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COMMENTS

Pathology of moyamoya disease (MMD) shows intimal thickening owing to cellular and extracellular matrix proliferation. The internal elastic lamina is fragmented and seems to be separated into layers, there may be lipid deposits in the intima, and the tunica media smooth muscle is decreased. These changes are observed at the end stage of the disease. Of course, they must be the cause of the angiographic narrowing observed, but the exact makeup of the changes over time and their etiology are unknown. Studies such as this provide only very small pieces of the puzzle. Whether or not the changes observed are a cause of the disease or consequences observed at the end stages cannot be determined from data such as this. This is a difficult problem for diseases such as MMD because there is no animal model, patients are rare, and it is impossible to obtain biochemical and molecular information over the course of the disease. Some of the methods could be improved by using additional immunohistochemical controls and stereological counting methods, but this is a waste of time because it will not change the results or add any important new information beyond that already presented.

R. Loch Macdonald
Chicago, Illinois

Takagi et al. studied potential pathophysiological events leading to intimal hyperplasia of the middle cerebral artery (MCA) of patients with MMD. The authors immunohistochemically analyzed MCA specimens in 12 MMD patients undergoing direct revascularization for the expression of hypoxia-inducible factor-1 HIF-1α, endoglin, vascular endothelial growth factor (VEGF), and transforming growth factor-β and compared these with MCA samples from 12 control subjects. They found that MCA specimens from MMD patients had marked intimal hyperplasia compared with those from the control patients. Endothelial expression of HIF-1α and endoglin was higher in samples from MMD patients and the immunoreactive cells were colocalized with transforming growth factor-β. There was, however, no VEGF immunoreactivity in samples from MMD patients. They conclude that intimal hyperplasia in MMD patients occurred through the HIF-1α and endoglin pathway.

HIF-1 is a well-known heterodimeric transcriptional factor consisting of an inducible HIF-1α subunit and a constitutive HIF-1β subunit. It has been shown that HIF-1α expression is exponentially induced as the oxygen concentration of cells decreases. HIF-1 targets genes leading to the transcriptional activation of several dozen genes such as erythropoietin, glucose transporter 1, glycolytic enzymes (aldolase A and enolase 1), and VEGF. Recent experimental work has shown that intimal hyperplasia can be induced by VEGF, and it is known that VEGF is a potent angiogenic factor. In rat models of chronic cerebral hypoperfusion, administration of VEGF combined with vasoreconstructive surgery significantly increased capillary density in the brain. In the current report, the investigators did not find expression of VEGF despite elevated HIF-1. A recent neuropathological case report also failed to demonstrate VEGF immunoreactivity in MMD vessels. We found that serum levels of the angiogenic proteins VEGF, basic fibroblast growth factor, and metalloproteinase were significantly elevated in patients with MMD. There could be several reasons for that discrepancy. First, it is conceivable that HIF-1 upregulates the expression of soluble VEGF. This diffusible signal induces neovascularization in areas at risk. Secondly, it is possible that VEGF is not expressed in well developed and stable MMD vessels. The same would be true for more distal MCA branches typically harvested for direct vascularization. Soluble VEGF, however, could be responsible for intimal hyperplasia in the intracranial circulation of MMD patients. The authors also explored an alternative pathway. Endoglin is a component of TGF-β and was first described as a candidate gene for hereditary hemorrhagic teleangiectasia. It is known to be important in vascular development and remodeling.

The authors are to be congratulated for this extremely novel histological and immunocytochemical study on intracranial arterial samples from MMD patients undergoing surgery. This is an important contribution to the literature, and further studies should be pursued to obtain better insight into molecular mechanisms underlying this debilitating disease.

Raphael Guzman
Gary K. Steinberg
Stanford, California

This study aimed to clarify the pathogenesis of MMD through an immunohistochemical analysis of human MCA samples. The authors compared 12 M4 samples obtained at the time of superficial temporal artery-MCA bypass in MMD patients with those obtained from patients with other causes of MCA or internal carotid occlusion. They report that the MMD samples showed a thicker intima, higher staining for HIF-α in the intima and endothelium, and higher staining for endoglin in the endothelium compared with the controls.

Although the results are interesting and add to the literature, their use in elucidating the mechanism of MMD is limited, owing in part to methodological problems with the study. First, the control patients represent a markedly different population than the MMD patients in that they are an average 18 years older and most of them are the opposite sex. It is possible that these disparities alone could have led to the differences in staining. Furthermore, the methods section mentions that control samples in some experiments were obtained from a 27-year old woman with an arteriovenous malformation. However, this patient is not accounted for in the summary of cases reported in *Table 1*. Secondly, the samples analyzed were from the fourth portion of the MCA. Although obtaining more proximal portions is impractical in humans, these are the portions that are classically implicated in the pathogenesis of MMD. Extrapolating M4 findings to more proximal segments, and thus to the mechanism of the disease, may not be valid.

The authors should be commended for their work on human tissue, an endeavor which is often fraught with challenges. The results of this descriptive study, however, are circumstantial suggestions that do not definitively implicate HIF-1α or endoglin as players in the pathogenesis of MMD. We hope this initial work encourages this group and others to further evaluate the specific pathways that may be involved in the mechanism of this disease.

Lance S. Governale
Robert M. Friedlander
Boston, Massachusetts

Neurol Med Chir (Tokyo) 47, 564~567, 2007

Histological Analysis of Microbleed After Surgical Resection in a Patient With Moyamoya Disease

—Case Report—

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Abstract

A 65-year-old male with moyamoya disease underwent surgical resection of a microbleed simultaneously with revascularization surgery. Histological examination identified several fragile arteries surrounding the microbleed. Microbleeds detected by T_2*-weighted magnetic resonance imaging are considered to be a general marker of vascular vulnerability in cerebral angiopathy with a tendency to bleeding. The microbleeds observed in patients with moyamoya disease probably originate in bleeding from the fragile arteries.

Key words: moyamoya disease, microbleeding, T_2*-weighted magnetic resonance, histopathology, surgical resection

Introduction

Microbleeds are defined as rounded foci of <5 mm diameter, that appear hypointense and distinct from vascular flow voids, leptomeningeal hemosiderosis, or nonhemorrhagic subcortical mineralization.[15] The incidence of cerebral microbleeds detected by gradient-echo T_2*-weighted magnetic resonance (MR) imaging is significantly higher in patients with primary intracerebral hemorrhage,[6,10,16] ischemic stroke,[7,14] Alzheimer disease,[5] and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[1,11] than in healthy individuals.[7,17,18] Microbleeds may be a potential risk factor of subsequent intracranial hemorrhage after ischemic stroke[2,14] and intra-arterial thrombolytic therapy,[8] and are considered to be a general marker of various types of bleeding-prone cerebral angiopathy.[19]

We previously reported the incidence of asymptomatic microbleeds in patients with moyamoya disease[4] as 43–44% regardless of the onset type, which is significantly higher than that in healthy individuals.[9] We defined asymptomatic microbleeds as hypointense foci of <10 mm in size detected by 3T T_2*-weighted MR imaging. Vascular flow voids can be excluded by 3T MR angiography and hemorrhagic mass lesions such as cavernous angiomas by T_1- and T_2-weighterd MR imaging. The definition of microbleeds also excludes hypointense foci located in areas of previous hemorrhage associated with hemorrhagic moyamoya disease.[9] Little is known about the histological character of microbleeds.[3]

We treated a patient with moyamoya disease who underwent surgical resection of a microbleed and discuss the histological properties.

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Case Report

A 65-year-old man had suffered episodes of recurrent transient motor weakness of the bilateral upper extremities in his childhood. He was suspected to have moyamoya disease in 1978 when his daughter was admitted to our institution under this diagnosis. Although the patient had been free from transient ischemic attacks (TIAs) for more than 50 years, intractable asthma attacks began in 2001, which caused recurrence of TIAs. Antiplatelet medication was started but the frequency of TIAs increased. On admission, he suffered from TIAs induced by asthma attacks almost every day.

