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Hemorrhagic Moyamoya Disease : A Recent Update

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Moyamoya disease (MMD) is a progressive cerebrovascular disease with unknown etiology, characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery and an abnormal vascular network formation at the base of the brain. MMD has an intrinsic nature to convert the vascular supply for the brain from internal carotid (IC) system to the external carotid (EC) system, as indicated by Suzuki's angiographic staging. Insufficiency of this 'IC-EC conversion system' could result not only in cerebral ischemia, but also in intracranial hemorrhage from inadequate collateral anastomosis, both of which represent the clinical manifestation of MMD. Surgical revascularization prevents cerebral ischemic attack by improving cerebral blood flow, and recent evidence further suggests that extracranial-intracranial bypass could powerfully reduce the risk of re-bleeding in MMD patients with posterior hemorrhage, who were known to have extremely high re-bleeding risk. Although the exact mechanism underlying the hemorrhagic presentation in MMD is undetermined, most recent angiographic analysis revealed the characteristic angio-architecture related to high re-bleeding risk, such as the extension and dilatation of choroidal collaterals and posterior cerebral artery involvement. We sought to update the current management strategy for hemorrhagic MMD, including the outcome of surgical revascularization for hemorrhagic MMD in our institute. Further investigations will clarify the optimal surgical strategy to prevent hemorrhagic manifestation in patients with MMD.

Key Words : Moyamoya disease · Hemorrhage · Revascularization surgery · Angiography.

INTRODUCTION

Moyamoya disease (MMD) is a progressive cerebrovascular disease with unknown etiology, characterized by bilateral steno-occlusive changes at the terminal portion of the internal carotid artery (ICA) and an abnormal vascular network formation at the base of the brain[33]. MMD has an intrinsic nature to convert the vascular supply for the brain from internal carotid (IC) system to the external carotid (EC) system, as indicated by Suzuki's angiographic staging established in 1969[10,11,33]. Insufficiency of this 'IC-EC conversion system' could result not only in cerebral ischemia, but also in intracranial hemorrhage from inadequate collateral anastomosis ('moyamoya vessels'), both of which represent the clinical manifestation of MMD[10].

In light of this dynamic pathology of MMD, EC-IC bypass such as superficial temporal artery-middle cerebral artery (STA-MCA) bypass potentially has a perfect concept to compliment this 'IC-EC conversion system' and thus prevents cerebral ischemia and/or hemorrhage[10,11]. In fact, STA-MCA by-

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pass is generally employed as the standard surgical treatment for ischemic MMD based on the guideline recommendation[30,36]. Regarding hemorrhagic MMD, it has been a controversy whether surgical revascularization could reduce the risk of re-bleeding, while recent multicenter randomized control trial strongly suggested that EC-IC bypass reduces the risk of re-bleeding in hemorrhagic MMD patients[28]. Based on these observations, we sought to focus on the currents status of revascularization surgery especially for hemorrhagic MMD in this review article. We further discuss the characteristic angioarchitectures of these patients and thus sought to clarify the optimal surgical strategy for the high risk patients with hemorrhagic MMD.

DIAGNOSIS OF MMD

Modern diagnostic criteria

Original diagnostic criteria of definitive MMD included steno-occlusive change at ICA bilaterally, which is associated with abnormal vascular network formation at the base of the brain[30]. While considering the increasing number of the MMD patients with unilateral involvement[16] as well as the evidence that substantial number of unilateral cases could progress to the bilateral presentation[25,26], diagnostic criteria of MMD was revised in 2015 to include patients demonstrating both bilateral and unilateral involvement of terminal ICA stenosis associated with the compensatory development of the abnormal vascular network formation at the base of the brain[36]. Diagnostic criteria also stated that definitive diagnosis of MMD requires catheter angiography in unilateral cases and/or cases with atherosclerotic changes while bilateral cases could be promptly diagnosed by either catheter angiography or magnetic resonance (MR) imaging/angiography[36].

