hemorrhagic MMD patients are not rare, with the rate of recurrent hemorrhage reported to be 16.9% at 5 years and 26.3% at 10 years. [36] Because some previous studies failed to support the effectiveness of revascularization for hemorrhagic MMD [38–40], the efficacy of bypass surgery in preventing rebleeding in hemorrhagic MMD remains controversial. However, some recently published studies have demonstrated the effectiveness of surgery in the treatment of hemorrhagic MMD.

Jiang et al. reported a hemorrhage recurrence rate of 1.9% at 2-year follow-up after combined, direct, or indirect revascularization. Therefore, this high-volume single-center study demonstrated a favorable clinical outcome following revascularization surgery for patients with hemorrhagic MMD compared with outcomes for conservative management previously reported in the literature. [41] More robust evidence for combined/direct revascularization in preventing rebleeding was observed in the Japan Adult Moyamoya Trial (JAM Trial). In this multicenter, prospective, randomized trial, annual rebleeding rates were estimated to be 2.7% in the surgical group and 7.6% in the non-surgical group ($p < 0.05$). [42••] Furthermore, according to a recent meta-analysis, revascularization surgery significantly reduced the risk of future stroke events in the surgical group compared with the non-surgical group (OR, 0.32;

Table 1. Treatment outcomes for moyamoya disease based on a literature review

Authors	Year	Number of patients	Method(s) of revascularization	Follow-up duration (months)	Number of strokes	Annual stroke rate (%)
Ischemic MMD						
Revascularization						
Lee et al. [45]	2012	39	CR/DR	56.4	3	1.6
Cho et al. [26]	2014	77	CR	63.7	3	0.7
Kim et al. [27]	2016	301	CR/DR	4	18	1.6
Lee et al. [45]	2012	50	IR	56.4	14	6.0
Conservative management						
Lee et al. [45]	2012	9		50.9	2	5.2
Cho et al. [32]	2015	144		82.5	31	4.2
Kim et al. [27]	2016	140		77	18	2.0
Hemorrhagic MMD						
Revascularization						
Lee et al. [45]	2012	17	CR/DR	56.4	2	2.5
Huang et al. [46]	2015	90	CR/DR	32.1	9	3.7
Kim et al. [36]	2017	30	CR/DR	83	1	0.5
Lee et al. [45]	2012	18	IR	56.4	4	4.7
Huang et al. [46]	2015	34	IR	32.1	7	7.7
Kim et al. [36]	2017	40	IR	83	5	1.8
Conservative management						
Kobayasi et al. [47]	2000	42		80	14	7.0
Morioka et al. [48]	2003	36		144	22	5.1
Lee et al. [45]	2012	9		59.6	4	8.9
Cho et al. [32]	2015	62		82.5	23	5.7
Huang et al. [46]	2015	28		32.1	6	8.0
Kim et al. [36]	2017	176		83	38	3.4
Asymptomatic MMD						
Revascularization						
Kuroda et al. [43]	2007	6	CR/DR	43.7	0	
Luo et al.	2017	52	CR/DR/IR	56.3	3	1.2
Conservative management						
Kuroda et al. [43]	2007	34		43.7	4	3.2
Jo et al. [49]	2014	35		32	0	
Cho et al. [32]	2015	35		82.5	7	3.4
Luo et al. [31]	2017	9		56.3	6	14.2

MMD moyamoya disease, *CR* combined revascularization, *DR* direct revascularization, *IR* indirect revascularization.

95% CI, 0.15–0.68; $p < 0.01$). [28••] Therefore, it is reasonable to suggest that revascularization surgery is helpful in preventing further hemorrhage in patients with hemorrhagic MMD.