Annual MR imaging with a 3-tesla unit had been performed on this patient before admission. MR an-

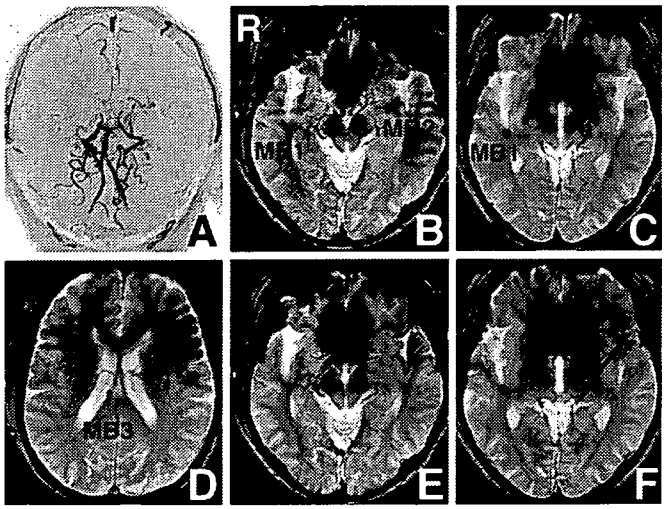

Fig. 1 **A: Magnetic resonance (MR) angiogram in November 2003 demonstrating typical angiographic findings of moyamoya disease. B–D: T_2*-weighted MR images showing three asymptomatic microbleeds in the right temporal operculum (MB1), the left insula (MB2, *arrowhead*), and the right corpus callosum (MB3). E, F: Follow-up T_2*-weighted MR images in November 2004 revealing asymptomatic subarachnoid hemorrhage in the left sylvian cistern (*arrow*), which seemed to be derived from MB2 in the left insula.**

giography demonstrated typical angiographic findings of moyamoya disease in November 2003 (Fig. 1A). T_2*-weighted MR imaging demonstrated three asymptomatic microbleeds in the right temporal operculum (MB1), the left insula (MB2), and the right corpus callosum (MB3) (Fig. 1B–D). Follow-up MR imaging revealed asymptomatic subarachnoid hemorrhage in the left sylvian cistern in November 2004 (Fig. 1E, F), which seemed to be derived from the MB2.

He was admitted to our institution in January 2005. Quantitative iodine-123 N-isopropyl-p-iodoamphetamine single photon emission computed tomography showed severe decreases in bilateral regional cerebral blood flows and cerebrovascular reserves, so surgical revascularization was planned. His daughter had experienced delayed hemorrhage after bypass surgery. One of the microbleeds in this patient showed hemorrhagic manifestation and the microbleed in the right temporal operculum (MB1) was situated near the recipient site of the right superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis. The presence of microbleeds is a risk factor for bleeding after ischemic stroke.[2,12] Accordingly, the patient became very afraid of cerebral hemorrhage after the revascularization surgery. Considering such special factors in this patient, we decided to try surgical resection of the MB1 combined with right STA-MCA anastomosis. Our preoperative explanation of the surgery to the patient emphasized that resection of the microbleed could not definitely reduce the risk of subsequent cerebral hemorrhage.

MB1 was located near the right optic radiation, so was resected through a transsylvian transinsular approach[12,13] under monitoring of the optic radiation using MR tractography-guided navigation (Fig. 2A, B). The microbleed was surrounded by many perforating arteries and frequent bleeding occurred during the operation. After resection of the microbleed, the right parietal STA was anastomosed to the posterior temporal artery in end-to-side fashion.

The postoperative course was uneventful. MR imaging at 1 month after surgery demonstrated removal of MB1 (Fig. 2C). 3T MR tractography obtained at 3 months after surgery demonstrated preservation of the right optic radiation (Fig. 2D). Postoperative angiography showed patency of the bypass. He was discharged from our institution in April 2005 with no neurological deficits including visual field loss. No cerebral hemorrhage had occurred up to January 2007.

Histological imaging of the microbleed revealed encapsulated hematoma containing small vessels (Fig. 3A). Many small vessels were located within the deposition of erythrocytes and the internal elastic lamina of the vessels was clearly visualized (Fig. 3B). Immunostaining with antibodies against human factor VIII and human alpha-smooth muscle actin showed the vessels had thick smooth muscle layers indicating arteries (Fig. 3C, D). Some of the vessels had disrupted internal elastic lamina (Fig. 3E).

Discussion

A previous study found focal deposition of hemosiderin in areas of signal loss on T_2*-weighted images and an old asymptomatic microbleed at the site of the largest area of hypointensity in an autopsy study.[3] The present histological study of microbleed in a patient with moyamoya disease found several arterioles associated with the microbleed, some with disrupted internal elastic lamina. These arterioles easily ruptured during the surgery, which indicated fragile vessels. Therefore, microbleeds associated with moyamoya disease might be produced by rupture of such arterioles.

Whether the presence of microbleeds is a risk

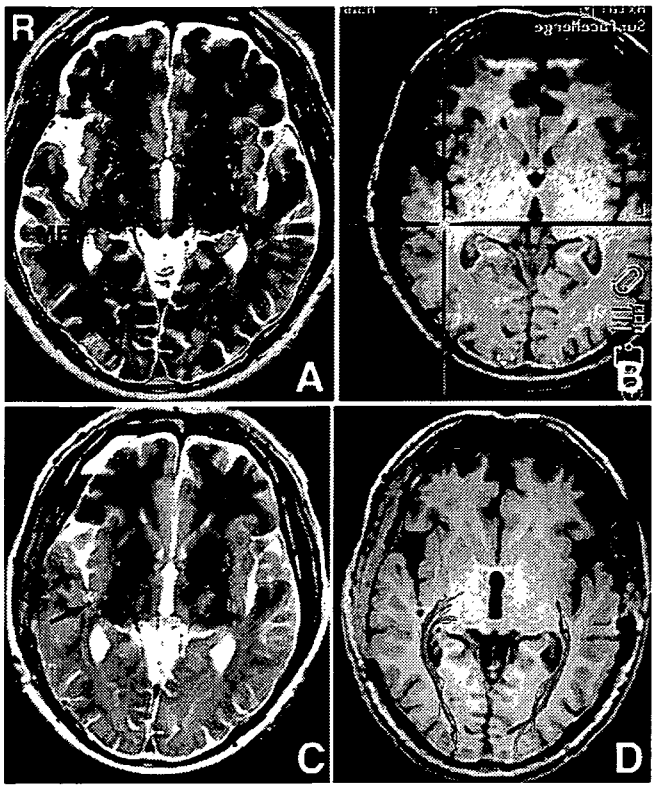

Fig. 2 **A: Preoperative T_2-weighted magnetic resonance (MR) image showing the microbleed in the right temporal operculum (MB1) located near the right optic radiation. B: MB1 was resected under monitoring of the optic radiation using a MR tractography-guided navigation system (blue bundles indicating optic radiation). C: Postoperative T_2-weighted MR image at 1 month after surgery showing removal of MB1 (*arrow*). D: MR tractography image at 3 months after surgery demonstrating preservation of the right optic radiation.**

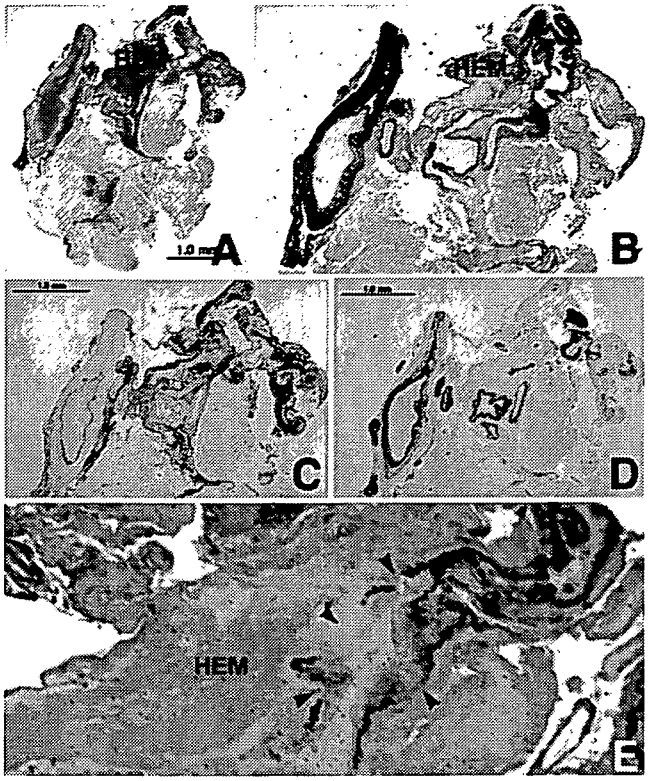

Fig. 3 **A, B: Photomicrographs of the microbleed revealing encapsulated hematoma (HEM) with small vessels (A: hematoxylin-eosin stain, ×20), and many small vessels within the deposition of erythrocytes and clearly visualized internal elastic lamina (B: elastica-van Gieson stain, ×30). C–E: Immunostaining with antibodies against human factor VIII (C: ×25) and human alpha-smooth muscle actin (D: ×25) showing thick smooth muscle layers in these vessels indicating arteries, and some arterioles with disrupted internal elastic lamina (*arrowheads*) (E: elastica-van Gieson stain, × 200).**

factor of cerebral hemorrhage in patients with moyamoya disease remains controversial, and whether extirpation of the microbleeds can reduce the risk of subsequent hemorrhage is also uncertain. We extirpated a microbleed in the present patient because another microbleed showed hemorrhagic manifestation, the target microbleed was situated near the recipient site of bypass surgery, and his daughter exhibited delayed hemorrhage after bypass surgery. Fortunately, the transsylvian transinsular approach combined with MR tractography-guided neuronavigation resulted in safe resection of the microbleed and preservation of the optic radiation. However, this is only an experimental treatment, so future attempts will require approval by the ethical committee.

