Table 3 continued

rs ID[a]	Allele	Populations	Controls					Cases					OR[d] (95% CI)	P^e
	1/2		11	12	22	Frequency[b]	P, HWE[c]	11	12	22	Frequency[b]	P, HWE[c]		
rs4890047	C/T	Japanese	147	176	61	0.39	0.546	16	52	22	0.53	0.206	1.80 (1.30–2.50)	4.00×10^{-4}
			38.28%	45.83%	15.89%			17.78%	57.78%	24.44%				
		Korean	78	104	41	0.42	0.612	8	20	13	0.56	1.000	1.79 (1.11–2.87)	0.016
			34.98%	46.64%	18.39%			19.51%	48.78%	31.71%				
		Chinese	31	49	20	0.45	1.000	8	15	0	0.33	0.063	0.60 (0.31–1.19)	0.141
			31.00%	49.00%	20.00%			34.78%	65.22%	0.00%				
		All Asian	256	329	122	0.41	0.389	32	87	35	0.51	0.156	1.53 (1.19–1.95)	8.00×10^{-4}
			36.21%	46.53%	17.26%			20.78%	56.49%	22.73%				
		Caucasian	91	60	13	0.26	0.585	15	8	2	0.24	0.822	0.89 (0.44–1.78)	0.739
			55.49%	36.59%	7.93%			60.00%	32.00%	8.00%				
rs4889863	A/G	Japanese	149	174	61	0.39	0.440	16	52	22	0.53	0.206	1.82 (1.31–2.53)	3.00×10^{-4}
			38.80%	45.31%	15.89%			17.78%	57.78%	24.44%				
		Korean	76	106	41	0.42	0.783	8	20	13	0.56	1.000	1.75 (1.09–2.82)	0.020
			34.08%	47.53%	18.39%			19.51%	48.78%	31.71%				
		Chinese	30	50	20	0.45	1.000	8	15	0	0.33	0.063	0.59 (0.30–1.16)	0.126
			30.00%	50.00%	20.00%			34.78%	65.22%	0.00%				
		All Asian	255	330	122	0.41	0.425	32	87	35	0.51	0.156	1.52 (1.19–1.95)	8.00×10^{-4}
			36.07%	46.68%	17.26%			20.78%	56.49%	22.73%				
		Caucasian	91	60	13	0.26	0.585	15	8	2	0.24	0.822	0.89 (0.44–1.78)	0.739
			55.49%	36.59%	7.93%			60.00%	32.00%	8.00%				
rs11655474	T/C	Japanese	24	148	212	0.74	0.920	2	30	58	0.81	0.691	1.47 (0.98–2.21)	0.062
			6.25%	38.54%	55.21%			2.22%	33.33%	64.44%				
		Korean	16	86	121	0.74	0.993	0	12	29	0.85	0.781	2.10 (1.10–4.01)	0.022
			7.17%	38.57%	54.26%			0.00%	29.27%	70.73%				
		Chinese	8	39	53	0.73	0.971	3	7	13	0.72	0.415	0.96 (0.47–1.96)	0.917
			8.00%	39.00%	53.00%			13.04%	30.43%	56.52%				
		All Asian	48	273	386	0.74	1.000	5	49	100	0.81	0.997	1.49 (1.10–2.03)	0.011
			6.79%	38.61%	54.60%			3.25%	31.82%	64.94%				
		Caucasian	19	61	84	0.70	0.175	2	10	13	0.72	1.000	1.11 (0.57–2.15)	0.754
			11.59%	37.20%	51.22%			8.00%	40.00%	52.00%				

Table 3 continued

rs ID[a]	Allele	Populations	Controls					Cases				OR[d] (95% CI)	P^e
	½		11	12	22	Frequency[b]	P, HWE[c]	11	12	22	Frequency[b]	P, HWE[c]	
rs8080957	A/G	Japanese	28	157	199	0.72	0.818	2	31	57	0.81	0.600	1.59 (1.06–2.38)	0.023
			7.29%	40.89%	51.82%			2.22%	34.44%	63.33%				
		Korean	16	98	109	0.71	0.449	0	14	27	0.83	0.525	2.00 (1.09–3.68)	0.024
			7.17%	43.95%	48.88%			0.00%	34.15%	65.85%				
		Chinese	9	45	46	0.69	0.893	4	8	11	0.65	0.434	0.86 (0.44–1.70)	0.667
			9.00%	45.00%	46.00%			17.39%	34.78%	47.83%				
		All Asian	53	300	354	0.71	0.390	6	53	95	0.79	0.916	1.51 (1.12–2.03)	0.007
			7.50%	42.43%	50.07%			3.90%	34.42%	61.69%				
		Caucasian	26	77	61	0.61	0.932	3	12	10	0.64	1.000	1.15 (0.62–2.14)	0.653
			15.85%	46.95%	37.20%			12.00%	48.00%	40.00%				

NA, Data not available

[a] rs ID, Reference single nucleotide polymorphism (SNP) accession identity number

[b] Frequency of risk allele 2

[c] P, Hardy–Weinberg Equilibrium (HWE) two-sided probability value from the test for deviation from the HWE

[d] OR, Allelic odds ratio with its 95% confidence interval (CI) except for ss161110142, which was calculated under the assumption of dominant effect because of very rare allele frequency

[e] P Cochran–Armitage trend test's P value

present at all in Chinese controls. Consequently, the A allele was associated with a very high odds ratio (OR) for MMD: 51.5 (95% CI 21.9–121.1) ($P = 2.08 \times 10^{-29}$) in Japanese and 84.1 (95% CI 28.1–251.8) ($P = 9.42 \times 10^{-22}$) in Koreans. Note that the genotype distribution of the ss161110142 SNP followed HWE in Asian controls but showed some deviation from HWE in Korean cases, which would not be unexpected if this SNP is truly associated with MMD. In contrast, the ss161110142 A allele was not detected in either the patients or the controls among the Caucasian participants in the study.

Haplotype frequencies derived from the seven studied *Raptor* SNPs are shown in Table 4. Due to the moderate size of the Chinese samples, haplotypes were inferred only in Japanese and Korean populations. The same *Raptor* haplotype structure was observed in Japanese and Koreans. Interestingly, the ss161110142 A allele was carried by only one haplotype that was very rare in controls but very frequent in cases, suggesting the existence of a founder haplotype spanning 65 kb common to Japanese and Korean subjects with MMD.

Population attributable risks were estimated to be 49% (44/90) for Japanese, 66% (27/41) for Koreans, and 9% (2/23) for Chinese.

Discussion

Here, we report the results of positional cloning based on tried and true tactics. We identified ss161110142 as a sensitivity SNP for MMD. Although the *Raptor* ss161110142 A allele was found to be a rare variant in East Asian general populations, it was very common in East Asian MMD patients, with approximately 50% of the Japanese and 66% Korean MMD patients being heterozygous for this allele. Intensive sequencing of coding regions and a promoter of *Raptor* did not reveal any variants specific for cases with MMD, with the exception of the ss161110142. The presence of this rare allele was found to elevate susceptibility to MMD by 52.2-fold. We thus tentatively conclude that ss161110142 of *Raptor* is very likely to confer susceptibility to MMD.

There might be a caveat, however, with respect to a causal role of ss161110142 in MMD. Sequencing was not conducted in genes around *Raptor*, and we also did not further explore the founder haplotype around *Raptor*. More importantly, the functional link was not explained pathologically. Those limitations to our study contribute to an uncertainty regarding the causal role of *Raptor*, leaving open the possibility that this variant of *Raptor* may simply be a marker having a very strong linkage disequilibrium with unknown causative mutations of unsequenced parts of *Raptor* or a nearby gene.

Table 4 Main *Raptor* haplotypes derived from the study of ss161110142, rs9911978, rs12950635, rs4890047, rs4889863, rs11655474, and rs8080957 in the Japanese and Korean case–control studies

Polymorphisms							Haplotype frequencies			
							Japanese		Korean	
ss161110142	rs9911978	rs12950635	rs4890047	rs4889863	rs11655474	rs8080957	Controls	Cases	Controls	Cases
G	G	C	T	G	C	G	0.366	0.274	0.395	0.219
G	A	C	C	A	C	A	0.021	0	0.025	0.024
G	A	C	C	A	T	A	0.248	0.181	0.261	0.146
G	A	T	C	A	C	G	0.336	0.272	0.291	0.268
A	G	C	T	G	C	G	0.009	0.253	0.011	0.329

Based on signaling by the mammalian target of the mTOR complex, it has been reported that *Raptor* is associated with vascular smooth muscle cell proliferation and intimal expansion mediated by interferon-γ [25] and with HLA class I antibody-mediated endothelial cell proliferation [24]. The ss161110142 variant is predicted to be located one base upstream of the GATA-1 site (http://www.cbs.dtu.dk/services/Promoter/) [26]. As such, this variant may modify signals mediated by mTOR complexes by changing gene expression levels in tissue-specific manners. The involvement of *Raptor* as a key molecule can potentially explain the smooth muscle cell proliferation observed in steno-occlusive lesions [27, 28] provide the basis of several immunological hypotheses [28, 29]. In fact, elevations of hypoxia-inducible factor [30] and basic fibroblast growth factor (bFGF) [31] have been reported in MMD. Therefore, it is possible that the mTOR signaling pathway may bridge the missing link between genetic factors and pathological consequences.

