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Vascular

Incidence and risk factors for symptomatic cerebral hyperperfusion after superficial temporal artery-middle cerebral artery anastomosis in patients with moyamoya disease

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Abstract

Background: Superficial temporal artery-middle cerebral artery anastomosis for moyamoya disease prevents cerebral ischemic attack by improving CBF, whereas recent evidence suggests that the temporary neurologic deterioration because of postoperative cerebral hyperperfusion could occur despite its low-flow revascularization. The present study investigates the incidence and the risk factors for symptomatic hyperperfusion after STA-MCA anastomosis in patients with moyamoya disease.

Methods: We prospectively performed *N*-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission computed tomography 1 and 7 days after STA-MCA anastomosis on 80 hemispheres of 58 consecutive patients with moyamoya disease (approximately 2-62 years old, 34.4 years old in average). Mean follow-up period was 22.7 months. Symptomatic cerebral hyperperfusion was defined as the presence of the significant increase in CBF at the site of the anastomosis that is responsible for the apparent neurologic sign.

Results: Twenty-one patients (22 sides, 27.5%) temporarily had symptomatic cerebral hyperperfusion, who were subjected to intensive blood pressure control. Postoperative magnetic resonance imaging/angiography showed the thick high signal of bypass without ischemic changes in all 21 patients. Adult-onset ($P = .013$) or hemorrhagic-onset patients ($P = .027$) had significantly higher risk for symptomatic hyperperfusion. There was no difference in intraoperative temporary occlusion time between each group. No patients had permanent neurologic deficit because of hyperperfusion.

Conclusion: The STA-MCA anastomosis is a safe and effective treatment of moyamoya disease, although adult-onset and/or hemorrhagic-onset patients had higher risk for symptomatic hyperperfusion. We recommend routine CBF measurement especially for these patients because the management of hyperperfusion is contradictory to that of ischemia.

Keywords: Moyamoya disease; Cerebral hyperperfusion; Risk factor; Extracranial-intracranial bypass

Abbreviations: BBB, blood-brain barrier; CBF, cerebral blood flow; CT, computed tomography; DWI, diffusion-weighted images; EDMS, encephalo-duro-myo-synangiosis; ICH, intracerebral hemorrhage; ^{123}I-IMP-SPECT, *N*-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission computed tomography; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; ROS, reactive oxygen species; SAH, subarachnoid hemorrhage; STA-MCA, superficial temporal artery-middle cerebral artery; TIA, transient ischemic attack.

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1. Introduction

Moyamoya disease is a chronic, occlusive cerebrovascular disease with unknown etiology characterized by bilateral stenoocclusive 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 prevents cerebral ischemic attacks by improving CBF, and STA-MCA anastomosis with or without indirect pial synangiosis is generally used as the standard surgical treatment of moyamoya disease [4,8,9,15,17]. Despite its favorable long-term outcome, increasing evidence suggest that direct revascularization surgery for moyamoya disease could result in temporary neurologic deterioration owing to focal cerebral hyperperfusion at the site of the anastomosis during the acute stage [3-6,12,14]. Because the clinical manifestation of cerebral hyperperfusion in patients with moyamoya disease includes transient focal neurologic deficit mimicking cerebral ischemic attack [4-6], it is clinically important to make accurate diagnosis of symptomatic hyperperfusion and to conduct its adequate management such as intensive blood pressure control [4,5]. Furthermore, it would be of great value to clarify the predictive factors for postoperative symptomatic hyperperfusion in moyamoya disease, although the exact incidence and the risk factors of hyperperfusion are totally undetermined in moyamoya disease.

To address this issue, we retrospectively investigated the incidence and the risk factors of symptomatic cerebral hyperperfusion in 58 consecutive patients with moyamoya disease, who were all treated by STA-MCA anastomosis on 80 hemispheres and were examined by ^{123}I-IMP-SPECT 1 and 7 days after 80 consecutive surgeries.

1.1. Patients and methods

The correlation between postoperative changes in CBF and clinical course was investigated in 58 consecutive patients (approximately 2-62 years old; mean 34.4 years) with moyamoya disease operated on 80 hemispheres by the same surgeon (MF) in Tohoku University Hospital (Sendai, Japan) from March 2004 to May 2007. All patients were strictly followed-up in our institute with the mean follow-up period of 22.7 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, Tokyo, Japan, except for 3 patients with "probable moyamoya disease" with unilateral involvement. All patients underwent STA-MCA anastomosis with or without EDMS and dural pedicle insertion. The CBF was routinely measured by ^{123}I-IMP-SPECT 1 and 7 days after surgery in all patients. The CBF was quantified by the autoradiographic method, the CBF in each subregion of the cerebral cortex was automatically calculated by Three-Dimensional Stereotactic Region of Interest Template (3D-SRT) software (version 2) provided by Daiichi Radio-Isotope (Tokyo, Japan), and the diagnosis of cerebral hemodynamics was made by 2 specialized radiologists. The 1.5 or 3 Tesla MRI and MRA were routinely performed 2 and 8 days after surgery. The MRI includes DWI, fluid attenuated inversion recovery, T1/T2-weighted images, and T2*-weighted images. The diagnostic criteria for symptomatic cerebral hyperperfusion include all of the following issues; (1) the presence of the significant increase in CBF at the site of the anastomosis that is responsible for apparent neurologic signs including focal neurologic deficit and/or severe headache because of hemorrhagic changes; (2) apparent visualization of STA-MCA bypass by MRA and the absence of any ischemic changes by DWI; and (3) the absence of other pathologies such as the compression of the brain surface by the temporal muscle inserted for indirect pial synangiosis, ischemic attack, and seizure. We evaluated the correlation between the occurrence of symptomatic cerebral hyperperfusion and patients' information including age, sex, side of the operated hemisphere, onset-type, and the period of temporary occlusion time of the recipient arteries during surgery. Statistical analysis was performed by χ^2 test or by Student t test.

2. Results

Among 58 consecutive patients with 80 surgeries, no patients had perioperative cerebral infarction, except for 3 patients (3.7%) presenting with pseudolaminar necrosis in a part of cerebral cortex supplied by STA-MCA bypass at the subacute stage, which did not affect their long-term neurologic status. All patients with the onset of TIA obtained disappearance or improvement of ischemic attack during the follow-up period. One hemorrhagic-onset patient had ICH on the contralateral side 3 months after surgery, which did not affect his neurologic status. The patency of STA-MCA bypass was confirmed in all 58 patients with 80 surgeries by MRA after surgery. Among the 58 consecutive patients with 80 surgeries, 21 patients (22 hemispheres, 27.5% of 80 operated hemispheres) had temporary neurologic deterioration because of postoperative cerebral hyperperfusion from 2 to 9 days after surgery, which sustained for several days (Table 1). Postoperative MRI/MRA showed no ischemic changes, and the thick high signal of STA on the operated hemisphere was evident in all 22 hemispheres except for one

Table 1
Incidence of symptomatic cerebral hyperperfusion in moyamoya disease

	No. of hemisphere sides (n = 80)	Initial symptom (d after surgery)	Permanent neurologic deficit
Symptomatic hyperperfusion	22 (27.5%)		
Focal neurologic deficit	18 (22.5%)	Approximately 2-7 d	None
SAH	3 (3.8%)	Approximately 1-2 d	None
ICH	1 (1.2%)	4 d	None

Table 2
Correlation between each factors and symptomatic hyperperfusion

	χ^2 value	P
Age		
Adult-onset (≥16 y)	6.1919	.0128*
Sex	1.3444	.2462
Onset-type		
Hemorrhage	4.9079	.0267*
Cerebral infarction	0.8868	.3463
Side of the operated hemisphere	1.3197	.2506

	Hyperperfusion +	Hyperperfusion −	P
Mean age (y)	39.8	28.8	.0134*
Temporary occlusion time (min)	28.9	29.5	.6217

case that required STA ligation 2 days after surgery to control cerebral hyperperfusion. Postoperative SPECT revealed significant intense increase in CBF at the sites of anastomosis on all 22 hemispheres. As summarized in Table 1, 17 patients (18 hemispheres, 22.5%) had transient focal neurologic deficit because of localized hyperperfusion that mimicked ischemic attack, which started from 2 to 9 days after surgery and sustained for several days. The anatomical location and the temporal profile of hyperperfusion were completely in accordance with the transient neurologic signs in these 17 patients. Four patients (4 hemispheres, 5.0%) complained of severe headache and had cerebral hyperperfusion syndrome associated with SAH in 3 patients or with ICH at right frontal subcortex in one patient. Symptoms were relieved by intensive blood pressure control with the use of free radical scavenger, edaravone (Mitsubishi Pharma Co, Tokyo, Japan), although one patient with ICH required rehabilitation to relive her transient left hemiparesis for 2 months. One patient with significant bilateral flow compromise manifested as SAH and required ligation of STA-MCA bypass 2 days after the first stage surgery to control postoperative cerebral hyperperfusion, who was rescued by marked development of pial synangiosis without complication. No patients had permanent neurologic deficit because of hyperperfusion. No patients had delayed neurologic deterioration because of cerebral hyperperfusion during the follow-up period. Correlation between each factor and the occurrence of symptomatic cerebral hyperperfusion is summarized in Table 2. Adult-onset patients who were 16 years old or older had significantly higher risk for hyperperfusion ($P = .0128$). The mean age of the patients with symptomatic hyperperfusion (39.8 years old) was significantly higher than that of without hyperperfusion (28.8 years old) ($P = .0134$). The average time of the intraoperative temporary occlusion of the recipient arteries showed no significant difference between patients with and without postoperative cerebral hyperperfusion (28.9 and 29.5 minutes, respectively; $P = .6217$). Regarding the onset

