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Review Article

Hemorrhage and risk of further hemorrhagic strokes following cerebral revascularization in Moyamoya disease: A review of the literature

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Abstract

Background: We sought to review the current literature with regards to future risks of hemorrhage following cerebral revascularization in Moyamoya disease (MMD).

Methods: We performed a comprehensive literature review using PubMed to inspect the available data on the risk of hemorrhage after revascularization in MMD.

Results: In this review, we identify the risk factors associated with hemorrhage in MMD both before and after cerebral revascularization. We included proposed pathophysiology of the hemorrhagic risk, role of the type of bypass performed, treatment options, and future needs for investigation.

Conclusions: The published cases and series of MMD treatment do show a risk of hemorrhage after treatment with either direct or indirect bypass both in the immediate as well as long-term future. While there are no discernible patterns in the rate of these hemorrhages, there is Class III evidence for the predictive effect of multiple microbleeds on preoperative imaging. Also, whereas revascularization, both direct and indirect, has been shown to reduce ischemic complications from MMD, there is not an association with the risk of hemorrhage after the procedure. Further studies need to be performed to help evaluate what the risk factors are and how to counsel patients as to the long-term outlook of this disease process.

Key Words: Angioarchitecture, cerebral hemorrhage, cerebral perfusion, moyamoya

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BACKGROUND, PRESENTATION AND EPIDEMIOLOGY

Moyamoya disease (MMD) is a rare, chronic, and progressive cerebrovascular disorder characterized by stenosis and occlusion of the distal carotid and proximal middle and anterior cerebral arteries, accompanied by the development of networks of small collateral vessels. The disease was first recognized in a Japanese case report by Takeuchi and Shimizu in 1957,[41] described pathologically by Kudo as the spontaneous occlusion of the circle of Willis in 1968,[23] and described as moyamoya (something hazy like a puff of smoke) based on the angiographic appearance of the collateral vessels by Suzuki and Takaku in 1969.[39] While the precise etiology remains unknown, to fulfill the most

commonly accepted diagnostic criteria for spontaneous MMD, arterial stenosis or occlusion and associated abnormal vascular networks must be bilateral and not the result of a known inciting disease or exposure.[7] Unilateral disease or that associated with other conditions such as Down's syndrome, neurofibromatosis, cranial radiation, or sickle cell anemia is classified as moyamoya syndrome. MMD presentations occur in a bimodal age distribution, with a peak in childhood around age 5 and a peak in adulthood around age 40.[42] Findings in Japanese populations suggest that childhood MMD usually presents with ischemic symptoms, with less than 10% rate of hemorrhage, while adults have a much higher rate of hemorrhagic presentation, between 30% and 60%.[35,38] While it is unclear whether adult MMD represents a progression from the juvenile form, one theory suggests that the bleeding in adults occurs from breakdown of collateral vessels formed at a younger age.[15] The incidence of the disease in Japan is between 0.54–0.94/100000/year.[1,42] Outside of Japan, the incidence is about one-tenth that seen in the Japanese population.[2,3,22,34] The phenotype also seems to be different, as the rate of hemorrhage in adults is lower, between 14% and 22%, with ischemic symptoms being more common on presentation, while the rate of hemorrhage in children remains rare.[12,18,32]

NATURAL HISTORY AND DIAGNOSIS

The initial diagnostic evaluation of patients usually consists of computed tomography (CT) and magnetic resonance (MR) imaging of the brain to identify areas of infarction or hemorrhage. CT or MR angiography can also reveal the intracranial stenosis of the internal carotid arteries and development of collateral circulation, and in some situations may be sufficient to make the diagnosis. However, formal catheter angiography provides definitive diagnosis of MMD and allows classification of disease severity based on the six stage scale of internal carotid artery stenosis and collateral vessel formation described by Suzuki and Takaku.[39] It also allows assessment of external carotid artery supply to the brain through collateral networks, and evaluation of potential donor vessels for revascularization procedures. Numerous tests have been developed to assess cerebral perfusion and hemodynamics in patients with MMD and can serve as a useful guide for following disease progression and the effect of treatment. These tests include transcranial Doppler (with CO_2 reactivity), xenon enhanced CT and single photon emission CT (with acetazolamide challenge), positron emission tomography, and CT or MR perfusion imaging.[32] There is no currently accepted gold standard for cerebral hemodynamic assessment, and the choice of test is usually institutionally dependent based on available resources.