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Vascular

Effects of intravenous anesthesia with propofol on regional cortical blood flow and intracranial pressure in surgery for moyamoya disease

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Abstract

Background: The aim of this study was to compare the effects of inhalation anesthesia with sevoflurane and intravenous anesthesia with propofol on ICP and rCoBF during revascularization surgery for patients with MMD.

Methods: Between 1999 and 2004, a total of 90 revascularization surgeries were performed on 58 patients. Among them, in 20 consecutive operations on 14 patients, continuous monitoring of ICP was performed with an ICP monitoring probe. Subsequently, in 14 consecutive operations on 9 patients (CoBF group), intraoperative monitoring of rCoBF was carried out with a laser Doppler flowmeter probe. The monitoring of ICP and rCoBF was performed for more than 20 minutes after the administration of anesthetic was changed from 1.5% to 2.5% sevoflurane to 6 mg/kg per hour of propofol. In all cases, the $PaCO_2$ of these patients was strictly maintained between 38 and 40 mm Hg throughout the operations.

Results: In both the ICP and the CoBF groups, the values of physiologic parameters obtained under inhalation anesthesia did not differ statistically from those obtained under intravenous anesthesia. The value for ICP under anesthesia with propofol was significantly lower than that under anesthesia with sevoflurane ($P < .0001$). The value for rCoBF in the frontal lobe under anesthesia with propofol was significantly higher than that under anesthesia with sevoflurane.

Conclusions: Intravenous anesthesia with propofol has potential to provide brain protection and preservation of rCBF in the frontal lobes in surgery for MMD. Whether choice of anesthetic agents might be important in surgery for MMD should be investigated further.

Keywords: Moyamoya disease; Anesthetic management; Propofol; Sevoflurane; Intracranial pressure; Cortical blood flow

1. Introduction

Moyamoya disease has been considered a progressive steno-occlusive disease at the terminal portions of the bilateral internal carotid arteries with the development of moyamoya vessels as collateral channels [5]. Because cerebral blood flow and metabolism are severely impaired in most cases of MMD, perioperative stroke occasionally occurs after surgery [8,15,16]. The importance of anesthetic management has therefore been emphasized [1,6,9]. Not only hypocapnia but also hypercapnia during the operation increases the risk of perioperative stroke because hypercapnia sometimes induces the steal phenomenon of the rCBF

Abbreviations: BT, body temperature; CBF, cerebral blood flow; CMR, cerebral metabolism; CoBF, cortical blood flow; CT, computed tomography; EMS, encephalomyosynangiosis; ICP, intracranial pressure; MAP, mean arterial pressure; MBP, mean blood pressure; MMD, moyamoya disease; MRI, magnetic resonance imaging; rCBF, regional cerebral blood flow; rCoBF, regional cortical blood flow; SPECT, single photon emission computed tomography; STA-MCA, superficial temporal artery–middle cerebral artery.

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Table 1
Characteristics of patients in the ICP group and the CoBF group

	ICP group	CoBF group
No. of patients	14	9
Age (y)	30.1 + 20.6	30 + 12
Sex (male:female)	4:10	1:8
No. of operations	20	14
STA-MCA + EMS	13	14
STA-MCA	7	0
Types of onset		
Ischemia	18	9
Hemorrhage	2	5

[8,9,11,13]. As a result, normocapnia with a $PaCO_2$ value of between 38 and 40 mm Hg has been recommended during surgery for MMD [12].

Regarding anesthetics, some investigators have reported inhalation anesthesia to be advantageous for surgery for MMD because of its cerebral vasodilatory activity [9], whereas others have recommended intravenous anesthesia with propofol because inhalation anesthesia induces the steal phenomenon [4,17]. In this article, we examine the difference between sevoflurane and propofol anesthesia on ICP and rCoBF during revascularization surgery for MMD.

2. Materials and methods

2.1. Patient characteristics

Between 1999 and 2004, 63 patients with MMD were admitted to our clinic. All patients underwent CT, MRI, SPECT studies, and cerebral angiography and were diagnosed with MMD according to the diagnostic criteria updated in 1997 [5]. A total of 90 revascularization surgeries were performed on 58 patients during this period. Among them, intraoperative ICP monitoring was performed in 20 consecutive operations for 14 patients between June 2002 and March 2003 (the ICP group). These 14 patients comprised 4 men and 10 women ranging in age from 4 to 66 years (mean age, 30.1 years). Eighteen operations were performed for ischemic MMD and 2 for hemorrhagic MMD. Intraoperative rCoBF monitoring was performed in the next 14 consecutive operations on 9 patients between October 2003 and November 2004 (the CoBF group). The 9 patients comprised 1 man and 8 women ranging in age from 17 to 58 years (mean age, 30.0 years). Nine operations were performed for ischemic MMD and 5 for hemorrhagic MMD. The characteristics of the patients in the ICP group and the CoBF group are shown in Table 1.

2.2. Intraoperative ICP monitoring

At the start of surgery, each patient was maintained on inhalation anesthesia with 1.5% to 2.5% sevoflurane, and the $PaCO_2$ value was stabilized at between 38 and 40 mm Hg. After completion of dissection of the donor artery and craniotomy, a small incision was made in the dura mater to avoid tearing the arachnoid membrane. An ICP monitoring probe (Ventrix™, Camino Laboratories, San Diego, Calif) was inserted into the subdural space, and the inhalation anesthesia was stopped [2]. When the endotidal sevoflurane concentration was decreased to less than 0.5%, intravenous anesthesia with propofol (a bolus of 30 mg plus infusion of 6 mg/kg per hour) was started. Intracranial pressure was monitored for more than 20 minutes until the value stabilized after the change in anesthetics. The values for MBP, PaO_2, $PaCO_2$ in blood gas, and BT under anesthesia with sevoflurane and with propofol were also recorded.

Table 2
Physiologic parameters and the value of ICP under inhalation anesthesia and under intravenous anesthesia in the ICP group

	ICP group (n = 20)		
	Sevoflurane	Propofol	*P*
MAP (mm Hg)	79.9 ± 11.6	80.5 ± 10.5	.78
PaO_2 (mm Hg)	189.11 ± 52.3	195.7 ± 47.2	.21
$PaCO_2$ (mm Hg)	38.9 ± 1.8	38.6 ± 1.7	.51
BT (°C)	36.3 ± 0.4	36.3 ± 0.5	.13
ICP (mm Hg)	6.33 ± 4.00	3.35 ± 3.59	.0001

The values for mean blood pressure, PaO_2, $PaCO_2$, and BT under inhalation anesthesia with sevoflurane were not statistically different from those under intravenous anesthesia with propofol. The value of ICP under anesthesia with propofol was significantly lower than that under anesthesia with sevoflurane ($P < .0001$).

2.3. Intraoperative CoBF monitoring

At the start of surgery, the patient was maintained on inhalation anesthesia with 1.5% to 2.5% sevoflurane, and the $PaCO_2$ value was stabilized between 38 and 40 mm Hg. After completion of dissection of the donor artery and craniotomy, a laser Doppler flowmeter probe (probe, CW; flowmeter, ALF21D; ADVANCE Co, Ltd, Tokyo, Japan) was placed on the brain surface of the frontal lobe and, in some cases, on the parietotemporal lobe as well [19]. The inhalation anesthesia was stopped, and intravenous anesthesia with propofol (bolus of 30 mg plus infusion of 6 mg/kg per hour) was started when the endotidal sevoflurane concentration had

Table 3
Physiologic parameters and the value of rCoBF under inhalation anesthesia and under intravenous anesthesia in the ICP group

	CoBF group (n = 14)		
	Sevoflurane	Propofol	*P*
MAP (mm Hg)	82.6 ± 9.5	86.6 ± 9.8	.09
PaO_2 (mm Hg)	195.1 ± 28.8	195.7 ± 27.3	.82
$PaCO_2$ (mm Hg)	38.6 ± 1.8	38.2 ± 1.6	.33
BT (°C)	36.3 ± 0.4	36.3 ± 0.5	.94
rCoBF (mL/100 g per min)			
Total (n = 22 points)	37.6 ± 26.6	43.1 ± 25.6	.0661
Frontal (n = 13 points)	30.9 ± 15.7	40.1 ± 24.2	.0138
Tempoparietal (n = 9 points)	47.2 ± 36.3	47.3 ± 28.5	.9856

The values for mean blood pressure, PaO_2, $PaCO_2$, and BT under inhalation anesthesia with sevoflurane were not statistically different from those under intravenous anesthesia with propofol. There was no significant difference between rCoBF under anesthesia with sevoflurane and that with propofol in rCoBF values in all 22 points, whereas the rCoBF value in the frontal lobe under anesthesia with propofol was significantly higher than that under anesthesia with sevoflurane ($P = .0138$).Various reactions in response to the change in anesthetics were observed in the regions of the temporoparietal lobe.

decreased to less than 0.5%. rCoBF was monitored for more than 20 minutes until the value stabilized after the change in anesthetics. The values for MBP, PaO_2, $PaCO_2$ and BT of the patients were also recorded under anesthesia with sevoflurane and with propofol.