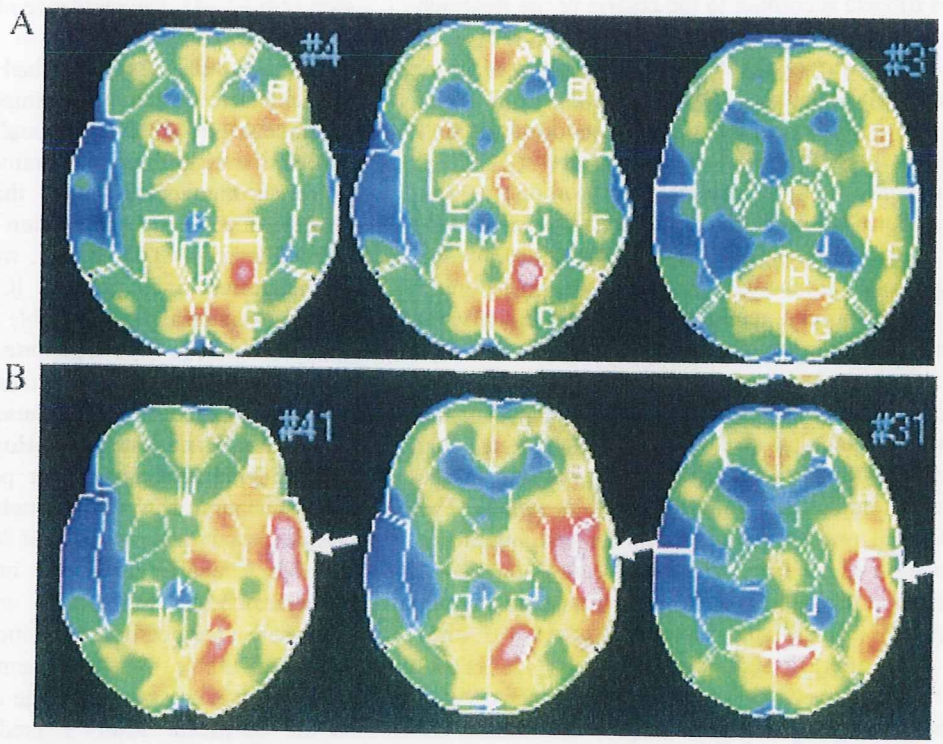

Fig. 1. *N*-isopropyl-p-[^{123}I]iodoamphetamine single-photon emission computed tomographic scans before (A) and after left STA-MCA anastomosis (B). As compared to preoperative finding in (A), marked increase in CBF at the site of the anastomosis was evident postoperatively (arrows in B) in accordance with the manifestation of aphasia. Symptoms completely disappeared 12 days after surgery.

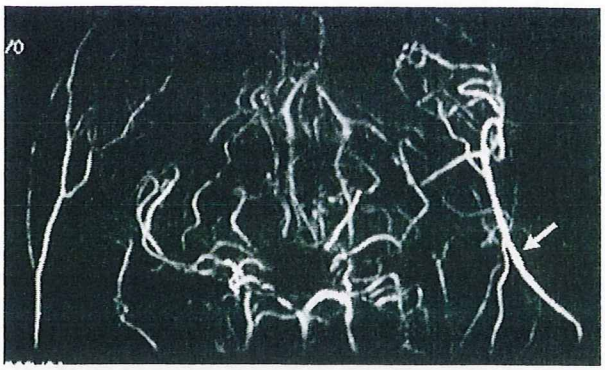

Fig. 2. Magnetic resonance angiography after left STA-MCA anastomosis with pial synangiosis. The STA-MCA bypass was apparently patent shown by thick high signals (arrow).

type, hemorrhagic-onset patients had higher risk for symptomatic hyperperfusion (P = .0267), whereas there was no difference between the patients with and without cerebral infarction (P = .346). There was no correlation of patients' sex (P = .246) or of side of the operated hemisphere (P = .251) to the risk for symptomatic hyperperfusion.

2.1. Representative case

A 39-year-old woman, presenting with left hemiparesis because of cerebral infarction at the right frontal lobe, was admitted to our hospital to undergo revascularization surgery for moyamoya disease. The diagnosis was stage III moyamoya disease according to the criteria of the Research Committee on Spontaneous Occlusion of the Circle of Willis, of the Ministry of Health, Labor, and Welfare, Japan. She had mild left hemiparesis and dysarthria on admission, whereas her activity of daily life was independent. Preoperative ^{123}I-IMP-SPECT showed decreased CBF at the corresponding lesion to cerebral infarction on the right hemisphere, but CBF at the adjacent cortex was preserved. Her CBF and cerebrovascular reserve capacities on the left hemisphere were markedly compromised on the entire middle cerebral artery territory. Thus she underwent revascularization surgery on the left hemisphere. The recipient artery at the M4 segment of the MCA was explored, and anastomosis was performed between the stump of the STA and the M4 segment that supplied the temporal lobe. Then EDMS and dural pedicle insertion were performed. She showed no neurologic deficit immediately after surgery. The ^{123}I-IMP-SPECT one day after surgery showed significant increase in CBF at the site of the anastomosis compared to the preoperative findings (Fig. 1A), and focal intense increase in CBF at the site of anastomosis was further evident 7 days after surgery (arrows in Fig. 1B). Postoperative MRA showed the apparently patent STA-MCA bypass as a thick high signal intensity sign (Fig. 2), and DWI showed no evidence of ischemic change (data not shown). She had aphasia, dysarthria, and numbness in the right upper limb 2 days after surgery. Based on the diagnosis of symptomatic cerebral hyperperfusion, the intensive blood pressure control and the use of free radical scavenger relieved her symptoms gradually that completely disappeared 12 days after surgery. Then she was discharged without neurologic deterioration compared to the preoperative status. She does not experience cerebrovascular event postoperatively, and she does not have any neurologic deterioration during the follow-up period of a year. The MRI/MRA 1 year after surgery showed left STA-MCA bypass as the thick high signal, and there was no abnormality of the cerebral cortex at the site of the hyperperfusion.

3. Discussion

Cerebrovascular reconstruction surgery including carotid endarterectomy or extracranial-intracranial bypass in patients with atherosclerotic cerebral stenoocclusive diseases can cause a rapid increase in CBF in the chronic ischemic brain, resulting in complications such as "cerebral hyperperfusion syndrome" [7,8,16,18,19,21]. Patients with poorer cerebrovascular reactivity are known to have potentially higher risk for hyperperfusion syndrome [8,11,13]. The severity of the intraoperative ischemia is also reported to be one of the predictive factors for postoperative hyperperfusion syndrome after carotid endarterectomy [11]. Recent evidence suggests that STA-MCA anastomosis for moyamoya disease, which usually provides low-flow revascularization because of the relatively small diameter of recipient artery, could also result in symptomatic cerebral hyperperfusion [3-6,12,14]. The incidence of symptomatic hyperperfusion is as high as 38.2% in patients with adult-onset moyamoya disease [4]. The final outcome of these patients was excellent despite their temporary deterioration during the acute stage [4,5]. But we sought to stress it is important to predict the risk for postoperative hyperperfusion and to make accurate diagnosis of this condition because the management of hyperperfusion is contradictory to that for ischemia [3-5,12]. In fact, we experienced one patient who manifested as delayed ICH 4 days after surgery owing to hyperperfusion (Table 1). Furthermore, Houkin and colleagues [10] have reported 2 cases of hemorrhagic-onset moyamoya disease manifesting as postoperative intracerebral hemorrhage because of unknown mechanism after STA-MCA anastomosis. However, the exact incidence and the predictive factors for postoperative symptomatic hyperperfusion are totally undetermined in moyamoya disease. In our present series of 80 consecutive surgeries of STA-MCA anastomosis, the incidence of symptomatic hyperperfusion was 27.5%, whereas no patients had permanent neurologic deterioration compared to preoperative status (Table 1). The present study also indicates, for the first time, that patients' age and the type of the onset are the significant factors to predict postoperative symptomatic hyperperfusion (Table 2). Adult-onset patients had significantly higher risk for symptomatic hyperperfusion compared to child-onset patients (P = .0128). Patients with

symptomatic hyperperfusion were significantly older (mean, 39.8 years old) than those without it (mean, 28.8 years old; $P = .0134$). Furthermore, the hemorrhagic-onset patients had significantly higher risk for symptomatic hyperperfusion compared to the other patients ($P = .0267$). On the contrary to the result in carotid endarterectomy [11], intraoperative temporary occlusion time did not correlate with the incidence of postoperative symptomatic hyperperfusion in patients with moyamoya disease.

