and EDMAPS are safe and feasible surgical procedures for pediatric and adult patients with moyamoya disease. These procedures include direct STA-MCA anastomosis and indirect synangiosis. Combined bypass can provide the advantages of both direct and indirect bypass procedures. Clinical results were described previously. Briefly, overall incidences of mortality and morbidity in 123 operations for 75 patients were 0% and 5.7%, respectively. The annual risk of cerebrovascular events during follow-up periods was very low, at 0% in pediatric patients and 0.4% in adults over about 67 months.[24] Here we discuss the theoretical basis and surgical techniques of direct and indirect bypass procedures separately.

Direct Bypass Procedure

Direct bypass is useful to improve cerebral hemodynamics and to resolve ischemic attacks immediately after surgery. The frequency of perioperative ischemic stroke is lower after direct or combined bypass than after indirect bypass.[9] Surgery can be technically challenging in a certain subgroup of pediatric patients, because their cortical branches have smaller diameters and are more fragile than those of adults. Therefore, thorough surgical training in vessel anastomosis is essential. To safely complete direct bypass procedures, the following techniques are quite important. First, complete hemostasis of the entire surgical route, including the scalp, muscle, cranium, and dura mater, is essential to prevent disturbance of fine manipulations during the procedures. Elimination of cerebrospinal fluid from the operative field also facilitates direct bypass procedures. Second, clear visualization of the orifice of arteriotomy by staining blue with methylrosaniline chloride (pyoctaninum blue) is quite useful. Blue silicone rubber should be placed beneath the recipient artery to clearly visualize the semi-translucent recipient vessel, especially in pediatric patients.[12] Our personal experience suggests that these preparations enable safe STA-MCA anastomosis even in a one-year-old baby (Fig. 1).

Although the incidence of ischemic stroke is lower after direct or combined bypass surgery, recent clinical studies have clarified that careful management of patients is quite important to avoid perioperative complications after bypass surgery because pronounced postoperative changes in cerebral hemodynamics may induce hyperperfusion syndrome, particularly in patients with profound ischemia before surgery.[1] Dramatic postoperative changes in cerebral hemodynamics may also cause rapid diminishment of the basal moyamoya vessels and lead to transient cheiro-oral syndrome or small frontal lobe infarction.[26,42] Therefore, pre- and postoperative blood flow studies can be important to identify and prevent such serious complications after direct or combined bypass surgery.

Moyamoya disease is often associated with altered cerebral hemodynamics in the frontal lobe, including the territory of the anterior cerebral artery (ACA).[26,39,47] However, direct STA-ACA anastomosis is not always essential in all patients with moyamoya disease,[10,11] probably because the surgical collaterals to the MCA territory may also provide blood flow to the ACA territory through the pial anastomosis. Thus, the collateral blood flow may be redistributed after surgery.[25,39] However, direct STA-ACA anastomosis is essential in specific patients with pronounced ischemia in the ACA territory, although the number of such cases may be rather small. The frontal branch of STA should be dissected from the scalp to as great a length as possible, which enables easier handling during STA-ACA anastomosis.[10,17] The frontal branch of STA can be anastomosed to the cortical branch of ACA close to the midline with the usual technique, but the direct bypass procedure should be performed more carefully, because the calibers of both donor and recipient vessels are often smaller than the usual situation in STA-MCA anastomosis (Fig. 2). Postoperative angiography and blood flow studies show improvement or normalization of the cerebral hemodynamics in the involved ACA territory.[10,17]

The posterior cerebral artery (PCA) is also involved in a certain subgroup of patients with moyamoya disease, and PCA lesions can be observed in approximately 25% to 60% of cases.[27,34,35,37,43] These patients are considered at higher risk for subsequent ischemic stroke, because the PCA functions as an important collateral route to the ICA territory in moyamoya disease. Some patients are known to develop cerebral infarction in the occipital lobe or temporo-occipital lobe at initial presentation. Surgical revascularization should be planned for both the ICA and PCA territories in these patients.[27,34,35,37,43] We have developed one-stage bypass surgery that can provide extensive collateral blood flow to the entire hemisphere, as reported elsewhere.[28] Briefly, the technique includes STA-MCA anastomosis targeted to the angular artery and indirect bypass through large craniotomy extended from the frontal to the temporo-parietal area. Follow-up cerebral angiography reveals that surgical collaterals supplied blood flow widely to the operated hemispheres including the posterior temporal and parietal lobes. Postoperative blood flow studies also demonstrated marked improvement of cerebral hemodynamics

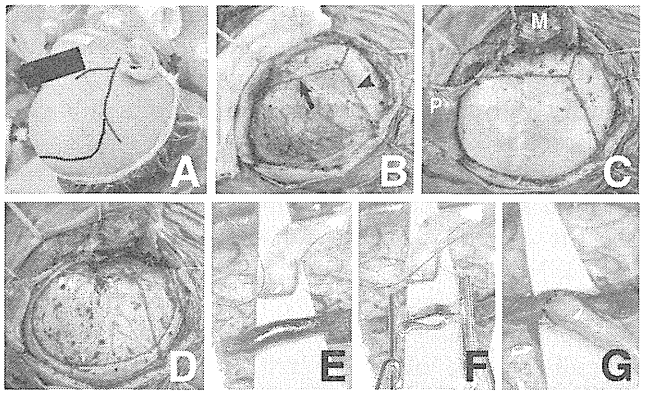

Fig. 1 Intraoperative photographs of superficial temporal artery to middle cerebral artery (STA-MCA) double anastomosis and encephalo-duro-myo-arteriopericranial synangiosis for a one-year-old baby who developed sudden onset of cerebral infarction. A: Skin incision is designed based on the course of the parietal branch of STA. *Red lines* represent the course of the frontal and parietal branches of STA. *Black line* represents the design of skin incision. B: Both the frontal (*arrow*) and parietal branches (*arrowhead*) of STA are carefully dissected under surgical microscope. Note that both branches remain patent even after complete dissection. C: The temporal muscle (M) and frontal pericranial flaps (P) are carefully dissected and the cranium is exposed. D: Fronto-temporal craniotomy is performed, leaving the STA and middle meningeal artery intact. Note the wide extension of craniotomy to the frontal area. E–G: Step-by-step photographs of STA-MCA anastomosis. Note that the orifice of the arteriotomy is clearly visualized by the use of pyoctaninum blue staining and blue silicone rubber.

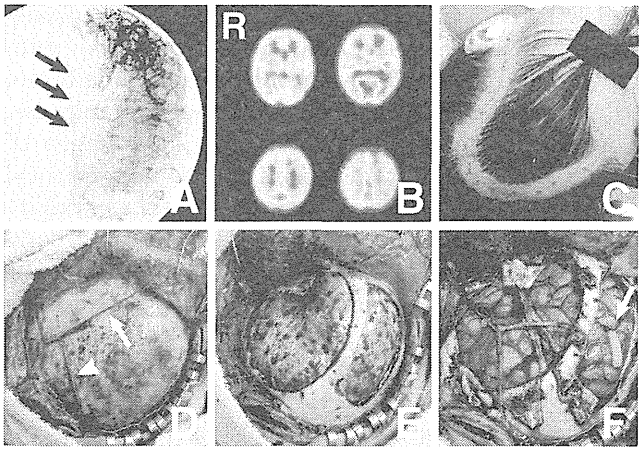

Fig. 2 Radiological and intraoperative findings of a 4-year-old girl who developed transient weakness of the right leg after crying. Her cousin was also diagnosed with moyamoya disease and was surgically treated at our hospital. A: Preoperative left internal carotid angiogram showing almost no filling of contrast material in the left anterior cerebral artery (ACA) territory even at late arterial phase (*arrows*). B: Iodine-123 N-isopropyl-p-iodoamphetamine single photon emission computed tomography scans demonstrating moderate reduction of cerebral blood flow in the left frontal lobe at rest (*left column*) and markedly impaired reactivity to acetazolamide in the bilateral frontal lobes (*right column*). C–F: Intraoperative photographs. Design of skin incision and partial hair shaving (C). The frontal (*arrow*) and parietal branches (*arrowhead*) of superficial temporal artery (STA) are carefully dissected under the surgical microscope (D). Note the very long graft of the frontal STA branch. Two-flap craniotomy is useful to widely expose the medial frontal lobe and perform STA-ACA anastomosis (E). The dura mater is opened, and the main branches of middle meningeal artery are kept intact (F). The frontal STA branch is passed beneath the cranial strip, and anastomosed to the cortical branch of the ACA near the midline.

and metabolism in the operated hemispheres including the occipital lobe (Fig. 3).[28]

Delayed wound healing or scalp necrosis is known as one of the most serious complications after STA-MCA anastomosis in patients with moyamoya disease.[19,29] We have used a modified surgical technique to dissect the STA to avoid this problem for 15 years. No serious complications of wound healing and scalp necrosis have occurred. First, the STA branches are carefully dissected from the surrounding galeal tissue under the surgical microscope. The dissected STA should be "naked," because the surrounding galeal tissue is quite important for wound healing. Next, the galeal "track" is always repaired after STA dissection by suturing the galeal tissue. The small amounts of time and effort contribute to the preservation of scalp blood flow, thus supporting wound healing (Fig. 4). The technique can be applied to STA-MCA anastomosis for patients with atherosclerotic carotid artery diseases (Kuroda et al., unpublished data).

In patients with advanced-stage moyamoya disease, the vault moyamoya vessels are frequently identified through the middle meningeal artery (MMA) and STA.[21] Therefore, the STA branches should be preserved during surgical revascularization if these vessels are involved in the vault moyamoya vessels. A representative case is presented in Fig. 5. This 52-year-old male had spontaneous collaterals to the ACA branches through the frontal branch of STA. Thus, the frontal branch of STA was preserved and used as the donor artery for encephalo-arterio-synangiosis by positioning on the brain surface.