Modern supportive diagnostic tools

Definitive diagnosis of MMD is not always easy, especially in patients with early stage of Suzuki's angiographic grading[33], when abnormal vascular network is not yet evident. Furthermore, one may wonder that revision of the diagnostic criteria might lead to the misdiagnosis of atherosclerotic patients with unilateral involvement to the definitive MMD, especially in elderly patients with intracranial arterial stenosis. To resolve these critical issues, it is essential to understand the diagnostic value of high resolution MR wall imaging focusing on vascular wall anatomy characteristic in MMD. Kaku et al.[21] proposed the constrictive remodeling theory that the outer diameter narrowing of the affected intracranial major arteries was the early characteristic of MMD, as demonstrated by three-dimensional (3D) constructive interference in steady-state (CIISS) MR imaging. Similar observation on 3D CIISS MR imaging in the diagnosis of MMD was reported by Kuroda and colleagues[27]. Ryoo and colleagues[31] reported that MMD was characterized by concentric enhancement on distal ICA and shrinkage of MCA, while atherosclerosis represented focal eccentric enhancement at the symptomatic segment of intracranial arteries. Yuan et al.[40] also reported that the vascular wall-thinning and the arterial outer diameter narrowing shown by high resolution MR imaging could be the early morphological changes characteristic to MMD. Taken together, the high resolution MR wall imaging may provide the important information for the accurate diagnosis of MMD, especially in the early angiographic stage and/or elderly patients with atherosclerosis. Alternatively, genetic analysis on the susceptibility gene, such as ring finger protein (RNF) 213 gene (*RNF213*) in the 17q25-ter region, would also provide supportive information for the diagnosis of MMD among East Asian population, although the exact function of *RNF213* is still undetermined[9,22].

REVASCULARIZATION SURGERY FOR HEMORRHAGIC MMD

Concept of revascularization surgery

Concept of surgical revascularization for MMD includes both microsurgical reconstruction by STA-MCA bypass and the consolidation for future vasculogenesis by indirect pial synangiosis such as encephalo-duro-myo-synangiosis (EDMS) and encephalo-duro-arterio-synangiosis[11,18]. Both procedures attempt to convert the vascular supply for the brain from IC system to the EC system. In hemorrhagic MMD patients, combined revascularization procedure could complement 'IC-EC conversion system', ameliorate the hemodynamic stress to the inadequate collateral anastomosis at the base of the brain, and thus reduce the risk of re-bleeding from the affected vessels[10,11].

Japan Adult Moyamoya (JAM) trial and guideline recommendation

Direct revascularization surgery such as STA-MCA bypass is established as an effective procedure for the MMD patients with ischemic symptoms, providing long-term favorable outcomes[18]. In fact, the most recent guideline for MMD in Japan recommends direct revascularization surgery for the patients with MMD manifesting as cerebral ischemic symptoms (recommendation grade B)[30,36]. Regarding hemorrhagic-onset patients, there had been a controversy whether surgical revascularization has potential role for reducing the risk of re-bleeding. The JAM trial was a unique randomized controlled trial, which examined the efficacy of direct EC-IC bypass for hemorrhagic MMD[28]. The inclusion criteria of JAM trial included all of the following items. 1) Adult (aged from 16 to 65 years old), 2) timing of bilateral revascularization within 1 to 12 months after the onset, 3) independent activity of daily living (modified Rankin Scale of 0 to 2), and 4) absence of major brain damage. The 80 patients were enrolled and randomized to non-surgical and surgical group who underwent bilateral direct EC-IC bypass. The result showed that the annual risk of re-bleeding was 2.7% in surgical group, and was significantly lower than that in non-surgical group (7.6%/year, p=0.042), although the result represented marginal significance[28]. Then pre-specified subgroup analysis of the JAM trial further indicated that patients with posterior hemorrhage demonstrated a much higher re-bleeding rate (17.1% per year) compared to those with anterior hemorrhage, and EC-IC bypass significantly reduced the risk of re-bleeding in patients with posterior hemorrhage (p=0.001)[34]. Based on these observations, the most recent guideline for MMD recommends direct revascularization surgery for hemorrhagic MMD patients with posterior hemorrhage (grade B)[36].