The natural history of MMD can be variable. The relative rarity of the disease and differences in presentation between age groups and ethnic backgrounds make it challenging to study, but evidence suggests it is progressive over time.[24,29] From diagnosis, most patients exhibit symptomatic progression within 5 years and the outcome without treatment remains poor. However, a large meta-analysis examining primarily pediatric patients found that symptomatic progression could be halted in the vast majority of this population following revascularization procedures.[8] Another study demonstrated that the strongest predictor of outcomes in MMD patients is the neurologic status at the time of treatment, suggesting that early recognition and intervention may be of benefit.[33] Despite this, specific indications for treatment, and indeed the optimal treatment method, have not been established. The strongest guidelines come from the Japanese Research Committee on Spontaneous Occlusion of the Circle of Willis that state in cases with both repeated clinical symptoms due to apparent cerebral ischemia, and a decreased regional cerebral blood flow, vascular response and perfusion reserve, based on the findings of a cerebral circulation and metabolism study, bypass surgery is indicated.[7] In cases of hemorrhagic presentation, initial treatment is symptomatic and aimed at resuscitation, and may include ventriculostomy or hematoma evacuation, and the role of revascularization therapy is unclear.

TREATMENT OPTIONS

There are currently no treatments that slow down or reverse the underlying pathological process in MMD, and therapies are directed at improving blood flow to vulnerable regions of the brain with the aim of reducing ischemic symptoms and strokes. Treatment options include observation, medical management, and surgery. Observation is typically only employed in asymptomatic, incidentally discovered cases, and as disease progression is common, development of symptoms warrants further investigations and management. Medical therapies include antiplatelet or anticoagulant agents to reduce emboli originating from the sites of intracranial stenosis, calcium channel blockers to reduce MMD-associated headache and transient ischemic attacks (TIA), and interventions to increase blood pressure and oxygenation and reduce cerebral vasoconstriction in an attempt to prevent ischemia.[7,32,43] Surgical treatment of MMD consists of revascularization procedures intended to improve the blood flow from the external to internal circulation and is divided into two main categories, direct and indirect.

TYPES OF REVASCULARIZATION

Indirect revascularization techniques aim to improve

cerebral blood flow in MMD by augmenting the natural process of collateral vessel formation by procedures that assist in the process of neovascularization. Indirect revascularization procedures are notable for their wide variability in the technique, with a recent review identifying 12 different variations used.[31] The most commonly employed technique is encephaloduroarteriosynangiosis (EDAS), followed by encephalomyosynangiosis (EMS) and multiple burr holes. EDAS involves dissection of an external carotid artery (ECA) vessel, usually the superficial temporal artery (STA), and a cuff of surrounding fascia, which is then sutured into a dural opening under a craniotomy flap to provide access to the surface of the brain for collateral vessel formation.[25] EMS similarly involves opening the dura, but the donor blood supply comes from a vascularised section of temporalis muscle which is placed over the brain to allow collateral angiogenesis to occur.[16] The multiple burr hole procedure was developed after the discovery of neovascularisation around burr holes performed for ventriculostomy in MMD patients, and expanded to locations all over the cranium; it has the advantage of being the least technically demanding.[5] All indirect revascularization techniques rely on the angiogenic properties of the underlying ischemic brain to promote the development of collateral circulation from the donor sites over time. A theoretical advantage of this gradual process is that the maximally dilated and often abnormal cerebral vessels are not exposed to a sudden dramatic increase in blood flow, which may help reduce the risk of reperfusion hemorrhage. A limitation of this technique is that acutely ischemic brain is not immediately revascularized, and temporizing measures to promote cerebral perfusion may be needed to prevent strokes while the collateral vessels develop. Indirect surgical procedures have been used with much success, especially in the pediatric age group, where small recipient vessels would make direct bypass challenging.[4,8,33] In North American, Chinese and some Japanese adults presenting primarily with ischemic symptoms, indirect bypass by EDAS has also been found to be very effective at restoring blood flow and preventing infarction.[3,13,37]