2.4. Statistical analysis

The data for the physiologic parameters, ICP, and rCoBF were statistically evaluated with the paired t test. Differences were considered significant at a value of $P < .05$.

3. Results

3.1. Physiologic parameters

In both the ICP group and CoBF groups, the values for MBP, PaO_2, $PaCO_2$, and BT under inhalation anesthesia with sevoflurane were not statistically different from those under intravenous anesthesia with propofol (Tables 2 and 3).

3.2. Effects of propofol on ICP

Intracranial pressure was successfully monitored in all 20 operations. The mean ICP in the 20 operations was 6.33 ± 4.00 mm Hg under inhalation anesthesia with sevoflurane and 3.35 ± 3.59 mm Hg under intravenous anesthesia with propofol. The ICP under anesthesia with propofol was slightly but significantly lower than that under anesthesia with sevoflurane ($P < .0001$) (Table 2).

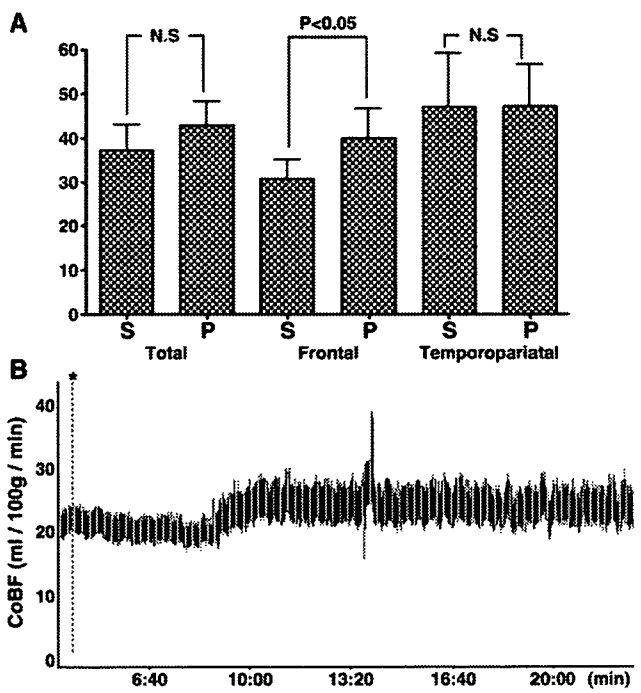

Fig. 1. There was no significant difference between rCoBF under anesthesia with sevoflurane and that with propofol in rCoBF values in all 22 points and in the 9 points in the temporoparietal lobes, whereas the rCoBF value in the frontal lobe under anesthesia with propofol was significantly higher than that under anesthesia with sevoflurane (A). Representative findings of intraoperative monitoring of rCoBF performed in the frontal lobe of a 49-year-old male with ischemic MMD (B). The value for rCoBF in the frontal lobe increased about six minutes after the change to propofol anesthetic and it staged at the level for more than 20 minutes. S, anesthesia with sevoflurane; P, anesthesia with propofol. *Start of propofol.

3.3. Effects of propofol on regional CoBF

Monitoring of rCoBF was successful from 13 regions of the frontal lobe and from 9 regions of the temporoparietal lobe. In total, data for intraoperative rCoBF were available from 22 points for evaluation of the change in rCoBF. As shown in Table 3, the mean value for rCoBF under anesthesia with sevoflurane in the 22 regions—in the 13 regions on the frontal lobe and in the 9 regions on the temporoparietal lobe—were 37.6 ± 26.6, 30.9 ± 15.7, and 47.2 ± 36.3 mL/100 g per minute, respectively. The values under anesthesia with propofol in all regions, in the frontal regions, and in the temporoparietal regions were 43.1 ± 25.6, 40.1 ± 24.2, and 47.3 ± 28.5 mL/100 g per minute, respectively. There was no significant difference between rCoBF under anesthesia with sevoflurane and that with propofol in rCoBF value in all 22 points, whereas the rCoBF value in the frontal lobe under anesthesia with propofol was significantly higher than that under anesthesia with sevoflurane ($P = .0138$). Various reactions in response to the change in anesthetics were observed in the regions of the temporoparietal lobe (Table 3, Fig. 1).

4. Discussion

Anesthetic management in revascularization surgery for MMD has been a popular topic in studies of MMD. Kansha et al [9] reported inhalation anesthesia to be favorable for its good cerebral vasodilatory activity. Sato et al [17] recommended intravenous anesthesia with propofol during surgery for MMD because inhalation anesthesia sometimes induced the steal phenomenon.

In this study, the $PaCO_2$ values of the patients were strictly maintained between 38 and 40 mm Hg in all operations. Under normocapnia conditions, the value of ICP under anesthesia with propofol was slightly but significantly lower than that under anesthesia with sevoflurane. It is well known that continuous intravenous infusion of high-dose propofol (20 mg/kg per hour) can induce a constant electroencephalographic burst-suppression pattern [7]. However, a lower dose of propofol can also suppress cerebral blood flow and metabolism [3]. Stephan et al [18] administered bolus plus infusion (2 mg/kg and 0.2 mg/kg/min, respectively) and observed average CBF and CMR decreases of 51% and 36%, respectively. The dose of propofol used in this study (bolus 30 mg plus infusion of 6 mg/kg per hour) likely induced a reduction in average CBF and CMR. Although neither CBF nor brain metabolism were globally measured in this study, the reduction in ICP by propofol appeared to reflect the decrease in average CBF and CMR induced by propofol.

Although propofol maintained the rCoBF in most regions of the brain, it increased the rCoBF in the frontal lobes significantly more than did sevoflurane. This might be, in part, caused by the steal phenomenon induced by sevoflurane during surgery for MMD [17]. However, recent reports have shown that the effects of propofol and of sevoflurane on rCBF were more varied than expected. Although propofol decreased rCBF in most regions of the brain, it increased rCBF in the medial temporal lobe in healthy volunteers [20,21]. Although sevoflurane has an intrinsic cerebral vasodilatory effect, it increased rCBF in all regions except in the parietal and frontal gray matter in normal volunteers [10,12,]. Although potent volatile anesthetics can act as pure cerebral vasodilators, they are noted for the differences in CBF and CMR associated with them [14]. Sevoflurane affects regional CMR differently than does propofol. It is probable that the different rCBF effects of the 2 anesthetics reflect the difference in brain metabolism in patients with MMD between them.

In this study, ICP and CBF data are collected from a separate group of patients. It was because change of anesthetic agents twice in the same operation prolonged the operation time and seemed hazardous. Therefore, it gave limitations in interpreting the data presented. In addition, our data did not show comparison of neurologic outcome between the 2 anesthetic agents but only comparision of rCoBF and ICP. Although intravenous anesthesia with propofol seemed to show brain protection and preservation of rCBF in the frontal lobes [13], our data was not enough to discuss clinical significance of anesthetic agents in surgery for MMD. Because it is widely accepted that management of ventilation and blood pressure during anesthesia for revascularization surgery for MMD are important to minimize adverse neurologic outcome [8,15], whether choice of anesthetic agents might be important in surgery for MMD should be investigated further.

5. Conclusions

In summary, intravenous anesthesia with propofol has potential to provide brain protection and preservation of rCBF in the frontal lobes in surgery for MMD. Whether choice of anesthetic agents might be important in surgery for MMD should be investigated further.

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Histological Features of Middle Cerebral Arteries From Patients Treated for Moyamoya Disease

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Abstract

Moyamoya disease (MMD) is a cerebrovascular occlusive disease characterized by progressive stenosis or occlusion at the distal ends of the bilateral internal carotid arteries. Vascular structural changes were previously detected using postmortem specimens. This study investigated 35 specimens of the middle cerebral artery (MCA) from 25 patients undergoing surgical treatment for MMD. Six MCA samples were also obtained from six control subjects. Histological examination showed that MCA specimens from patients with MMD had significantly thinner media and thicker intima than control specimens. In addition, abnormal findings of the internal elastic lamina and eosin-positive deposits in the intima were detected. Medial thinness and intimal hyperplasia occurred in the MCA of patients with MMD.

Key words: moyamoya disease, middle cerebral artery, media, intima

Introduction

Moyamoya disease (MMD) is a cerebrovascular occlusive disease characterized by progressive stenosis or occlusion at the distal ends of the bilateral internal carotid arteries (ICAs), resulting in the development of an unusual vascular network at the base of the brain (moyamoya vessels), which is called "moyamoya" because of its hazy, puff of smoke-like angiographic appearance due to the many collaterals of the basal perforating arteries and arterioles.[12] The etiology of the disease is undefined. The incidence of the disease is highest in, but not confined to, the Japanese population and the condition is frequently familial, suggesting the involvement of a genetic factor in its pathogenesis.[12]

Histological investigations of autopsy specimens have demonstrated that the main vascular lesion in MMD is stenosis or occlusion caused by fibrocellular intimal thickening.[6,8,15,19] Patients with MMD are usually treated by superficial temporal artery-middle cerebral artery (STA-MCA) bypass surgery or indirect revascularization.[7,9] During this surgery, the MCA is often observed to have a thin wall and to appear transparent.[16] Several studies on extracranial vessels have been reported,[1-5,11] but few on the intracranial arteries from patients with MMD except those based on autopsy specimens.[6,8,15,19]

The present study histologically analyzed a series of samples of MCA walls obtained from patients treated for MMD to explore the characteristics of the intracranial arterial walls in MMD.