The reason why adult-onset and/or hemorrhagic-onset patients had higher risk for hyperperfusion is unclear. Because the vulnerability of the BBB in patients subjected to the chronic ischemia is thought to be one of the important factors for cerebral hyperperfusion [21], it is conceivable that similar mechanism regarding BBB maintenance, which facilitate hemorrhage in patients with moyamoya disease, could also contribute to the occurrence of postoperative cerebral hyperperfusion. Because ROS has been implicated in cerebral ischemia/reperfusion injury [2], excessive production of ROS during revascularization may also affect vascular permeability and thus result in transient neurologic deterioration and/or hemorrhagic complications. In fact, antioxidant agent is reported to prevent cerebral hyperperfusion syndrome after carotid endarterectomy in patients with atherosclerotic occlusive disease and markedly affected cerebrovascular reserve capacity [13]. Therefore, we treated our patients with edaravone, a novel free radical scavenger, to ameliorate the unfavorable effects of hyperperfusion on the affected brain [4]. From biochemical viewpoint, certain specific conditions such as the overexpression of proteins including angiogenic factors and extracellular matrix proteins, which not only contribute to angiogenesis but also affect vascular permeability in the chronic ischemic cortex [1], may be involved in these intrinsic responses to vascular reconstruction against chronic ischemic brain in moyamoya disease. These issues remained to be elucidated in the future study. By delineating these cascades, prophylactic blockade of these deleterious molecules in high-risk patients may be helpful to avoid unfavorable complications including postoperative cerebral hyperperfusion after STA-MCA anastomosis in patients with moyamoya disease, which could be the new therapeutic approach in combination with surgery for moyamoya disease.

In conclusion, the STA-MCA anastomosis is a safe and effective treatment of moyamoya disease, although adult-onset and/or hemorrhagic-onset patients had higher risk for symptomatic hyperperfusion. We recommend routine CBF measurement especially for these patients because the management of hyperperfusion is contradictory to that of ischemia.

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Efficacy of the revascularization surgery for adult-onset moyamoya disease with the progression of cerebrovascular lesions

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ABSTRACT

Object: In moyamoya disease, despite its progressive nature of the occlusive lesions in pediatric patients, the prevalence of the progression in adult patients is undetermined. Furthermore, the optimal timing of the revascularization surgery for progressive cases is controversial. To address these issues, we retrospectively investigate four cases with the adult-onset moyamoya disease manifesting as progression before revascularization surgery.

Methods: From March 2004 to May 2007, 49 patients with adult-onset moyamoya disease aged from 19 to 62 years old (mean 40.5) underwent superficial temporal artery–middle cerebral artery (STA–MCA) anastomosis on 63 hemispheres. All patients were strictly followed up by magnetic resonance (MR) imaging/angiography postoperatively. Twenty-seven hemispheres of 15 adult patients without surgery were also followed up at outpatient service during the same period. If the patients manifest as the progression of the steno-occlusive lesion on the hemisphere without surgery, they undergo revascularization surgery after the confirmation of hemodynamic compromise.

Results: During this period, 47 hemispheres including those of outpatient cases were conservatively followed up after initial diagnosis. Among them, six hemispheres (12.8%) of four patients had been proven to show apparent progression of steno-occlusive lesion and were subjected to revascularization surgery. Postoperative courses were uneventful in all four cases, and no patient suffered cerebrovascular event on the operated hemisphere after surgery.

Conclusion: Adult-onset moyamoya disease, either bilateral or unilateral, has a substantial risk for progression, and careful follow-up is necessary for asymptomatic hemisphere. Once the patient manifests as the progression of cerebrovascular occlusive lesions or ischemic symptoms, we recommend revascularization surgery after the confirmation of the hemodynamic compromise.

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 [1]. In pediatric patients, the occlusive lesions frequently progress or unilateral lesions become bilateral lesions. On the other hand, the progression of steno-occlusive lesion has been believed to be quite rare among adult patients [2–4], while recent evidence suggests that adult patients with moyamoya disease and unilateral moyamoya disease also have substantial risk for the progression of steno-occlusive lesion [5–16].

Surgical revascularization for moyamoya disease is believed to prevent cerebral ischemic attacks by improving cerebral blood flow (CBF), and superficial temporal artery–middle cerebral artery (STA–MCA) anastomosis with or without indirect pial synangiosis is generally employed as the standard surgical procedure for moyamoya disease [17–21]. Regarding the timing of the revascularization surgery for moyamoya disease, however, it is undetermined when the patients should undergo surgery during the course owing to the uncertainty of the natural course of this rare entity, which may be completely distinct from atherosclerotic occlusive cerebrovascular disease. There is no consensus on surgical indication and on the optimal timing of revascularization surgery especially in patients with adult-onset moyamoya disease manifesting as the progression of steno-occlusive lesion. Thus we retrospectively investigated four cases with the adult-onset moyamoya disease operated on six hemispheres, which had been proven to show apparent progression of steno-occlusive lesion during the observational period before revascularization surgery.

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Table 1
Summary of patients manifested as the progression of steno-occlusive lesions before surgery.

Case	Age/gender	First onset			Progression		
		Types of stroke	Side of lesion	Bypass surgery	Progressive lesion	Types of stroke	Bypass surgery
1	24/F	INF (Lt)	Blt	Left	Rt. MCA	TIA (Rt)	Rt
2	31/F	TIA (Lt)	Lt	None	Rt. MCA Lt MCA	TIA (Rt)	Blt
3	33/M	TIA (Lt)	Blt	None	Rt. MCA Lt. PCA	TIA (Blt)	Blt
4	53/M	TIA (Rt)	Rt	None	Rt. MCA Lt. ICB	TIA (Rt)	Rt

Lt, left; Rt, right; Blt, bilateral; TIA, transient ischemic attack; INF, cerebral infarction; Lt, Rt, and Blt in column of types of stroke indicate the side of symptomatic hemisphere; ICB, internal carotid artery bifurcation; MCA, middle cerebral artery; PCA, posterior cerebral artery.

2. Materials and methods/case material

From March 2004 to May 2007, revascularization surgery was performed on 80 hemispheres of 58 consecutive patients (2–62 years old, mean 34.4) with moyamoya disease by the same surgeon (M.F.) in Tohoku University Hospital [22,23]. In this study, we focused on 49 adult-onset patients (19–62 years old, mean 40.5) operated on 63 hemispheres and exclude 9 pediatric patients operated on 17 hemispheres. All patients underwent diagnostic angiogram on admission, and 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 three patients with 'probable moyamoya disease' with unilateral involvement. All patients underwent STA–MCA anastomosis with or without encephaloduromyosynangiosis (EDMS) [22,23]. Our surgical indication includes all of the following items: (1) the presence of ischemic symptoms, (2) apparent flow compromise by single-photon emission computed tomography, (3) independent activity of daily life (modified Rankin Score 0–2), and (4) absence of major cerebral infarction. All the hemispheres which did not match these criteria were excluded from initial surgery. All patients were strictly followed up by routine outpatient services every 6 months using 1.5 or 3 T magnetic resonance (MR) imaging and MR angiography. During the same period, 27 hemispheres of 15 adult-onset patients with moyamoya disease (including those of unilateral involvement) and without surgery were also followed up conservatively at outpatient service. If the patients manifest as the progression of the steno-occlusive lesion on the hemisphere without surgery, they were immediately subjected to the CBF analysis using N-isopropyl-p-[^{123}I] iodoamphetamine single-photon emission computed tomography (^{123}I-IMP-SPECT). The cerebral perfusion reserve capacity was evaluated by the administration of acetazolamide. The CBF was quantified by the autoradiographic method, and the CBF in each subregion was automatically calculated by 3DSRT (three-dimensional stereotactic region of interest template) software (version 2) provided by Daiichi Radio-Isotope (Tokyo, Japan). When the CBF at rest is under 80% of normal CBF (about 42 ml per 100 g/min) and reactivity to acetazolamide is under 10%, we regard the CBF state as hemodynamic compromise. Once the flow compromise is confirmed, the patients underwent revascularization surgery.

We retrospectively investigate the clinical feature and efficacy of revascularization surgery for the patients who had been proven to have the apparent progression of steno-occlusive lesion during the observational period by routine MR imaging/angiography before revascularization surgery.

3. Results

During this period, 47 hemispheres including those of outpatient cases were conservatively followed up after initial diagnosis with the mean follow-up period of 25.4 months. Among them, six hemispheres (12.8%) of four patients (male/female = 2/2, 24–53 years old) had been proven to show apparent progression of steno-occlusive lesion and were subjected to revascularization surgery (Table 1). Two patients had definitive moyamoya disease (definite cases), and the remaining two patients had "unilateral" moyamoya disease (probable cases) at the initial diagnosis. The type of the onset was ischemia in all four patients, including one patient with cerebral infarction and the other three patients with transient ischemic attack (TIA). The interval periods from the initial diagnosis to the revascularization surgery for the affected hemispheres with progression ranged from 21 months to 44 months. Progression of steno-occlusive lesion was noticed by MRA on TIA in three patients, and the other one patient underwent MRA due to the epileptic attack. The flow compromises were confirmed in all for patients on six hemispheres. Six hemispheres with progression of arterial stenosis in this study, all matched our surgical indication criteria

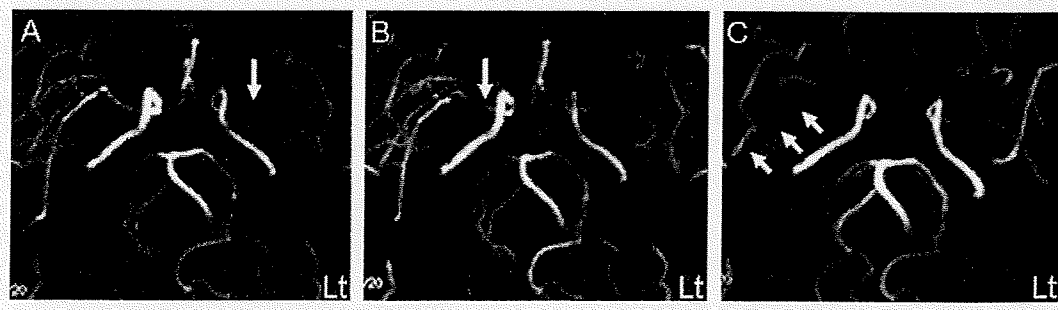

Fig. 1. Magnetic resonance angiography showed the stenosis on horizontal segment of only the left middle cerebral artery (MCA) 7 months after the onset (arrow in A). One year later, follow-up MRA showed stenosis on horizontal segment of the right MCA as well as the left side (arrow in B). Two years and 5 months after the onset, MRA showed progressed steno-occlusive lesion of the right MCA and weak signals of MCA branches (arrows in C).

