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Impact of posterior cerebral artery involvement on long-term clinical and social outcome of pediatric moyamoya disease

Clinical article

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Object. In the study of pediatric moyamoya disease, information on long-term social outcomes and risk factors for unfavorable social outcomes remains insufficient. The authors analyzed the long-term results of surgical revascularization for pediatric patients with moyamoya disease to determine whether the involvement of a stenoocclusive lesion in the posterior cerebral artery (PCA), relatively common in pediatric moyamoya disease, represents an underlying predictor for unfavorable social outcomes.

Methods. Prospectively collected data on 61 consecutive patients with moyamoya disease who had undergone combined bypass surgery were analyzed. Neuroradiological features and other baseline clinical factors were incorporated into univariate and multivariate analyses to determine any association with an unfavorable social outcome, defined as difficulty attending regular school or obtaining regular employment.

Results. Posterior cerebral artery involvement detected by angiography on admission was noted in 22 (36.1%) of the 61 patients. Follow-up data were acquired in 56 patients (91.8%), and the mean follow-up period was 15.8 years. While transient ischemic attacks were eliminated in 52 (92.9%) of these 56 patients after surgery, and late-onset ischemic stroke was observed in only 1 patient during the follow-up period, 10 (17.9%) experienced an unfavorable social outcome. Although younger age at onset, longer duration between onset and surgery, infarction present on preoperative neuroradiological images, and PCA involvement had been identified as risk factors for an unfavorable social outcome in univariate analysis, only infarction present on preoperative images and PCA involvement remained statistically significant after multivariate adjustment.

Conclusions. Posterior cerebral artery involvement can be considered one of the underlying risk factors for unfavorable social outcome and should be studied further to improve social outcome in pediatric moyamoya disease. *(http://thejns.org/doi/abs/10.3171/2013.9.PEDS13111)*

Key Words • **moyamoya disease** • **cerebral revascularization** • **social prognosis** • **posterior cerebral artery**

Moyamoya disease, characterized by progressive spontaneous occlusion of bilateral internal carotid arteries (ICAs) and development of abnormal collateral vessels, is one of the major causes of stroke in childhood. Surgical revascularization is believed to benefit pediatric patients with moyamoya disease. Such surgery is classified into 3 categories: direct, indirect, and combined bypass. While indirect bypass is more commonly applied to pediatric patients than direct or combined bypass, both types of surgery are equally effective for pediatric patients.[5] Recent studies have reported favorable long-term results for both direct and indirect bypasses in terms of preventing strokes or transient ischemic attacks.[3,6,13,16,18,25,31,32,36] However, social outcomes vary in terms of education and employment at adulthood, and a substantial portion of the patients suffer from social adaptation difficulties even after surgery.[27,29] Although reports associate several factors with unfavorable social or functional outcomes,[10,13,14,17,29] studies addressing this issue are lacking.

Involvement of a stenoocclusive lesion in the posterior circulation, especially in the posterior cerebral artery (PCA), is a relatively specific finding in juvenile-onset

Abbreviations used in this paper: ACA = anterior cerebral artery; EMS = encephalomyosynangiosis; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale; PCA = posterior cerebral artery; STA = superficial temporal artery.

moyamoya disease.[19] The PCA usually provides much collateral flow to the anterior circulation in moyamoya disease, and recent studies revealed a higher prevalence of ischemic and hemorrhagic stroke in patients with such PCA involvement.[7,22] However, any association between long-term outcomes and PCA involvement in moyamoya disease has not yet been closely examined.

We hypothesized that PCA involvement in pediatric moyamoya disease represents an underlying factor for poor social outcome. To test this hypothesis, we analyzed long-term follow-up data on consecutive patients who had survived at least 10 years after undergoing combined bypass surgery in childhood. Combined bypass surgery is superficial temporal artery (STA) to middle cerebral artery (MCA) anastomosis with encephalomyosynangiosis (EMS) Since the 1980s, our group has consistently adopted combined bypass as the first-choice treatment for pediatric patients with moyamoya disease.[12,13] This was, to the best of our knowledge, the longest follow-up study among the previous reports on direct or combined bypass for pediatric moyamoya disease.[3,6,11,13,16]

Methods

Patient Population

Between 1984 and 2003, the senior author (S.M.) performed combined bypass surgery on 61 pediatric patients with moyamoya disease at Kyoto University Hospital in Kyoto, Japan, and its satellite hospital. The senior author created a personal database by collecting data on these consecutive cases including patient identification number, age at admission, sex, age at symptom onset, primary clinical manifestations at onset, clinical condition at admission (translated later into the modified Rankin scale [mRS] score with age-specific modification[2,37]), date and procedure of surgery, and angiographic findings upon each patient's first or second admission. These patients were followed prospectively at our hospital. This study was approved by the ethics committee of the Kyoto University Graduate School of Medicine.