As described above, direct STA-MCA and/or STA-ACA anastomoses are considered to contribute to

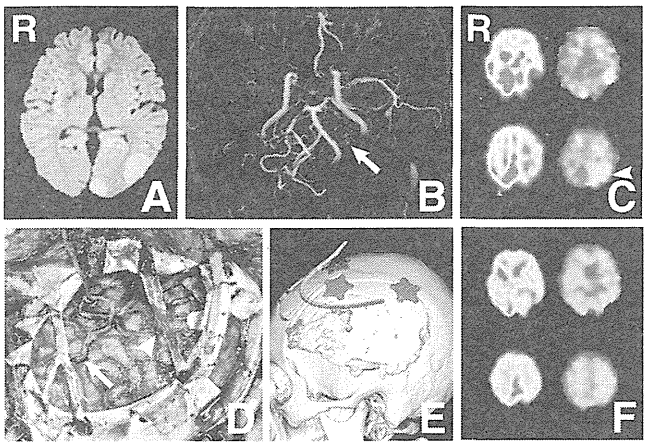

Fig. 3 Radiological and intraoperative findings of a 38-year-old female who developed ischemic stroke. A: Diffusion-weighted magnetic resonance (MR) image demonstrating cerebral infarction in the left posterior temporal and occipital lobes at onset. B: MR angiogram revealing severe stenosis of the left posterior cerebral artery (*arrow*) as well as occlusive lesions in the bilateral internal carotid arteries. C: Preoperative oxygen-15 gas positron emission tomography (^{15}O-gas PET) scans showing marked reduction of cerebral blood flow in the entire left hemisphere (*left column*). Oxygen extraction is elevated in the left parieto-occipital lobe (*right column, arrowhead*). D: Intraoperative photograph showing a wide craniotomy exposing the posterior temporal and parietal lobes. The parietal branch of the superficial temporal artery (STA) is anastomosed to the angular artery to directly supply blood flow to the oxygen extraction-elevated area (*arrow*). The frontal branch of STA is anastomosed to the prefrontal artery (*arrowhead*). E: Postoperative three-dimensional skull computed tomography scan demonstrating the extent of craniotomy. F: Postoperative ^{15}O-gas PET scans showing improvement of the cerebral hemodynamics (*left column*) and oxygen metabolism (*right column*) in the operated hemispheres.

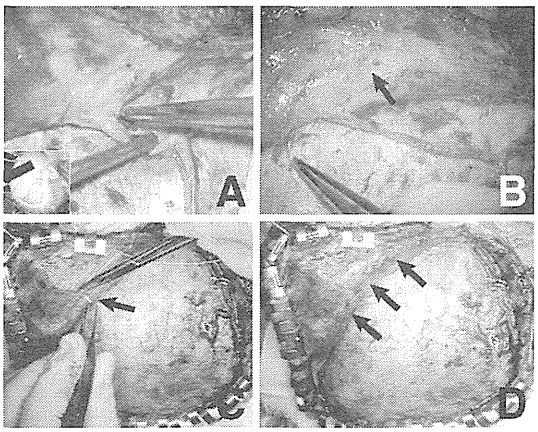

Fig. 4 Intraoperative photographs of left superficial temporal artery (STA) to middle cerebral artery double anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis for a 6-year-old boy who developed transient weakness of the left extremities. A: The main trunk of STA and its two main branches are carefully dissected from the surrounding galeal tissue under surgical microscope. Note that there are no galeal tissues around the dissected STA branches. B: The main trunk of STA and its frontal and parietal branches are still patent after complete dissection. Note that dissection of the STA branch resulted in the track-like galeal injury, where subcutaneous fatty tissue is exposed (*arrow*). C: After STA dissection, the galeal injury should be carefully repaired to preserve blood flow in the scalp, using absorbable surgical sutures (*arrow*). D: The galeal injury after dissection of the frontal STA branch is completely repaired, contributing to good wound healing (*arrows*).

good short- and long-term outcomes of patients with moyamoya disease. However, the course of the frontal STA branch should carefully be checked prior to surgery. As reported before, the frontal branch of STA runs tortuously upward and forward to the forehead, where it supplies the muscles, integument, and pericranium in this region, and anastomoses with the supraorbital and frontal arteries.[18] In a certain subgroup of patients, it runs in an extremely caudal direction. In such cases, full dissection of the frontal STA branch may injure the temporal branch of the facial nerve and cause postoperative palsy of the frontalis muscle.[50] Therefore, only the distal portion of the frontal STA branch should be dissected from the scalp to avoid postoperative frontalis palsy, if the course is extremely caudal. The artery close to the temporal branch of the facial nerve should be left intact (Fig. 6). The dissected length is enough for direct bypass to the frontal branches of the MCA. After STA-MCA anastomosis, the frontal branch of STA can be guided into the intracranial space through the burr hole at the pterion (Fig. 6).

Indirect Bypass Procedure

Surgical procedures for indirect bypass are specific for moyamoya disease. Indirect bypass surgery that induces spontaneous angiogenesis between the brain surface and the vascularized donor tissues is technically simple to do and has been widely used. Donor tissues include the STA, dura mater, temporal muscle, and galeal tissue.[8,13,16,20,32] However, several important issues should be considered when performing indirect bypass procedures. First, the beneficial effects are not immediate because surgical collaterals require 3 to 4 months to develop,[6,7,48]

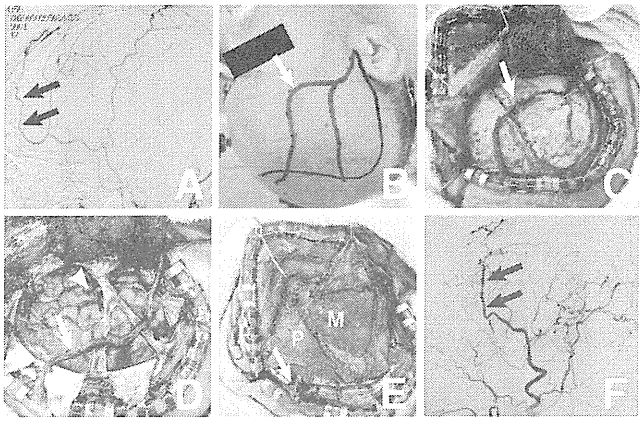

Fig. 5 Intraoperative photographs of superficial temporal artery to middle cerebral artery (STA-MCA) single anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis for a 52-year-old male who developed minor ischemic stroke. A: Preoperative right external carotid angiogram showing the collateral circulation to the anterior cerebral artery branches spontaneously developed through the frontal branch of STA (*arrows*). B: Skin incision (black line) and course of two branches of STA (*red lines*). Note that the frontal branch of STA (*arrow*) is crossing the line of the skin incision. C: The STA branches are carefully dissected, and the scalp flap is reflected. Then, the temporal muscle and frontal pericranial flap are dissected. The frontal branch of STA is still intact (*arrow*). D: The dura mater is opened, leaving the middle meningeal artery branches intact. The parietal branch of STA is anastomosed to the cortical branch of MCA (*arrowhead*). The frontal branch of STA is still intact (*arrow*). E: The dural window is covered by the temporal muscle (M) and frontal pericranium (P). Note that the frontal branch of STA is still intact (*arrow*) and is used as the donor artery for encephalo-arterio-synangiosis. F: Postoperative right external carotid angiogram demonstrating collateral blood flow through the STA-MCA anastomosis and indirect bypass. Note the preserved frontal branch of the STA (*arrows*).

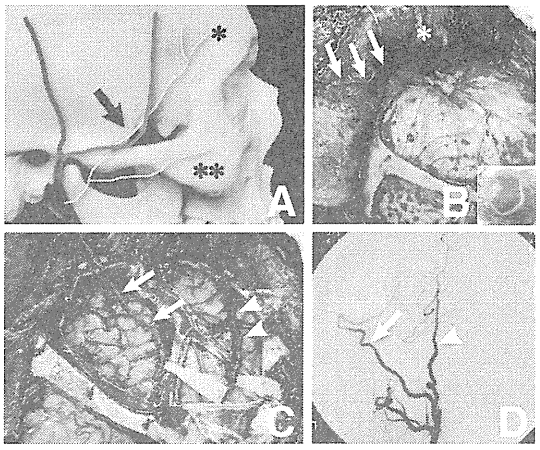

Fig. 6 A: Anatomy of the superficial temporal artery (STA; *red*) and facial nerve (*yellow*). The facial nerve has the temporal branch (*) and zygomatic branch (**). Note that the frontal branch of the STA runs very close to the temporal branch of the facial nerve because of its unusually caudal course in some patients (*arrow*). B: Intraoperative photograph of a 54-year-old female who experienced transient weakness of the left extremities. The frontal branch of STA runs very caudally, and only the distal part is dissected from the scalp (*arrows*). C: Intraoperative photograph showing that STA to middle cerebral artery double anastomosis is completed. Note that the frontal STA branch is guided into the intracranial space through the burr hole made at the pterion (*arrows*). The parietal branch of STA follows the usual course (*arrowheads*). D: Postoperative right external carotid angiogram showing that the frontal branch of the STA (*arrow*) is guided into the subdural space through the burr hole at the pterion. The parietal branch of the STA is guided into the intracranial space with a usual fashion (*arrowhead*).

suggesting that there is a potential risk of perioperative ischemic stroke.[9,41] Second, previous studies have demonstrated that collateral pathways through indirect bypass extensively develop in almost all pediatric patients, but not in about 40% to 50% of adult patients.[36] In fact, combined, but not indirect, bypass surgery could reduce the incidence of rebleeding in adult moyamoya disease.[15] Third, surgical design is quite important because the extent of surgical collateral pathways depends on the size of the craniotomy and the extent of the indirect bypass. Thus, the revascularized area is confined to the craniotomy field after indirect bypass. Recent multivariate analysis has proven that "small craniotomy" surgery can be an independent predictor for poor intellectual outcome in pediatric moyamoya disease, probably because of persistent cerebral ischemia in the frontal lobes even after surgery.[23] Figure 7 shows representative cerebral angiography and three-dimensional skull computed tomography findings after various types of indirect bypass surgery, demonstrating that indirect bypass through a smaller craniotomy develops less extensive surgical collaterals.