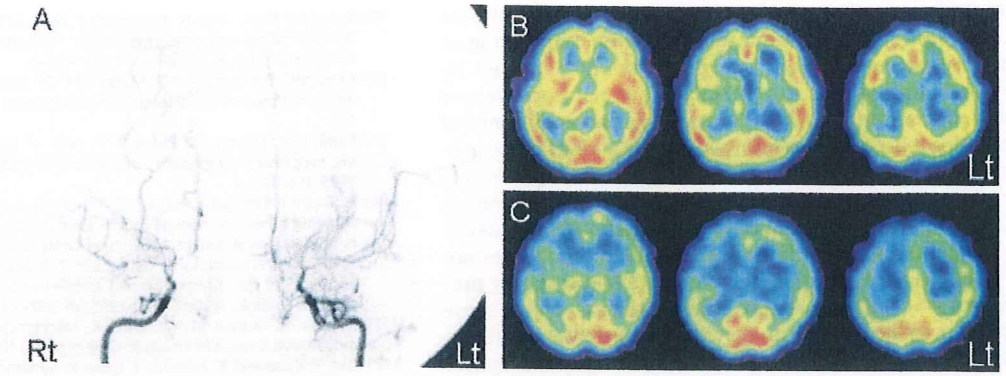

Fig. 2. Preoperative cerebral angiography showed stenosis of bilateral internal carotid arteries, middle cerebral arteries and anterior cerebral arteries. Basal moyamoya vessels were developed obviously on the left and slightly on the right (A). Preoperative ^{123}I-IMP-SPECT showing mildly decreased cerebral blood flow (B) and severely compromised reserve capacity of bilateral cerebral hemispheres (C).

after the progression, thus we operated all four patients STA–MCA anastomosis and EDMS on six hemispheres subsequently. Postoperative courses were uneventful in all cases, and no patients suffered from cerebrovascular event on the operated hemisphere after surgery.

3.1. Representative case (case 2)

A 28-year-old woman suffered TIA of the right hemiparesis. Cerebral angiography showed unilateral moyamoya disease on the left side. She visited another hospital for the second opinion 7 months after the onset. The MRA showed the stenosis on horizontal segment of the left MCA (Fig. 1A). The next year, follow-up MRA showed stenosis on horizontal segment of the right MCA as well as on the left side (Fig. 1B). After that, she underwent follow-up MRA every 6 months for 1.5 years, and steno-occlusive lesion of the right MCA became more severe and signal of MCA branches (Fig. 1C) weakened. Around the same time, she began to present TIA of sensory disturbance of left hand. Cerebral angiography (Fig. 2A) revealed stenosis of bilateral internal carotid artery, MCA and anterior cerebral artery. Basal moyamoya vessels were developed obviously on the left and slightly on the right. Based on these findings, she was diagnosed as definitive moyamoya disease. ^{123}I-IMP-SPECT demonstrated decreased cerebral blood flow and compromised reserve capacity of bilateral cerebral hemispheres (Fig. 2B and C). First, she underwent STA–MCA anastomosis and EDMS on the right hemisphere, and then on the left hemisphere 3 months later. Postoperative MRA (Fig. 3) showed the patent STA–MCA bypass on both hemispheres. Postoperative course was uneventful and her TIA was completely disappeared after surgery. She had no cerebrovascular event during the follow-up period of 1 year.

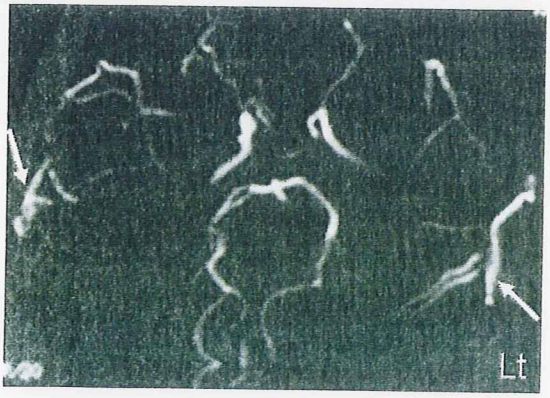

Fig. 3. Postoperative magnetic resonance angiography showed patency of STA–MCA bypass bilaterally (arrows).

4. Discussion

Six hemispheres (6/47, 12.8%) of four patients had been proven to show apparent progression of steno-occlusive lesion associated with hemodynamic compromise during the mean follow-up period of 25.4 months, and were subjected to revascularization surgery. Two patients were found to be the definitive moyamoya disease, and the other two patients were probable moyamoya disease with unilateral involvement at the initial diagnosis. Strict follow-up by ischemic symptoms and radiological examinations indicated the adequate timing for surgery. All four patients have not shown ischemic event after surgery.

Disease progression in adult-onset moyamoya disease was believed to be very rare previously. But the increasing evidence suggests that substantial number of the patients with adult-onset moyamoya disease also presented progression of steno-occlusive lesions [8–16], and that disease progression occurs in about 20% of patients during a mean follow-up period of 6 years [5]. During follow-up periods (mean 73.6 months), the occlusive lesions in the major intracranial arteries progressed in 15 of 86 sides (17.4% per hemisphere) or in 15 of 63 patients (23.8% per patients) [5]. Steno-occlusive lesions progress in both anterior and posterior circulation, in both bilateral and unilateral types, and in both symptomatic and asymptomatic patients [5]. A nation-wide questionnaire survey collected 2193 cases of definite moyamoya disease in Japan and 33 cases of them (33/2193 = 1.5%) were asymptomatic [24], and 7 patients (7/33 = 21.2%) became symptomatic during 3 years and 8 months follow-up periods on average. It is also reported that 5 of 13 patients with adult-onset unilateral moyamoya disease presented angiographic progression from unilateral to bilateral disease during radiological follow-up of 19.3 months [7]. Multivariate analysis in the recent study, the incidence of disease progression was significantly higher in female patients than in male patients [5]. In our study, six hemispheres (6/47, 12.8%) of four adult-onset patients, including two male and two female patients, underwent revascularization surgery due to progression of steno-occlusive lesion. Therefore strict and long-term follow-up should be given for patients with even adult-onset, asymptomatic or unilateral moyamoya disease.

The STA–MCA anastomosis is considered to be effective for improving cerebral blood flow and metabolism and preventing

ischemic stroke in patients with adult-onset moyamoya disease [25,26]. A case of adult-onset moyamoya disease manifesting as the repetitive ischemic symptoms was successfully treated by direct revascularization surgery [27]. But there is no consensus on indication and optimal timing of revascularization surgery of patients with adult-onset moyamoya disease manifesting the progression of arterial stenosis. Our surgical indication includes (1) presence of ischemic symptoms, (2) apparent flow compromise by SPECT, (3) independent activity of daily life, and (4) absence of major cerebral infarction. But our surgical indication does not include intellectual/cognitive impairment. We are evaluating pre- and postoperative higher function in pediatric cases, and these issues remain to be solved in the future study. Nevertheless, recent report suggests that careful follow-up for the hemisphere without ischemic symptom is an acceptable choice based on the retrospective data of pediatric cases [4]. In our study, once the patient manifests as the progression of arterial stenosis or ischemic symptoms, we confirmed the compromised CBF and performed revascularization surgery on the progressed hemisphere. Six hemispheres of four adult-onset patients underwent revascularization surgery after the progression of arterial stenosis and all four patients had good prognosis. Thus we recommend revascularization surgery for the affected hemisphere after the confirmation of the presence of flow compromise in patients with adult-onset moyamoya disease manifesting as the progression of steno-occlusive changes. Future study with large number of series including the patients with probable moyamoya disease is necessary to clarify the natural history of moyamoya disease and to establish surgical indication for progressive cases among adult patients.

5. Conclusions

The present study indicates that adult-onset moyamoya disease, either bilateral or unilateral, has a substantial risk for progression, and careful follow-up is warranted for asymptomatic hemisphere by routine radiological study. Once the patient manifests as the progression of cerebrovascular occlusive lesion or ischemic symptoms, we recommend revascularization surgery for the affected hemisphere after the confirmation of the flow compromise by CBF analysis.

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Vascular

Increased expression of serum matrix metalloproteinase-9 in patients with moyamoya disease

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Abstract

Background: Moyamoya disease is a chronic occlusive cerebrovascular disease with unknown etiology characterized by an abnormal vascular network at the base of the brain, which can manifest both as ischemic stroke and as cerebral hemorrhage. It was also reported that the patients with moyamoya disease are more vulnerable to cerebral hyperperfusion such as postoperative hemorrhagic complication after extracranial-intracranial bypass surgery despite its low flow revascularization. However, the underlying mechanisms of its pathologic angiogenesis and the occurrence of hemorrhage are undetermined. Excessive degradation of the vascular matrix by MMPs, proteolytic enzymes that degrade all the components of extracellular matrix, can lead to instability of the vascular structure and can thereby cause bleeding. The MMPs also play an important role in tissue remodeling including angiogenesis in both physiologic and pathologic condition.