Direct revascularization procedures involve creating an anastomosis from an ECA branch, usually the STA, to a cortical artery, most often the middle cerebral artery (MCA).[11] An advantage of this technique is that it immediately provides augmented blood flow to areas of hypoperfusion identified on the preoperative workup, and can thus rapidly reverse ischemic symptoms.[30] For this reason, it is considered by many authors to be the first choice of the revascularization procedure for MMD.[13,17] However, it has several drawbacks; it is more technically demanding than indirect techniques and may not be feasible in all patients, especially children, due to limitations in donor or recipient artery characteristics. In addition, the sudden introduction of high flow blood to abnormal vessels has been considered a potential mechanism for postoperative reperfusion hemorrhages seen in a small number of patients. Most follow-up studies demonstrate a marked improvement in cerebral perfusion characteristics and angiographic imaging of collateral vessel supply in patients treated with direct bypass, and a significant improvement of ischemic symptoms in both pediatric and adult patients.[10,26] No trial has ever compared the efficacy of direct versus indirect revascularization for MMD, and in many reports, both types of the procedure are used together; the superiority of one treatment method has not been demonstrated.[36]

HEMORRHAGE RISKS

Hemmorhage on presentation is a common finding in Japanese adults with MMD, and in up to 1/5 of adults in the rest of the world, and is a major risk for morbidity and mortality.[35,42] The natural history of this form of MMD is poor, with only 45% of patients making a good recovery after their first presentation, an annual rebleeding rate of 7% and only 21% of patients making a good recovery after subsequent events.[21] Mortality after an initial hemorrhage was 7% and increased to 29% after rebleeding.[21] The most common location of hemorrhage is periventricular, in the basal ganglia and thalamus, and intraventricular bleeding alone or in combination with intracerebral hemorrhage is often seen; subarachnoid hemorrhage is rare, but may be seen over the cerebral convexities.[14] The precise pathophysiology that leads to hemorrhage in MMD is still not fully understood, but major underlying features that have been postulated include development of microaneurysms on dilated perforating arteries, especially in the periventricular region, and fibrinoid necrosis of the arterial wall in the basal ganglia.[44] Pathological studies of collateral vessels demonstrate signs of stress from increased flow, including break down of the internal elastic lamina and thinning of the media, predisposing to microaneurysm formation.[40] More typical saccular berry aneurysms have also been described arising from abnormal moyamoya vessels, but are thought to be a rare source of hemorrhagic presentation; if present, these aneurysms should be treated by surgical or endovascular methods to prevent rebleeding.[15] Long-term ischemia also seems to play a role in making anastomotic arteries vulnerable, and chronic maximal dilation has been implicated in predisposing these vessels to rupture when exposed to periods of hypertension that may be tolerated by normal arteries.[9] In patients with recurrent episodes of hemorrhage, two patterns of rebleeding have been identified.[15] The first is rebleeding at the same site as the original hemorrhage, which usually occurs within 2 months of the initial event and is thought to be due to small aneurysms or pseudoaneurysms of the feeding vessels. The second pattern of rebleeding is at a site in the brain remote from the initial hemorrhage, occurs more than 2 months and often many years after the initial event, and is thought to be related to altered

hemodynamic forces on the abnormal collateral vessels. Clearly, an effective treatment paradigm must identify and remove the major causative factor, either the small aneurysms or the hemodynamic stress on collateral vessels, in order to prevent rebleeding.