Diagnosis and Radiological Assessment

Moyamoya disease was diagnosed in the patients according to criteria proposed by the Research Committee on Moyamoya Disease in Japan.[4,28,34] The diagnoses were confirmed by cerebral angiography in all cases. Children with a typical occlusive finding in the unilateral ICA alone were also considered to have moyamoya disease.[30] Children with autoimmune disease, meningitis, brain tumor, Down syndrome, neurofibromatosis Type 1, or a history of head irradiation were excluded from the present study.

For all patients, we recorded the presence and distribution of infarction before surgery as revealed through CT in early cases or MRI. The hemisphere in which infarctions was dominantly distributed and the presence of bilateral infarctions were also recorded. In cases in which either the original CT scans or MR images were preserved, one of the authors (T.F.) quantitatively assessed the size of infarction on preoperative images in which the patient name was hidden. The area of infarction was measured with Adobe Photoshop software through manual tracing of the lesion on the image slice with the maximum lesion size. If the targeted slice contained more than 2 lesions, the total area of all visible lesions was calculated.

Findings of all angiograms, which had first been reviewed by the senior author on patient admission, were checked again by a coauthor (K.Y.) who was blinded to all clinical information. Unilateral lesion of the ICA was defined as unilateral stenosis or occlusion of the terminal portion of the ICA with the formation of moyamoya vessels accompanied by no or a subtle lesion around the contralateral terminal portion of the ICA. The severity of disease progression in the ICA was evaluated with a 4-stage system,[24] with a higher ICA stage representing more advanced stenoocclusive lesions in the anterior circulation. If the two hemispheres were classified as different ICA stages, the higher stage was recorded. Involvement of the PCA was defined as the presence of occlusion or stenosis greater than 50% in the P_1 to P_3 segment of either PCA (Fig. 1).

Treatment Protocol

Surgical revascularization was indicated for patients with cerebral ischemic manifestations. Single photon emission computed tomography (SPECT) was performed in all but the first few cases to detect hemodynamic impairment, which was considered an indicator suggesting surgical revascularization. All patients underwent direct or combined bypass consisting of STA-MCA anastomosis with or without EMS in each MCA territory as a first-line treatment. Encephalomyosynangiosis, an indirect bypass procedure using the pedicle flap of the temporalis muscle, was usually combined with STA-MCA anastomosis for patients under 10 years of age. All surgeries were performed by the senior author (S.M.). Previously published studies detail the surgical procedure.[13] Briefly, a horseshoe-shaped scalp incision is made surrounding the parietal branch of the STA, and the temporalis muscle is dissected along the horseshoe incision to make the pedicle flap. The dura is widely opened, preserving the main branch of the meningeal arteries. After a conventional

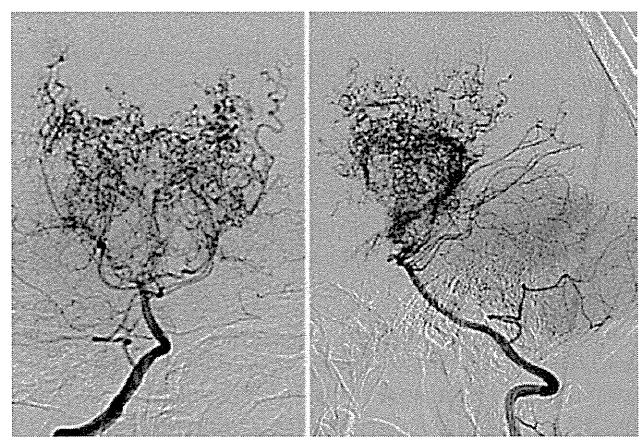

Fig. 1. Anteroposterior **(left)** and lateral **(right)** views of a vertebral artery angiogram revealing heavy involvement of bilateral PCAs characterized by occlusion at the P_3 segment and extensive development of collateral moyamoya vessels.

procedure of STA-MCA single anastomosis, the pedicle flap of the temporalis muscle is placed over the brain surface and sutured to the edge of the remaining dura.