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Methods

Twenty-five patients underwent surgical procedures for the standard indications of MMD at Kyoto University Hospital. All patients were symptomatic with reduction of cerebrovascular reserve assessed by single photon emission computed tomography with diamox challenge. Clinical data of the patients are summarized in Table 1. This study was performed under the guidelines of the ethics committee of Kyoto University School of Medicine. All patients gave informed consent.

During STA-MCA bypass surgery, an 11-0 nylon monofilament was passed around the wall of the recipient MCA (M_4 portion, 0.5–1.0 mm in diameter). The vessel was pulled up by lifting the monofilament with forceps, and the operator (Y.T. or K.K.) performed arteriotomy with microscissors. Tiny samples of the MCA were obtained without disruption of the recipient MCA after the surgery. The 35 specimens were fixed in 10% formalin overnight and then embedded in paraffin the next day. The specimens were stored at room temperature. Six control MCA samples were also obtained in

Table 1 Summary of cases

		No.
Moyamoya disease	Samples	35
	Cases	25
	Onset	
	ischemia	23
	hemorrhage	2
	Age (mean ± SD, yrs)	38.4 ± 15.8
	Sex	
	male	7
	female	18
	Surgery	
	STA-MCA bypass	35
	others	0
Control	Samples	6
	Cases	6
	Disease	
	meningioma	1
	astrocytoma	2
	aneurysm	3
	Age (mean ± SD, yrs)	59.1 ± 9.3
	Sex	
	male	1
	female	5

SD: standard deviation, STA-MCA: superficial temporal artery-middle cerebral artery.

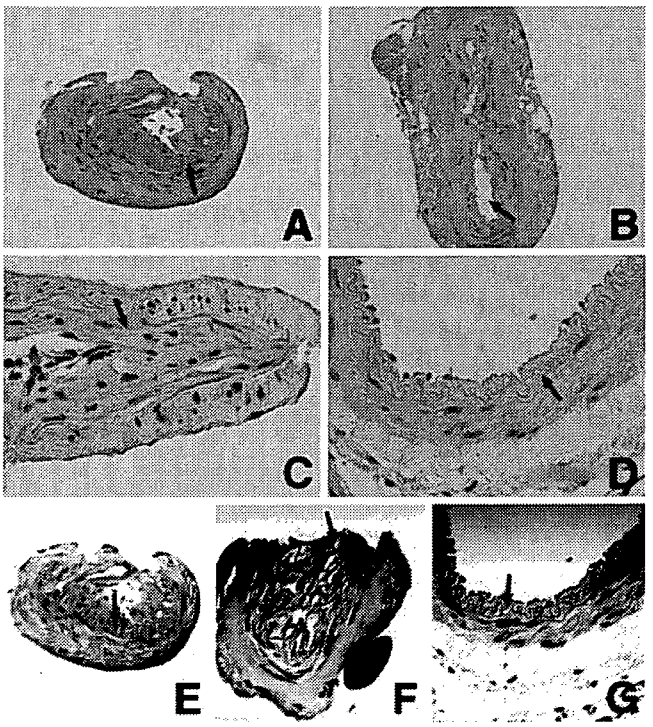

Fig. 1 A-D: Photomicrographs of specimens of the middle cerebral artery taken from patients with moyamoya disease showing intimal hyperplasia (A, *arrow* indicates internal elastic lamina) and disrupted internal elastic lamina (C, *arrow*), and specimens of the middle cerebral artery taken from control subjects (B, D, *arrows* indicate internal elastic lamina). Hematoxylin and eosin stain, original magnification A, B: × 200, C, D: ×400. E-G: Photomicrographs taken by interference differential microscopy of specimens of the middle cerebral artery taken from patients with moyamoya disease showing obvious intimal hyperplasia and thin media (E, F, *arrows* indicate internal elastic lamina), and specimens of the middle cerebral artery taken from control subjects (G, *arrow* indicates internal elastic lamina). Original magnification E, G: ×200, F: ×400.

the same way from the six control subjects described in Table 1.

Multiple, sequential, 6-μm thick tissue sections were cut from the paraffin blocks and deparaffinized in xylene, rehydrated, and stained with hematoxylin and eosin. The sections were examined under a BX51 fluorescent microscope (Olympus Optical Co., Tokyo) or a Fluoview FV300 laser confocal microscope (Olympus Optical Co.) and the histological images were captured with a computer. Intimal and medial thickness was analyzed with an Image-Pro image-analyzing system (Media Cybernetics, Silver Spring, Md., U.S.A.).

Mann-Whitney and Fisher's exact tests were used for statistical analysis (StatView; SAS Institute, Cary, N.C., U.S.A.). $P < 0.05$ was considered statistically significant.

Results

The mean thickness of the MMD intima was 19.4 ± 9.7 μm and significantly greater than that of the control intima of 8.0 ± 4.7 μm ($p = 0.0041$). The mean thickness of the MMD media was 23.0 ± 7.7 μm and significantly less than the control intima of 61.8 ± 30.4 μm ($p = 0.0009$). Histological examination of the MMD samples showed the internal elastic lamina was normal in seven samples, disrupted in 10 samples, and thin in 14 samples compared to the control samples, with eosin-stained intimal deposits in five samples (Fig. 1).

Discussion

The present study of surgical samples of MCAs from patients with MMD found thinner media and thicker intima compared to the control specimens. In

addition, changes in the internal elastic lamina were more frequent in MMD specimens than in control specimens. These results indicate that remodeling of vascular wall occurred in the intima and media of the MCA in patients with MMD as previously reported using autopsy samples.

Examination of autopsy samples of the MCA from patients with MMD found fewer than normal smooth muscle cells in the media and thick intima.[15] Fragmented elastic lamina and attenuated media were also reported.[19] The present study also found intimal hyperplasia and medial thinness in the M_4 portion of the MCA. These changes were predominantly observed in the terminal portion of ICA in the previous autopsy studies. Therefore, the characteristics of arterial changes are similar between the M_4 and ICA. We analyzed the thicknesses of intima and media in patients under 30 years old, from 30 years old to 40 years old, and over 40 years old, and in males and females, but could not detect any significant differences between the groups (results not shown). The incidence of abnormal internal elastic lamina was also assessed. Twenty percent of the patients under 30 years old, 40% of the patients from 30 years old to 40 years old, and 11% of the patients over 40 years old showed abnormal internal elastic lamina. These results may indicate intimal hyperplasia and medial thinness occur even in young patients with MMD. However, this abnormality of internal elastic lamina may occur as a secondary effect.

The molecular mechanism underlying MMD has been investigated, but not fully clarified. We reported that basic fibroblast growth factor (bFGF) may be involved, as bFGF expression is elevated in the cerebrospinal fluid (CSF) and STA of patients with MMD.[5,14] In addition, FGF receptors are overexpressed in MMD.[11] FGF is a strong mitogen and is thought to promote intimal thickening and angiogenesis. Transforming growth factor-beta (TGF-β) is also involved in MMD, because elevated levels of TGF-β in the CSF and TGF-β expression in the STA are found in patients with MMD.[4] TGF-β mediates MMD through elastin synthesis, as elastin accumulates via the TGF-β pathway and results in the intimal thickening in MMD.[18] Moreover, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and elastin levels increase in the CSF of patients with MMD.[10] Other findings indicate that an inflammatory response or endothelial activation occurs, as the production of prostaglandin E_2 and interleukin-1β is greater in the smooth muscle cells of patients with MMD.[17]

Patients with MMD often present systemic arterial lesions including the STA or renal artery.[3,13] However, the main characteristic of MMD is intracranial stenosis, so intracranial arterial samples are the most important. Autopsy specimens tend to be degraded during the fixation process, so proteins and messenger ribonucleic acid in good condition are very difficult to collect. Our specimens were fresh and messenger ribonucleic acid was easy to collect. In this study, we only showed the evidence of reorganization of the arterial walls. We are planning to investigate the molecular mechanisms of intimal thickening, medial thinning, and angiogenesis in the future analysis using our samples.

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Commentary

The authors histologically analyzed 35 specimens of the middle cerebral arteries from patients with moyamoya disease, which were obtained during bypass surgery and were freshly fixed with formalin. They found hyperplasia of the intima and narrowing of the media of the middle cerebral arteries. These findings are consistent with previous histological findings in autopsy specimens. In autopsy cases, these histological changes are typically observed in the terminal portion of the internal carotid arteries, which is the essential characteristic of moyamoya disease. The similarity of histological findings may justify the importance of investigating such specimens in search of the causes of moyamoya disease.

The unique feature that the specimens were fresh would have great advantages in investigating proteins, DNAs, and RNAs in the vessels, because they are less likely to be denatured. As they have stated in the last part of the discussion, further investigation using these specimens is awaited.