Based on these observations, we have recently developed a novel indirect bypass procedure by using the vascularized frontal pericranial flap, named EDMAPS (see above).[24] The frontal pericranial flap is large enough to widely cover the frontal lobe (Figs. 2, 3, and 5). Postoperative cerebral angiography and blood flow studies have shown that the pericranial flap functions well as a donor tissue for indirect bypass, especially in pediatric patients with

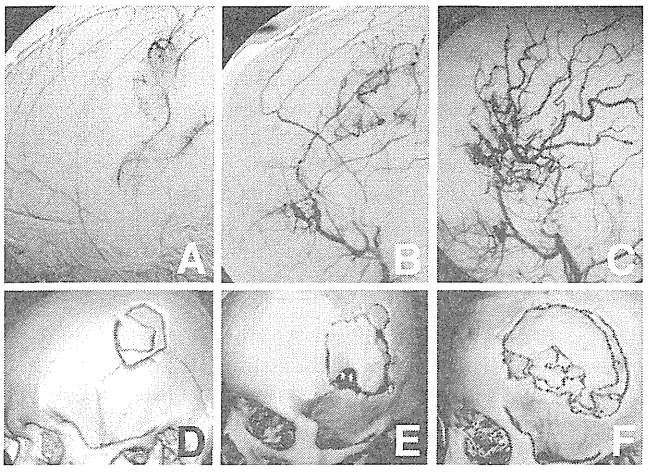

Fig. 7 Postoperative external carotid angiograms (A–C) and three-dimensional skull computed tomography scans (D–F) showing the relationship between craniotomy size and the extent of surgical collaterals through indirect bypass after encephalo-duro-arterio-synangiosis (A, D), encephalo-myo-synangiosis (B, E), and encephalo-duro-arterio-myo-synangiosis (C, F).

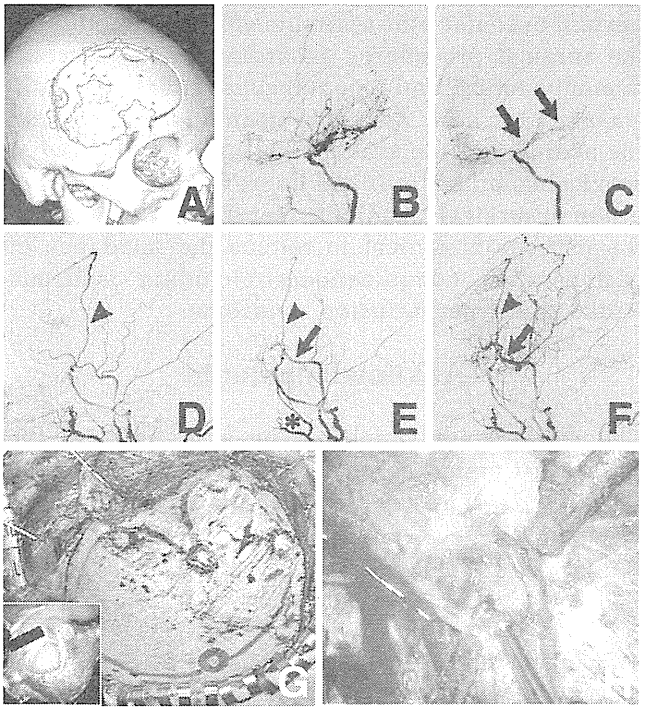

Fig. 8 Radiological findings of a 55-year-old female who developed transient ischemic attacks followed by right thalamic hemorrhage. She underwent right superficial temporal artery to middle cerebral artery (STA-MCA) single anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis (EDMAPS) safely. A: Postoperative three-dimensional skull computed tomography scan showing the extent of craniotomy. B, C: Pre- (B) and postoperative (C) right internal carotid angiograms revealing marked diminishment of the basal moyamoya vessels after surgery (C, *arrows*). D–F: Pre- (D) and postoperative (E, F) right external carotid angiograms showing extensive developments of the surgical collaterals through the STA-MCA anastomosis (E, F; *arrow*) and indirect bypass. Note that the middle meningeal artery (MMA) is preserved even after surgery (D–F, *arrowhead*) and that the deep temporal artery has increased diameter after surgery (E, *asterisk*). G, H: Intraoperative photographs of right STA-MCA single anastomosis and EDMAPS. Fronto-temporal craniotomy is designed to avoid injury of the MMA during craniotomy (G). The MMA can be preserved intact by carefully drilling out the bone surrounding the MMA (H).

moyamoya disease. Figure 8 demonstrates the representative radiological findings before and after STA-MCA single anastomosis and EDMAPS in an adult patient with hemorrhagic onset. Surgical collateral pathways have extensively developed and provide blood flow widely to the operated hemisphere. Finally, the basal moyamoya vessels are markedly diminished.

The MMA can function as one of the important surgical collaterals through the dura mater. Therefore, the MMA should carefully be preserved during craniotomy. However, the course of the anterior (frontal) branch of the MMA in the region of lesser wing of the sphenoid and adjacent parietal bone greatly varies in adults. Generally, the anterior branch of the MMA is believed to run within the groove in the medial surface of bone, but this pattern is observed in less than 30% of adults. Alternatively, the course of the anterior branch of the MMA is completely enclosed within a bony canal in the lesser wing of the sphenoid and parietal bone in about 50% to 75% of adults.[30,45] Therefore, the MMA can easily be damaged during usual fronto-temporal craniotomy. As shown in Fig. 8G and H, we have modified the design of fronto-temporal craniotomy to avoid this problem. The MMA can be kept intact by carefully drilling out the lesser wing of the sphenoid. Figure 8E and F demonstrate that the dilated anterior branch of the MMA remains intact and functions as one of collateral pathways even after surgery.

Conclusions

In this article, we describe the basic concepts of surgical revascularization for moyamoya disease. In particular, STA-MCA anastomosis combined with a novel indirect bypass, EDMAPS, can be a safe and effective procedure for pediatric and adult patients with moyamoya disease. However, it is quite im-

portant to achieve the optimum effects by modifying the surgical procedures according to the cerebral hemodynamics and spontaneous collateral pathways in each case. Also, it is essential to understand the anatomy of the scalp, STA, and MMA to avoid surgical complications and improve outcome. In addition to surgical techniques, careful management of the patients is critical to reduce the incidence of perioperative complications, including ischemic stroke and hyperperfusion syndrome.

Acknowledgments

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Incidence, Locations, and Longitudinal Course of Silent Microbleeds in Moyamoya Disease

A Prospective T2*-Weighted MRI Study

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Background and Purpose—Clinical significance of silent microbleeds is unknown in moyamoya disease. This study was aimed to clarify the incidence, locations, and longitudinal course.

Methods—This prospective cohort study included 78 nontreated patients with moyamoya disease. The incidence and locations of silent microbleeds were evaluated on T2*-weighted MRI. MR examinations were repeated every 6 or 12 months during a mean follow-up period of 43.1 months.

Results—T2*-weighted MRI identified silent microbleeds in 17 (29.3%) of 58 adult patients with moyamoya disease, but in none of 20 pediatric patients. During follow-up periods, de novo silent microbleeds developed in 4 (6.9%) of 58 adult patients. Hemorrhagic stroke occurred in 4 patients (6.9%), all of who had silent microbleeds on initial examination. The presence of silent microbleeds was a significant predictor for subsequent hemorrhagic stroke in adult moyamoya disease ($P<0.001$).

Conclusions—Careful and long-term follow-up of silent microbleeds would be essential to improve their outcome in adult patients with moyamoya disease. **(*Stroke*. 2013;44:516-518.)**

Key Words: microbleeds ■ moyamoya disease ■ MRI ■ outcome

Moyamoya disease is characterized by progressive occlusion of the supraclinoid internal carotid artery and its main branches, resulting in the formation of moyamoya vessels at the base of the brain.[1] The majority of pediatric patients develop transient ischemic attack and ischemic stroke, whereas about half of adult patients develop intracranial bleeding.[1] The moyamoya vessels may rupture because of persistent hemodynamic stress, thus intracranial bleeding occurs in the basal ganglia, thalamus, and periventricular region.[2,3]

According to recent studies, silent microbleeds are identified on T2*-weighted MRI in moyamoya disease.[4–6] They are found in the basal ganglia, thalamus, and periventricular region, where intracranial bleeding often occurs.[4–6] They may predict subsequent hemorrhagic stroke.[6] However, the information on their clinical significance is still limited. Especially, none of previous studies could disclose actual features of silent microbleeds, because the majority of subjects in these studies had already undergone surgical revascularization before initial MR examination.[4–6] Therefore, this study enrolled nontreated patients and prospectively assessed the incidence, locations, and longitudinal course of silent microbleeds in moyamoya disease.

Methods

This prospective cohort study included 78 patients who were admitted to our hospital because of moyamoya disease between November 2003 and October 2011. All met the guideline for the diagnosis set by the Research Committee on Moyamoya Disease of the Ministry of Health, Labor and Welfare of Japan. There were 18 males and 60 females. There were 20 children and 58 adults. The mean ages were 10.1±5.6 and 46.6±14.0 years in pediatric and adult patients, respectively. All pediatric patients developed transient ischemic attack or ischemic stroke. In adult patients, clinical diagnosis included asymptomatic in 20, transient ischemic attack or ischemic stroke in 27, and intracranial bleeding in 11.

MR imaging was performed before surgery, using a 1.5-Tesla scanner, as reported previously.[4] The involved hemisphere with impaired reactivity to acetazolamide was considered as the candidate for surgical revascularization. Totally 46 patients underwent surgical revascularization after initial examinations.[7] All patients were followed up in the outpatient clinic. Both MRI and magnetic resonance angiography were repeated every 6 or 12 months. Hypertension was noted in 10 adult patients. None of them received antiplatelets and anticoagulants.

Continuous data were expressed as mean±SD. Categorical data were compared by using χ^2 test. Cumulative hemorrhagic stroke-free survival rate was compared between 2 groups with the Kaplan-Meier method and Cox-Mantel log-rank statistics. Multivariate analysis using the Cox proportional hazards model determined the joint effect of multiple variables on hemorrhagic stroke over time. Differences were considered statistically significant when P value was <0.05.