The high prevalence of the ss161110142 variant can explain the large prevalence of MMD among East Asian populations compared with Caucasian populations. In particular, the high PARs can explain the greater prevalence of MMD in Japanese (49%) and Koreans (66%) compared with other ethnicities. However, the issue of whether this variant is a single risk factor for MMD should be addressed because of the large gap between the prevalence of carriers of the ss161110142 A allele (2%) and the prevalence of MMD (as low as 6.03 per 100,000 persons) [10]. The large gap in the estimated frequencies (330-fold) strongly indicates that other factors contribute to the development of MMD. Although we were unable to demonstrate direct evidence for the involvement of ss161110142 in MMD, it may be that this allele elevates the risk of MMD synergistically with unknown factors. Pathologic clues are expected to be identified by functional characterization of *Raptor*.

Kraemer et al. [32] recently reported the clinical features and course of MMD in Caucasians. MMD in Caucasian differs from Asian MMD in the timing of onset of vasculopathy and lower rate of hemorrhage. Although we could not confirm such differences in this study—mainly due to limitations in the size of the study population—it is plausible to assume that the *Raptor* gene may modify the clinical features and course of MMD.

The present study clearly demonstrated a founder haplotype harboring *Raptor* ss161110142 variant in East Asian patients with MMD, giving an explanation for high prevalence in Asian. Further studies including functional analysis are required to envisage the gene–environment interactions in the process of MMD.

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Multiple Coronary Stenosis in Infantile Moyamoya Disease

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A 3-year-old girl was referred to our institution for evaluation of mitral valve regurgitation. A heart murmur was observed when she visited a pediatrician for treatment of a respiratory infection, and it was diagnosed as mitral valve regurgitation. The regurgitation gradually became worse and she was referred to the hospital. An echocardiographic examination showed moderate mitral valve regurgitation. Because her ECG demonstrated a slight ST depression on the left chest leads, dipyridamole stress thallium imaging was performed. However, it was interrupted when an aminophylline injection was required because of chest pain with ST depression on leads II, III, aVf, and V4 through V6. This strongly suggested ischemic mitral valve regurgitation, and coronary angiography was performed. A coronary angiogram demonstrated multiple stenoses in both coronary arteries (Figure 1). Because her 16-year-old sister was suffering from moyamoya disease, intracranial magnetic resonance angiography was performed.[1] The image showed severe stenosis of the bilateral internal carotid arteries with small collateral vessels (Figure 2), and she was therefore with the early stages of moyamoya disease.

Although she had been suffering from chest pain, the administration of aspirin, an angiotensin-converting enzyme inhibitor, a β-blocker, nicorandil, and a calcium channel antagonist relieved her symptoms.

Moyamoya disease is characterized by progressive stenoocclusive changes at the terminal portions of the bilateral internal carotid arteries with arterial collateral vessels, called *moyamoya vessels*, at the base of the brain. Familial occurrence is reported in about 15% of patients with moyamoya disease. Therefore, the patient's family history led to the diagnosis, although she had had no neurological symptoms.[2] The scant collateral arteries probably indicate an early stage of the disorder, which is consistent with the fact that she demonstrated no neurological symptoms.

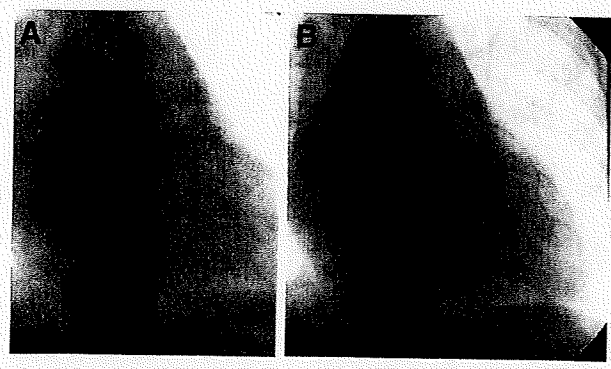

Figure 1. Coronary angiograms of the right coronary artery (A) and left coronary artery (B). There are multiple stenotic lesions and collateral vessels.

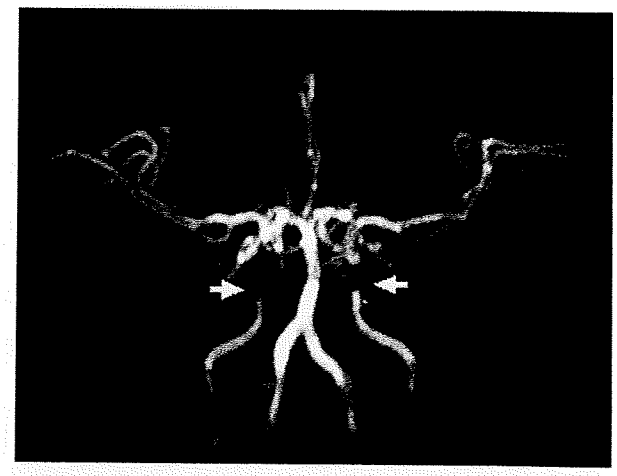

Figure 2. Magnetic resonance angiogram of the head. The image demonstrated stenosis of the terminal portion of the bilateral internal carotid arteries (arrow).

Cases of moyamoya disease associated with coronary artery disease, coronary stenosis, and spastic angina have only rarely been reported.[3] The present report demonstrated the first case of multiple coronary artery stenosis in a young patient with moyamoya disease. A coronary artery disease is rare in small children, and it is important to consider moyamoya disease as a potential cause of ischemic heart disease even in children.

Disclosures

None.

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Novel Bypass Surgery for Moyamoya Disease Using Pericranial Flap: Its Impacts on Cerebral Hemodynamics and Long-term Outcome

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OBJECTIVE: We reviewed our 11-year experience with a novel bypass procedure, superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and encephalo-duro-myo-arterio-pericranio-synangiosis (EDMAPS), for moyamoya disease regarding cerebral hemodynamics and long-term outcome.

METHODS: This prospective study included 75 patients with moyamoya disease, including 28 children and 47 adults. We performed STA-MCA anastomosis and EDMAPS on 123 hemispheres of 75 patients. In addition to conventional STA-MCA anastomosis and indirect bypass for the MCA territory, the medial frontal lobe was revascularized using the frontal pericranial flap through medial frontal craniotomy. Surgical results were analyzed with magnetic resonance imaging, cerebral angiography, and single-photon emission computed tomography/positron emission tomography.

RESULTS: Overall incidences of mortality and morbidity were 0% and 5.7%, respectively. The annual risk of cerebrovascular events during the follow-up periods was very low: 0% in pediatric patients and 0.4% in adults over approximately 67 months. Postoperative cerebral angiography showed that the pericranial flap functioned well as donor tissue for indirect bypass, especially in pediatric patients. Follow-up single-photon emission computed tomography/positron emission tomography studies revealed that cerebral blood flow and its reactivity to acetazolamide markedly improved in both the MCA and anterior cerebral artery territories.

CONCLUSION: These findings strongly suggest that STA-MCA anastomosis and EDMAPS using a frontal pericranial flap is a safe and effective surgical procedure to further improve the long-term prognosis in moyamoya disease by improving cerebral hemodynamics in both the MCA and anterior cerebral artery territories.

KEY WORDS: Bypass surgery, Cerebral hemodynamics, Moyamoya disease, Outcome, Pericranial flap

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Moyamoya disease is an uncommon cerebrovascular disorder characterized by progressive occlusion of the supraclinoid internal carotid artery (ICA) and its main branches within the circle of Willis. This occlusion results in the formation of a fine vascular network (the moyamoya vessels) at the base of the brain. The moyamoya vessels are the dilated perforating arteries that function as collateral pathways. There are no effective medical therapies for moyamoya disease. Surgical revascularization is believed to be the most effective therapy to improve cerebral hemodynamic and to reduce the risk of subsequent stroke.[1,2]

Surgical procedures can be classified into 3 categories: direct bypass, indirect bypass, and combined bypass. Direct bypass such as superficial

ABBREVIATIONS: ACA, anterior coronary artery; **CBF**, cerebral blood flow; **CVR**, cerebrovascular reactivity; **EDAS**, encephalo-duro-arterio-synagiosis; **EDAMS**, encephalo-duro-arterio-myo-synangiosis; **EDMAPS**, encephalo-duro-myo-arterio-pericranio-synangiosis; **EGPS**, encephalogaleo(periosteal)synangiosis; **EMS**, encephalo-myo-synangiosis; **ICA**, internal carotid artery; **MMA**, middle meningeal artery; **SPECT**, single-photon emission computed tomography; **STA-MCA**, superficial temporal artery to middle cerebral artery; **TIA**, transient ischemic attacka

temporal artery to middle cerebral artery (STA-MCA) anastomosis is useful to improve cerebral hemodynamics and to resolve ischemic attacks immediately after surgery. Surgical procedures for indirect bypass are specific for moyamoya disease. The STA, dura mater, temporal muscle, and galeal tissue have been used as the pediculate donor tissues. Combined procedures, which include direct and indirect, have the advantages of both.[1] However, surgical procedures should be further advanced to improve long-term outcome in patients with moyamoya disease. Thus, the majority of previously reported procedures have aimed to improve blood flow in the MCA territory. As pointed out before, however, cerebral hemodynamics in the anterior cerebral artery (ACA) territory is also important to resolve lower-extremity motor weakness and to prevent intellectual deficits, especially in pediatric patients with moyamoya disease.[3-5] On the basis of these considerations, we used the frontal pericranial flap as donor tissue for additional indirect bypass through medial frontal craniotomy to revascularize the ACA territory. During these 11 years, we operated on 75 patients with moyamoya disease using combined procedures, including STA-MCA anastomosis and encephalo-duro-myo-arterio-pericranio-synangiosis (EDMAPS). We review the effects of STA-MCA anastomosis and EDMAPS on cerebral hemodynamics and long-term outcome in moyamoya disease.