For patients with bilateral ICA involvement, the more symptomatic or hemodynamically impaired side is revascularized first. The second revascularization for the contralateral MCA territory is performed at least 1 month after the first revascularization. To assess bypass patency and improvement of cerebral blood flow, angiography and SPECT were performed 3 months after the second revascularization. In most cases these bypasses widely covered the brain surface beyond the MCA territory.[21] If SPECT reveals insufficient hemodynamic improvement in the anterior or posterior cerebral artery territories, additional direct revascularizations are considered to the territories of the anterior cerebral artery (ACA) or PCA using the frontal branch of the STA or occipital artery.

Follow-Up Data Collection

All follow-up data were acquired through a medical interview and neurological examination at the outpatient neurosurgical clinic. The data obtained at the last visit were used for analysis. Transient ischemic attacks were classified into 4 categories by frequency: eliminated, rare (several times per year), frequent (several times per month or per week), or exacerbated after surgery. The mRS score for each patient was recorded. Late-onset stroke was defined as ischemic stroke or intracranial hemorrhage occurring more than 30 days after surgery, causing certain neurological symptoms, and identified by neuroradiological modalities.

The patients were interviewed about educational background, employment history, and current occupation. Educational background was assessed in all patients and classified by type of school: regular class at ordinary school, special class, or school for the disabled. Employment was assessed in all patients except homemakers and those currently enrolled as students. An unfavorable social outcome was defined as patient difficulty in either attending regular classes or obtaining regular employment.

Statistical Analysis

To compare baseline characteristics, a t-test, the Wilcoxon rank-sum test, or the Fisher exact test was used as appropriate. The mRS scores at the last follow-up evaluation and those at first admission were compared by means of the Wilcoxon signed-rank test. Variables including sex, age of onset, time interval between onset and first bypass surgery, presence of infarction in the preoperative image, infarction area, side of infarction, bilateral infarction, unilateral ICA lesion, ICA stage, involvement of the PCA, and late-onset stroke were incorporated into univariate analysis to identify factors associated with an unfavorable social outcome. The Fisher exact test and logistic regression analysis were used for univariate analysis. Variables with a p value < 0.1 on univariate analyses were selected for further multivariate analysis. The ICA stage was incorporated into multivariate analysis regardless of its p value in univariate analysis in light of the likelihood of correlation between ICA stage and PCA involvement.[24] Variables including missing data were not incorporated into multivariate analysis. Multiple logistic regression analysis was used for multivariate analysis. Two-sided p values < 0.05 were considered statistically significant. All statistical analyses were performed with JMP software (version 9, SAS Institute Inc.).

Results

Patient Background

Table 1 summarizes patient backgrounds before surgery. The female-to-male ratio was 1.3 to 1, and the median age at onset was 6 years (mean 6.5 years, range 0–15 years). No patient experienced intracranial hemorrhage at disease onset. At the time of first admission, 47 patients (77.0%) had an mRS score of 0, 6 (9.8%) a score of 1, 6 (9.8%) a score of 2, and 2 (3.3%) a score of 3. Involvement of the PCA was detected in 22 patients (36.1%).

Infarction, assessed preoperatively with CT in 25 patients (41.0%) and with MRI in 36 patients (59.0%), was detected in 34 patients (55.7%). At the time of retrospective assessment of the infarction area, the original image was not available in 8 of the 61 patients because of the expiration of the film storage period. The median and mean areas of preoperative infarction measured in the remaining cases were 6.4 mm^2 and 206.1 mm^2, respectively (range 0–1652.9 mm^2).

Surgery

A total of 119 surgeries were performed for 61 patients. Table 2 summarizes the number of revascularization surgeries. All patients underwent at least 1 STA-MCA anastomosis. Forty-three patients (76.8%) underwent bypass surgeries twice, while 5 (8.2%) underwent additional revascularization to the ACA or PCA territory. One patient experienced a small infarction in the temporooccipital region immediately after STA-MCA anastomosis, resulting in transient disorientation but no permanent deficit. The patency of the bypasses was confirmed in all cases by means of postoperative angiography.