Results

No silent microbleeds were detected in 20 pediatric patients, whereas silent microbleeds were detected in 17 (29.3%) of

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Table. Clinical Data of 8 Patients With Clinical or Radiological Events During Follow-Up Periods

	Age, Sex	Initial Presentation	Silent Microbleeds	Surgical Treatment	Follow-up (mo)	De Novo Silent Microbleeds	Hemorrhagic Sstroke
De novo silent microbleeds during follow-up periods							
1	36, F	Hemorrhagic stroke	Left putamen	Yes	23	Left periventricular white matter	
2	62, F	Asymptomatic	Corpus callosum	None	6	Right insula, right periventricular white matter	
3	51, F	Asymptomatic	None	None	8	Right periventricular white matter	
4	29, F	TIA	None	None	32	Right peduncle	
Hemorrhagic stroke during follow-up periods							
1	56, F	Hemorrhagic stroke	Right periventricular white matter	Yes	11		Right periventricular white matter
2	33, F	Asymptomatic	Left putamen, Bilat. periventricular white matter	None	72		Left putamen
3	52, F	TIA	Right thalamus	None	0.2		Right thalamus
4	83, M	TIA	Right periventricular white matter	None	15		Right periventricular white matter

Bilat indicates bilateral; and TIA, transient ischemic attack.

58 adult patients. Of these 17 patients, 11 had 1 silent microbleed and the other 6 had >2 silent microbleeds (total number of silent microbleeds =27). Silent microbleeds were found in the basal ganglia, thalamus, and periventricular white matter. There were no significant differences in clinical variables between patients with silent microbleeds and those without. Silent microbleeds were found in 5 (25.0%) of 20 asymptomatic patients, in 6 (22.2%) of 27 ischemic-type patients, and in 6 (54.5%) of 11 hemorrhagic-type patients. The incidence of silent microbleeds did not differ among them, although the incidence of silent microbleeds in hemorrhagic-type patients was higher (P=0.121).

During follow-up periods, T2*-weighted MRI did not detect any new microbleeds in pediatric patients. However, radiological and clinical events occurred in 8 (13.8%) of 58 adult patients during a mean follow-up period of 48.8 months (Table). Thus, silent microbleeds newly developed in 4 adult patients (6.9%). Two of them had silent microbleeds on initial examination, and de novo silent microbleeds were identified in the area apart from the original ones. These de novo silent microbleeds were identified in 2 asymptomatic, 1 ischemic-type, and 1 hemorrhagic-type patients. The annual incidence of de novo microbleeds was 1.7% in adult patients. Hemorrhagic stroke occurred in other 4 patients (6.9%). Their clinical diagnosis included transient ischemic attack in 2 patients, hemorrhagic stroke in 1, and asymptomatic in 1. All of these 4 patients had silent microbleeds on initial examination, but had no de novo ones during follow-up periods. Of 11 patients with single microbleeds, 3 (27.3%) developed hemorrhagic stroke. Of 6 patients with multiple microbleeds, 1 (16.7%) developed it. Their locations did not differ among them. Therefore, there were no associations with the number and location of silent microbleeds on initial examination (Table). Two of them were fatal. Another developed severe hemiparesis (Figure 1). The

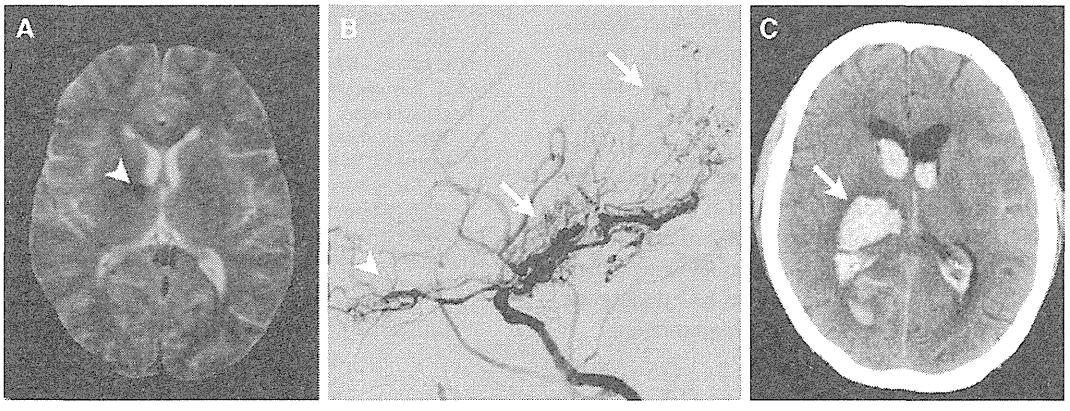

Figure 1. Radiological findings in a 52-year-old female who experienced transient ischemic attack attributable to moyamoya disease. Silent microbleed in the right thalamus on initial T2*-weighted MRI (**A**, arrowhead). Markedly dilated moyamoya vessels originating from the lenticulostriate, anterior and posterior choroidal arteries (**B**, arrows) and ethmoidal arteries (**B**, arrowhead) on right cerebral angiography. One week later, she developed right thalamic hemorrhage (**C**, arrow).

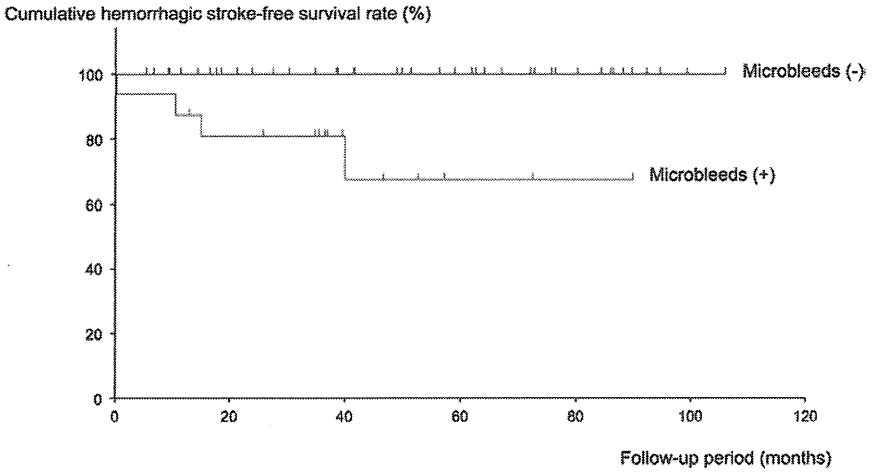

Figure 2. Kaplan-Meier cumulative hemorrhagic stroke-free survival rate curves of microbleeds-positive group (black) and microbleeds-negative group (gray). Cox-Mantel test revealed that adult patients with silent microbleeds were significantly at higher risk for hemorrhagic stroke ($P<0.001$).

annual risk of hemorrhagic stroke was 1.7% in whole adult patients with moyamoya disease. The value was 6.6% in adult patients with silent microbleeds on initial T2*-weighted MRI, being significantly higher than those without ($P<0.001$; Figure 2).

Discussion

This study prospectively investigated clinical features of silent microbleeds in patients with moyamoya disease. Silent microbleeds were detected in about 30% of adult patients. The lesions were identified in the hemorrhagic stroke-prone areas.[1] Ishikawa et al[4] found them in 4 (14.8%) of 27 adult patients. They were detected in 2 (33.3%) of 6 nonoperated patients, but in 2 (9.5%) of 21 operated patients. There was a significant difference in their incidence between them.[4] Subsequently, Kikuta et al[5] also reported that their incidence was 28% and 44% on 1.5- and 3.0-Tesla MR apparatus, respectively. No silent microbleeds were identified in pediatric moyamoya disease. Shorter disease periods in pediatric patients may explain no or very low incidence of silent microbleeds.[1]

The principle finding in this study is that de novo silent microbleeds occurred even in asymptomatic patients, in patients without silent microbleeds on initial examination, or in surgically treated patients. Furthermore, hemorrhagic stroke occurred in 4 patients who had silent microbleeds on initial examination. Annual risk of hemorrhagic stroke was quite high, 6.6% in adult patients with silent microbleeds on initial examination. The value was significantly higher than those without. Intracranial hemorrhagic is still one of the most serious events that cause poor outcome in adult moyamoya disease. The present finding strongly suggests that the adult patients with silent microbleeds may carry the high risk for hemorrhagic stroke. Kikuta et al[6] also reported that hemorrhagic stroke occurred in totally 4 (8.0%) of 50 patients during a mean follow-up period of 16.6 months. However, their study included 23 (46%) of 50 patients who had undergone surgical revascularization before initial MR examination.

In conclusion, silent microbleeds are not rare and may predict subsequent hemorrhagic stroke in adult moyamoya patients. The incidence of de novo silent microbleeds is not small. Careful and long-term follow-up of silent microbleeds would be essential to improve their outcome in adult moyamoya disease.

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Disclosures

None.

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Effective Surgical Revascularization Improves Cerebral Hemodynamics and Resolves Headache in Pediatric Moyamoya Disease

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Key words
- Bypass surgery
- Cerebral hemodynamics
- Headache
- Moyamoya disease

Abbreviations and Acronyms
ACZ: Acetazolamide
CBF: Cerebral blood flow
CVR: Cerebrovascular reactivity
EDAS: Encephalo-duro-arterio-synangiosis
EDMAPS: Encephalo-duro-myo-arterio-pericranial synangiosis
MR: Magnetic resonance
PET: Positron emission tomography
SPECT: Single-photon emission computed tomography
STA-MCA: Superficial temporal artery to middle cerebral artery
TIA: Transient ischemic attack

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BACKGROUND: Headache is one of the major clinical presentations in pediatric Moyamoya disease. However, the clinical features and underlying mechanisms are not fully understood. This study aimed to clarify the clinical feature of headache in pediatric Moyamoya disease and the effect of surgical revascularization.

METHODS: This study included 29 pediatric patients who underwent superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and indirect bypass for Moyamoya disease. Their medical records were precisely evaluated to identify the clinical features of their headache. The findings on magnetic resonance imaging, positron emission tomography, and single-photon emission computed tomography also were analyzed.

RESULTS: Preoperative headache was documented in 11 (38%) of 29 patients. The majority of them complained of severe headache in the frontal or temporal region in the morning. Headache was significantly related to more advanced disease stage and to the decreases in cerebral blood flow and its reactivity to acetazolamide. Surgical revascularization completely resolved headache in all 11 patients.