Surgery compared with conservative treatment for asymptomatic patients

Few studies have compared conservative treatment with surgery in adults with asymptomatic MMD. In a multicenter survey conducted in Japan, the annual risk of any stroke was 3.2% in the non-surgical group and no cerebrovascular events occurred for 44 months in the six patients who underwent surgical revascularization (although this is admittedly a small number of patients). [43] In another recent study, 33.3% of asymptomatic patients in the non-surgical group showed symptomatic progression and 11.5% of asymptomatic patients in the surgical group experienced TIAs across 56 months. Survival analysis showed that patients in the surgery group had a longer symptom-free period than did those in the conservative treatment group ($p = 0.02$). [31]

There is no guideline for how asymptomatic patients with MMD should be followed up. The results of a multicenter survey in Japan [43] suggested that cerebrovascular events (CVEs) occurred in 15.0% of asymptomatic patients with impaired cerebrovascular reactivity for acetazolamide, while CVEs occurred in 8.3% of asymptomatic patients with normal cerebrovascular reactivity. Furthermore, silent infarction or ICH on follow-up magnetic resonance imaging (MRI) was detected in 20.6% of asymptomatic patients treated conservatively. [43] Kuroda et al. has shown that disease progression occurs in 18.2% of asymptomatic patients during a mean follow-up period of 6 years, and they emphasized that disease progression may occur silently leading to stroke, even in asymptomatic patients. [44] These findings suggest that it is important to repeat MRI and cerebrovascular reactivity examinations at regular intervals in asymptomatic patients who are conservatively followed-up to detect disease progression before ischemic stroke occurs.

Surgical revascularization can be considered, at least, in patients who have disturbed cerebral hemodynamics with newly occurring symptoms because the procedure is considered effective for preventing ischemic stroke and improving cerebral blood flow and metabolism. Nevertheless, the number of patients in the non-surgical groups of previous studies was small and only non-randomized studies have been conducted. Therefore, the efficacy of surgical treatment for asymptomatic MMD patients remains unclear. Table 1 summarizes the recent literature.

Treatment for moyamoya syndrome

Although the optimal treatment of MMS is not clear, surgical treatment for symptomatic MMS is known to have similar outcomes to that for MMD. Koss et al. reported that in 22 patients with long-term follow-up who underwent pial synangiosis for NF1 associated with MMS, 21 (95%) showed a stable or improved neurological status. [50] The largest study on Down's syndrome with MMS included 16 surgically treated patients and demonstrated that 85% of the surgically treated hemispheres had radiological evidence of good to excellent cerebral revascularization in angiography conducted a year after surgery. [51] Another study of 5-year outcomes in children with MMS after pial synangiosis

reported that only two late-onset strokes occurred in all 46 patients followed for more than 5 years.

Perioperative complications

Perioperative stroke

In previous studies of adult patients diagnosed with MMD, the rate of perioperative stroke, including ischemic and hemorrhagic stroke, after bypass surgery varied from 2.6 to 23.9%. [14, 15•, 26, 27•, 29–31, 34, 42••, 52–57] It is suspected that direct revascularization may be associated with higher rates of perioperative complications than is indirect revascularization because of technical difficulties such as the requirement for temporary cortical vessel occlusion and hyperperfusion. [57] However, it remains difficult to determine the preferred surgical approach based on differences in rates of perioperative complications between the direct and indirect revascularization groups. Perioperative ischemic stroke events were reported in 1.3–13.0% of those receiving combined/direct revascularization, and 4.1–7.1% of those receiving indirect revascularization. In addition, perioperative hemorrhagic strokes were reported in 0.6–4.6% in those undergoing combined/direct revascularization group, and 0–7.1% in those undergoing indirect revascularization. [14, 15•, 26, 34, 41, 42••, 52, 53, 56, 57] Most previous studies have demonstrated no statistically significant difference in rates of perioperative stroke between the two methods of revascularization, although the direct revascularization group tends to show slightly higher rates of complications. [15•, 29, 34, 57]

Research suggests that multiple ischemic episodes and the presence of infarct visible on low-density computed tomography (CT) or high-signal intensity diffusion MRI in the pre-operative state are significant risk factors for perioperative ischemic complications after revascularization surgery. In addition, multiple pre-operative cerebral ischemia events have been noted as risk factors. [56] Accordingly, patients with these risk factors require very close monitoring to avoid non-surgical hemodynamic risk factors, such as hypercapnia, hypocapnia, hypotension, and hypovolemia, because they have unstable cerebral blood flow and disturbance of normal autoregulation.