Follow-Up

The mean follow-up period (± SD) was 15.8 ± 7.0 years, and the mean age at last follow-up was 24.0 ± 6.8 years. Follow-up information was not available in 5 patients (8.2%): 2 were followed up by institutes outside Japan, and 3 were lost to follow-up when their attendant doctors in the outpatient clinic were transferred after surgery. The remaining 56 patients for whom follow-up data were acquired were assessed for further analysis. Baseline characteristics were not statistically different between patients with and without follow-up data (Table 1).

Outcome

Transient ischemic attacks were eliminated in 52 cases (92.9%) and rare in 4 (7.1%) during the follow-up period. Late-onset ischemic or hemorrhagic stroke occurred in 4 patients (7.1%). One patient suffered from acute subdural hematoma due to a traffic accident 33 months af-

TABLE 1: Comparison of baseline characteristics of groups with and without follow-up data

Variable	Total	Followed Up	Lost to Follow-Up	p Value
no. of patients	61	56	5	NA
females (%)	35 (57.4)	33 (58.9)	2 (40.0)	0.642
mean age of admission in yrs ± SD	8.6 ± 3.7	8.7 ± 3.7	7.8 ± 3.1	0.596
mean age of onset in yrs ± SD	6.5 ± 3.5	6.6 ± 0.5	5.8 ± 1.5	0.629
median delay in yrs until surgery (IQR)	1 (0–3)	1 (0–3)	1 (0.5–4)	0.756
infarction on preop image (%)	34 (55.7)	32 (57.1)	2 (40.0)	0.647
median area in mm^2 (IQR)*	6.4 (0–156.0)	7.6 (0–167.9)	0 (0–128.5)	0.351
lt hemisphere infarction (%)	29 (47.5)	26 (46.4)	3 (60.0)	0.662
bilat infarction (%)	6 (9.8)	5 (8.9)	1 (20.0)	0.415
unilat ICA lesion (%)	6 (9.8)	6 (10.7)	0	1.000
ICA stage (%)				
I	7 (11.5)	6 (10.7)	1 (20.0)	
II	29 (47.5)	27 (48.2)	2 (40.0)	
III	23 (37.7)	21 (37.5)	2 (40.0)	
IV	2 (3.3)	2 (3.6)	0	
≥III	25 (41.0)	23 (41.1)	2 (40.0)	1.000
PCA involvement	22 (36.1)	21 (37.5)	1 (20.0)	0.645

* Data on the infarction area were not available in 8 of the 61 patients. IQR = interquartile range; NA = not applicable.

ter STA-MCA anastomosis, which resulted in ischemic stroke in the affected hemisphere. Three patients suffered from intracranial hemorrhage at the mean age of 26 years (range 24–29 years). One patient experienced a second hemorrhage, which resulted in a fatal outcome. The overall incidence of late-onset stroke was not significantly associated with an unfavorable social outcome (Table 3). At the time of the last follow-up, 40 patients (71.4%) had an mRS score of 0, 5 (8.9%) a score of 1, 8 (14.3%) a score of 2, 2 (3.6%) a score of 3, and 1 (1.8%) a score of 6. Among the patients with follow-up, no significant difference in mRS scores was evident between first admission and last follow-up ($p = 0.182$).

Seven (18.9%) of 37 patients who were not currently students or homemakers encountered difficulty in obtaining regular employment. Six patients (10.7%) currently or previously attended special classes or a school for the disabled. In summary, 10 (17.9%) of 56 patients had an unfavorable social outcome: 4 had difficulty obtaining regular employment, 3 had difficulty attending regular classes, and 3 had both difficulties. Univariate analysis revealed that younger age at onset, longer delay between onset and surgery, infarction present on the preoperative image, and PCA involvement were significantly associated with an unfavorable outcome (Table 3). The area of infarction was also significantly larger in patients with an unfavorable outcome than in those with a favorable outcome, although the infarction area could not be measured in 7 of the patients with follow-up because original images were no longer available. Advanced ICA lesion (Stage III or IV), unilateral ICA lesion, left hemisphere infarction, and bilateral distribution of infarction were not significantly associated with outcome.