CONCLUSIONS: These findings strongly suggest that disturbed cerebral hemodynamics may play key roles in developing severe headache in pediatric Moyamoya disease. STA-MCA anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis may be effective procedures to rapidly resolve headache by widely supplying collateral blood flow to the operated hemispheres.

INTRODUCTION

Moyamoya disease is an uncommon cerebrovascular disease that is characterized by progressive steno-occlusion of the supraclinoid internal carotid artery 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. Clinical presentations of Moyamoya disease are very unique. Most children with Moyamoya disease develop transient ischemic attack (TIA) or cerebral infarction, whereas about half of adult patients develop intracranial bleeding, and half develop TIA or cerebral infarct (11). On the other hand, headache is one of the serious symptoms associated with Moyamoya disease, especially in pediatric patients. Typically, they present with migraine-like severe headache in the frontal area in the morning. They cannot go to school because of severe headache. Headache is often associated with vomiting and spontaneously resolves within several hours (1, 23, 27, 30, 35). Migraine-like headache is also observed in some adult patients with Moyamoya disease (27, 31, 35). According to previous studies, persistent cerebral ischemia may be closely related to the occurrence of headache in pediatric Moyamoya disease because surgical revascularization may improve or resolve it (30). However, there are almost no studies that denote the relationship between cerebral hemodynamics and headache in pediatric patients with Moyamoya disease. Therefore, the authors believe that it is important to explore the underlying mechanism to establish more effective treatment and improve quality of life. Based on these considerations, this study aimed to clarify the role of cerebral hemodynamics in headache and to survey the effects of surgical revascularization on headache in pediatric Moyamoya disease.

PATIENTS AND METHODS

Patients

This study included 29 pediatric patients who were admitted because of Moyamoya disease and underwent surgical revascularization at Hokkaido University Hospital between 1997 and 2010. All of them were Japanese and met the guidelines for the diagnostic criteria of the Research Committee on Moyamoya Disease of the Ministry of Health, Labor, and Welfare of

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Japan. There were 7 boys and 22 girls. Their ages ranged from 5 to 17 years, with a mean age of 10.0 years.

Before surgery, the frequency, timing, region, and severity of headache were precisely evaluated in all patients. Based on functional impairment, severity of Q2 headache was classified into 4 categories: 1) mild, patient is aware of a headache but is able to continue daily routine with minimal alteration; 2) moderate, the headache inhibits daily activities but is not incapacitating; 3) severe, the headache is incapacitating; and 4) status, a severe headache that has lasted more than 72 hours (4).

Radiological Examinations

Before surgery, all patients underwent precise neuroradiological examinations, including magnetic resonance (MR) imaging, MR angiography, and cerebral angiography. Disease was classified into 6 stages according to Suzuki angiographic stage (33). Using ^{133}xenon or ^{123}I-IMP single-photon emission computed tomography (SPECT) or ^{15}O-gas positron emission tomography (PET), cerebral blood flow (CBF) before and after intravenous injection of 10 mg/kg acetazolamide was quantitatively measured, as reported previously (12, 15-18). In this study, the involved hemisphere was considered as the candidate for surgical revascularization when having impaired reactivity to acetazolamide (13, 28). Cerebrovascular reactivity (CVR) to acetazolamide was determined as follows: CVR (%) = 100 × (CBF_{ACZ} − CBF_{rest}) / CBF_{rest}, where CBF_{rest} and CBF_{ACZ} represent CBF before and after intravenous injection of acetazolamide, respectively. Because a normal CBF value dramatically changes with growth in children, CBF was rated as reduced when the value was lower than 80% of the cerebellum in each patient (9, 16, 26). CVR was rated as reduced when it was lower than 14% (17).

Surgical Procedures

The patients underwent superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and encephalo-duro-myo-arterio-pericranial synangiosis (EDMAPS) for surgical revascularization, as described previously (13, 28). Briefly, the skin incision was 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. The parietal branch of the STA was dissected from the surrounding tissues, being kept patent, and 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. The temporal muscle was dissected as widely as possible and was made as a vascularized flap. Then, the vascularized frontal pericranium was also dissected. A standard frontotemporal craniotomy was made, preserving the middle meningeal artery. 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. The dura was incised, preserving the main braches of the middle meningeal artery. 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 used as the recipients of anastomoses because cerebral hemodynamics are impaired, especially in the frontal lobe, in Moyamoya disease. The clamping time was about 20 minutes. Then, the dural flaps were turned into the epiarachnoid space to make an indirect bypass. The dural opening through the frontotemporal craniotomy was covered with the temporal muscle flap. The dural opening through the medial frontal craniotomy was covered with the frontal pericranial flap. Cranioplasty was performed for both craniotomies, and the wound was closed. Total surgery time ranged from 5 to 7 hours. No blood transfusion was performed.

Follow-Up

After surgical revascularization, all patients were followed up in the outpatient clinic. The mean follow-up period was 85.3 ± 45.7 months, ranging from 3 months to 162 months. Episodes of TIA, cerebral infarction, and intracranial hemorrhage as well as the clinical features of headache during follow-up periods were precisely recorded. Overall clinical outcomes were classified into 4 categories: 1) excellent, preoperative symptoms (such as TIA) had totally disappeared without fixed neurological deficits; 2) good, symptoms had totally disappeared but neurological deficits remained; 3) fair, symptoms persisted, albeit less frequently; and 4) poor, the symptoms remained either unchanged or worsened (20).

Cerebral angiography and blood flow study were repeated 3 to 6 months after surgery. Both MR imaging and MR angiography were performed every 6 or 12 months with a 1.5-T whole-body MR imager.

Statistical Analysis

Continuous variables were expressed as mean ± SD. Statistical analysis was performed using a χ^2 test and a Kruskal-Wallis test as appropriate. The statistical level of significance was set at $P < .05$.

RESULTS

Clinical Results

STA-MCA anastomosis and EDMAPS were performed on 50 hemispheres of 29 patients. Perioperative ischemic stroke occurred in 3 (6.0%) of these 50 surgical procedures. Cerebral infarct developed in the ipsilateral hemisphere in 2 patients and in the contralateral hemisphere in another. However, their neurological sequelae completely disappeared within 30 days after surgery.

During follow-up periods, 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 ischemic or hemorrhagic stroke occurred in 29 patients during follow-up periods. Therefore, clinical outcome was categorized as excellent in 26 patients (89.7%) and good in 3 (10.3%). Three patients categorized as having good outcomes had mild neurological sequelae because of their initial ischemic stroke, but were independent in their daily life.

Clinical Features of Preoperative Headache

Before surgery, headache was observed in 11 (37.9%) of 29 patients. Their clinical data are shown in Table 1. The clinical diagnosis was TIA in 10 patients and ischemic stroke in 1. The frequency of headache widely varied: once every day in 2 patients (18%), a few times per week in

Table 1. Summary of Clinical Data in 11 Pediatric Patients with Preoperative Headache

Number	Age, Sex	Clinical Diagnosis	Region of Headache	Severity of Headache	Decreased CBF	Impaired CVR	Postoperative Headache	Postoperative CBF	Postoperative CVR	Follow-Up (months)
1	6, Male	TIA	Bilateral frontal	3	F, T, P	F, T, P	0	Improved	Improved	4
2	8, Female	TIA	Right temporal	3	F, T, P	Not done	0	Improved	Not done	6
3	12, Female	TIA	Bilateral frontal	3	F, T, P	F, T, P	0	Improved	Improved	16
4	14, Female	TIA	Bilateral frontal	3	F, T	F, T, P	0	Unchanged	Improved	20
5	16, Female	TIA	Right temporal	3	F, T	F, T, P	0	Improved	Improved	35
6	7, Female	TIA	Right frontal	3	F, T	F, T	0	Improved	Improved	55
7	8, Male	TIA	Right frontal → left frontal	3	F	F	0	Improved	Improved	100
8	12, Male	Ischemic stroke	Right frontal	3	F, T	F, T, P	0	Improved	Unchanged	100
9	17, Female	TIA	Left temporal	3	T, P	T, P	0	Improved	Improved	116
10	11, Male	TIA	Left frontal	3	F, T	F, T	0	Improved	Improved	117
11	8, Female	TIA	Left frontal	3	F, T, P	F, T, P	0	Improved	Improved	139

The headache was classified as 0) no pain; 1) mild pain, does not interfere with usual activities; 2) moderate pain, inhibits but does not wholly prevent usual activities; 3) severe pain, prevents all activities.

CBF, cerebral blood flow; CVR, cerebrovascular reactivity; F, frontal lobe; T, temporal lobe; P, parietal lobe.

6 (54%), and a few times per month in 3 (27%). Headache developed in the morning in 9 (81.8%) of 11 patients and during hyperventilation such as exercising in 1 patient (9.1%). The timing of headache could not be defined in another patient (9.1%). Severity of headache was graded as severe in all 11 patients because they could not go to school or kindergarten during a headache attack. Nausea and vomiting were often associated with headache. Abdominal pain was simultaneously observed in 1 patient. Headache could be localized in the bilateral frontal area in 3 patients (27.3%), the frontal area in 5 (45.5%), and the temporal area in 3 (27.3%). Headache spontaneously resolved within 3 to 4 hours after onset in all 11 patients (Figure 1).

Preoperative demographic and radiological data were precisely evaluated between 11 patients with headache and 18 patients without. There were no significant differences in age, gender, and clinical diagnosis between them (Table 2). As the next step, the relationships between headache and cerebral hemodynamics were assessed between 14 hemispheres with headache and 44 without (Table 2). Suzuki angiographic stage in the hemispheres with headache was significantly more advanced than in those without ($P = .029$). Furthermore, a decreased CBF ($P < .01$) and impaired CVR ($P = .028$) were significant predictors for headache. Localization of headache closely correlated with the area with disturbed cerebral hemodynamics in all 11 patients.

Surgical Effects on Headache

Surgical effects on headache in each patient are shown in Table 1. Headache completely disappeared in all 11 patients within 2 weeks after surgery. Patients did not complain of headache during follow-up periods. Postoperative cerebral angiography revealed that surgical collaterals supplied blood flow to the areas where headache was repeated before surgery. Follow-up SPECT/PET also showed that both CBF and CVR normalized or improved in the hemispheres that underwent surgery, including the area where patients complained of headache before surgery (Table 1).