MATERIALS AND METHODS

Patients

This prospective study included 75 patients who were admitted to our hospital and were surgically treated for moyamoya disease between 1998 and 2009. All were Japanese and met the guidelines for the diagnosis set by the Research Committee on Moyamoya Disease of the Ministry of Health, Labor, and Welfare of Japan. Their clinical data are summarized in Table 1. There were 19 men and 56 women. Of these 75 patients, 28 were <20 years of age at onset. Their age ranged from 3 to 16 years. Their clinical diagnosis was transient ischemic attack (TIA) in 25 patients and ischemic stroke in 3. The remaining 47 patients were >20 years of age at onset, and their age ranged from 22 to 68 years. Their clinical diagnosis included TIA in 8 patients, ischemic stroke in 24, intracranial bleeding in 12, and asymptomatic in 3.

TABLE 1. Summary of Clinical Data in 75 Patients Who Underwent STA-MCA Anastomosis and EDMAPS for Moyamoya Disease[a]

Clinical Data	
Children (<20 y at onset), n	28
Mean age, y	10.1 (3-16)
Sex, n	
Male	7
Female	21
Clinical diagnosis, n	
TIA	25
Cerebral infarct	3
Intracranial bleeding	0
Asymptomatic	0
Mean follow-up period, mo	72.8 (1-128)
Cerebrovascular events, n	
Cerebral infarct	0
Intracranial bleeding	0
Adults (>20 y at onset), n	47
Mean age, y	44.8 (22-68)
Sex, n	
Male	12
Female	35
Clinical diagnosis, n	
TIA	8
Cerebral infarct	24
Intracranial bleeding	12
Asymptomatic	3
Mean follow-up period, mo	63.1 (1-127)
Cerebrovascular events, n	
Cerebral infarct	1
Intracranial bleeding	0

[a] STA-MCA, superficial temporal artery to middle cerebral artery; EDMAPS, encephalo-duro-myo-arterio-pericranio-synangiosis; TIA, transient ischemic attack.

Radiological Examinations

Cerebral angiography, magnetic resonance imaging, and magnetic resonance angiography (1.5-T apparatus) were performed on all patients before surgery. Cerebral blood flow (CBF) before and after intravenous injection of 10 mg/kg acetazolamide was also measured in all patients at least 4 weeks after the last onset with (123)I-IMP single-photon emission computed tomography (SPECT) or (15)O-gas positron emission tomography, as reported previously.[6,7] Regional CBF was determined by designating 10-mm-diameter circular regions of interest in the MCA and ACA territories and was expressed as the ratio to mean hemispheric CBF (regional CBF/mean CBF ratio) because the absolute values of CBF are known to depend largely on both methodology and patient age. Cerebrovascular reactivity (CVR) to acetazolamide was determined as follows: CVR (%) = 100 × (CBFACZ − CBFrest)/CBFrest, where CBFrest and CBFACZ represent CBF before and after intravenous injection of acetazolamide, respectively.[8]

Surgical Procedures

The involved hemisphere was considered the candidate for surgical revascularization when having impaired reactivity to acetazolamide. As a result, we performed STA-MCA anastomosis and EDMAPS on 123 hemispheres of 75 patients.

All patients received intravenous drip overnight before surgery to avoid dehydration before surgery. After induction of general anesthesia, $PaCO_2$ was strictly maintained around 40 mm Hg. The

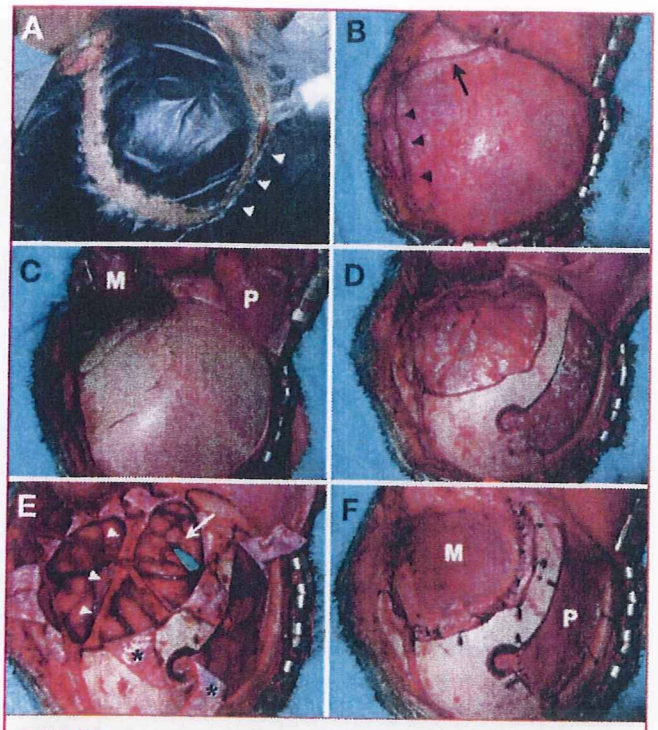

FIGURE 1. *Intraoperative photographs showing the step-by-step procedures of superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis (EDMAPS) in this study.* **A**, *a skin incision is made along the course of the parietal branch of the STA and extended upward to the midline (arrowheads).* **B**, *The parietal (arrowheads) and frontal (arrow) branches of the STA are carefully dissected from the surrounding tissue, maintaining their patency.* **C**, *the temporal muscle (M) and frontal pericranium (P) are dissected from the skull and preserved as the vascularized flaps.* **D**, *Two-flap craniotomies are performed. The size of bone windows fits that of the muscular and pericranial flaps for indirect bypass.* **E**, *The dura mater is opened. Note that the main branches of the middle meningeal artery are preserved (arrowheads). The dural flaps are prepared for indirect bypass (asterisks). The frontal branch of the STA is anastomosed to the frontal branch of the MCA (arrow).* **F**, *The dural windows are closed by suturing the temporal muscle (M) and frontal pericranium (P).*

course of the STA was identified with a Doppler ultrasound probe. The skin incision was then made along the course of the parietal branch of the STA and extended upward to the midline near the bregma and then along the midline downward to the hairline (Figure 1A). The parietal branch of the STA was dissected from the surrounding tissues, being kept patent at the point where the STA crosses the skin incision. After the scalp flap was reflected laterally, the frontal branch of the STA was also dissected under a surgical microscope (Figure 1B). The temporal muscle was dissected as widely as possible and was made as a vascularized flap for encephalo-myo-synangiosis (EMS). Then, the vascularized frontal pericranium, consisting of the cranium periosteum and the overlying loose areolar layer, was also dissected for subsequent encephalo-pericranio-synangiosis (Figure 1C). Careful dissection is essential to preserve the arterial and venous pedicles of the pericranial flap.[9]

A standard frontotemporal craniotomy was made, preserving the middle meningeal artery (MMA). The size of craniotomy was matched to that of the temporal muscle flap. Then, a medial frontal craniotomy was made separately, which should fit the size of the pericranial flap (Figure 1D). The dura was incised and rolled back, preserving the main branches of the MMA. Subsequently, STA-MCA single or double anastomosis was performed in an end-to-side fashion with 10-0 or 11-0 nylon threads. The frontal branches of the MCA were usually selected as the recipients of anastomoses because cerebral hemodynamics are impaired, especially in the frontal lobe, in moyamoya disease. The diameter of the recipients ranged from 0.5 to 1.1 mm. The blue dye was put onto the surface of cut ends of the donor and recipient to visualize them clearly. A green silicon sheet was inserted beneath the recipient for the same purpose.[10] Furthermore, each needle was left keeping the surface of both cut ends in good position until the next needle was placed, like a pin fastens pieces of cloth together when sewing.[11] The clamping time of recipient was approximately 20 minutes (Figure 1E). Then, the dural flaps were turned into the epiarachnoid space. The dural opening through frontotemporal craniotomy was covered with the temporal muscle flap. The dural opening through medial frontal craniotomy was covered with the frontal pericranial flap (Figure 1F). Cranioplasty was performed for both craniotomies, and the wound was closed. Total operation time ranged from 5 to 7 hours. Blood transfusion was not performed.

FOLLOW-UP

All 75 patients were followed up in the outpatient clinic. The mean follow-up period was 66.7 ± 43.2 months, ranging from 1 to 128 months. Episodes of TIA, cerebral infarction, and intracranial hemorrhage during follow-up periods were precisely recorded.