Cerebral hyperperfusion syndrome

Studies suggest that clinical cerebral hyperperfusion syndrome (CHS) is experienced by 21.5–50% of patients who have undergone revascularization surgery and is most frequently observed on the third post-operative day. [18, 58–62] Transient dysfunction of cerebral autoregulation has been suggested as the underlying mechanism for CHS.

In MMD, the intracranial arteries undergo atrophy and become thin. Accordingly, moyamoya vessels are formed when long-term ischemia occurs due to the metabolic insufficiency of blood perfusion. The relatively excessive amount of increased perfusion in the chronically ischemic cortical area provokes various clinical symptoms, which can manifest as headaches, neurological deficits, and intracerebral hemorrhage. These symptoms are resolved after

restoration of autoregulation of arteries and normalization of perfusion. [60, 62]

After CHS is diagnosed, cerebral blood flow should be controlled by adequate use of fluids and control of systemic arterial blood pressure within the normal or lower range according to pre-operative levels. [63] Nonetheless, careful monitoring of blood pressure is required because lowering systemic blood pressure can cause ischemic stroke. Fortunately, most cases of CHS in MMD patients after revascularization surgery are reversible with effective treatment, and the symptoms usually resolve within two post-operative weeks. However, intracranial hemorrhage in approximately 3% of patients with CHS is often associated with a bad prognosis. [59]

Endovascular treatment for MMD

Several investigators have assessed the use of intracranial stenting for specific MMD patients presenting with symptomatic focal stenosis of the ICA or MCA. Most cases have undergone stenting with bare metal stents. Although such a technique appears to be successful in restoring blood flow in the affected area, longer term follow-up data provided disappointing results mainly due to in-stent restenosis or progressive stenosis at the adjacent segments. [64] Given the pathophysiology of MMD, intimal hyperplasia and in-stent restenosis could easily develop when a stent is deployed at the active pathologic segment.

Therefore, a drug-eluting stent embedded with immunosuppressive agent has been used for intracranial stenting in MMD patients. In this case, although no significant in-stent restenosis was observed, de novo stenosis developed at the distal segment. [65] Moreover, maintaining dual antiplatelets to prevent in-stent thrombosis is required, and this adjunctive therapy is required for longer with a drug-eluting stent. This can represent another danger because potential hemorrhage can occur among MMD patients. As such, intracranial stenting cannot be recommended generally for MMD patients.

Another role of endovascular treatment for MMD is to prevent further bleeding in patients with hemorrhagic MMD. As described earlier, fragile collateral vessels are prone to rupture. As most collateral channels arise from the choroidal system, most hemorrhage occurs as intraventricular hemorrhage with or without parenchymal hemorrhage. The formation of a pseudoaneurysm is detected with digital subtraction angiography in a certain proportion of such patients. For example, we identified collateral pseudoaneurysms in about 26% (31 out of 119) of hemorrhagic MMD patients.

The presence of a pseudoaneurysm is known to be an independent risk factor for recurrent bleeding. [36] Although surgical clipping can be considered, the usual location of the collateral pseudoaneurysm is too deep to access without causing additional damage. Therefore, endovascular obliteration of pseudoaneurysms can be helpful to prevent recurrent bleeding. [66] During endovascular obliteration, the microcatheter should be located as close as possible to the pseudoaneurysm, because the parent artery of the pseudoaneurysm is a part of the properly functioning collateral channels. As

such, to avoid trapping the parent artery due to poor accessibility, the surgeon should evaluate the territory supplying the target vessel carefully to weigh the benefits and risks of such a procedure.

Summary

MMD is known as a progressive disease and it requires revascularization surgery to prevent both ischemic and hemorrhagic stroke in adult patients. Furthermore, endovascular treatment for hemorrhagic MMD patients who are diagnosed with pseudoaneurysms can be also helpful to prevent further hemorrhage. Although randomized clinical trials for ischemic MMD have not been conducted, cumulative reports strongly support the benefit of revascularization surgery. A randomized trial (the JAM trial) has provided evidence for the efficacy of revascularization surgery for hemorrhagic MMD. However, further research is required to develop effective treatments for asymptomatic MMD because previous studies have provided inconclusive results.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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