Variables including the age of onset, delay between onset and surgery, infarction present in the preoperative image, ICA stage, and PCA involvement were incorporated into a further multivariate analysis (Table 4). In this analysis, only infarction present on the preoperative image (OR 9.96, 95% CI 1.08–355.82) and PCA involvement (OR 7.44, 95% CI 1.22–67.79) were identified as significant factors associated with an unfavorable social outcome. The frequency of an unfavorable social outcome was stratified by PCA involvement and delay between onset and surgery to estimate the impact of the combination of these factors on social outcome. The frequency of an unfavorable social outcome reached 50% when PCA involvement and a surgical delay exceeding 3 years were combined, while that in patients with neither risk factor was 0% (Table 5).

TABLE 2: Number of revascularization surgeries by type*

Mode of Revascularization Surgery	No. of Surgeries
STA-MCA anastomosis w/ EMS	97
STA-MCA anastomosis w/o EMS	13
STA-ACA bypass	2
OA-PCA bypass	1
other	6

* OA = occipital artery.

Discussion

Despite the favorable long-term outcomes overall, our results reveal that 17.9% of pediatric patients with moyamoya disease continued to suffer from social adaptation difficulties as they matured, even after bypass surgery. The results also suggest that PCA involvement and presence of infarction on preoperative images are independently associated with an unfavorable social outcome.

TABLE 3: Univariate analyses for factors associated with long-term social outcome in all patients with follow-up*

Variable	Favorable Outcome (n = 46)	Unfavorable Outcome (n = 10)	p Value
female	26 (56.5)	7 (70.0)	0.500
mean age of onset in yrs ± SD	7.1 ± 3.6	4.1 ± 1.8	0.021
median delay until surgery in yrs (IQR)	1 (0–2)	3 (1.5–9.25)	0.015
infarction on preop image	23 (50.0)	9 (90.0)	0.021
median area in mm^2 (IQR)†	0 (0–67.9)	370.1 (58.8–1220.5)	0.028
lt hemisphere infarction	20 (43.5)	6 (60.0)	0.487
bilat infarction	3 (6.5)	2 (20.0)	0.214
unilat ICA lesion	6 (13.0)	0 (0)	0.578
ICA stage ≥3	17 (37.0)	6 (60.0)	0.288
PCA involvement	13 (28.3)	8 (80.0)	0.004
overall late-onset stroke	2 (4.4)	2 (20.0)	0.142

* All data given as number of patients (%) unless otherwise indicated.

† Data regarding the infarction area were not available in 7 of the 56 patients with follow-up.

Our results indicating that more than 80% of patients had a favorable social outcome appear comparable to those of past studies, in which the frequency of patients with a normal intelligence quotient or capable of independent daily activities remained 63.5%–87%.[13,17,25,31] Nevertheless, our results, along with those of several pioneering studies, shed light on the salient issue of social adaptation in pediatric moyamoya disease. Nakashima et al. reported that approximately 10% of patients had severe difficulty in social or school life because of intellectual impairment.[27] While Phi et al. reported good long-term social outcomes in terms of education and employment, their results also revealed that a certain proportion of patients had difficulty planning their marriages and acquiring driver's licenses, and that approximately 20% of the respondents were dissatisfied with their treatment outcomes.[29]

Several factors, including preoperative neurological impairment,[10,17,29] infarction,[13,14] age of symptom onset,[10,13] and duration after onset,[9] have been reported as affecting social or functional outcomes. Our result in univariate analysis is consistent with these reports. In addition, our result in multivariate analysis suggests that PCA involvement, which has so far received less attention in long-term follow-up studies, is also an independent risk factor for unfavorable social outcomes. Involvement of the PCA is more likely to occur in younger children[19,22] and thus may act as a potential confounder affecting social outcome in the previous studies. Although several studies reported that PCA involvement is associated with a high prevalence of preexisting infarction at diagnosis,[22,23] our results from the multivariate analysis suggest that both the preexisting infarction and PCA involvement are independently associated with an unfavorable social outcome.