Three-dimensional skull computed tomography (CT) was performed after surgery to confirm the extent of craniotomy. Cerebral angiography and blood flow study were repeated 3 to 6 months after surgery. On postoperative cerebral angiography, the extent and distribution of collateral circulation through direct and indirect bypass in the MCA and ACA territories were analyzed. They were graded according to the scales described previously.[12,13] Thus, collaterals were considered grade A if they supplied more than two thirds of the MCA territory, grade B if they supplied between one third and two thirds of the MCA territory, and grade C if they supplied less than one third of the MCA territory. Postoperative CBF and CVR were also determined in the MCA and ACA territories and were compared with preoperative values. Both magnetic resonance imaging and magnetic resonance angiography were performed every 6 or 12 months with a 1.5-T whole-body magnetic resonance imager.

STATISTICAL ANALYSIS

All values were expressed as mean ± standard deviation. A paired t test was used to compare CBF and CVR before and after surgery. A value of $P < .05$ was considered statistically significant.

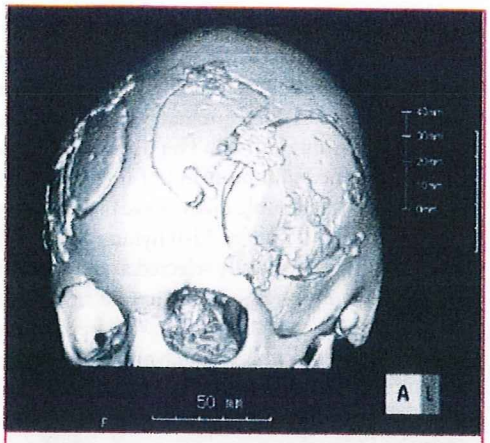

FIGURE 2. *Postoperative 3-dimensional computed tomography scans of the skull of an 8-year-old girl who underwent superficial temporal artery to middle cerebral artery anastomosis and encephalo-duro-myo-arterio-pericranio-synangiosis on both sides. Note the wide cranial windows for surgical revascularization.*

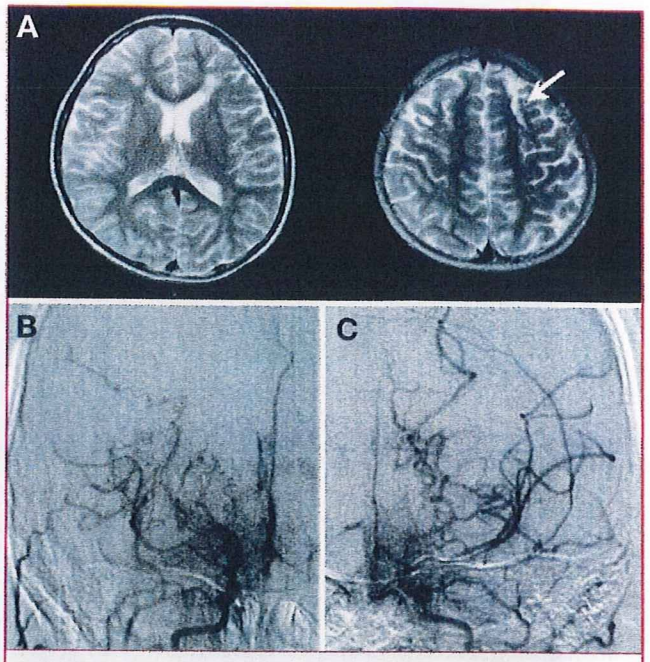

FIGURE 3. *Preoperative radiological findings of an 8-year-old girl who developed transient weakness of the right extremities.* **A**, *T2-weighted magnetic resonance imaging shows cortical infarction in the left frontal lobe (arrow). A small infarction can be seen in the deep white matter of the bilateral frontal lobes. Towne's views of right* (**B**) *and left internal carotid angiograms* (**C**) *demonstrate typical findings of moyamoya disease, ie, severe stenosis of the terminal portion of the internal carotid artery and marked development of moyamoya vessels on both sides.*

RESULTS

Clinical Results

STA-MCA anastomosis and EDMAPS were performed on 47 hemispheres of 28 pediatric patients. Perioperative ischemic stroke occurred in 2 of these 47 surgical procedures. Cerebral infarct developed in the ipsilateral parietal lobe in 1 patient and in the contralateral temporal lobe in another after surgery. As a result, 3-month mortality and morbidity were 0% and 4.3% in pediatric patients, respectively. Forty-seven adult patients underwent surgical revascularization on 76 hemispheres. Of these, cerebral infarct developed in 2 ischemia-type patients and intracerebral hemorrhage occurred in 3 bleeding-type patients. Therefore, 3-month mortality and morbidity were 0% and 6.6% in adult patients, respectively.

TIA completely disappeared in all but 1 patient. Only a 7-year-old girl continued to develop transient weakness of the bilateral legs for 1 year after surgery, although its frequency decreased markedly. No cerebrovascular events occurred in pediatric patients during a mean follow-up period of 72.8 months (Table 1). Of 47 adult patients, 46 experienced no episodes of ischemic or hemorrhagic stroke during a mean follow-up of 63.1 months. Only a 55-year-old female patient suffered cerebral infarct in the right occipital lobe caused by progression of an occlusive lesion in the right posterior cerebral artery 11 months after STA-MCA anastomosis and EDMAPS for both sides. No intracranial bleeding occurred (Table 1). Therefore, the annual risk for subsequent stroke in adults was 0.4% per year per patient.

Radiological Findings

Postoperative 3-dimensional skull CT clearly demonstrated that craniotomy widely covered the MCA and ACA territories (Figure 2). Postoperative external carotid angiography revealed that STA-MCA anastomosis was patent in 40 of 47 operated hemispheres (85.1%) of pediatric patients. However, extensive development of surgical collaterals through indirect bypass was observed in all pediatric patients. The calibers of the STA, MMA, and deep temporal artery increased markedly. As a result, surgical collaterals in the MCA territory were grade A in 43 hemispheres (91.5%) and grade B in 4 (8.5%). Surgical collaterals in the ACA territory were grade A in 28 hemispheres (60.0%), grade B in 10 (22.7%), and grade C in 9 (18.3%). The moyamoya vessels disappeared or diminished in all pediatric patients (Figure 4). Uniquely, postoperative external carotid angiography demonstrated that the branches of the facial artery markedly increased their calibers, anastomosed with the supraorbital artery, and primarily supplied blood flow to the ACA areas (Figure 4). In other cases, postoperative internal carotid angiography showed that the branches arising from the ophthalmic artery increased their caliber and supplied blood flow to the ACA areas (Figure 5). Table 2 summarizes the number of hemispheres that showed the increase in caliber of these branches on postoperative angiography.

STA-MCA anastomosis was patent in all 76 operated hemispheres of adult patients. However, surgical collaterals through indirect bypass developed in 45 (59.2%). In these hemispheres,

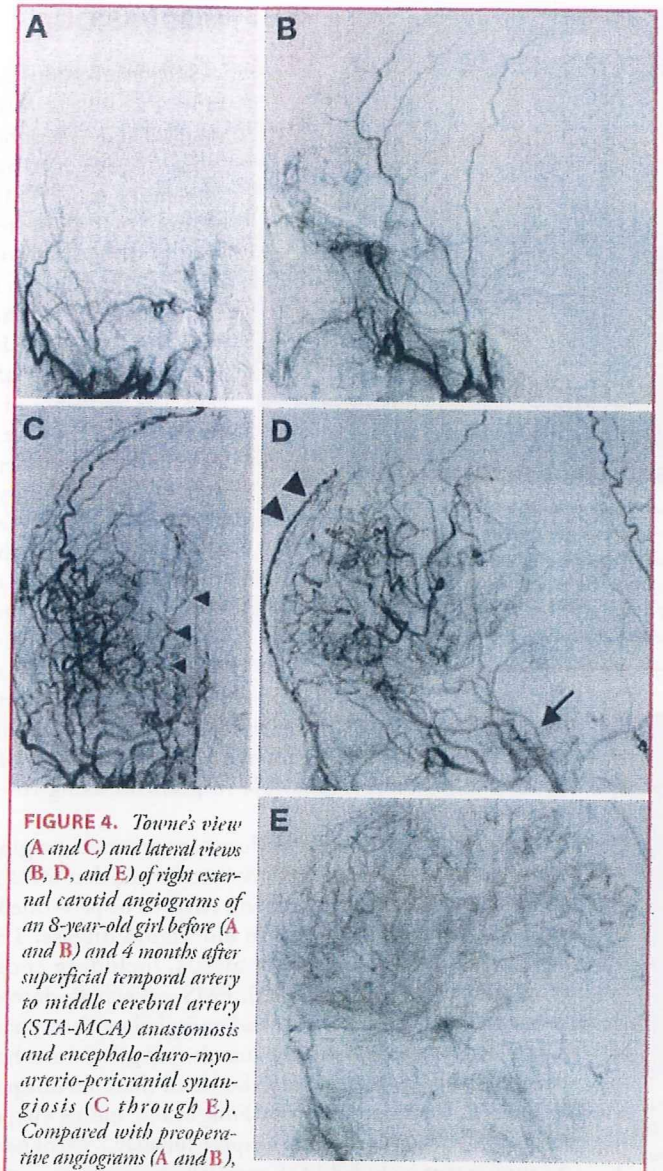

FIGURE 4. *Towne's view (A and C) and lateral views (B, D, and E) of right external carotid angiograms of an 8-year-old girl before (A and B) and 4 months after superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis (C through E). Compared with preoperative angiograms (A and B), postoperative angiograms demonstrated that STA-MCA anastomosis and indirect bypass widely supply collateral blood flow to the operated hemisphere, especially to the frontal lobe. Note that the branch of facial artery markedly increased its caliber and supplies blood flow to the medial frontal lobe through encephalo-pericranio-synangiosis (arrowheads in C and D). The internal carotid artery diminished its caliber and is almost occluded (arrow in D). Wide opacification of contrast material in the internal carotid artery territory can be seen in the late arterial phase (E).*

the calibers of the STA, MMA, and deep temporal artery increased. Indirect bypass was effective in 21 (65.6%) of 32 hemispheres of patients <40 years of age and in 24 (54.5%) of 44 hemispheres of those >40 years of age. Therefore, patient age was not directly related to the formation of surgical collaterals through indirect bypass in adult patients with moyamoya disease. As a result, surgical collaterals in the MCA territory were grade A in 50 hemispheres (65.8%), grade B in 22 (28.9%), and grade C in 4 (5.3%). Surgical collaterals in the ACA territory were grade A in 36 hemispheres (47.4%), grade B in 24 (31.6%), and grade C in 16 (21.0%).