OUTCOME OF REVASCULARIZATION SURGERY FOR MMD PATIENTS SATISFYING JAM CRITERIA

Based on the JAM criteria, we attempted revascularization surgery for the hemorrhagic MMD patients since 2014, in principal for the affected hemispheres with posterior hemorrhage. Surgical indication for hemorrhagic MMD in our institute is specified in Table 1. Among 172 consecutive revascularization surgeries performed from 2014 to 2018 by single surgeon (M.F.), 16 patients with hemorrhagic MMD aged from 22 to 65 (mean, 39.5 years old) underwent STA-MCA bypass with EDMS for 18 hemispheres. The sites of the hemorrhage at the initial onset were para-ventricle area in nine, temporal lobe in four, thalamus in two, and frontal lobe (subarachnoid hemorrhage) in one patient. The sites of the anastomosis were M4 segment of frontal lobe in 14, parietal lobe in three, and temporal lobe in one patient. There was no surgical complication including peri-operative cerebral infarction and cerebral hyperperfusion syndrome in 18 consecutive surgeries. None of the 16 patients developed re-bleeding in the hemisphere operated on during the follow-up period of 22.4 months. These results indicated that direct revascularization surgery for hemorrhagic MMD patients satisfying JAM criteria is a safe and effective management, although further evaluation with long-term follow-up in necessary to validate this strategy. Representative case of a 45-year-old woman with repeated hemorrhage in the bilateral hemispheres had been conservatively followed up in our institute. In light of the posterior location of the hemorrhage on the left hemisphere (Fig. 1), she underwent left STA-MCA bypass with EDMS without complication. The stump of STA was anastomosed to the M4 segment of left MCA with the temporary occlusion time of 21 minutes (Fig. 2). Post-operative MR angiography demonstrated STA-MCA bypass with thick high signal intensity, and cerebral blood flow (CBF) was normalized after surgery (Fig. 3).

Table 1. Surgical indication for hemorrhagic Moyamoya disease

1. Adult (16 to 65 years old)
2. Within 1 year after hemorrhage (1–12 months)
3. Independent ADL (mRS 0–2)
4. Absence of major brain damage
5. Posterior hemorrhage

ADL : activity of daily living, mRS : modified Rankin Scale

MECHANISM UNDERLYING HEMORRHAGIC PRESENTATION IN MMD

Angiographic characteristics of MMD patients with posterior hemorrhage

Since the first supplemental study of JAM trial indicated the

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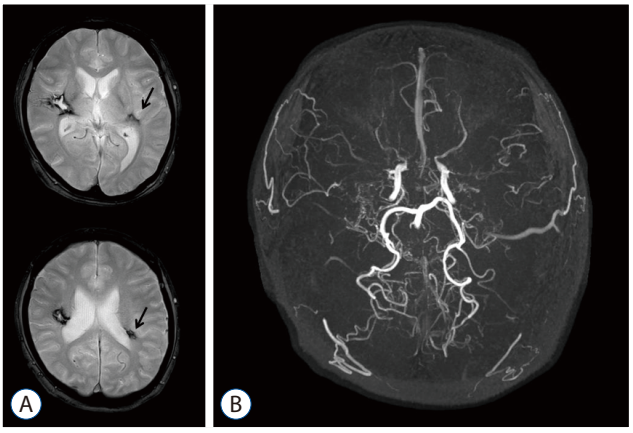

Fig. 1. A : Representative finding of T2*-weighted magnetic resonance (MR) imaging of a 45-year old woman with hemorrhagic MMD. Among the multiple hemorrhages, posterior hemorrhage was evident on the left hemisphere (arrows). B : MR angiography demonstrating terminal internal carotid artery stenosis and abnormal vascular network formation bilaterally.

extremely high annual re-bleeding rates in MMD patients with posterior hemorrhage[34], it was important to understand the characteristic angiographic pattern of this patient population. To address this critical issue, JAM trial group attempted comprehensive analysis of the angiographic findings in hemorrhagic MMD patients who were enrolled to JAM trial. They focused on the abnormal collaterals at the base of the brain, and classified them into three types : lenticulostriate anastomosis, thalamic anastomosis, and choroidal anastomosis[15]. Then the development of each collateral anastomosis was compared between MMD patients with anterior hemorrhage and those with posterior hemorrhage. The results showed that choroidal anastomosis was developed in 35 of 75 hemorrhagic hemispheres of 75 patients (46.7%). The development of choroidal anastomosis, as characterized by dilatation and extension of anterior choroidal artery beyond the level of lateral ventricle, as well as the PCA involvement were significantly associated with posterior hemorrhage, suggesting that choroi-