Of 18 patients without headache before surgery, 17 did not complain of headache after surgery. However, a 5-year-old boy developed severe headache on the right side after surgical revascularization on both sides. He often had severe headache, although postoperative examinations revealed a marked improvement of both CBF and CVR.

Illustrative Cases

Case 7. A 7-year-old girl experienced transient weakness of the left extremities and severe right frontal headache. She often complained of severe headache when she woke up in the morning. MR imaging revealed no cerebral infarction (Figure 2A). MR angiography and cerebral angiography showed severe stenosis of the terminal portion of the ICA and marked development of Moyamoya vessels on the right side, defined as Suzuki stage 3. The lesion was less pronounced on the left side, defined as Suzuki stage 2 (Figure 2B). On ^{15}O-gas PET, both CBF and CVR were reduced in the right cerebral hemisphere, especially in the right frontal lobe, where she complained of headache (Figure 2C).

The patient underwent STA-MCA anastomosis and EDMAPS on the right side. The postoperative course was uneventful. After surgery, she has experienced neither TIA nor headache. Follow-up examinations were repeated 4 months after surgery. Both CBF and CVR almost normalized on ^{123}I-IMP SPECT (Figure 2D). On cerebral angiography, surgical collaterals widely supplied blood flow to the operated hemisphere, including the frontal lobes (Figure 2E).

Case 8. A 12-year-old boy had complained of right frontal headache and involuntary

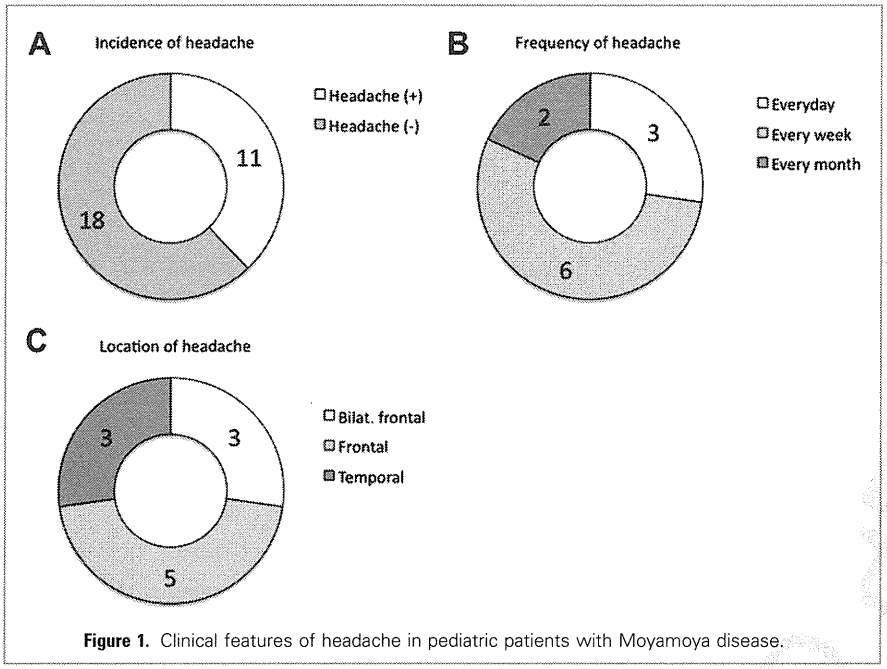

Figure 1. Clinical features of headache in pediatric patients with Moyamoya disease.

movement of the left arm since he was 5 years old. His headache gradually increased in severity and frequency, and he was admitted to our hospital. MR imaging showed a small cerebral infarct in the right frontal lobe (Figure 3A). Cerebral angiography showed severe stenosis of the terminal portion of the ICA and marked development of Moyamoya vessels on both sides, defined as Suzuki stage 3. On ^{133}Xe SPECT, both CBF and CVR were reduced in the right frontal lobe, where he often complained of headache (Figure 3B). He underwent STA-MCA anastomosis and EDMAPS on the right side. The postoperative course was uneventful, and he became free from headache and involuntary movement.

However, the patient started to complain of severe headache in the left frontal area 4 months after the first surgery. The patient could not go to school because of severe headache. MR imaging showed the development of cerebral infarction in the left caudate head and putamen (Figure 3C). MR angiography showed progression of disease stage in the left side. Repeated ^{133}Xe SPECT revealed that surgical revascularization almost normalized cerebral hemodynamics in the right frontal lobe, but both CBF and CVR markedly deteriorated in the left frontal lobe (Figure 3D). Therefore, STA-MCA anastomosis and EDMAPS were performed on the left side. Headache attack completely disappeared after the second surgery. Follow-up ^{123}I-IMP SPECT demonstrated normalization of cerebral hemodynamics on both sides (Figure 3E). Cerebral angiography also showed well-developed surgical collaterals in the operated hemispheres, including the bilateral frontal lobes.

DISCUSSION

This study explores new aspects of headache in pediatric Moyamoya disease. About 40% of pediatric patients with Moyamoya disease complain of headache before surgery. Although the frequency widely varies among patients, most of them complain of severe morning headache in the frontal area. Headache spontaneously resolves within 3 to 4 hours. The hemispheres with headache have a more advanced disease stage. The incidence of reduced CBF and CVR is significantly higher in the hemispheres with headache than in those without. The location of headache correlates very well with the area with disturbed cerebral hemodynamics. STA-MCA anastomosis and EDMAPS completely resolved headache in all patients who complained of it before surgery. This is the first report that denotes the close relationship between headache and cerebral hemodynamics in pediatric patients with Moyamoya disease.

Clinical Features of Headache in Pediatric Moyamoya Disease

As described earlier, there are a limited number of studies that precisely analyzed clinical features of headache in pediatric Moyamoya disease. The incidence of headache in pediatric Moyamoya disease widely varied among previous studies, probably because of different methods of survey and different definitions of headache. Matsushima et al. have precisely reported its clinical features. A total of 47 (34.3%) of 137 pediatric patients complained of headache at initial diagnosis. A morning headache was recorded in more than 60%. Headache significantly affected the activities of daily life in more than 60%. Headache was localized in the frontal region in 40% and in the temporal region in 25%. Headache spontaneously resolved within 1 hour in 25%, within 2 to 3 hours in 22%, and within 4 to 5 hours in 25% (24). Recently, Seol et al. also reported that headache was described in 44 (21.6%) of 204 pediatric patients with Moyamoya disease before surgery. A morning headache was observed in 14 patients. However, headache could be localized in only 5 patients (2 frontal, 1 parietal, and 2 temporal) (30).

The type of headache in pediatric Moyamoya disease can often be categorized into migraine-like headache with or without an aura (1, 19, 24, 30) and hemiplegic migraine (2). However, the underlying mechanisms are still unknown. Park-Matsumoto et al. reported a 49-year-old woman in whom severe migraine with aura developed due to Moyamoya disease. Brain CT scans revealed cerebral infarction in the left occipital lobe. It was speculated that borderline perfusion of the occipital lobe cortex could be a trigger for the development of migraine with aura-like headache in susceptible patients, although it is unclear whether or not this hypothesis can be adapted to pediatric Moyamoya disease (27). The present study precisely analyzed the clinical data of pediatric patients with or without headache. No significant differences in age, gender, or clinical diagnosis were observed among them. However, disease stage was significantly more advanced in the hemispheres with headache than in those without, although the difference was very small (3.2 ± 0.4 and 2.6 ± 1.1, respectively). More importantly, a decreased CBF and

Table 2. Determinants of Preoperative Headache in Pediatric Moyamoya Disease

Clinical Factors	Preoperative Headache: Yes (n = 11)	Preoperative Headache: No (n = 18)	Significance
Age	10.8 ± 3.7	9.2 ± 3.4	NS
Gender			NS
Boy	3	3	
Girl	8	15	
Clinical diagnosis			NS
Asymptomatic	0	1	
Transient ischemic attack	10	15	
Ischemic stroke	1	2	

Clinical Factors	Preoperative Headache: Yes (n = 14)	Preoperative Headache: No (n = 44)	Significance P
Angiographic stage	3.2 ± 0.4	2.6 ± 1.1	.029
Cerebral blood flow			.01
Normal	0	28	
Reduced	14	16	
Cerebrovascular reactivity			.028
Normal	0	15	
Impaired	14	29	

Age, gender, and clinical diagnosis were analyzed between the patients with headache and those without. Angiographic stage, cerebral blood flow, and cerebrovascular reactivity were analyzed between the hemispheres with headache and those without. NS, not significant.

impaired CVR were closely related to headache. Therefore, persistent cerebral ischemia may be one of the powerful inducers of headache attack in pediatric Moyamoya disease. In fact, as presented in illustrative cases, the localization of headache was closely associated with the area with disturbed cerebral hemodynamics in all 11 patients. However, other factors would be involved in the development of their headache, because many of the patients without headache also had disturbed cerebral hemodynamics. Further study is necessary to fully understand the precise mechanism of headache in pediatric Moyamoya disease.

Effects of Surgical Revascularization on Headache in Pediatric Moyamoya Disease

In this study, postoperative courses in the subjects strongly support the involvement of cerebral hemodynamics in the development of headache in pediatric Moyamoya disease. Thus, STA-MCA anastomosis and EDMAPS normalized or significantly improved both CBF and CVR in the operated hemispheres, as reported previously (13). The beneficial effects on cerebral hemodynamics could widely be observed in the operated hemispheres, including the frontal lobe. After surgery, headache completely resolved in all 11 patients (Table 1). Especially, the clinical course of case 8 is quite interesting when considering the underlying mechanism of headache in pediatric Moyamoya disease. He complained of severe headache in the right forehead at onset. Blood flow measurements revealed disturbed cerebral hemodynamics in the right frontal lobe. STA-MCA anastomosis and EDMAPS on the right side improved cerebral hemodynamics and completely resolved his headache. However, the progression of disease stage in the left side led to a marked reduction of cerebral perfusion pressure in the left frontal lobe, causing frequent headache in the left forehead. Additional surgery on the left side also normalized cerebral hemodynamics in the left frontal lobe and resolved his headache (Figure 3).