TABLE 2. Number of Hemispheres That Showed the Increase in Caliber on Postoperative External and Internal Carotid Angiograms

Source of Branches	Children (n = 47), n	Adults (n =76), n
Facial and superficial temporal arteries	25	23
Ophthalmic artery	35	34

Postoperative blood flow studies demonstrated that regional CBF/mean CBF ratio in the MCA and ACA territories significantly increased from 0.97 ± 0.03 to 1.10 ± 0.04 ($P < .01$) and from 0.96 ± 0.04 to 1.08 ± 0.02 ($P < .01$), respectively. Postoperative improvements in CVR were more notable. Thus, CVR in the MCA and ACA territories increased significantly from 10.2 ± 14.0% to 22.3 ± 10.5% ($P < .01$) and from 2.5 ± 11.0% to 18.3 ± 8.8% ($P < .01$), respectively (Figure 5).

Illustrative Case 1

An 8-year-old girl frequently experienced transient weakness of the right extremities and was admitted to our hospital. Preoperative magnetic resonance imaging revealed cortical infarction in the left frontal lobe. Cerebral angiography demonstrated severe stenosis of the terminal portion of the ICA and marked development of moyamoya vessels on both sides (Figure 3). On (123)I-IMP SPECT, both CBF and CVR were reduced in the right frontal lobe and left cerebral hemisphere (Figure 5). She underwent STA-MCA anastomosis and EDMAPS on the left side. The postoperative course was uneventful. Repeated SPECT revealed significant improvement in CBF in the left cerebral hemisphere 1 week after surgery. She underwent STA-MCA anastomosis and EDMAPS on the right side 3 weeks after the first surgery. The postoperative course was uneventful. After surgery, her ischemic attacks completely disappeared. Follow-up examinations were repeated 4 months after the second surgery. On cerebral angiography, surgical collaterals widely supplied blood flow to the operated hemisphere, including the frontal lobes, through both direct and indirect bypass. The facial branch of the STA markedly increased its caliber and supplied blood flow to the medial frontal lobe through the pericranial flap (Figure 4). On (123)I-IMP SPECT, both CBF and CVR significantly improved (Figure 5).

Illustrative Case 2

A 14-year-old girl frequently complained of frontal headache and transient weakness of the left extremities and was admitted to our hospital. She was diagnosed with moyamoya disease and underwent STA-MCA anastomosis and EDMAPS on both sides. The interval between the 2 surgeries was 2 months. Her postoperative

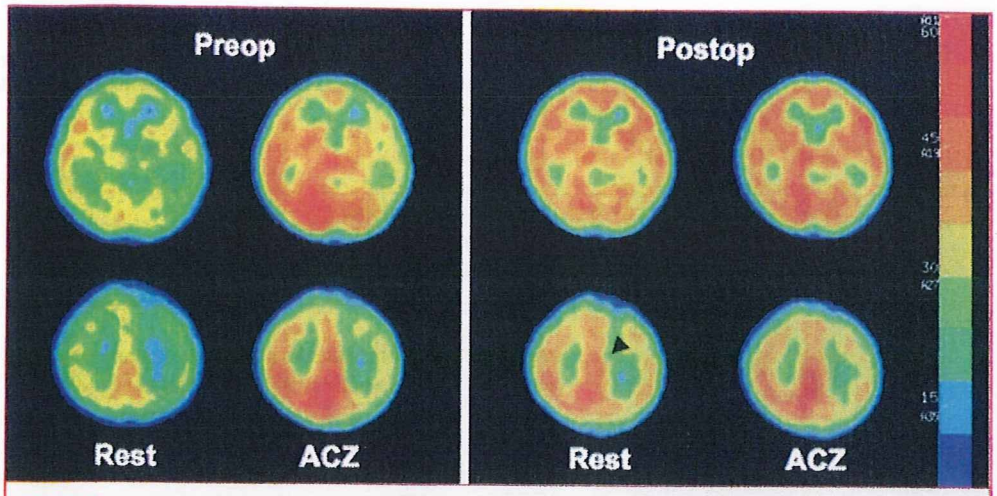

FIGURE 5. *Pre- (left) and postoperative (123)I-IMP single-photon emission computed tomography (right) of an 8-year-old girl who underwent superficial temporal artery to middle cerebral artery anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis on both sides. Before surgery, both cerebral blood flow and its reactivity to acetazolamide (ACZ) were reduced in the right frontal lobe and the entire territory of the left internal carotid artery. These parameters significantly improved or normalized 4 months after surgery, except for a small cortical infarction in the left frontal lobe. Note that both cerebral blood flow and its reactivity to ACZ also improved in the anterior coronary artery territories (arrowhead).*

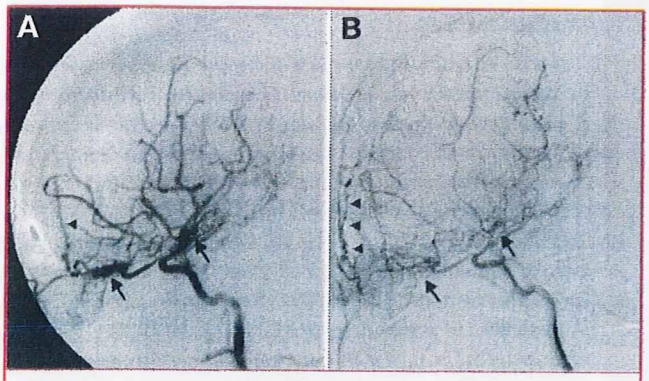

FIGURE 6. *Lateral view of right internal carotid angiograms of a 14-year-old girl before (A) and 6 months after superficial temporal artery to middle cerebral artery anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis (B). A, preoperative angiogram showed a marked development of ethmoid and basal moyamoya vessels (arrows) and a dilatation of anterior falcian artery (arrowhead). B, postoperative angiogram demonstrated the decrease in ethmoid and basal moyamoya vessels (arrows) and the development of collateral vessels through the pericranial flap (arrowheads). In contrast, the anterior falcian artery decreased its caliber.*

course was uneventful, and her symptoms resolved after surgery. Cerebral angiography was performed 4 months after the second surgery. On external carotid angiograms, surgical collaterals widely supplied blood flow to the operated hemisphere through the STA, MMA, and deep temporal artery. On internal carotid angiograms, the branches from the ophthalmic artery increased their caliber and extended into the ACA area through the pericranial flap (Figure 6).

DISCUSSION

Surgical procedures for moyamoya disease can roughly be classified into 3 categories: direct bypass, indirect bypass, and combined bypass.[1,2] STA-MCA anastomosis is most frequently used as direct bypass procedures.[14] Direct bypass is useful to improve cerebral hemodynamics and to resolve ischemic attacks immediately after surgery. The incidence of perioperative ischemic stroke is lower after direct or combined bypass than after indirect bypass.[15] Direct bypass may be essential in adult patients with moyamoya disease because indirect bypass starts to function in only about 50% of them (see below). STA-MCA anastomosis can be technically challenging in some pediatric patients because their cortical branches have a smaller caliber and are more fragile than those of adults. However, it is not impossible to perform using the abovementioned procedures.[11]

Indirect bypass surgery induces spontaneous angiogenesis between the brain surface and the vascularized donor tissues. The procedures are technically easy and can even be performed by surgeons with little experience in moyamoya disease. There are various methods for indirect bypass, including encephalo-duro-arterio-synagiosis (EDAS), EMS, encephalo-duro-arterio-myo-synangiosis (EDAMS), and encephalo-galeo-synangiosis. The STA, dura mater, temporal muscle, and galeal tissue have been used as the pediculate donor tissues in these techniques.[16-19] According to a recent review by Fung et al,[20] indirect bypass procedures have been performed in approximately 75% of patients in 57 studies that included 1448 surgically treated patients between 1966 and 2004. However, the beneficial effects are not immediate because surgical collaterals require 3 to 4 months to develop,[2,21,22] and there is a higher risk of perioperative ischemic stroke after indirect bypass than after direct or combined bypass.[15,23] Furthermore, indirect bypass does not develop collateral pathways in about 40% to 50% of adult patients, although it provides extensive surgical collaterals in almost all pediatric patients.[24,25] More important, surgical design is critical because the extent of surgical collateral pathways depends on the size of craniotomy and the extent of the indirect bypass. Thus, the revascularized area is confined to the craniotomy field after indirect bypass.[13,26-28] For example, indirect bypass such as EDAS and EMS is performed through temporoparietal craniotomy and is useful to resolve ischemic attacks such as hemiparesis because surgical collaterals

develop in and around the primary motor cortex after surgery. However, the procedures do not improve disturbed cerebral hemodynamics in the frontal lobe even after surgery.[3,28] Recent multivariate analysis has proven that such "small craniotomy" can be an independent predictor for poor intellectual outcome in pediatric moyamoya disease because it does not improve cerebral hemodynamics in the frontal lobes.[3]