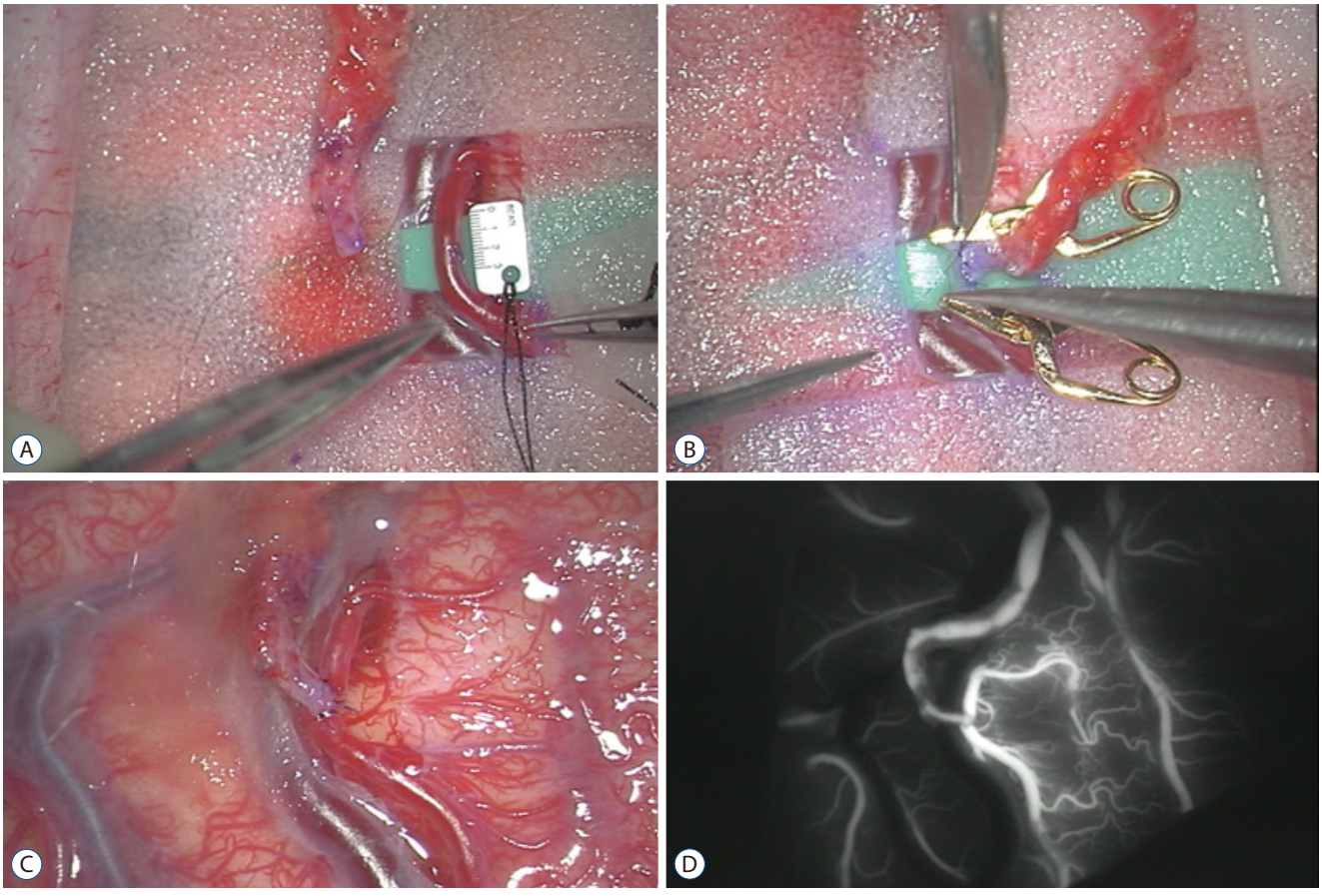

Fig. 2. Intra-operative view of microsurgical revascularization. Surgical view before (A), during (B), and after left superficial temporal artery-middle cerebral artery bypass (C and D). Indocyanine green video-angiography demonstrated apparently patent bypass with favorable distribution of bypass flow (D).