Methods: We examined the serum levels of MMP-2 and MMP-9 in 16 cases with definitive moyamoya disease by enzyme-linked immunosorbent assay and compared them with those from healthy controls.

Results: The serum MMP-9 level was significantly higher in moyamoya disease (40.18 ng/mL) than in healthy controls (13.75 ng/mL, $P = .0372$). There was no difference in serum MMP-2 level between moyamoya disease (646.65 ng/mL) and healthy control (677.60 ng/mL). Immunohistochemistry on the surgical specimens showed significant increase in MMP-9 expression within the arachnoid membrane of moyamoya disease.

Conclusion: The increased expression of MMP-9 may contribute to pathologic angiogenesis and/or to the instability of the vascular structure and could thereby cause hemorrhage in moyamoya disease.

Keywords: Moyamoya disease; Matrix metalloproteinase; Enzyme-linked immunosorbent assay; Immunohistochemistry

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 [14]. It can manifest not only as ischemic stroke owing to the steno-occlusive changes at the major cerebral arteries, but also as spontaneous hemorrhage from collateral vessels or from cerebral aneurysm [3,14,16]. An abnormal vascular network shows two different patterns of histological change: either dilated, thin-walled arteries or obstruction from recent thrombi or mural thickening with or without elastosis or fibrosis, suggesting the hemodynamic changes in the moyamoya vessels during the clinical course [6]. On the

Abbreviations: BBB, blood-brain barrier; CNS, central nervous system; MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinases.

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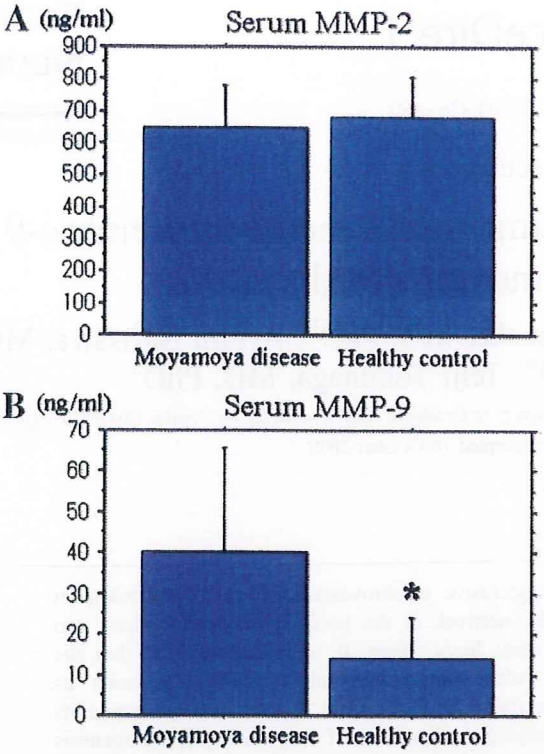

Fig. 1. Serum level of MMP-2 (A) and MMP-9 (B) in patients with moyamoya disease (n = 16) and healthy controls (n = 5). Serum MMP-9 level was significantly higher in patients with moyamoya disease (40.18 ng/mL) than in healthy controls (13.75 ng/mL, $P = .0372$).

other hand, histopathological evidence also suggests the presence of lipohyalinosis and multiple microaneurysms in small moyamoya vessels with diameters of 50 to 1500 μm, indicating the intrinsic vulnerability of this abnormal vascular network [6,10]. However, the underlying mechanism of such abnormal vascular network formation and the occurrence of spontaneous hemorrhage, both of which are characteristic of moyamoya disease, is undetermined. Furthermore, it was reported that patients with moyamoya disease could be more vulnerable to cerebral hyperperfusion including vasogenic edema and hemorrhagic transformation after extracranial-intracranial bypass surgery, despite its low flow revascularization obtained by this standard procedure [3-5,12]. These observations together raise the possibility that patients with moyamoya disease have an intrinsic background that can facilitate angiogenesis and blood-brain barrier (BBB) disruption including vasogenic edema and spontaneous hemorrhage.

Matrix metalloproteinases (MMPs) are a family of zinc-binding proteolytic enzymes that are capable of degrading all the components of extracellular matrix in a variety of physiologic and pathophysiological conditions of the CNS [1,2,8,9,11,13,15,17]. But the expression of MMPs in moyamoya disease has not been examined previously. In the present study, we sought to examine the serum levels of MMP-2 and MMP-9 in patients with moyamoya disease, both of which can digest endothelial basal lamina by their collagenase activities and are implicated in many pathophysiological conditions in CNS disorders including intracerebral hemorrhage [9,13], cerebral aneurysm [17], traumatic brain injury [15], cerebral cavernous malformation [2], and vasogenic edema formation and hemorrhagic transformation after cerebral stroke [1,11].

2. Materials and methods

The present study included 16 patients with definitive moyamoya disease aged from 8 to 62 years (mean, 39.8 years) and 5 healthy controls. All patients with moyamoya 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. Serum was collected at an outpatient service. There were 6 patients with hemorrhagic-onset moyamoya disease (21-62 years old; mean, 46.0 years) and 10 patients with ischemic-onset moyamoya disease (8-57 years old; mean, 36.0 years). To avoid the biological effect of cerebrovascular event including cerebral infarction and cerebral hemorrhage [1,11], all samples were collected at least 6 months after the onset when the MMP-2 and MMP-9 were suspected to return to the

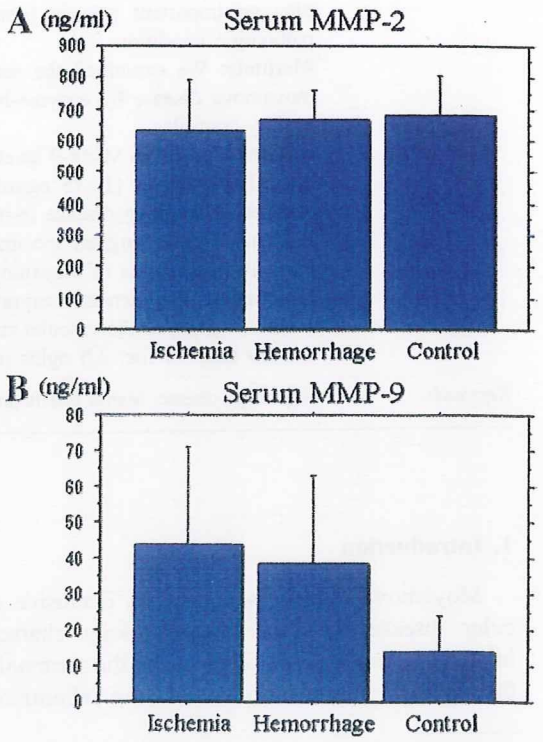

Fig. 2. Serum level of MMP-2 (A) and MMP-9 (B) in patients with ischemic-onset moyamoya disease (*ischemia*; n = 10), those with hemorrhagic-onset moyamoya disease (*hemorrhage*; n = 6), and healthy controls (*control*; n = 5). There was no difference in serum MMP-2 levels ($P = .82$) between each group (A). There was no difference either in serum MMP-9 levels ($P = .089$) between each group (B).

baseline level. The experiments were conducted in accordance with the Declaration of Helsinki.

Serum MMP-2 was measured using an enzyme-linked immunosorbent assay kit obtained from Daiichi Fine Chemical Co Ltd (Takaoka, Japan), which specifically detects pro-MMP-2. Serum MMP-9 was measured using the MMP-9 Biotrak Activity Assay Kit (Amersham Biosciences, Piscataway, NJ), which allows us to detect total MMP-9 level. We quantified the MMP-2 and MMP-9 levels twice in each patient, and the mean level of each marker was used as the result, which was analyzed by unpaired *t* test using StatView software (SAS Institute, Inc, Cary, NC) in patients with moyamoya disease and healthy controls. We also compared the result of healthy controls, hemorrhagic-onset patients, and ischemic-onset patients between each group, which was analyzed by 1-factor analysis of variance using Excel 2003 software (Microsoft, Inc, Redmond, Wash). A P value less than .05 was considered to be significant.

We performed immunohistochemistry for MMP-9 using paraffin-embedded sections of the surgical specimens as previously described [2]. Before superficial temporal artery–middle cerebral artery anastomosis [3-5], arachnoid membrane around the site of the anastomosis was carefully collected. The samples were sectioned by cryostat and were incubated with a blocking solution and reacted with anti–MMP-9 mouse monoclonal antibody (Toyama Pharmaceutical Co, Takaoka, Japan) at a dilution of 1:100. Immunohistochemistry was performed using the avidin-biotin technique, and then the nuclei were counterstained with methyl green solution for 10 minutes. As a negative control, specimens from the same patients were incubated without primary antibody. We also performed immunohistochemistry for MMP-9 on arachnoid membranes on normal brain obtained during frontal lobectomy for glioma. The study complies with the Declaration of Helsinki, and the research protocol was approved by the ethics committee of Tohoku University Graduate School of Medicine.