On the basis of these observations, we performed combined bypass, including STA-MCA anastomosis and EDAMS, through frontotemporal craniotomy for patients with moyamoya disease between 1988 and 1997. Combined bypass can provide the advantages of both direct and indirect procedures. Clinical results were more favorable than before, as reported in detail elsewhere.[3,11,15,24,27,29,30] However, surgical collaterals were not always sufficiently induced in the ACA territory because the temporal muscle, a main donor tissue for indirect bypass, covered mainly the MCA territory.[11] In fact, our previous report has shown that ischemic attacks in lower legs persisted in 56% of pediatric patients after EDAS or EMS and in 10% after STA-MCA anastomosis and EDAMS.[15] Therefore, since 1998, we have extended the exposure of the brain surface to the medial frontal area through additional craniotomy and covered the brain surface with the vascularized pericranial flap. Previously, various surgical procedures targeting the ACA territory have been proposed. Ideally, the best way to revascularize the ACA territory is to perform direct anastomosis of STA in the interhemispheric space to a branch of the ACA.[4,31] However, STA-ACA anastomosis is technically more difficult than STA-MCA anastomosis in moyamoya disease. Thus, the peripheral STA is too small to provide enough blood flow to the ACA territory immediately after surgery. Furthermore, perioperative complications resulting from cerebral ischemia in the ACA territory are very rare.[32] Therefore, STA-ACA anastomosis may be one surgical option for specific patients who have marked hemodynamic compromise in the ACA territory before surgery but not a routine procedure for all patients.[4] Several tissues for indirect bypass have been used to revascularize the ACA territory, including the dura mater, galea aponeurotica, and omentum, through multiple burr holes or craniotomy. Clinical and radiological findings were rather favorable, but the small sample size and short follow-up periods make it difficult to draw final conclusions in each study.[4,5,33-37]

A pericranial flap has been widely used to reconstruct the anterior cranial fossa because of its simplicity, reliability, and low morbidity.[9] In this study, the pericranial flap was large enough to cover the frontal lobe through medial frontal craniotomy (Figure 1). As reported by Yoshioka and Rhoton,[9] the frontal pericranium receives blood flow mainly from the supraorbital and supratrochlear arteries. The supraorbital artery has the vascular anastomosis between the deep branches of STA. Therefore, we attempted to prepare the pericranial flap based anteriorly and widely to preserve its vascular supply. Previously, Korean groups have used the galeopericranial flap in the parietal region to revascularize the ACA territory [encephalogaleo(periosteal)synangiosis; EGPS]. However, they have not considered the vascular supply of the pericranial flap.[5,35,36] We analyzed the radiological findings and long-term outcomes in 75 patients who underwent this novel bypass surgery, STA-MCA anastomosis and EDMAPS, for moyamoya disease. The sample size and follow-up period are believed to be sufficient to discuss the efficacy of this surgical procedure on long-term outcome in patients with moyamoya disease. Surgical collaterals widely supplied blood flow to the operated hemisphere, and cerebral hemodynamics significantly improved in both the MCA and ACA territories after surgery. Overall incidences of mortality and morbidity were 0% and 5.7%, respectively. The annual risk of cerebrovascular events was very low, 0% in pediatric patients and 0.4% in adults, when they were strictly followed up for approximately 67 months.

According to the literature review by Fung et al,[20] perioperative complications, including ischemic stroke and hemorrhage, occurred in 6.1% of 680 pediatric patients who underwent any surgical revascularization. Matsushima et al[38] reported that 6 of 81 pediatric patients (7%) developed cerebral infarction in the perioperative period after EDAS. Kim et al[5] performed combined EDAS and bifrontal EGPS on 92 children and reported that 12 (13%) developed cerebral infarction within 14 days after surgery. Okada et al[39] reported that 2 of 30 adult patients (6.7%) developed intracerebral hemorrhage on the second day after direct bypass. There was the possibility that the surgical procedures presented in this study would increase the risk for perioperative complications because it required longer operative times and wider surgical fields. However, its incidence was lower than or comparable to previous data.

The pericranial flap was used to revascularize the medial frontal lobes and to improve blood supply to the ACA territory, especially in pediatric patients who frequently develop ACA territory symptoms. Transient attack of paraparesis was repeated in only 1 of 28 pediatric patients (3.6%) within 1 year after surgery. No adult patients experienced any further TIA after surgery. The clinical results were supported by postoperative radiological findings. Thus, surgical collaterals widely covered the operated hemispheres (see also Table 2), and both CBF and CVR significantly improved in both the MCA and ACA territories after surgery. Previously, ACA territory symptoms were known to repeat in up to 10% after effective bypass surgery.[11,15,40] Kim et al[5] reported that 19% of pediatric patients repeated ACA territory symptoms and required, maximally, 18 months even after combined EDAS and bifrontal EGPS.

There is a scarcity of randomized clinical trials to confirm the beneficial effects of bypass surgery on subsequent ischemic stroke in both pediatric and adult patients with moyamoya disease.[1] On the basis of previous studies, however, surgical revascularization is thought to improve cerebral hemodynamics and to reduce the incidence of subsequent ischemic stroke.[11,15,39-46] In this study, the incidence of cerebrovascular events was very low during a mean postoperative follow-up period of approximately 67 months. Thus, no pediatric patients experienced further ischemic or hemorrhagic stroke. Only 1 adult patient developed cerebral infarction in the occipital lobe because the stenosis in the posterior cerebral artery progressed (annual risk, 0.4%/y). Recent observational studies show that about 20% of adult patients with moyamoya disease

experience disease progression in both anterior and posterior circulation, even if they are asymptomatic or are diagnosed with unilateral moyamoya disease. Therefore, careful and long-term radiological follow-up is essential to prevent additional stroke events and to improve prognosis even in patients with favored postoperative course.[47,48] Recurrent hemorrhagic stroke (rebleeding) is still a serious problem in adult patients with moyamoya disease. Rebleeding is known to occur in about 30% to 65% of the conservatively treated patients during follow-up periods of 2 to 20 years.[49-52] Rebleeding significantly worsens their functional outcome and increases mortality.[50,52] Rebleeding can occur at the original bleeding site and at a different site.[24,53] Some clinical studies have suggested that surgical revascularization may reduce the incidence of rebleeding to 12.5% to 20%, although their evidence level is not very high.[24,39,52,54] Direct or combined bypass may have the potential to reduce the risk of rebleeding and to resolve the "peripheral" aneurysms located within the collaterals or moyamoya vessels.[55,56] Presently, the Japan Adult Moyamoya trial, a multicenter, randomized clinical trial, is underway to evaluate whether direct or combined bypass surgery can reduce the risk of rebleeding in adult patients with moyamoya disease.[57]

CONCLUSION

Our study demonstrates that STA-MCA anastomosis and EDMAPS using a frontal pericranial flap is a safe and effective surgical procedure that improves the long-term prognosis in moyamoya disease by improving cerebral hemodynamics in both the MCA and ACA territories.

Disclosure

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COMMENTS

This article introduces encephalo-duro-myo-arterio-pericranio-synangiosis (EDMAPS), a variation of combined direct and indirect bypass for moyamoya disease that uses pericranium as an onlay graft over the medial frontal lobe in addition to direct superficial temporal artery--middle cerebral artery bypass and temporalis muscle onlay grafts. A second medial frontal craniotomy is needed for the pericranial flap, which increases the revascularized area of brain to include the anterior cerebral artery territory. The results in this 11-year experience in 75 patients are excellent, with improved cerebral blood flow by positron emission tomography and single-photon emission computed tomography imaging and infrequent clinical events after treatment. The authors suggest that by extending revascularization to include the anterior cerebral artery territory, EDMAPS might improve blood flow to the frontal lobes and improve intellectual outcome in pediatric patients. This provocative idea was not tested here but deserves further study. EDMAPS appears to be a useful technique to consider in the management of patients with moyamoya disease.

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特集　もやもや病

側頭葉から後頭葉にかけて高度の虚血を有するもやもや病に対する脳血行再建術

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Revascularization Surgery for Moyamoya Disease with Cerebral Ischemia in Temporo-occipital Lobes

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Summary: We report a novel surgical technique for patients with profound cerebral ischemia in the temporo-occipital lobes due to significant stenosis of the ipsilateral posterior cerebral artery (PCA) in moyamoya disease. The technique includes STA-MCA anastomosis targeted to the angular artery and indirect bypass through large craniotomy extended towards the temporo-parietal area. Over the past 10 years, we applied the surgical technique for 4 patients who exhibited transient ischemic attacks or ischemic stroke involving the temporo-occipital lobes. Following surgery, none of them developed any cerebrovascular events during follow-up periods of up to 8 years. Cerebral angiography revealed that surgical collaterals widely supplied blood flow to the operated hemispheres, including the posterior temporal and parietal lobes. Postoperative SPECT and/or PET studies also demonstrated marked improvement of cerebral hemodynamics and metabolism in the operated hemispheres, including the occipital lobe.