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Moyamoya disease with its characteristic feature of bilateral progressive stenosis and occlusion of the supraclinoidal internal carotid arteries has been recognized for many decades. Yet, the etiology of this disease is not well understood.

In this article, instead of using specimens from autopsy, Takagi and colleagues from Kyoto studied specimens of intracranial arterial wall obtained from arteriotomy during extracranial-intracranial vascular bypass surgery. The results of the present study revealed the peripheral branch of the middle cerebral artery (M4 segment) in patients with moyamoya disease has a thinner media and thicker intima than the normal controls. Changes such as disruption and thinning of the internal elastic lamina and eosin-positive deposits in intima were also found. These findings are similar to the previous autopsy studies on distal internal carotid arteries.

However, whether these results represent the etiology or the consequences of moyamoya disease cannot be elucidated from this morphological study. It also cannot be explained why similar morphological changes are observed in proximal and distal arteries, but not in the clinical setting where stenosis and occlusion always start from the supraclinoidal internal carotid artery. As the authors mentioned, further molecular study would probably provide solutions for these questions.

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ORIGINAL PAPER

Efficacy of superficial temporal artery–middle cerebral artery anastomosis with routine postoperative cerebral blood flow measurement during the acute stage in childhood moyamoya disease

Miki Fujimura · Tomohiro Kaneta · Teiji Tominaga

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Abstract
Object Surgical revascularization for moyamoya disease prevents cerebral ischemic attacks by improving cerebral blood flow (CBF). It is undetermined, however, how rapid increase in CBF affects chronic ischemic brain during the acute stage in childhood moyamoya disease.
Materials and methods The present study includes nine consecutive cases of patients with childhood moyamoya disease (2~8 years old, 6.2 in average), who underwent superficial temporal artery–middle cerebral artery (STA–MCA) anastomosis on 17 hemispheres. We prospectively performed single-photon emission computed tomography 1 and 7 days after 17 surgeries. The follow-up period ranged from 12 to 37 months (24.9 in average).
Results The outcome of 17 surgeries was excellent (disappearance of transient ischemic attack) in 14 hemispheres (82.4%) and good (reduction of transient ischemic attack) in three hemispheres (17.6%). No patient suffered perioperative infarction, except for one (5.9%) manifesting as pseudolaminar necrosis in a part of the cerebral cortex supplied by STA–MCA bypass at the subacute stage, which did not affect his long-term neurological status. One patient (5.9%) presented with transient facial palsy due to hyperperfusion, which resolved within several days. No patient manifested permanent neurological deterioration during the follow-up period.
Conclusion The STA–MCA anastomosis is a safe and effective treatment for childhood moyamoya disease. We recommend routine CBF measurement for avoiding surgical complications including both cerebral ischemia and hyperperfusion.

Keywords Moyamoya disease · Pediatrics · Extracranial–intracranial bypass · Cerebral blood flow · Superficial temporal artery–middle cerebral artery anastomosis · Single-photon emission computed tomography

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Introduction

Moyamoya disease is a chronic, occlusive 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 at the base of the brain [19]. Surgical revascularization for moyamoya disease is believed to prevent cerebral ischemic attacks by improving cerebral blood flow (CBF), and superficial temporal artery (STA)–middle cerebral artery (MCA) anastomosis with or without indirect pial synangiosis is generally employed as the standard surgical treatment for moyamoya disease [4, 9–11, 20].

The immediate improvement of cerebral hemodynamics by STA–MCA anastomosis is considered to be one of the major advantages of this procedure [9, 11] compared to the indirect pial synangiosis [1, 12, 13, 17, 18], the alternative treatment for pediatric moyamoya disease. However, it is undetermined how rapid increase in CBF affects chronic ischemic brain during the acute stage in childhood moyamoya disease. To address this issue, we prospectively performed *N*-isopropyl-*p*-[^{123}I] iodoamphetamine single-photon emission computed tomography (^{123}I-IMP-SPECT)

within 1 week after STA–MCA anastomosis in nine consecutive cases with childhood moyamoya disease operated on 17 hemispheres. In this report, we sought to evaluate the outcome of STA–MCA anastomosis for childhood moyamoya disease, especially focusing on the neurological events during the acute stage including peri-operative ischemic complication and cerebral hyperperfusion.

Materials and methods

The present study includes nine consecutive patients (2~8 years old, mean 6.2) with childhood moyamoya disease operated on 17 hemispheres by the same surgeon (M.F.) in Tohoku University Hospital from November 2004 to November 2006. All patients were strictly followed up in our institute with the mean follow-up period of 24.9 months (12~37 months). All patients satisfied the diagnostic criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health, Labor, and Welfare, Japan, except for one patient with akin-moyamoya disease with neurofibromatosis type-I (case-1 in Table 1). All patients underwent STA–MCA anastomosis with encephalo-duro-myo-synangiosis (EDMS) and dural pedicle insertion [4]. The CBF was routinely measured by ^{123}I-IMP-SPECT 1 and 7 days after surgery in all patients. The 1.5 or 3 T magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were routinely performed 2 and 8 days after surgery. The MRI includes diffusion-weighted images (DWI), fluid attenuated inversion recovery, T1-/T2-weighted images, and T2*-weighted images.

Results

Among nine consecutive patients with 17 surgeries, all patients obtained the disappearance (six cases, 66.6%) or reduction of ischemic symptoms (three cases, 33.3%) during the follow-up period (Table 1). The outcome of 17 surgeries was excellent (disappearance of transient ischemic attack (TIA)) in 14 hemispheres (82.4%) and good (reduction of TIA) in three hemispheres (17.6%). No patients suffered from peri-operative cerebral infarction, except for one patient (5.9%) presenting with pseudolaminar necrosis in a part of cerebral cortex supplied by STA–MCA bypass at the subacute stage, which did not affect his long-term neurologic status (case-6). There were no radiological changes including cerebral infarction and hemorrhage in 17 operated hemispheres as well as in one hemisphere without surgery in nine cases during the follow-up period after discharge. The patency of STA–MCA bypass was confirmed in all 17 hemispheres by MRA after surgery. One patient (one hemisphere, 5.9%) suffered from transient left facial palsy due to postoperative cerebral

Table 1 Summary of nine cases with pediatric moyamoya disease operated on 17 hemispheres

	Age/sex	Preoperative presentation	Surgery	Outcome	Complication
Case 1	2/M	Infarction, TIA	Left STA–MCA bypass/EDMS	Excellent	Subcutaneous effusion (~1 month)
Case 2	8/F	Infarction, TIA	Left STA–MCA bypass/EDMS	Excellent	None
			Right STA–MCA bypass/EDMS	Excellent	None
Case 3	7/F	TIA	Left STA–MCA bypass/EDMS	Excellent	None
			Right STA–MCA bypass/EDMS	Excellent	None
Case 4	7/M	TIA	Right STA–MCA bypass/EDMS	Good	None
			Left STA–MCA bypass/EDMS	Excellent	None
Case 5	4/F	TIA	Right STA–MCA bypass/EDMS	Excellent	Transient left facial palsy (POD5~9)[a]
			Left STA–MCA bypass/EDMS	Excellent	None
Case 6	8/M	Infarction, TIA	Right STA–MCA bypass/EDMS	Good	Transient left monoparesis (POD9~3 months)[b]
			Left STA–MCA bypass/EDMS	Excellent	None
Case 7	6/F	Infarction, TIA	Left STA–MCA bypass/EDMS	Good	None
			Right STA–MCA bypass/EDMS	Excellent	None
Case 8	8/F	TIA	Right STA–MCA bypass/EDMS	Excellent	None
			Left STA–MCA bypass/EDMS	Excellent	None
Case 9	6/M	TIA	Right STA–MCA bypass/EDMS	Excellent	None
			Left STA–MCA bypass/EDMS	Excellent	None

Excellent Disappearance of TIA after surgery, *Good* reduction of TIA after surgery, *M* male, *F* female
[a] Cerebral hyperperfusion
[b] Pseudolaminar necrosis

hyperperfusion from 5 to 9 days after right STA–MCA anastomosis (case-4). The detail of this case was previously reported elsewhere [5]. One patient suffered from subcutaneous effusion (case-1), which spontaneously resolved without infectious sign within 1 month after surgery.

Representative cases

Case-2

An 8-year-old girl presented with repeated TIA on her right hand and subsequent minor completed stroke. MRI on admission demonstrated cerebral infarction at the left occipital lobe with multiple ischemic changes at the bilateral paraventricular region, and MRA demonstrated steno-occlusive changes at the terminal portions of the bilateral internal carotid arteries as well as at the left posterior cerebral artery with the abnormal network-like vessels at the bilateral basal ganglia, which satisfied the diagnostic criteria for moyamoya disease [19]. The STA–MCA anastomosis with pial synangiosis was performed on the left hemisphere without complication. Postoperative ^{123}I-IMP-SPECT showed significant increase in CBF on the operated hemisphere (Fig. 1b), and MRA/MRI demonstrated apparently patent STA–MCA bypass without ischemic change. She underwent right STA–MCA bypass 4 weeks later without complication, which also resulted in significant increase in CBF on the right hemisphere (Fig. 1c) with apparently patent STA–MCA bypass without ischemic change as shown by postoperative SPECT and MRA/MRI. Her TIA completely disappeared after surgery, and she did not suffer neurological deterioration during the follow-up period of 34 months. MRA 12 months after the initial surgery showed apparently patent STA–MCA bypass with significant development of pial synangiosis bilaterally (Fig. 2a).