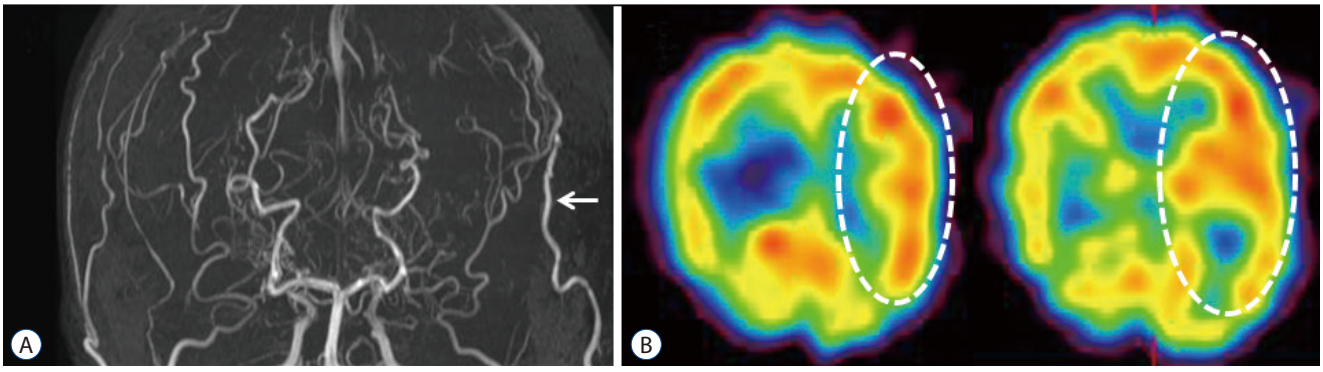

Fig. 3. A : Postoperative MR angiography demonstrating STA-MCA bypass as thick high signal intensity (arrow). B : N-isopropyl-p-[^{123}I] iodpamphetamine single-photon emission computed tomography seven days after left STA-MCA bypass demonstrating marked improvement in cerebral blood flow on the hemisphere operated on (dotted circles). STA-MCA : superficial temporal artery-middle cerebral artery.

dal anastomosis might be considered a potential source of posterior hemorrhage at high risk of re-bleeding[13]. In fact, subsequent supplemental analysis of a non-surgical cohort in the JAM trial showed that the re-bleeding rate was as high as 13.1% per year in the choroidal collateral-positive group as compared with 1.3% in the choroidal collateral-negative group (p=0.008)[14].

Intrinsic angio-architecture in hemorrhagic MMD patients

Before JAM trial, it has been reported that dilatation and/or extension of choroidal artery could be one of the characteristic angiographic findings of hemorrhagic MMD. Irikura et al.[20] reported the high prevalence of choroidal artery dilatation in hemorrhagic MMD patients by their comparative angiographic study between hemorrhagic and ischemic MMD patients. Morioka and colleagues[29] further attempted a comparative angiographic study in a larger series including 37 ischemic and 70 hemorrhagic MMD patients, and found a significant association between hemorrhagic manifestation with dilatation and abnormal branching of anterior choroidal artery. In fact, more recent high resolution MR imaging studies suggested that these collateral vessels were the source of the hemorrhage[15]. Based on these observations, JAM trial group attempted a case-control study which compared the data set of the JAM trial with the angiographic data of the adult MMD patients presenting with ischemia. As a result, hemorrhagic MMD patients showed a significantly higher proportion of choroidal anastomosis (<0.001) and thalamic anastomosis (p=0.043) compared to ischemic MMD patients[1]. The result also showed that Suzuki's angiographic staging was significantly higher in hemorrhagic MMD patients than that in the ischemic-onset patients (p<0.038). These results indicated that the characteristic pattern of abnormal vascular anastomosis at the base of the brain was apparently distinct between each onset-type of MMD[1]. Angiographic characteristics associated with hemorrhage in MMD are summarized in Table 2.

Table 2. Angiographic characteristics associated with hemorrhage in Moyamoya disease

1. Hemorrhagic presentation
1) Development of thalamic and/or choroidal collaterals
2) Higher Suzuki's angiographic staging
2. Posterior hemorrhage
1) Development of choroidal collateral
2) Posterior cerebral artery involvement

ADL : activity of daily living, mRS : modified Rankin Scale

SURGICAL COMPLICATIONS AND PERIOPERATIVE MANAGEMENT

Potential complications of surgical revascularization for MMD

Surgical complications of MMD include peri-operative cerebral ischemia and cerebral hyperperfusion syndrome[3,5,7,18,24]. Perioperative cerebral ischemia could be caused by at least three distinct mechanisms; 'watershed shift phenomenon'[17,37], thrombo-embolism at the site of the anastomosis[7], and mechanical compression of the brain surface by swollen temporal

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muscle used for indirect bypass procedure[4]. Among them, 'watershed shift' is a characteristic pathophysiological phenomenon in MMD patients, which is an intrinsic hemodynamic ischemia at the adjacent cortex to the STA-MCA bypass for MMD[17,37]. Retrograde blood supply from STA-MCA bypass may interfere with the anterograde blood flow from proximal MCA, and thus result in the temporary decrease in CBF at the cortex supplied by the adjacent branch of MCA[17]. To avoid ischemic complications, it is essential to attempt proper perioperative hydration, hemoglobin concentration maintenance, and routine use of anti-platelet agent[30,36]. It is important to differentiate these distinct pathologies by CBF measurement and MR imaging/angiography in the acute stage for the accurate diagnosis and prompt perioperative management[6,36].