The presented surgical technique can effectively improve cerebral hemodynamics and metabolism in the frontal, temporal, and occipital lobes at once in patients with cerebral ischemia in the temporo-occipital lobes due to PCA stenosis in moyamoya disease.

Key words:
- moyamoya disease
- posterior cerebral artery
- temporo-occipital lobes
- cerebral ischemia
- surgical revascularization

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はじめに

もやもや病は両側内頸動脈終末部に生じる進行性の狭窄病変であり，前頭葉に高度の脳虚血をきたすことがよく知られている[11)15)]．今日においては虚血型もやもや病の多くは前方循環に対する脳血行再建術を実施することにより，自然歴を有意に改善して良好な長期予後を得ることができることも広く認知されている[4)5)8)10-12)15)17)]．一方，内頸動脈を中心に血管病変が存在するもやもや病では，後大脳動脈がきわめて重要な側副血行路として機能していることもよく知られた事実である[20)21)]．その後大脳動脈にも狭窄病変を合併した例では，側頭葉から後頭葉にかけても高度の脳虚血を合併することがあり，これまでにも後頭動脈-後大脳動脈吻合術(occipital artery to posterior cerebral artery anastomosis; OA-PCA anastomosis)など，後方循環への脳血行再建術が報告されている[3)7)13)]．しかし，発症の時点で前頭葉から側頭葉・後頭葉にかけて広範な脳虚血を有している症例では，前方循環，後方循環両者に対する一期的術式が必要になるが，具体的な術式に関する報告はきわめて少ない[6)]．今回，われわれは，このような症例に対する新たな脳血行再建術の工夫について報告する．

対象と方法

1998年4月より2008年7月の約10年間に，もやもや病と診断されて当科で脳血行再建術を実施された71例117側のうち，同側後大脳動脈に高度の狭窄を有し，側頭葉から後頭葉にかけての神経症状と著しい脳虚血を有していた4例(5.6%)を対象とした(**Table 1**)．いずれも女性で年齢は8-38歳であった．同側の側頭部痛，感覚性失語症，同名半盲などの発作や神経症状が主訴であった．ただし，case 1はすでに前方循環に対する脳血行再建術は実施されていたが，新たに後大脳動脈に狭窄が出現したために，側頭葉から後頭葉にかけての脳虚血が出現したため，追加手術を実施した例である．

われわれが通常のもやもや病に実施しているSTA-MCA anastomosis＋encephalo-duro-myo-arterio-pericranial synangiosis (EDMAPS)では，前頭部に拡大した前頭側頭開頭の後端は外耳道よりもやや後方である[10)11)]．これら4例では開頭をさらに後方に拡大して側頭部後半から頭頂部の脳表が露出できるようにデザインした．脳表を広範に露出したのち，基本的にはSTAのparietal branchをMCAのangular arteryに，STAのfrontal branchをMCAのprefrontal arteryに端側吻合した．そののち，dural pedicles, temporal muscle, frontal pericraniumを順次，脳表に接着させて間接バイパス術を完成させた．手術所要時間は6-7時間であった．輸血は実施しなかった．術前および術後3-4カ月後に脳MRI/MRA，^{15}O-gas PET，DSAを実施し，その後は6-12カ月ごとに脳MRI/MRAを実施した．^{15}O-gas PETでは，脳血流量(cerebral blood flow; CBF)，脳血液量(cerebral blood volume; CBV)，脳酸素摂取率(cerebral metabolic rate for oxygen; $CMRO_2$)，脳酸素抽出率(oxygen extraction fraction; OEF)のほか，acetazolamide負荷試験による脳血管反応性(cerebrovascular reactivity; CVR)を測定した．

結　果

術前の脳MRIでは2例では脳梗塞は認められなかったが，ほかの2例では後頭葉から側頭葉下面にかけて脳梗塞を認めた．^{15}O-gas PETでは通常の前頭部の虚血に加えて，側頭葉および後頭葉でCBF，CVRの低下，CBVの増加，OEFの上昇など，著しい脳虚血を認めた．

いずれの症例においても周術期に新たな脳虚血発作は出現しなかった．また，術後1.5-8年間の経過観察期間中，新たな頭痛，一過性脳虚血発作，脳梗塞は出現しなかった．

経過観察期間中，脳MRIでは新たな脳梗塞や脳出血は確認されなかった．術後3-4カ月後に実施した外頸動脈撮影では，STA-MCA anastomosisおよび間接バイパス術を介して，前頭部のみならず側頭部から後頭部にかけて側副血行路が広範に形成されていた．同時期の^{15}O-gas PETでも側頭葉，頭頂葉，後頭葉を含めてCBF，CVRの改善，CBV，OEFの正常化などの改善が確認された．

代表的症例を呈示する．

〈**症例3**〉33歳女性．小児期に脱力発作のエピソードがあったが，もやもや病とは診断されずに経過していた．最

Table 1 Summary of 4 cases who underwent STA-MCA anastomosis and indirect bypass extended to the temporo-parietal regions because of severe cerebral ischemia in the temporo-occipital lobes

Case	Age/Sex	Diagnosis	Main symptoms	PCA lesion	Follow-up	TIA/stroke
1	8/F	TIA	temporal headache	yes	3.5 yr	none
2	15/F	ischemic stroke	sensory aphasia	yes	8.0 yr	none
3	33/F	TIA	hemianopsia, numbness	yes	5.0 yr	none
4	38/F	ischemic stroke	hemianopsia, sensory aphasia	yes	1.5 yr	none

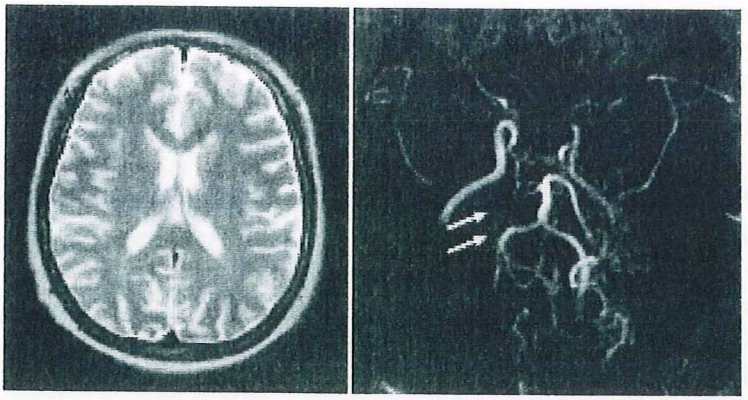

Fig. 1 MRI (A) and MR angiography (B) of a 33-year-old female who developed transient left hemianopsia and numbness of the left extremities. Note severe stenosis of the right posterior cerebral artery (arrows).

A | B

近，数分間持続する左上下肢のしびれ，左同名半盲を主訴に来院した．神経学的には陽性所見を認めず，脳MRIでも脳梗塞などの器質的病変を認めなかった．脳MRAにて両側内頸動脈終末部の高度狭窄に加えて，中大脳動脈，前大脳動脈のflow signalが著明に減弱していた．さらに右後大脳動脈に高度狭窄を認めた(**Fig. 1**)．^{15}O-gas PETでは，両側大脳半球にCBF，CVRの低下，CBVの増加などの脳虚血の所見を認めたが，右大脳半球で顕著であった．特に，右側頭葉から後頭葉にかけて，CBF低下，CBV増加，OEF上昇が著しかった(**Fig. 2**)．

前頭部から頭頂部を広くカバーする皮膚切開を実施して，耳介後方に及ぶ大きな前頭側頭開頭を実施した．STA-MCA double anastomosisののち間接バイパス術を実施した(**Fig. 3**)．術後経過は良好でTIAは消失した．

術後の右外頸動脈撮影では直接および間接バイパス術を介して前頭部のみならず，側頭部，頭頂部および後頭部に及ぶ広範な側副血行路が形成されていた(**Fig. 4**)．術後の^{15}O-gas PETでも，後頭葉を含む右大脳半球全体において各パラメータが明らかに改善した(Fig. 2)．左大脳半球に対する脳血行再建術は実施せずに経過観察中であるが，術後5年間，脳血管イベントは発生していない．

考　察

もやもや病では，後大脳動脈はきわめて重要な側副血行路として機能しており，なかでも側頭葉下面および後頭葉内側面からpial anastomosisを介するルートは側頭葉や頭頂葉への重要な血流の供給源となっていることは周知の事実である．これまでの報告によれば，後大脳動脈に有意な狭窄病変を合併するもやもや病の頻度は25-60%とされている[9)12-14)16)20)21)]．また，後大脳動脈に有意な狭窄が生じた症例では，同側大脳半球の脳循環動態が不良でTIAや脳梗塞といった脳虚血症状をきたしやすいことが判明している[9)21)]．しかし，確定診断に時間を要した以前に比べると，実際に後頭葉などの当該領域の脳虚血症状をきたす症例はそれほど多くはないのが現状である[9)]．

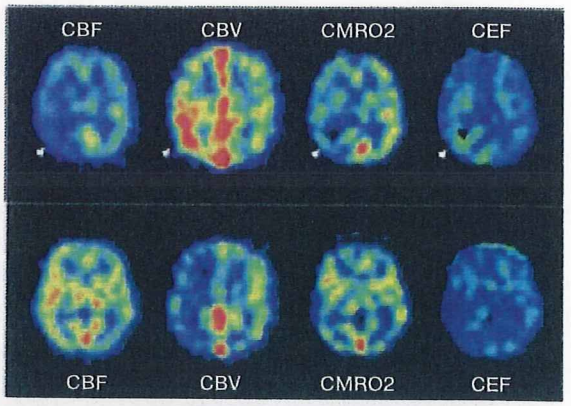

Fig. 2 Pre- (A) and postoperative findings on ^{15}O-gas PET (B) of a 33-year-old female who developed transient left hemianopsia and numbness of the left extremities. Note a marked CBF decrease, CBV increase and OEF elevation in the right temporo-occipital lobes (arrowheads). Note postoperative improvement of the findings even in the right occipital lobe.