Case-6

An 8-year-old boy presented with TIA on his left extremities and subsequent minor completed stroke. MRI on admission demonstrated cerebral infarction at the right parieto-occipital lobe, and MRA demonstrated steno-occlusive changes at the terminal portions of the bilateral internal carotid arteries and the presence of abnormal network-like vessels at the bilateral basal ganglia, which satisfied the diagnostic criteria for moyamoya disease [19]. The STA–MCA anastomosis with pial synangiosis was performed on the right hemisphere. The anastomosis was performed between the stump of the STA (0.8 mm in diameter) and the proximal portion of the M4 segment (0.8 mm in diameter) that supplied the frontal lobe. The ^{123}I-IMP-SPECT 1 day after surgery showed no apparent change in CBF on the operated hemisphere compared to the pre-operative findings. Postoperative MRA showed the apparently patent STA–MCA bypass (Fig. 3a, arrow). Eight days after surgery, however, he suffered from severe monoparesis on his left hand when DWI demonstrated a linear high-intensity lesion at the right pre-central gyrus (arrow in Fig. 4a), which was not evident by the previous MRI (Fig. 4a). The use of anti-platelet agent and edaravone, a novel free radical scavenger, gradually relieved the symptom, and the linear high-intensity lesion by DWI disappeared 5 days later (Fig. 4c). His symptom returned to

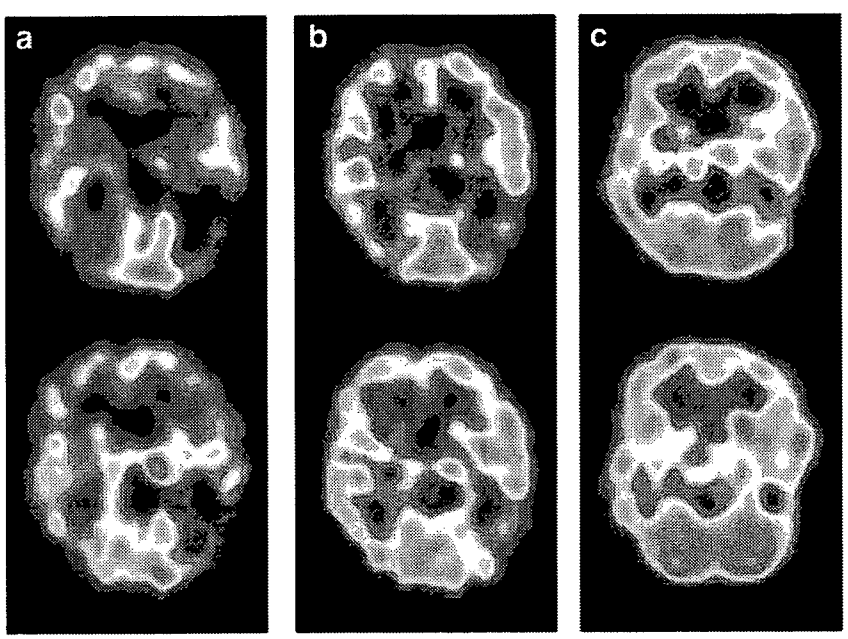

Fig. 1 Case 2. ^{123}I-IMP-SPECT scans before surgery (**a**), 7 days after left STA–MCA anastomosis (**b**), and 7 days after right STA–MCA anastomosis (**c**). The significant increase in CBF on the operated hemispheres was evident after surgery

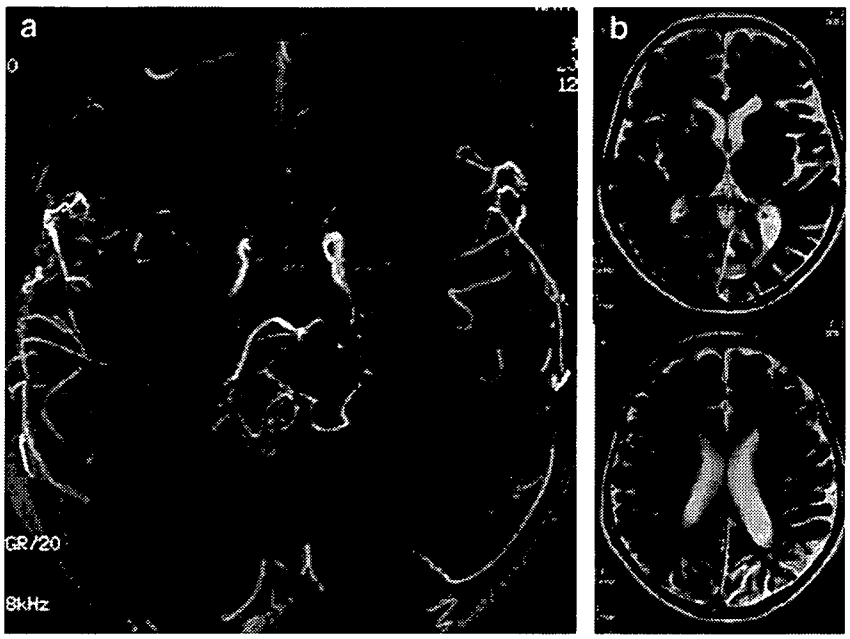

Fig. 2 Case 2. Postoperative MRA 1 year after surgery (**a**) demonstrating the patent STA–MCA bypasses and significant development of pial synangiosis bilaterally. Postoperative T2-weighted images (**b**) showed no change on both hemispheres compared to pre-operative finding

pre-operative status 3 months after the initial surgery. He underwent left STA–MCA anastomosis on the left hemisphere 4 months after initial surgery without complication. MRA 10 months after the initial surgery showed apparently patent STA–MCA bypass with significant development of pial synangiosis (arrow in Fig. 3b), when the right precentral gyrus showed atrophic change, consistent with the pseudolaminar necrosis (arrows in Fig. 4d and h). There was no stroke during the follow-up period, and he obtained the improvement of TIA.

Discussion

The present study demonstrated the favorable outcome of STA–MCA anastomosis with routine postoperative CBF evaluation by SPECT in patients with childhood moyamoya disease (Table 1). Despite the safety and the long-term efficacy of STA–MCA anastomosis reported in the previous literatures [9–11, 20], a substantial number of children with moyamoya disease, as much as 59.3% of patients with STA–MCA anastomosis, were reported to suffer transient neurological deterioration during the acute stage after surgery [20]. The exact mechanism of this transient deterioration has been totally undetermined due to the lack of postoperative CBF analysis and MR study during the acute stage after STA–MCA anastomosis [20]. In our series, the final outcome of 17 surgeries was excellent (disappearance of TIA) in 14 hemispheres (82.4%) and good (reduction of TIA) in two hemispheres (17.6%). No patient suffered from permanent neurological deficit postoperatively, while two patients (11.8%) manifested transient neurological deterioration due to cerebral hyperperfusion in one patient (5.9%) and pseudolaminar necrosis in the other (5.9%), as diagnosed

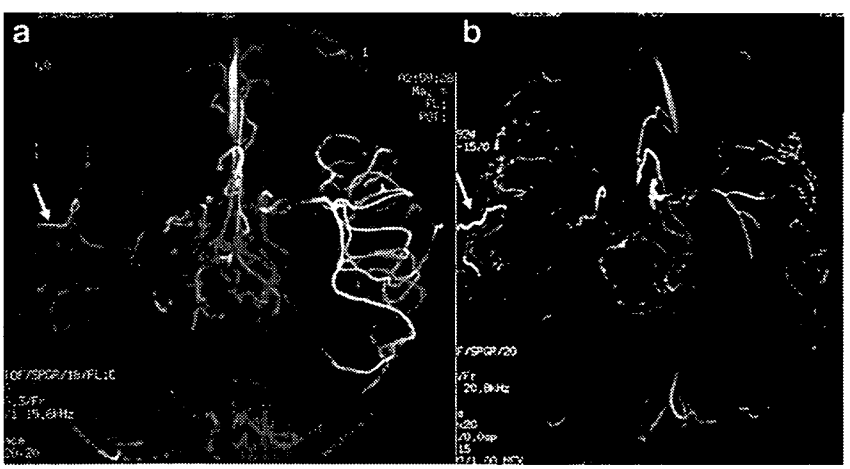

Fig. 3 Case 6. MRA 1 day (**a**) and 10 months (**b**) after right STA–MCA anastomosis demonstrating patent STA–MCA anastomosis postoperatively (*arrows*). Significant development of indirect pial synangiosis was evident as well as the patent STA–MCA bypasses after bilateral revascularization (**b**)