We speculate on several possible reasons why PCA involvement is associated with unfavorable social outcomes. Involvement of the PCA may more accurately represent the overall progression of a stenoocclusive lesion in pediatric moyamoya disease.[20,23] The other possible explanation is that PCA involvement may cause further reduction in cerebral blood flow because the PCA usually provides important collateral flow to the affected anterior circulation via leptomeningeal anastomosis in patients with moyamoya disease. In particular, a pair of posterior pericallosal arteries, branches of the PCA, is well developed in moyamoya disease as a collateral pathway to the medial frontal cortex. The medial frontal cortex involves various executive, emotional, and behavioral functions,[33] and decreased cerebral blood flow in this area may impede social adaptation abilities even with minimal infarct. Interestingly, Nakagawara et al. speculated that long-standing mild hemodynamic ischemia in the medial frontal lobe could lead to selective neuron loss detected by SPECT imaging with benzodiazepine receptor radioligand, and cognitive dysfunction in patients with moyamoya disease.[26]

Our study has some limitations. First, the result of our multivariate analysis has a relatively large confidence interval, which can be attributed to the limited number of cases. However, the baseline characteristics of this study,

TABLE 4: Multivariate analyses for factors associated with unfavorable long-term social outcome in all patients with follow-up

Variable	p Value	Adjusted OR (95% CI) for Unfavorable Social Outcome
mean age of onset	0.122	0.80 (0.58–1.06) for every yr
median delay until surgery	0.118	1.32 (0.94–2.03) for every yr
infarction on preop image	0.042	9.96 (1.08–355.82)
ICA stage ≥3	0.704	0.67 (0.07–5.11)
PCA involvement	0.029	7.44 (1.22–67.79)

TABLE 5: Frequency of unfavorable social outcomes stratified by PCA involvement and delay until bypass surgery

Length of Delay (yrs)	Without PCA Involvement	With PCA Involvement
<3	0	30.8%
≥3	28.5%	50.0%

such as peak age of onset and female-to-male ratio, were similar to those in previous large epidemiology studies.[1,15,38] Our sample thus can be considered reflective of the general population of pediatric patients with moyamoya disease. Second, our analysis did not include 8.2% of patients because of loss of follow-up, which could cause a certain bias if the trends of these patients differed significantly from those of the analyzed patients. Given that the baseline characteristics did not differ statistically between patients with and without follow-up data, however, such bias is likely minimal. Third, whether our results can be generalized to patients treated with an indirect bypass, such as encephaloduroarteriosynangiosis, is debatable. Generalization of our results may be partially allowed because recent reviews show that direct and indirect bypasses are equally effective over the long term.[5,30,35]

Viewed from a practical perspective, early revascularization may be required for patients with PCA involvement because the risk of an unfavorable social outcome markedly increases with the combination of PCA involvement and a delay in surgical treatment (Table 5). An aggressive revascularization strategy to the PCA or even ACA territory can also be proposed for patients with PCA involvement. A more recent study revealed that a stenoocclusive lesion of the PCA could progress even after surgery and reduce cerebral blood flow.[8] Careful follow-up is needed to minimize an unfavorable social outcome after bypass surgery of pediatric moyamoya disease.

Conclusions

The results of the present study support the hypothesis that the involvement of a stenoocclusive lesion in the PCA is one of the possible risk factors for an unfavorable social outcome from pediatric moyamoya disease. The finding of PCA involvement in pediatric moyamoya disease should receive more attention to ensure further improvement in social outcomes at adulthood.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Funaki. Acquisition of data: Funaki. Analysis and interpretation of data: Funaki. Drafting the article: Funaki. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Funaki. Statistical analysis: Funaki.

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Rapid Progression of Unilateral Moyamoya Disease in a Patient with a Family History and an *RNF213* Risk Variant

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Introduction

Moyamoya disease (MMD) is a progressive steno-occlusive vasculopathy that involves large intracranial arteries accompanied by moyamoya collaterals [1, 2]. It was demonstrated that the p.R4810K missense variant (rs 112735431) in the *RNF213* gene on the 17q25.3 locus [3–5] increases susceptibility to MMD in East Asian populations [6]. Genetic diagnosis enabled us to find presymptomatic patients with MMD.

Case Report

A 36-year-old woman, who had no past medical history, received MRI screening examination to check for MMD because her mother and her aunt had the disease. The initial examination in August 2005 showed no apparent intracranial arterial stenosis (fig. 1a). One year later, she received the second MRI scan, which showed proximal right middle cerebral artery (MCA) occlusion (fig. 1b). Conventional angiography confirmed MCA occlusion with minor moyamoya collaterals at the base of the brain (fig. 1c). No stenosis was observed on the contralateral side. Despite rapid progression of the arterial occlusion, the patient did not develop any neurological symptoms or ischemic brain lesions on MRI. She was conservatively followed up by annual MRI examinations without surgical intervention. The occlusive lesion has remained stable for 6 years without any progression.