A / B

後頭葉に脳虚血を有する症例に対する脳血行再建術は，これまでに直接バイパス術としてOA-PCA anastomosis，間接バイパス術として脳-腱膜接着術(encephalo-galeal synangiosis: EGS)，大網移植術(omental transplantation)などが実施され，それぞれの有用性が報告されている[3)7)13)]．しかし，これらの術式の大部分は腹臥位での手術法であり，同時に前頭部を中心とする脳虚血を合併した症例に対して，一期的に前頭部から側頭部・後頭部にかけて脳循環動態を改善させるための術式の報告はほとんどなされ

ていないのが現状である[6]．今回，われわれが報告した術式は，これまでに実施してきたSTA-MCA anastomosis＋EDMAPSと比較すると，①開頭範囲をさらに後方に拡大させて側頭葉後半部から頭頂葉の一部を露出する，②STA-MCA anastomosisの少なくとも1つは側頭葉や頭頂葉への血流を術直後から改善させるためにangular arteryをrecipientとする，③通常の手術では使用していない側頭筋の後半部をも間接バイパス術のdonorとして利用することが特徴である．この方法により，術後の脳血管撮影上，側頭葉後半部から頭頂葉を含めて，通常よりも広い範囲に側副血行路を形成させることが可能であった．その所見は，術後，側頭葉や後頭葉の虚血に起因すると考えられる側頭部の頭痛，感覚性失語，同名半盲といった発作が消失し，これらの領域の脳循環代謝が改善したこととともよく一致していた．

興味深い点として，呈示した症例でも明らかなように，この術式による手術のあと，術前に存在していた後頭葉内側面の虚血も改善した点があげられる．後頭葉を栄養する後大脳動脈に対して直接なんらかの処置を加えたわけではないが，術後に側頭葉や頭頂葉の脳循環動態が改善するとともに後頭葉においても脳循環動態が改善したと考えられる．そのメカニズムに関しては推論の域を脱しないが，後大脳動脈にとっては有意な狭窄病変を有するにもかかわらず，側頭葉における脳灌流圧(cerebral perfusion pressure)が低いために，その分枝のposterior temporal arteryなどを介して側頭葉へ血流を供給していたために十分な血流が本来の灌流域である後頭葉にまで供給できなかったと考えられる．それに反して，術後は側頭葉などの灌流圧が改善したために後頭葉への血流が十分に確保されたと考えられる．過去にも類似した病態は報告されている．すなわち，内頸動脈閉塞症の症例の一部で，椎骨脳底動脈系に血管病変を合併していないにもかかわらず，椎骨脳底動脈循環不全(vertebrobasilar insufficiency; VBI)をきたすことが以前から知られている[1)2)19)]．これは，内頸動脈領域のCPP低下のために後交通動脈が介して椎骨脳底動脈系から内頸動脈系へ頭蓋内盗血現象が生じるためといわれており，"steal VBI"と呼称されている[1)2)19)]．われわれも内頸動脈系に対する脳血行再建術によって，術前，後頭葉におけるCBFが改善したsteal VBIの2症例を経験して報告している[18)]．

結　　語

後大脳動脈の狭窄病変のために，前頭葉のみならず側頭葉や後頭葉にも高度の脳虚血を有し，その領域に起因する脳虚血発作を呈する例においては，一期的に実施する後方に拡大した複合的脳血行再建術は，周術期の脳虚血合併症

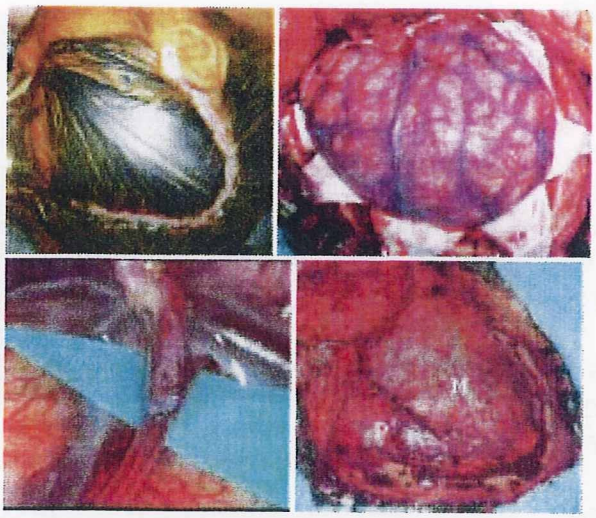

Fig. 3 Intraoperative photographs showing skin incision (A), craniotomy and exposure of the brain (B), STA-MCA anastomosis (C) and indirect bypass using vascularized temporal muscle and pericranium (D).

A | B
C | D

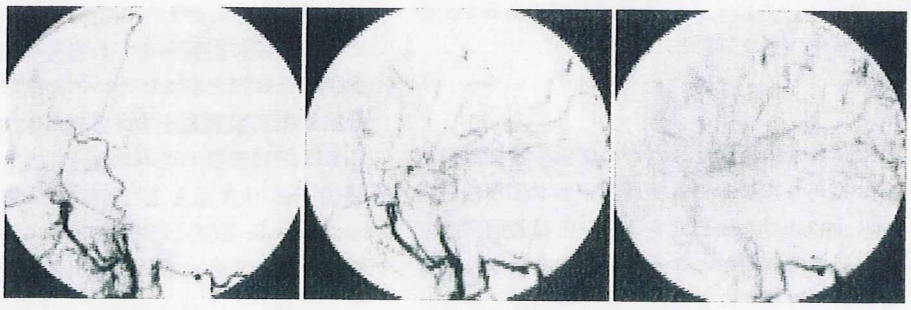

Fig. 4 Pre- (A) and postoperative cerebral angiography (B, C) of a 33-year-old female who developed transient left hemianopsia and numbness of the left extremities. Note that surgical collaterals widely cover the operated hemisphere through STA-MCA anastomosis and indirect bypass (B, C).

A | B | C

を予防して脳虚血発作を消失させるうえで有用な治療オプションと考えられた.

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特別寄稿

もやもや病(ウイリス動脈輪閉塞症)診断・治療ガイドライン

厚生労働科学研究費補助金　難治性疾患克服事業
ウイリス動脈輪閉塞症における病態・治療に関する研究班

Recommendations for the Management of Moyamoya Disease
A Statement from Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease)

Research on intractable diseases of the Ministry of Health, Labour and Welfare, Japan

第一章　疾患概念

1. 疾患概念

もやもや病(ウイリス動脈輪閉塞症，cerebrovascular "moyamoya" disease)は1957年に脳血管撮影上の特徴が初めて報告され[1]，1960年代に疾患としての概念が確立された[2-6]．その病態は，両側内頚動脈終末部に慢性進行性の狭窄を生じ，側副路として脳底部に異常血管網(脳底部もやもや血管)が形成される(脳血管撮影検査でこれらの血管が立ちのぼる煙のようにもやもやと見えるためこの病気がもやもや病と名づけられた[5])．ついには両側内頚動脈の閉塞とともに内頚動脈からの脳底部もやもや血管も消失し，外頚動脈系および椎骨脳底動脈系に脳全体が灌流されるにいたる疾患である[2-7]．当疾患は厚生労働省の定める難治性疾患克服研究事業，および特定疾患治療研究事業の対象疾患の1つである．現在，もやもや病(ウイリス動脈輪閉塞症)に関する調査研究班による診断基準は以下のようになっている[8]．

2. 診断基準[4]

(1) 診断上，脳血管撮影は必須であり，少なくとも次の所見がある．

①頭蓋内内頚動脈終末部，前および中大脳動脈近位部に狭窄または閉塞がみられる．

②その付近に異常血管網が動脈相においてみられる．

③①と②の所見が両側性にある．

(2) ただし，磁気共鳴画像(MRI)と磁気共鳴血管撮影(MRA)の所見が下記のすべての項目を満たしうる場合は脳血管撮影は省いてもよい．「MRI・MRAによる画像診断のための指針」を参照のこと．

①MRAで頭蓋内内頚動脈終末部，前および中大脳動脈

厚生労働科学研究費補助金　難治性疾患克服事業　ウイリス動脈輪閉塞症における病態・治療に関する研究班〔連絡先：〒606-8507 京都市左京区聖護院川原町54 京都大学 脳神経外科　高木康志〕[Address correspondence: Yasushi TAKAGI, M.D., Department of Neurosurgery, Faculty of Medicine, Kyoto University, 54 Shogoin Kawahara-cho, Kyoto 606-8507, Japan]