PREDICTORS OF HEMORRHAGE

Attempts have been made to identify risk factors for hemorrhage based on imaging characteristics during the workup of MMD. One such marker is the presence of multiple microbleeds on gradient-echo T2* weighted MRI scan. Microbleeds are asymptomatic, but have been regarded as a marker of microvascular vulnerability, and their incidence has been found to be higher in patients with MMD (40–50%) compared with healthy subjects (3–7%), and similar in incidence to patients with hypertension (56%), another disease associated with angiopathy.[19] Their appearance has also been identified as a risk factor for cerebral hemorrhage in conditions including postischemic stroke, postintra arterial thrombolytic therapy, and cerebral amyloid angiopathy. A prospective study of patients with MMD imaged with MRI scans found that the presence of multiple microbleeds was an independent risk factor for subsequent hemorrhage, and that hemorrhages tended to occur at the sites of previously identified microbleeds.[20] While not powered to look at the effect of bypass on development of new microbleeds, the authors reported that only 1 of 13 patients undergoing MRI within 3 months following a revascularization procedure developed a new microbleed. While the optimal treatment to prevent symptomatic bleeding in the setting of multiple microbleeds remains unclear, careful observation and ongoing surveillance of these patients are warranted.

A second imaging marker that has been suggested as a predictor for hemorrhage is dilatation and abnormal branching of the anterior choroidal and posterior communicating arteries. A study of 107 MMD patients that identified abnormal dilatation and branching of the anterior choroidal and posterior communicating arteries yielded a 86% specificity and 84% sensitivity in predicting hemorrhagic events.[28] Collaterals from these two arteries frequently supply the basal ganglia, thalamus, and periventricular areas, the most common sites of bleeding in MMD. It is believed that when the disease process affects these normally small vessels by greatly increasing demand and maximally dilating them, the risk of hemorrhage is greatly increased.

ROLE OF REVASCULARIZATION SURGERY IN PREVENTING RECURRENT HEMORRHAGE

In contrast to the clearly demonstrated benefit of both direct and indirect revascularization procedures in preventing further symptoms in patients presenting with ischemic attacks from MMD, the best treatment for preventing recurrent hemorrhage remains unclear. There is considerable debate in the literature, and results between groups have varied widely in their reports of efficacy, from great benefit to no improvement in rebleeding rate following revascularization. The small sample sizes, variations in the surgical technique and lack of consistent follow-up and outcomes measures make comparisons between the reports difficult. For example, in a nationwide survey of Japan in 1995, Ikezaki *et al*. found no difference in rebleeding rates (16.2% vs. 16.8%) between conservative management and bypass procedures for hemorrhagic MMD, although the small number of cases prevented distinguishing direct from indirect revascularization.[14] Another questionnaire based study in Japan reported a trend towards lower rebleeding following bypass surgery, but the difference was not statistically significant (28% vs. 19%, conservative vs. bypass).[6] This was also the case in another small series with long-term follow-up, in which one patient in the bypass group and five patients in the conservative management group suffered rebleeding, a nonstatistically significant difference.[45] In a study of STA–MCA bypass for hemorrhagic MMD, Okada *et al*. found that despite significant improvements in cerebral blood flow and vascular resistance, and a 60% reduction in moyamoya vessels after surgery, 20% of patients suffered repeat hemorrhage in the long-term follow-up.[30] This is similar to the one of five patients that suffered repeat bleeding 2 months after successful STA–MCA bypass with angiographic improvement in collateral vessels in a series from the North Western U.S.[26] Why this rebleeding occurs despite apparent resolution of abnormal collaterals following bypass surgery is unclear, although persistence of microaneurysms and damaged vessel walls, loss of cerebral autoregulation, and underlying microangiopathy with microbleeds are all possible etiologies. In contrast to these studies, some authors believe revascularization is an effective treatment in hemorrhagic MMD. Houkin *et al*. reported a rate of 14.3% recurrent hemorrhage following combined direct and indirect revascularization and declared this a significant improvement over historical controls, who had recurrent bleeding in the range of 33%.[13] These authors argue that reducing the hemodynamic stress on abnormal collaterals is an important facet in hemorrhagic MMD treatment and is best accomplished with direct bypass, and while some recurrent bleeding may occur, it is an improvement over the natural history of the disease. Echoing the importance of direct revascularization, a small study from Japan comparing STA–MCA bypass with EDAS and conservative therapy found no instances of recurrent hemorrhage in the direct bypass group but two rebleeds in each of the other