The patient and her family members, including unaffected members, received both genetic testing for *RNF213* and MRI examination in 2005; the family is pedigree 18 in our previous paper [6]. Sequencing of *RNF213* in the patient's mother and aunt revealed two haplotypes carrying p.R4810K: allele A_2, which is common among patients with MMD, and allele A_1, which is rare among patients with MMD [6]. The patient inherited an A_1 allele for p.R4810K (fig. 1d). On the other hand, her elder and younger sisters inherited an A_2 allele from their mother for p.R4810K, and no arterial stenosis was identified in either the initial or annual follow-up MRI examinations.

Ethical approval for this study was given by the Institutional Review Board and Ethics Committee of the Kyoto University School of Medicine, Kyoto University, Japan.

Discussion

Due to incomplete penetrance of the p.R4810K variant, *RNF213* is considered to be a susceptibility gene and other genetic or environmental factors may be associated with MMD. However, the genome-wide linkage and association analysis only showed a significant signal in *RNF213* on 17q25.3, indicating that other genetic factors have a much lower effect as compared with *RNF213* [3, 6]. p.R4810K or other mutations in *RNF213* were observed in all familial cases of MMD including Japanese, Korean and European populations and p.R4810K was associated with an increased risk of MMD with an odds ratio of as much as 338.9 for a Japanese population [6], which was confirmed in independent studies [5, 7]. These results indicate that p.R4810K screening would be a most appropriate approach to identify asymptomatic patients, especially those who have a family history of MMD.

In the present study, a 36-year-old woman, who was positive for *RNF213*, had de novo progression of unilateral MMD within only a year. In the past reports, a 59-year-old woman showed de novo progression of bilateral MMD within a 5-year interval and a 46-year-old woman developed unilateral MMD between 2004 and 2009 [8, 9]. Albeit not adult cases, Amlie-Lefond et al. [10] reported a 3-month-old patient with MMD and reviewed other 8 cases of early infancy before the age of 1 year, suggesting that MMD can develop very rapidly. Therefore, frequent follow-ups by MRI should be recommended for those who were diagnosed as having genetic risk factors for MMD.

Although the elder and younger sisters of the patient had the p.R4810K variant, they have not developed MMD. Since they may develop MMD several years later, a close follow-up is necessary. Alternatively, the discordant phenotype of the sisters may represent allelic differences between A_1 and A_2 [6]. The patient and the affected mother and aunt share p.R4810K on the same allele (A_1), whereas the unaffected sisters have A_2, suggesting a possibility that the 5′ portion of *RNF213* may have a modifier effect on the steno-occlusive phenotype. Still another possibility includes environmental factors, which may affect the pene-

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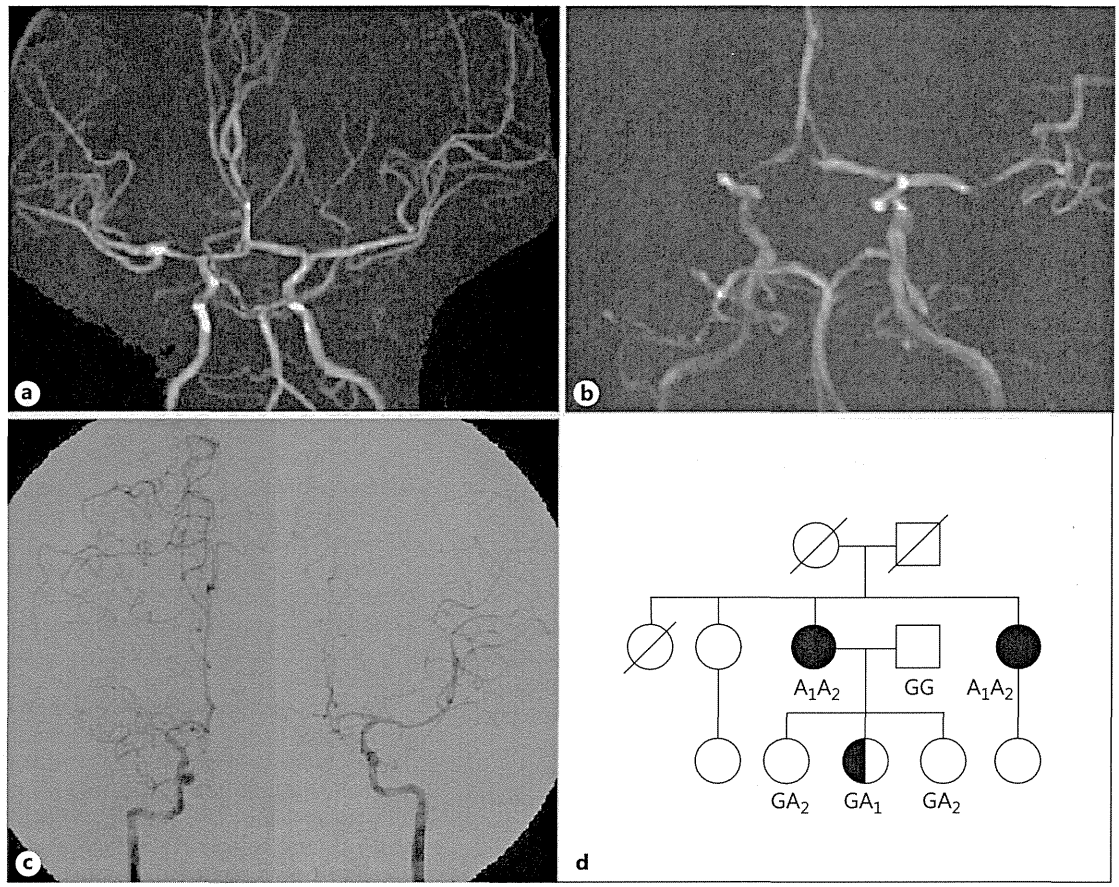