Previously, Matsushima et al. also reported the beneficial effect of surgical revascularization on headache in pediatric Moyamoya disease (25). Subsequently, they also reported that headache improved or completely disappeared in 75% of pediatric patients after indirect bypass procedure, encephalo-duro-arterio-synangiosis (EDAS) (22). Seol et al. recently surveyed their clinical data after EDAS and found that postoperative headache was observed in more than 60% of the patients with preoperative headache (30). Therefore, there is a significant difference in postoperative improvement of headache between the present and previous studies. The discrepancy may result from the difference in surgical procedures. Thus, the majority of patients in these previous studies underwent bilateral EDAS (22, 25, 30). Indirect bypass surgery induces spontaneous angiogenesis between the brain surface and the vascularized donor tissues and is known to function well in most pediatric patients with Moyamoya disease. The procedures are technically easy and can even be performed by surgeons with little experience with Moyamoya disease. According to a recent review by Fung et al., indirect bypass procedures have been performed in about 75% of patients in 57 studies including 1448 surgically treated patients between 1966 and 2004 (3). However, indirect bypass such as EDAS is performed through temporoparietal craniotomy, and the revascularized area is confined to the craniotomy area. Thus, EDAS is useful for resolving ischemic attacks such as hemiparesis because surgical collaterals develop in and around the primary cortex after surgery. As pointed out by several investigators, however, the procedures do not improve disturbed cerebral hemodynamics in the frontal lobe even after surgery (8, 10, 12-14, 21, 29, 34). Considering the high incidence of frontal headache in pediatric Moyamoya disease, it is most likely that many pediatric patients still suffered headache due to impaired cerebral hemodynamics in the frontal lobe after EDAS. In fact, we have developed STA-MCA anastomosis and EDMAPS by extending the exposure of the brain surface

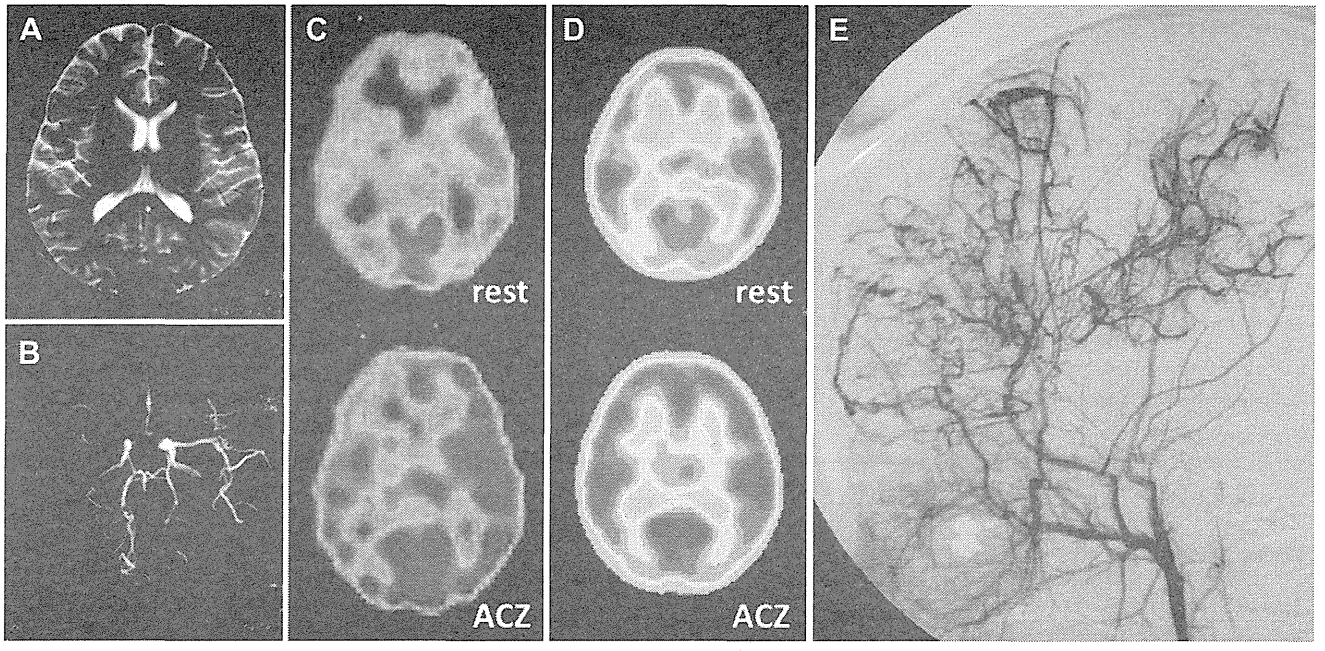

Figure 2. Radiological findings from a 7-year-old girl who underwent right superficial temporal artery to middle cerebral artery anastomosis and indirect bypass for Moyamoya disease. (**A**) Preoperative magnetic resonance imaging showed no parenchymal lesion. (**B**) Preoperative magnetic resonance angiography showed marked stenosis in the right carotid fork. (**C**) Preoperative ^{15}O-gas positron emission tomography showed that cerebral blood flow and its reactivity to ACZ were reduced in the right cerebral hemisphere, especially in the right frontal lobe. (**D**) Postoperative ^{123}I-IMP single-photon emission computed tomography performed 4 months after surgery showed the normalization of cerebral blood flow before and after ACZ injection. (**E**) Postoperative right external carotid angiogram showed that surgical collaterals widely supplied blood flow to the operated hemisphere, including the frontal lobes. ACZ, acetazolamide.

to the medial frontal area and covering the brain surface with the vascularized pericranial flap. Postoperative angiography showed that surgical collaterals supply blood flow to the frontal lobe very widely. Blood flow studies also showed significant improvement in cerebral hemodynamics in both the MCA and the ACA territories after surgery (13). Therefore, STA-MCA anastomosis and indirect bypass through large frontotemporal craniotomy may play a critical role in resolving headache after surgery in pediatric Moyamoya disease. Very recently, Shirane and Fujimura reported that STA-MCA anastomosis and indirect bypass markedly improved headache in 11 (84.6%) of 13 patients with Moyamoya disease (32).

In addition, the present study demonstrated that headache resolved within 2 weeks after STA-MCA anastomosis and EDMAPS. However, previous a study concluded that EDAS required a mean period of about 2 months to resolve headache after surgery (24, 25). Direct STA-MCA anastomosis may explain the difference between the 2 studies. Thus, a direct bypass procedure may be technically challenging in some pediatric patients because their cortical branches have a smaller caliber and are more fragile than those of adults. However, direct bypass is useful to improve cerebral hemodynamics, reduce the incidence of perioperative complications, and resolve ischemic attacks immediately after surgery (5, 8, 13). On the other hand, indirect bypass requires 3 to 4 months to develop surgical collaterals (6, 7). Therefore, direct STA-MCA anastomosis may improve or resolve headache as well as ischemic attacks more promptly.

Postoperative Headache in Pediatric Moyamoya Disease

In this study, surgical revascularization completely resolved headache in 11 patients who complained of headache before surgery. However, 1 of 18 patients without preoperative headache started to experience headache after surgery. Blood flow measurements demonstrated that he had normal CBF and CVR after surgery. Indeed, newly developed headache after surgery has been reported previously. Matsushima et al. reported 2 patients who started to develop headache attack after EDAS, although they did not complain of it before surgery (22). Seol et al. also reported that postoperative headache was observed in 10 (6.3%) of 160 patients without preoperative headache after EDAS (30). These facts strongly indicate that headache in pediatric Moyamoya disease may partly occur through mechanisms other than cerebral ischemia. Further study is warranted to fully explore the mechanism of postoperative headache in pediatric Moyamoya disease.

CONCLUSIONS

This study clearly demonstrates clinical features of headache in pediatric patients with Moyamoya disease. Persistent disturbance of cerebral hemodynamics may be one of the powerful factors that induce headache. STA-MCA anastomosis and EDMAPS can rapidly resolve headache by widely supplying collateral blood flow to the operated hemispheres, including the frontal lobes. Bypass surgery should be