3. Results

As shown in Fig. 1A, there was no difference in serum MMP-2 level between moyamoya disease (mean ± SD, 646.65 ± 133.42 ng/mL) and healthy control (mean ± SD, 677.60 ± 128.66 ng/mL). The serum MMP-9 level was significantly higher in patients with moyamoya disease (mean ± SD, 40.18 ± 25.5 ng/mL) than in healthy controls (mean ± SD, 13.75 ± 10.14 ng/mL) (P = .0372) as shown in Fig. 1B. As compared between each onset type and healthy control using analysis of variance, there was no difference in serum MMP-2 levels (P = .82) between patients with ischemic-onset moyamoya disease (633.60 ± 161.31 ng/mL), those with hemorrhagic-onset moyamoya disease (664.83 ± 96.03 ng/mL), and healthy controls (667.60 ± 128.66 ng/mL) (Fig. 2A). There was no difference either in serum MMP-9 levels (P = .089) between patients with ischemic-onset moyamoya disease (43.84 ± 27.08 ng/mL),

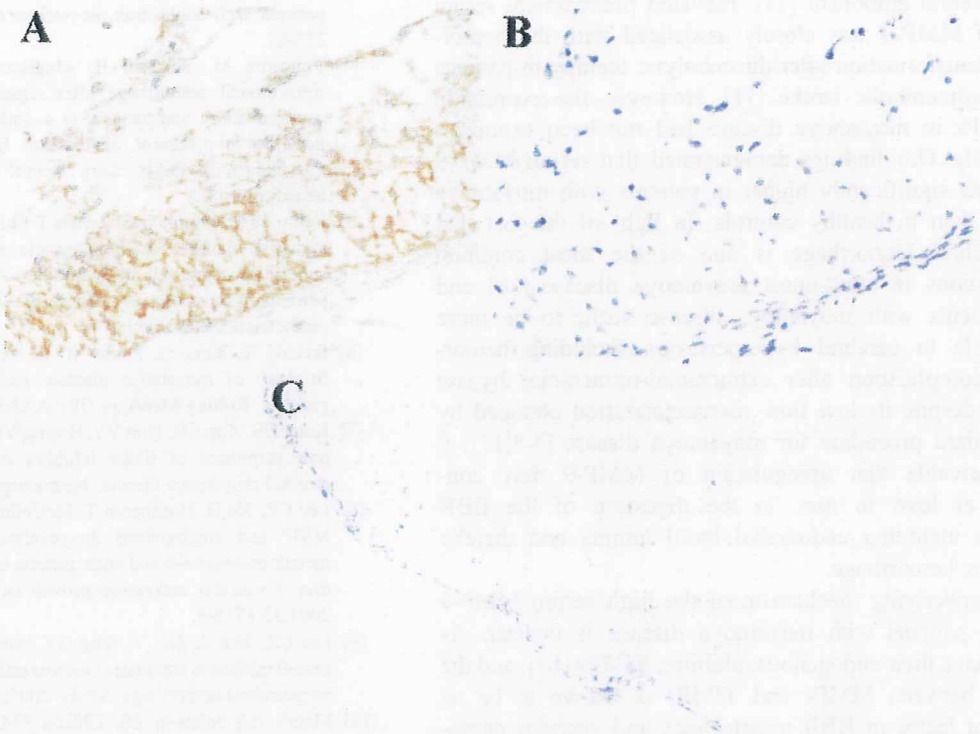

Fig. 3. A: Immunohistochemical analysis for MMP-9 on the surgical specimen obtained from patients with moyamoya disease demonstrating increased expression of MMP-9 within the arachnoid membrane. B: Negative control incubated without primary antibody showing no immunostaining. C: MMP-9 expression on normal arachnoid membrane, demonstrating less immunostaining compared to that from patients with moyamoya disease.

those with hemorrhagic-onset moyamoya disease (38.25 ± 24.64 ng/mL), and healthy controls (13.75 + 10.14 ng/mL) (Fig. 2B). Finally, immunohistochemistry on the surgical specimens from 7 patients with moyamoya disease showed a significant increase in MMP-9 expression within arachnoid membrane in all seven cases (Fig. 3A), whereas there was no immunostaining on negative control incubated without primary antibody (Fig. 3B). The MMP-9 expression was barely observed in arachnoid membrane on normal brain (Fig. 3C).

4. Discussion

The present study demonstrated, for the first time, that serum MMP-9 level is significantly higher in patients with moyamoya disease than in healthy controls. Matrix metalloproteinases are a family of zinc-binding proteolytic enzymes that are capable of degrading all the components of extracellular matrix in a variety of physiologic and pathophysiological conditions. Among MMPs, gelatinase A (MMP-2) and gelatinase B (MMP-9) are able to digest the endothelial basal lamina, which plays a major role in maintaining BBB impermeability, by regulating tight junctions leading to the opening of BBB [13]. Both MMP-2 and MMP-9 are implicated in many pathophysiological conditions in CNS such as cerebral ischemia [1], traumatic brain injury [15], formation and rupture of cerebral aneurysm [17], hemorrhage from cerebral cavernous malformation [2], and hemorrhagic transformation after cerebral embolism [11]. Elevated pretreatment serum level of MMP-9 was closely associated with the hemorrhagic transformation after thrombolytic therapy in patients with cardioembolic stroke [11]. However, the expression of MMPs in moyamoya disease had not been examined previously. Our findings demonstrated that serum MMP-9 level was significantly higher in patients with moyamoya disease than in healthy controls. In light of the fact that intracerebral hemorrhage is one of the most common presentations in adult-onset moyamoya disease [16] and that patients with moyamoya disease seem to be more vulnerable to cerebral hyperperfusion including hemorrhagic complication after extracranial-intracranial bypass surgery despite its low flow revascularization obtained by the standard procedure for moyamoya disease [3-5,12], it is conceivable that upregulation of MMP-9 may contribute, at least in part, to the digestion of the BBB structure including endothelial basal lamina and thereby facilitates hemorrhage.

The underlying mechanism of the high serum MMP-9 level in patients with moyamoya disease is unclear. As MMPs have their endogenous inhibitor, TIMPs [13], and the balance between MMPs and TIMPs is known to be an important factor of BBB maintenance and vascular angiogenesis [8], it would be of great value to evaluate TIMP expression in patients with moyamoya disease. In fact, the investigation of single nucleotide polymorphism of the TIMP-2 gene, located at chromosome location of familial moyamoya disease (17q25), delineated the presence of G/C heterozygous genotype at −418 in TIMP-2 promoter, which could be a genetic predisposing factor for familial moyamoya disease [7]. These observations raise the possibility that dysfunction of the TIMP-2 gene could affect the balance between TIMPs and MMPs, and then lead to abnormal increase in MMP-9 expression in familial moyamoya disease. Although the present study included no patient with familial moyamoya disease, a similar mechanism could be involved in the increased expression of MMP-9 and then facilitate the occurrence of hemorrhage and the formation of abnormal vascular network in patients with sporadic moyamoya disease. Further evaluation with larger number of patients with both sporadic and familial moyamoya disease would address this important issue.

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Commentary

In this study, the authors demonstrated that serum-MMP-9 is significantly elevated in patients with moyamoya disease and further showed that MMP-9 expression is highly elevated in the arachnoid membrane of these patients.

In the field of cerebral ischemia, MMPs have become a target of intense study. These MMPs are expressed in glial and inflammatory cells, and are supposed to disintegrate the BBB, leading to hemorrhagic transformation and edema formation [1,3,4]. They are also suggested to be involved in tissue neurovascular remodeling [6]. In addition, direct toxic effect of MMP-9 on cultured neurons has recently been shown [5]. These observations would suggest a detrimental role of upregulated MMP-9 in cerebral stroke. In this regard, this article would contribute greatly to our understanding of moyamoya disease. Although one might expect that patients presenting with hemorrhage have higher levels of MMP-9, this was not the case in this study. Although we do not know whether MMP-9 contributes directly to hemorrhagic complication in moyamoya disease from this study, this finding may explain that ischemic patients are always at risk of hemorrhagic complication. Further study would be required to clarify this issue. As inhibitor of MMP, such as minocycline, has been shown to attenuate hemorrhage stroke in the animal models [2], therapeutic approaches from this field would be of great interest.

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CASE REPORT

Cerebral ischemia owing to compression of the brain by swollen temporal muscle used for encephalo-myo-synangiosis in moyamoya disease

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Abstract Compression of the brain by swollen temporal muscle used for indirect pial synangiosis is a rare complication after the revascularization surgery for moyamoya disease, and its mechanism and clinical presentation are undetermined. A 26-year-old woman, who had been suffering transient ischemic attack (TIA), underwent superficial temporal artery-middle cerebral artery anastomosis with encephalo-myo-synangiosis (EMS) on the affected hemisphere. The ^{123}I-IMP-SPECT 1 day after surgery demonstrated an improvement of cerebral blood flow (CBF) on the operated hemisphere. Two days later, however, she suffered fluctuating aphasia when computed tomography scan revealed marked swelling of the temporal muscle used for EMS. The ^{123}I-IMP-SPECT 4 days after surgery showed significant decrease in CBF by the compression of the brain. Then, we performed revision of EMS. The base of the temporal muscle was markedly compressed by the edge of the free bone flap, which resulted in swelling of the entire temporal muscle used for EMS. We drilled out the edge of the free bone flap for decompression. Her aphasia disappeared postoperatively, and CBF normalized 7 days after the initial surgery. Her TIA disappeared, and there was no deterioration during the follow-up period. The STA-MCA bypass has been patent since the initial surgery. Surgical revascularization including EMS has a substantial risk for cerebral ischemia owing to compression of the brain by temporal muscle swelling. Relative wide bone window for temporal muscle insertion is necessary to avoid this rare complication. Once the flow compromise is confirmed, we recommend early decompression by the revision of EMS.