groups.[17]

Given the uncertainty of best management for hemorrhagic MMD, more research is clearly needed. This includes ongoing basic science and pathologic examinations to better elucidate the cause of bleeding in this disease, and further understanding the prognostic significance of arterial dilatation and the appearance of microbleeds on MRI scanning. However, in order to best guide clinical decision making and provide accurate counselling to patients with this disease, a multicenter, randomized controlled trial with clearly defined inclusion and exclusion criteria, evaluation methods, treatment protocols, and endpoints is required. To this end, the Japan Adult Moyamoya Trial is under way, enrolling patients with hemorrhagic MMD, stabilized at least one month from presentation, to be randomized to best medical management, or best medical management and direct bypass, with the addition of indirect bypass at the surgeon's discretion.[27] It is hoped that this trial will provide strong guidance for the treatment of hemorrhagic MMD, but further worldwide studies may be prudent, given the apparent differences observed between expression of MMD in Japan and the rest of the world.

CONCLUSIONS

The published cases and series of MMD treatment do show a risk of hemorrhage after treatment with either direct or indirect bypass both in the immediate as well as long-term future. While there are no discernible patterns in the rate of these hemorrhages, there is Class III evidence for the predictive effect of multiple microbleeds on pre-operative imaging. Also, whereas revascularization, both direct and indirect, has been shown to reduce ischemic complications from MMD, there is not an association with the risk of hemorrhage after the procedure. Further studies need to be performed to help evaluate what the risk factors are and how to counsel patients as to the long-term outlook of this disease process.

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Commentary

The authors are congratulated on the extensive and nice review in regards to future risk of hemorrhage following cerebral revascularization in Moyamoya disease. They concluded that the published cases and series of Moyamoya disease treatment showed a risk of hemorrhage after treatment with either direct or indirect bypass both in the immediate as well as in the long-term future. While there are no discernible patterns in the rate of these hemorrhages, there is Class III evidence for the predictive effect of multiple microbleeds on preoperative imaging.

As the authors mentioned, it has been clearly demonstrated benefit of both direct and indirect revascularization procedures in preventing further symptoms in patients presenting with ischemic attacks from Moyamoya disease; however, the best treatment for preventing recurrent hemorrhage remains unclear. In adults, hemorrhagic onset is predominant and prevention is therefore important. The rationale for the revascularization to prevent further hemorrhagic event is to reduce the hemodynamic stress to the fragile moyamoya vessels by re-distributing or normalizing the circulation after vascular reconstruction. In Japan as we have many patients with Moyamoya disease,[3] there have been several papers to see the protective effect of the revascularization as the authors already cited;[1,2,5,7] however, the effect was not significantly demonstrated. There is also a case report of re-hemorrhage after vascular reconstruction.[6] The Japan Adult Moyamoya Trial (JAM Trial), multicenter, prospective randomized trial, has been conducted,[4] to clarify the protective effect of direct STA–MCA anastomosis in patients of 16- to 65 years old, suffering intracerebral hemorrhage within the previous one year. In the study, patients are to be followed up for 5 years. Although the study is not finalized, when the result comes it will give us strong guidance for the treatment of patients with hemorrhagic Moyamoya disease.

Considering the fact that the incidence of Moyamoya disease varies among the races, other prospective studies may also be needed in countries other than Japan.

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