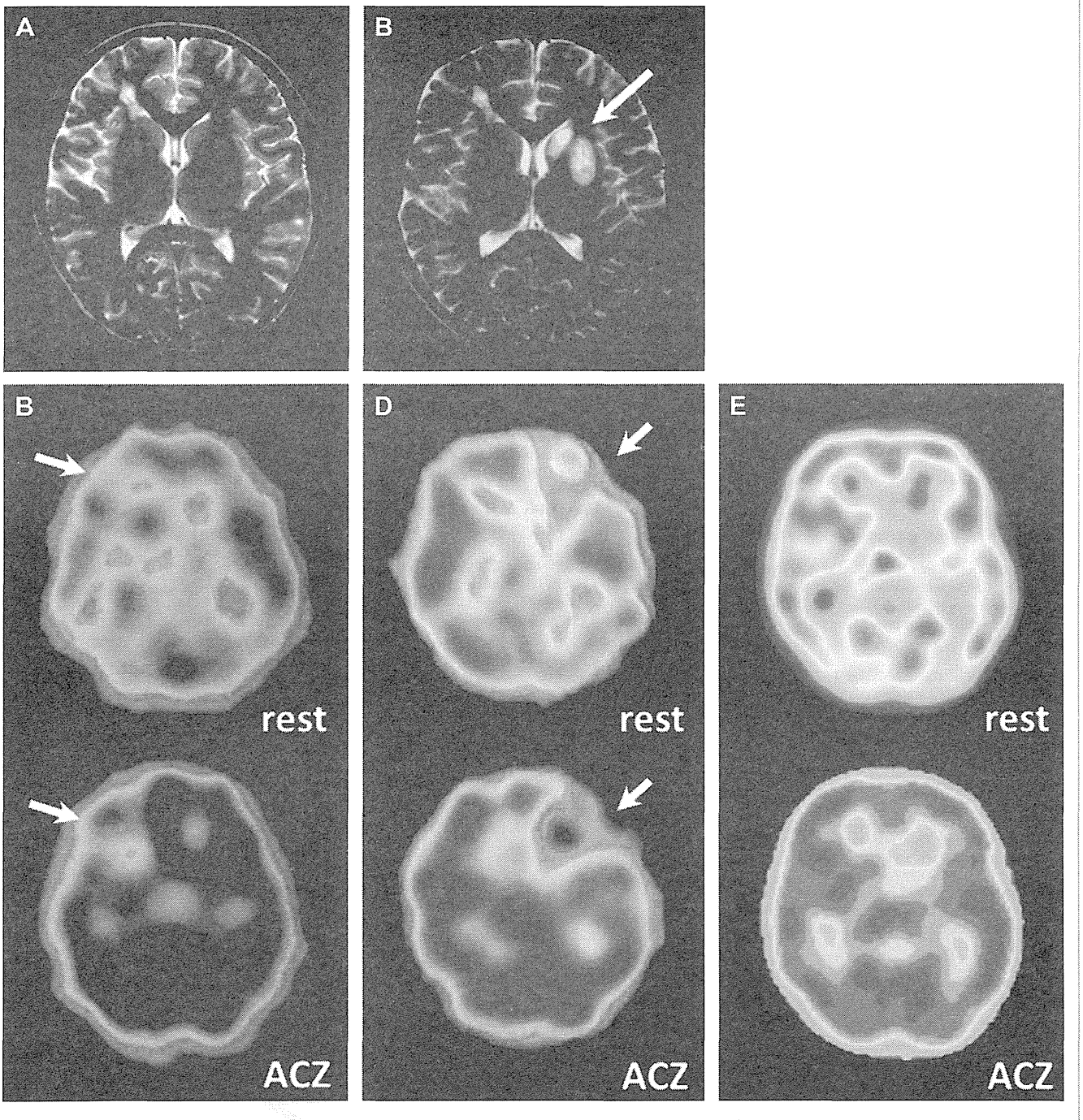

Figure 3. Radiological findings from a 12-year-old boy who complained of right frontal headache and involuntary movement of the left arm. His headache gradually increased in severity and frequency, and he was admitted to our hospital. (**A**) Preoperative magnetic resonance imaging showed a small cerebral infarct in the right frontal lobe. (**B**) Preoperative ^{133}Xe SPECT showed that CBF and its reactivity to ACZ were reduced in the right frontal lobe (*arrows*). He underwent right superficial temporal artery to middle cerebral artery anastomosis and indirect bypass. He became free from headache and involuntary movement. However, he started to complain of severe headache in the left frontal area 4 months after the first surgery. (**C**) Follow-up MRI showed the development of cerebral infarction in the left caudate head and putamen. (**D**) Follow-up ^{133}Xe SPECT revealed that bypass surgery markedly improved cerebral hemodynamics in the right frontal lobe, but both CBF and its reactivity to ACZ markedly deteriorated in the left frontal lobe (*arrows*). Therefore, he underwent left superficial temporal artery to middle cerebral artery anastomosis and indirect bypass. Headache attack completely disappeared after the second surgery. (**E**) Follow-up ^{123}I-IMP SPECT demonstrated normalization of cerebral hemodynamics on both sides. ACZ, acetazolamide; CBF, cerebral blood flow; SPECT, single-photon emission computed tomography.

planned to revascularize the whole area with cerebral ischemia, especially in patients who complain of headache. However, these patients should be carefully followed up because a certain subgroup of patients may develop postoperative headache. Furthermore, these results should be confirmed by analyzing the data in a greater number of patients in the future.

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Pregnancy and Delivery in Moyamoya Disease: Results of a Nationwide Survey in Japan

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Abstract

Stroke during pregnancy associated with moyamoya disease (MMD) has been reported sporadically, but no systematic surveys have been undertaken. To reveal the current clinical situation, the authors conducted Japan's first nationwide survey of pregnancy and delivery associated with MMD. A questionnaire was sent to all 270 perinatal medical centers across Japan to survey their experiences with delivery associated with MMD within the preceding 5 years (Survey I); another questionnaire was sent to 554 adult female patients with MMD regarding their experience with childbirth (Survey II). Survey I included 59 deliveries among patients with previously diagnosed MMD. The incidence of perinatal neurological events and morbidity was 5.1% and 1.7%, respectively. In another five cases, newly diagnosed after perinatal attacks, disability was noted in three cases, including one death from intracranial hemorrhage. Survey II included 278 deliveries. The perinatal attack rate was 6.6% in 76 previously diagnosed cases and 2.0% in 202 cases undiagnosed at pregnancy, but neither group reported permanent morbidity. Caesarean section in previously diagnosed cases accounted for 76.3% of deliveries in Survey I and 69.7% in Survey II, but no significant difference in event rate was found between caesarean section and vaginal delivery in either survey. Although the incidence of perinatal neurological events is low when MMD has been diagnosed, careful monitoring is required in light of the potential for stroke. Serious events, especially intracranial hemorrhage, can occur if MMD has not been diagnosed at pregnancy. Further efforts to establish management guidelines are required to ensure safer childbirth in patients with MMD.

Key words: delivery, intracranial hemorrhage, moyamoya disease, pregnancy, stroke

Introduction

Moyamoya disease (MMD) is a cerebrovascular disease characterized by progressive bilateral stenoocclusion of the terminal internal carotid arteries accompanied by the extensive formation of collateral vessels (moyamoya vessels) at the base of the brain.[2,13] MMD causes cerebral ischemic attacks as well as intracranial hemorrhage that is supposedly the result of excessive long-term hemodynamic stress to the moyamoya vessels.[8] MMD is more prevalent in females than in males and occurs most frequently during childhood and early adulthood[16]; thus, it is not uncommon for patients to become pregnant and give birth. Pregnancy and delivery are known to significantly affect a woman's physical condition, and the incidence of brain attacks can increase in the perinatal period.[5,17] Since the 1970s, several cases of stroke in pregnant patients with MMD have been reported,[1,12] and these sporadic reports were reviewed in 1998.[6] However, no systematic surveys have ever been conducted, and no guidelines have been established for managing pregnancy and delivery associated with MMD. Even recommendations regarding delivery method (natural labor, painless labor, or caesarean section), for example, seem to differ between hospitals. Consequently, the authors designed and conducted a nationwide survey in Japan on the management of pregnancy and delivery in patients with MMD.

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Methods

This survey comprises two sections: a survey of perinatal medical centers (Survey I) and a survey of

Table 1 List of questions for obstetricians regarding pregnancy, delivery, and moyamoya disease (MMD)

I.	Number of deliveries associated with MMD during the preceding 5 years
II.	Clinical data for each patient
1.	Age at delivery
2.	Weeks of gestation at delivery
3.	Number of previous deliveries
4.	MMD diagnosed before pregnancy
5.	Had undergone bypass surgery (when diagnosed before pregnancy)
6.	Detailed information on perinatal cerebral events leading to the diagnosis (when not previously diagnosed)
7.	Selection of delivery method
8.	Information on cerebral events during gestation
9.	Information on cerebral events during labor and puerperium
10.	Clinical outcome of patient at discharge (mRS)
11.	Clinical outcome of child at discharge

mRS: modified Rankin scale.

adult female patients with MMD (Survey II). The survey was conducted with the approval of the Ethical Committee of the National Cerebral and Cardiovascular Center, and great care was taken to protect all personally identifiable information.

I. Survey I

The survey questionnaires were sent to all 270 centers for maternal, fetal, and neonatal medicine across Japan regarding their experience during the preceding 5 years (January 2003–December 2007). These centers are designated to deal with high-risk pregnancies and deliveries. The questionnaire sought to determine the number of deliveries associated with MMD in each unit, the demographics of these patients, the details of any cerebrovascular events that occurred, and their clinical outcomes. Table 1 shows the questions contained in the questionnaire.

II. Survey II

This survey was conducted in cooperation with the Association of Persons with Moyamoya Disease and Their Families, which is the only Japanese association for patients with MMD, and represents 1,300 patients and their family members. The survey questionnaires regarding experiences with pregnancy and delivery were sent from the association's headquarters to all 554 adult female members. Table 2 lists the questions contained in the questionnaire. All reply forms were collected at the headquarters, and the data were provided to the authors for analysis after all personally identifiable information had been deleted.

Table 2 Questions for female patients with moyamoya disease (MMD) about their experiences with pregnancy and delivery

I.	Age at time of questionnaire
II.	Age upon diagnosis of MMD
III.	Clinical type of MMD (ischemic, hemorrhagic, hemorrhagic transformation from ischemic type, others)
IV.	Occurrence and timing of EC-IC bypass surgery
V.	Ongoing medication for MMD
VI.	Previous delivery (yes or no)
VII.	Detailed information about previous deliveries
1.	Number of deliveries before diagnosis of MMD, method of each delivery, details of any perinatal cerebral events
2.	Number of deliveries after diagnosis of MMD, method of each delivery, details of any perinatal cerebral events
3.	Please describe any problems you experienced during your pregnancy and delivery.

EC-IC: extracranial-intracranial.

III. Statistical analysis

The maternal prognosis was expressed with the modified Rankin scale (mRS)[15] at discharge. The data were presented as frequency or means ± standard deviation. Fisher's exact probability test was applied for categorical data. The analyses were performed with Statcel 3 (OMS Publishing Inc., Tokorozawa, Saitama).

Results of Survey I

Feedback was obtained from 132 medical centers (for a response rate of 48.9%). Among these centers, 33 (25.0%) had experienced a delivery associated with MMD, and 64 cases were recruited. These cases were divided into two groups: 59 cases in which MMD had been diagnosed before pregnancy (Group I-A); and 5 cases in which MMD had been newly diagnosed as a result of neurological incidents during pregnancy, delivery, or puerperium (Group I-B).

I. Group I-A (cases of MMD diagnosed previously)

Table 3 shows the clinical data. The mean age of the patients at delivery was 29.2 ± 4.1 years, with 54.2% being primipara. Thirty-four (57.6%) patients had previously undergone extracranial-intracranial (EC-IC) bypass surgery. Fourteen (23.7%) cases were managed with vaginal delivery (natural labor in 3 cases and painless labor with spinal epidural anesthesia in 11), whereas 45 (76.3%) cases were managed with caesarean section (scheduled in 41 cases, emergent change from vaginal delivery in 2, and others in 2). Although caesarean section tended to be selected more frequently for those who had not