Keywords Moyamoya disease · Cerebral ischemia · Compression · Surgical complication · Indirect bypass

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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 [7, 11]. Surgical revascularization for moyamoya disease prevents cerebral ischemic attack by improving cerebral blood flow (CBF), and both direct bypass and indirect pial synangiosis are known as the standard surgical procedures for moyamoya disease [1, 3, 5, 8, 10]. Despite the favorable outcome of revascularization surgery for moyamoya disease, it is also reported to result in transient neurologic deterioration due to cerebral hyperperfusion or cerebral ischemia during the acute stage after surgery [1–5, 10]. Since indirect pial synangiosis such as encephalo-myo-synangiosis (EMS) requires the insertion of temporal muscle under the bone flap [8], it has a substantial risk for compression of the brain if it gets swollen [12, 13]. However, the detail of such complication has not been reported except for the limited cases including the chronic stage after

surgery [12, 13]. Here, we report a case of moyamoya disease which manifested as cerebral ischemia owing to compression of the brain by swollen temporal muscle used for EMS during the acute stage after direct–indirect revascularization surgery. Time sequential performance of *N*-isopropyl-*p*-[^{123}I] iodoamphetamine single-photon emission computed tomography (^{123}I-IMP-SPECT) allowed us to reveal the cerebral hemodynamics during and after this rare complication and provided important information to decide the timing for the revision of EMS.

Case report

A 26-year-old woman, who had been suffering from transient ischemic attack (TIA) during the past 10 years, was admitted to our service. Neurological examination found no abnormality, and initial magnetic resonance angiography (MRA) demonstrated steno-occlusive changes at the terminal portion of the bilateral internal carotid arteries (Fig. 1a). Fluid attenuated inversion recovery (FLAIR) by magnetic resonance imaging (MRI) found "ivy sign" predominantly on the left hemisphere, while there was no cerebral infarction (Fig. 1b). Preoperative ^{123}I-IMP-SPECT found that her CBF and cerebrovascular reactivity were markedly compromised on the left hemisphere (Fig. 1c). Digital subtraction angiography confirmed the diagnosis of moyamoya disease (data not shown). Based on the diagnosis of moyamoya disease with apparent flow compromise and ischemic symptoms, she underwent superficial temporal artery-middle cerebral artery (STA-MCA) anastomosis with EMS on the left hemisphere [1]. The patency of the STA-MCA bypass was confirmed by IRIS-V infrared imaging system during surgery [9], and the postoperative ^{123}I-IMP-SPECT showed increase in CBF on the operated hemisphere (Fig. 2b) compared to the preoperative finding (Fig. 1c). The patient did not suffer neurologic deficit immediately after surgery. Postoperative MRA showed the apparently patent STA-MCA bypass as a thick high signal intensity sign and diffusion weighted image showed no evidence of ischemic change (data not shown). Two days later, however, she suffered from fluctuating aphasia. The computed tomography (CT) scan revealed marked swelling of the temporal muscle used for indirect pial synangiosis which compressed the surface of the left brain (Fig. 2c). The ^{123}I-IMP-SPECT 4 days after surgery showed significant decrease in CBF by the compression of the brain (arrows in Fig. 2d). Based on these findings, we considered that her aphasia was due to cerebral ischemia owing to compression of the brain by swollen temporal muscle used for EMS. Then, we performed revision of indirect bypass 4 days after initial surgery. The base of the temporal muscle was markedly compressed by the edge of the free bone flap, which resulted in swelling of the entire temporal muscle flap used for EMS. We drilled out the edge of the free bone flap and designed relatively wide bone window. We also drilled out the inner layer of the free bone flap for further decompres-

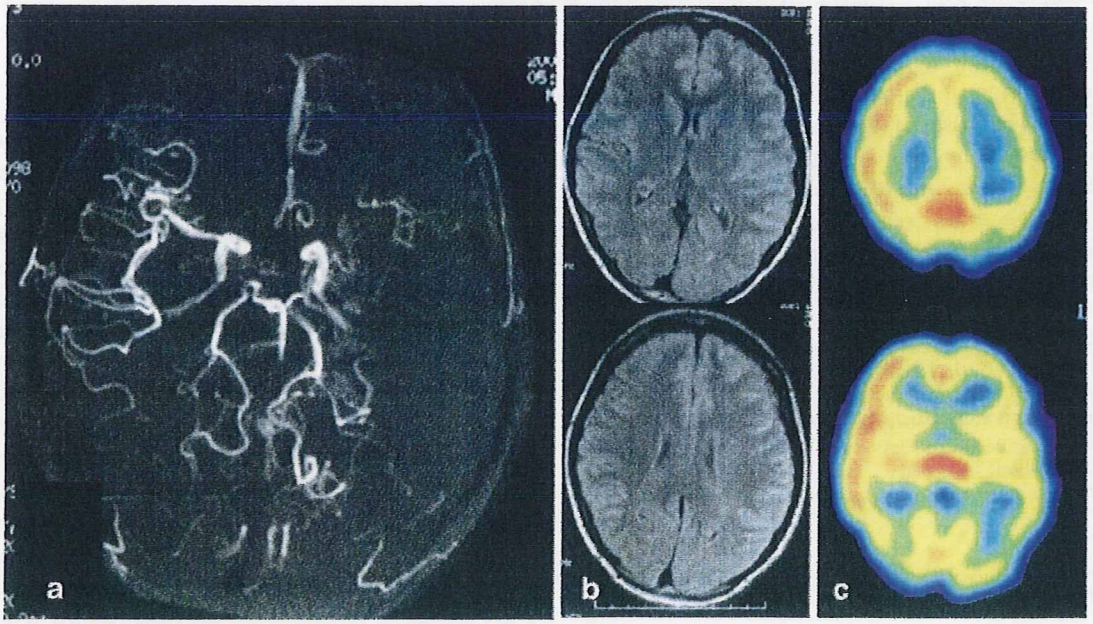

Fig. 1 Preoperative MRA (**a**), FLAIR of MRI (**b**), and ^{123}I-IMP-SPECT at rest (**c**); steno-occlusive changes at the terminal portion of the internal carotid artery were evident bilaterally (**a**). FLAIR demonstrated "ivy sign" predominantly on the left hemisphere, while there was no cerebral infarction (**b**). CBF was decreased in the MCA and ACA territories on the left hemisphere

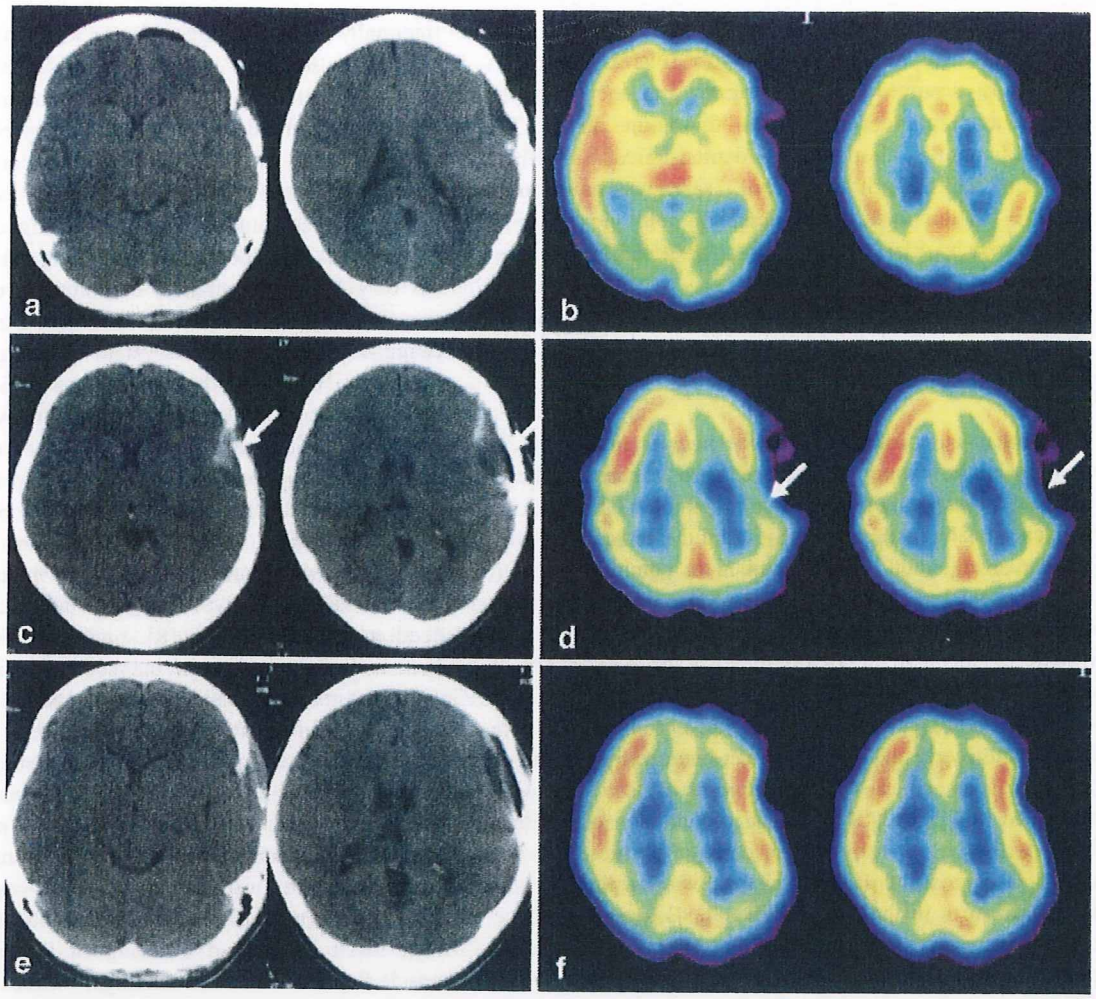

Fig. 2 Temporal profile of CT (**a**, **c**, **e**) and ^{123}I-IMP-SPECT (**b**, **d**, **f**) at 1 day (**a**, **b**), 4 days (**c**, **d**), and 1 week (**e**, **f**) after left STA-MCA anastomosis with indirect pial synangiosis; CBF was increased on the operated hemisphere as early as 1 day after surgery (**b**), but it markedly reduced 4 days after surgery (*arrows* in **d**) when compression of the brain by swollen temporal muscle was apparent by CT (*arrows* in **c**). Revision of indirect bypass with bone flap drilling relieved the compression (**e**), and CBF was significantly increased after decompression (**f**)