Besides peri-operative cerebral ischemia, rapid focal increase in CBF at the site of the anastomosis could result in focal hyperemia associated with vasogenic edema and/or hemorrhagic conversion in MMD[3,5,7,8]. Now it is well known that cerebral hyperperfusion syndrome is one of the most serious complications of revascularization surgery for MMD, especially in adult patients[3,5,7,24,30,36]. The incidence of cerebral hyperperfusion syndrome after STA-MCA bypass was reported to be significantly higher in MMD patients than that in patients with atherosclerotic occlusive cerebrovascular diseases[7]. Because the symptoms due to hyperperfusion become evident between 2 to 6 days after surgery in most cases, we recommend routine CBF study within 24 hours after surgery[3,7]. Prognosis of the focal neurological deficit due to hyperperfusion is generally favorable, but it could lead to delayed intracerebral hemorrhage and/or subarachnoid hemorrhage in a rare occasion[3,7,8]. The risk factors for hyperperfusion syndrome in MMD were reported as follows : adult-onset[5,38], increased preoperative cerebral blood volume[38], hemorrhagic-onset[5], operation on the dominant hemisphere[6,19], and smaller diameter of the recipient artery[6]. Therefore, it is particularly important to manage hemorrhagic MMD promptly to avoid deleterious effect of hyperperfusion during the peri-operative period.

Peri-operative management

Concept of the peri-operative management for MMD is to afford favorable 'IC-EC conversion' without causing deleterious impact to the affected hemisphere[10]. Blood pressure lowering definitely resolve cerebral hyperperfusion[3,5,7], while the excessive blood pressure lowering may increase the risk for perioperative infarction at the remote area from STA-MCA bypass[6,36]. We have shown that prophylactic blood pressure control between 110 to 130 mmHg of the systolic blood pressure in the awake state significantly reduced the incidence of cerebral hyperperfusion syndrome after STA-MCA bypass in MMD patients[2]. To further ameliorate the reperfusion injury to the affected brain, minocycline hydrochloride and edaravone (a free radical scavenger) were reported to reduce the risk of hyperperfusion syndrome in MMD patients[6,39]. We introduced minocycline hydrochloride, a neuro-protective antibiotic, to block the deleterious inflammatory cascade caused by the activation of matrix metalloproteinase-9 (MMP-9) to prevent both hyperperfusion syndrome and cerebral ischemia at the remote area[6]. This strategy is based on the previous findings that serum level of MMP-9, a type IV collagenase participating in blood brain barrier disruption in cerebrovascular diseases, was significantly elevated in MMD patients compared to the healthy control[12,23]. By the prophylactic blood pressure control combined with minocycline hydrochloride administration, the incidence of cerebral hyperperfusion syndrome was significantly reduced without increasing the ischemic complication[6]. Nevertheless, concomitant manifestation of local cerebral hyperperfusion with cerebral ischemia at the remote area, such as contralateral hemisphere and/or adjacent cortex affected by 'watershed shift phenomenon', is still one of the major issues to avoid peri-operative neurological deterioration[37]. Furthermore, most recent reports suggested the complexity of peri-operative pathology after surgical revascularization for MMD such as paradoxical association of local vasogenic edema with global cerebral hypoperfusion and/or without local hyperperfusion, thus further investigation for elucidating the exact mechanism of peri-operative pathology is needed in the future study[32,35].

CONCLUSION

Recent evidence suggests that surgical revascularization such as STA-MCA bypass could powerfully reduce the risk of re-bleeding in MMD patients with posterior hemorrhage, who potentially have extremely high annual re-bleeding rate (17% per year). Outcome of surgical revascularization for hemor-

rhagic MMD is favorable, while prompt perioperative management is essential to avoid surgical complications including cerebral hyperperfusion syndrome.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

This type of study does not require informed consent.

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