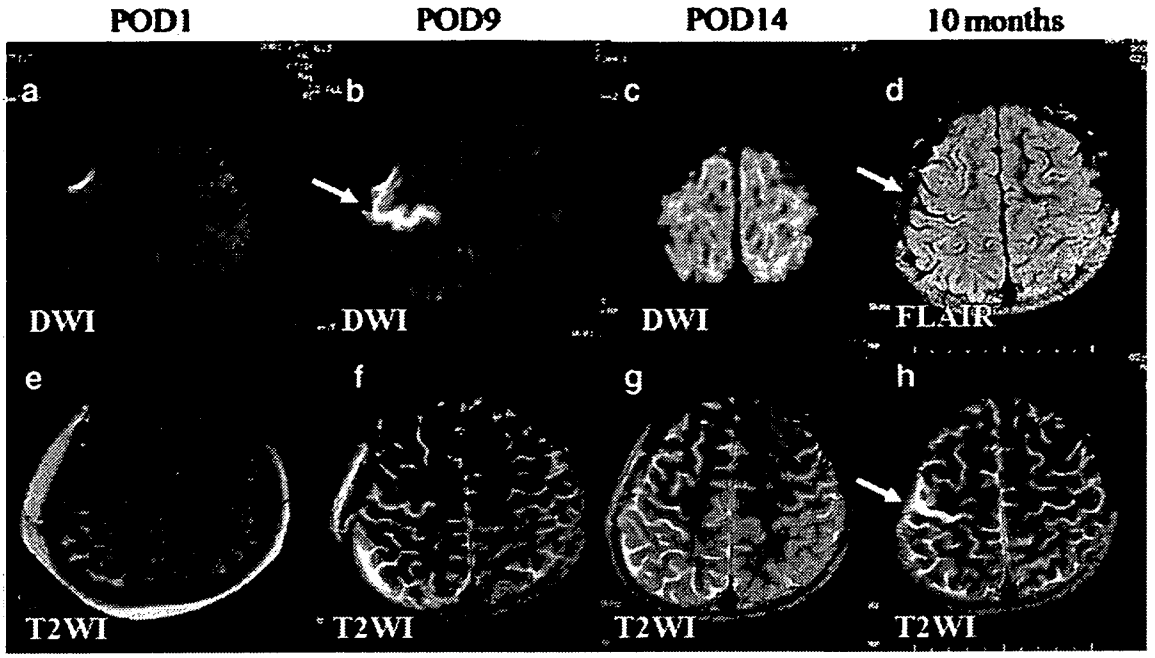

Fig. 4 Case 6. MR imaging 1 day (**a**, **e**), 9 days (**b**, **f**), 14 days (**c**, **g**), and 10 months (**d**, **h**) after right STA–MCA anastomosis. Linear high signal intensity sign by DWI transiently appeared at pre-central gyrus 9 days after right STA–MCA anastomosis (*arrow* in **b**), where delayed atrophic change was evident 10 months after surgery (*arrows* in **d**, **h**), consistent with pseudolaminar necrosis

by the routine postoperative ^{123}I-IMP-SPECT and MRA/MRI. Postoperative management based on these evaluations successfully led to the resolution of the symptoms. Thus, we recommend routine ^{123}I-IMP-SPECT and MR angiography/imaging during the acute stage, as the clinical manifestation of hyperperfusion and ischemia is similar but the management of each condition is contradictory [4].

Postoperative hyperperfusion syndrome [8, 21] has been considered to be less common in patients with moyamoya disease [9, 10] due to the relatively low flow revascularization obtained by surgery for moyamoya disease. However, increasing evidences suggest that STA–MCA anastomosis for moyamoya disease, especially in adult cases, could also result in symptomatic cerebral hyperperfusion such as transient focal neurological deficit [4, 5, 7, 15] or delayed intracerebral hemorrhage [6]. The incidence of symptomatic hyperperfusion is as high as 38.2% in patients with adult-onset moyamoya disease [4], while the final outcome of these patients was excellent despite their temporary deterioration during the acute stage [4]. Contrary to adult-onset moyamoya disease, symptomatic hyperperfusion was reported only in a limited case among children [5], and the incidence of such phenomenon was undetermined among patients with childhood moyamoya disease. The present study indicated, for the first time, that the incidence of symptomatic cerebral hyperperfusion was 5.9% in childhood moyamoya disease, which was much lower that that of adult-onset moyamoya disease [4]. The reason why adult-onset patients are more vulnerable to cerebral hyperperfusion is totally undetermined. Certain biological background in adult patients may contribute to the high incidence of symptomatic hyperperfusion, and this issue remained to be elucidated in the future study.

Long-term follow-up of the neurological function including cognitive functions and the anatomical changes in the affected brain is needed, because exposure to sublethal levels of reactive oxygen species during reperfusion to the chronic ischemic brain can affect organelles, and thus lead to delayed neuronal damage by apoptosis [2, 3]. In fact, case-6 manifested as delayed pseudolaminar necrosis in a part of the cerebral cortex supplied by STA–MCA bypass at the subacute stage, suggesting the involvement of reperfusion injury. Besides this particular case, however, no patient in this series showed delayed cortical damages such as the expansion of cerebral infarction and the atrophic change at the chronic stage. Postoperative cerebral hyperperfusion could also be associated with impairment of cognitive function in patients undergoing carotid endarterectomy [16], which was reported to be prevented by pre-administration of a free radical scavenger [14]. Thus, we use edaravone, a novel free radical scavenger [14], to counteract the deleterious effect of reperfusion into the chronic ischemic brain of moyamoya patients during the acute stage. Further evaluation is necessary to clarify the underlying mechanism of both pseudolaminar necrosis and cerebral hyperperfusion after STA–MCA anastomosis in childhood moyamoya disease in a future study.

Conclusion

The STA–MCA anastomosis is a safe and effective treatment for pediatric moyamoya disease, although it has a substantial risk for cerebral hyperperfusion and delayed cortical damage such as pseudolaminar necrosis. We recommend routine CBF measurement for the differential diagnosis between cerebral hyperperfusion and ischemic attack, as the treatments for these conditions are contradictory.

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Vascular

Temporary neurologic deterioration due to cerebral hyperperfusion after superficial temporal artery-middle cerebral artery anastomosis in patients with adult-onset moyamoya disease

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Abstract

Background: Surgical revascularization for moyamoya disease prevents cerebral ischemic attacks by improving CBF, but little is known about the change in CBF and its effect on neurologic status during the acute stage after revascularization.

Methods: ^{123}I-IMP-SPECT was performed 1 and 7 days after STA-MCA anastomosis on 34 sides of 27 consecutive patients with adult-onset moyamoya disease (6 men, 21 women; 22-62 years old). The follow-up period ranged from 5 to 28 months (mean, 17.6 months).

Results: Thirteen patients (13 sides, 38.2%) suffered temporary neurologic deterioration due to hyperperfusion several days after surgery, which was sustained for several days (7.4 days in average). Postoperative magnetic resonance imaging/angiography showed the STA as a higher intensity signal than the preoperative finding without ischemic changes in all 13 patients. Postoperative SPECT revealed focal intense increase in CBF at the sites of anastomosis in all 13 patients. Eleven patients (32.4%) had transient focal neurologic deficit mimicking ischemic attack. Two patients (5.9%) had cerebral hyperperfusion syndrome associated with subarachnoid hemorrhage extending to the ipsilateral sylvian cistern. Symptoms were relieved by intensive blood pressure control, and no patients had permanent neurologic deficit or delayed neurologic deterioration during the follow-up period.

Conclusions: Surgical revascularization including STA-MCA anastomosis is a safe and effective treatment for moyamoya disease, although temporary neurologic deterioration due to hyperperfusion could occur at a substantial rate. Routine CBF measurement is recommended for accurate diagnosis of postoperative hyperperfusion in moyamoya disease because its treatment is contradictory to that for ischemia.

Keywords: Cerebral blood flow; Cerebral hyperperfusion; Moyamoya disease; Superficial temporal artery-middle cerebral artery anastomosis; Hyperperfusion; Single-photon emission computed tomography

1. Introduction

Moyamoya disease is a chronic, occlusive 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 at the base of the brain [20]. Surgical revascularization for moyamoya disease is believed to be beneficial to prevent cerebral ischemic attacks by improving CBF, and STA-MCA anastomosis with or without indirect bypass is generally used as

Abbreviations: CBF, cerebral blood flow; CT, computed tomography; 3DSRT, 3-dimensional stereotactic region of interest template; DTA, deep temporal artery; DWI, diffusion-weighted imaging; EDMS, encephalodur-omyosynangiosis; FLAIR, fluid-attenuated inversion recovery; ^{123}I-IMP-SPECT, *N*-isopropyl-*p*-[^{123}I]iodoamphetamine single-photon emission computed tomography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; PWI, perfusion-weighted imaging; ROS, reactive oxygen species; STA-MCA anastomosis, superficial temporal artery-middle cerebral artery anastomosis.

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