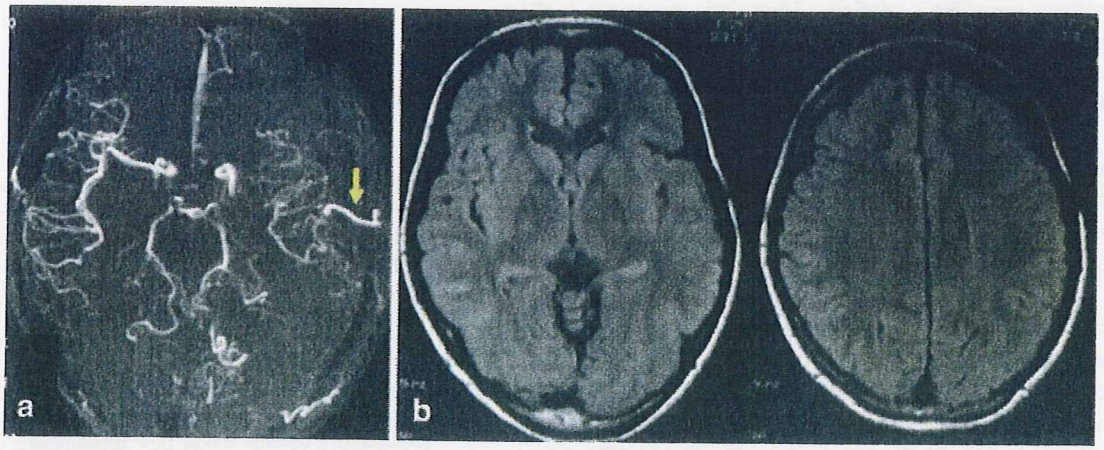

Fig. 3 Postoperative MRA (**a**) and MRI (FLAIR) (**b**) 3 months after revascularization surgery demonstrating that left STA-MCA bypass and the branches of left MCA were well visualized (*arrow* in **a**) and that ivy sign on the left hemisphere was disappeared

sion. Her aphasia was relieved postoperatively and CBF normalized 7 days after initial surgery (Fig. 2f). Her TIA completely disappeared after surgery, and there was no cerebrovascular event during the follow-up period. The MRA 3 months after surgery demonstrated STA-MCA bypass as a thick high signal (Fig. 3a) There was no brain damage on the operated hemisphere, and the ivy sign disappeared by FLAIR (Fig. 3b), suggesting the improvement of cerebral ischemia.

Discussion

The present case indicated that the indirect revascularization procedure for moyamoya disease has a substantial risk for cerebral ischemia owing to compression of the brain by temporal muscle used for EMS during the acute stage after surgery, even when it is performed in combination with direct revascularization procedure. Since recent evidence suggests that surgical revascularization for moyamoya disease could result in temporary neurologic deterioration due to cerebral hyperperfusion during the acute stage after surgery [1–4, 10], it is clinically important to make accurate diagnosis of cerebral hyperperfusion and cerebral ischemia [1], especially when the compression of the brain was suspected by CT or MRI. Clinical presentation of cerebral hyperperfusion in moyamoya disease mimics that of cerebral ischemia, while the management of hyperperfusion is contradictory to that of ischemia [1, 4]. Based on these observations, we have stressed the importance of routine postoperative CBF measurement during the acute stage after revascularization surgery for moyamoya disease [1–3]. In the present case, time sequential ^{123}I-IMP-SPECT allowed us to monitor the alteration of cerebral hemodynamics and provided important information to decide the timing for the revision of EMS. In fact, CBF normalized after the revision of EMS, and the patients was discharged without neurologic deficit. Thus, we recommend CBF analysis during the acute stage after revascularization surgery for moyamoya disease, when the patients manifest as neurologic sign after surgery.

A variety of techniques of indirect revascularization procedure such as EMS [1, 13], encephalo-duro-arterio-synangiosis [8], and multiple burr holes surgery [6] has been reported previously. The combination surgery of direct and indirect revascularization procedures has been getting more standard [1, 3, 5, 9] in light of the observation that the indirect techniques may further improve the postoperative cerebral hemodynamics by additional revascularization form meddle meningeal artery and/or deep temporal artery in wider territory on the ischemic hemisphere [5, 8]. Since we employed EMS in combination with STA-MCA anastomosis, which is one of the most common and minimally invasive indirect bypass techniques, we consider that the most of the indirect revascularization procedures have a substantial risk for the similar complication. Alternatively, multiple-burr-holes surgery could be a treatment of choice to avoid such complication [6] when it is employed without direct procedure. The exact mechanism by which the temporal muscle swelling occurred in the present case is undetermined. Venous congestion caused not only by the mechanical compression of the temporal muscle at the site of the insertion but also by the coagulation of the venous system of the temporal muscle during the manipulation may play a critical role in the pathophysiology of the temporal muscle swelling. Thus, it would be particularly important to preserve venous structure on the temporal muscle as well as to construct wider bone window at the site of temporal muscle insertion during this procedure for avoiding this rare complication.

Indirect revascularization procedure including EMS was reported to be effective especially in patients with childhood moyamoya disease [8], but this procedure has not been well discussed from the cosmetic viewpoint. Bone window for the insertion of temporal muscle used as EMS could result in linear indentation and thus cause aesthetic complaint especially in children and young women with moyamoya disease. The present case was a 26-year-old woman who had just married, and we do not rule out the possibility that minimization of the bone window for temporal muscle insertion in the present case might cause, in part, the compression of the temporal muscle base and, thus, result in marked swelling of the entire temporal muscle flap. Based on our findings, we recommend to drill out the inner layer of bone flap as well as to keep thorough bone window to avoid the risk for this rare complication, as long as the bone window is located behind the hair line. This issue remained to be solved in the future modification of surgical procedure for moyamoya disease also from the aesthetic viewpoint.

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Comments

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The authors report an unusual complication following otherwise uncomplicated left-sided STA-MCA bypass surgery with additional encephalo-myo-synangiosis (EMS) by subdural placement of the temporal muscle in a 26-year old patient who suffered from moyamoya disease: Two days after surgery and after initially documented improvement of CBF thanks to the functioning bypass, she developed aphasia. This was obviously due to considerable swelling of the temporal muscle which was compressed at the inferior level of the bon flap. Thus, they took the patient to the OR again and drilled off the inferior edge and some part of the inner table of the bone flap. This has lead to clinical improvement of the patient's condition that was then discharged without neurological deficits. In the discussion the authors highlight the differential diagnosis for postoperative deterioration in moyamoya patients, which should include not only the well-known complication of postoperative hyperperfusion but swelling of the temporal muscle as well if EMS has been performed.

Having a lower incidence in Europe than in Japan, moyamoya disease is being seen at centers with dedicated teams for neurovascular treatment mainly. There is a regain of interest, however, in the performance of EC-IC bypasses, with more and more unruptured complex aneurysms detected, which are not all amenable to endovascular therapy and with more elaborate tests for the precise diagnostics of cerebrovascular insufficiency now available, which does also contribute to the increasing numbers of EC-IC bypasses performed recently. Although local compression of the bypass with consecutive muscular swelling is more likely to occur with EMS, it may as well occur due to venous stasis or subgaleal rebleeding in EC-IC bypass surgery alone without additional EMS. Thus, I see the very practical aspect of this case description and on how the authors have successfully managed this unusual postoperative complication. This includes the knowledge of two important differential diagnoses for clinical deterioration following primarily successful bypass surgery with or without additional EMS: hyperperfusion or ischemia. They have successfully ruled out hyperperfusion by IMP-SPECT, which showed ischemia, whereas MRA revealed the patent STA-MCA bypass. We perform postoperative perfusion MRI and Duplex sonography in our bypass patients regularly, and I think the analogous problem might not have gone unnoticed as well. I think this report is a nice technical contribution and of interest for those of us who deal with neurovascular diseases.

Masao Sugita, Hiroyuki Kinouchi, Yamanashi, Japan

The authors provide a thoughtful analysis of a case with moyamoya disease suffered from rare postoperative complication. This study contains two kinds of essential information. First, they indicated the importance to evaluate the cerebral blood flow alteration in the acute stage following revascularization procedure especially when the symptoms appeared in order to differentiate ischemia from hyperperfusion since their clinical presentation is similar. Second, they successfully demonstrated that cerebral ischemia by muscle compression could be responsible for postoperative neurologic deterioration, which could be relieved by decompressive encephalo-myo-synangiosis (EMS) revision. The ischemic complications after direct and indirect anastomosis in this disease are commonly by technical failure; however, the mass effect of the swollen vascular supply materials, especially muscle for EMS, could be a cause for cerebral ischemia. Therefore, we should keep in mind of this rare complication.