Fig. 1. a Initial magnetic resonance angiography (MRA; 1.5 tesla) of the patient. No arterial stenosis was observed. **b** Second MRA (1.5 tesla) study 1 year after the initial examination showed disruption of the right MCA. **c** Digital subtraction angiography following the second MRA examination revealed right MCA occlusion and the formation of collateral circulation at the base of the brain. Distal MCA was filled with contrast media via collaterals. **d** The family with familial MMD. Filled symbols indicate patients with MMD; half-filled symbols, patients with unilateral MMD; circles, women; squares, men; crossed symbols, deceased people. The half-filled symbol in the third generation represents the 36-year-old patient in this report. Genotypes of the risk allele of *RNF213* are shown. GG represents wild type; GA, homozygote for the risk variant, AA heterozygote for the risk variant. Numbers are attached to the variant 'A' to discriminate the two different alleles. The patient and her affected mother and aunt share the risk variant on the same allele (A_1).

trance, although we could not identify any environmental differences between the affected patient and the unaffected sisters. The patient had one A allele (heterozygote) and developed unilateral MMD, whereas her mother and aunt had two A alleles (homozygote) and developed bilateral MMD. Miyatake et al. [7] reported that the number of risk alleles in *RNF213* is associated with earlier age at onset and a severe form of the disease. Bilateral progression may also be associated with the number of risk alleles. Further follow-ups and investigations are warranted for this family.

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Disclosure Statement

None.

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Effects of Surgical Revascularization on Cerebral Oxygen Metabolism in Patients With Moyamoya Disease

An ^{15}O-Gas Positron Emission Tomographic Study

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Background and Purpose—This prospective study was aimed to evaluate the effects of surgical revascularization on cerebral oxygen metabolism in moyamoya disease.

Methods—This study included totally 69 hemispheres of 42 patients who underwent superficial temporal artery to middle cerebral artery anastomosis and indirect bypass for moyamoya disease between 2000 and 2011. There were 12 children and 30 adults. MRI and ^{15}O-gas positron emission tomography were performed before and 3 to 4 months after surgery. Hemodynamic and metabolic parameters were precisely quantified and statistically analyzed.

Results—Preoperative positron emission tomographic scans revealed that cerebral blood flow was decreased, cerebral blood volume was increased, and cerebral metabolic rate for oxygen was decreased in both pediatric and adult patients. Cerebral metabolic rate for oxygen reduction was observed in ≈80% of pediatric (16/21; 76%) and adult hemispheres (38/48; 79%). Surgical revascularization resolved hemodynamic compromise in all operated hemispheres. Cerebral metabolic rate for oxygen significantly improved in pediatric patients without parenchymal lesions (n=8), but not those with parenchymal lesions (n=8). Multivariate analysis revealed that cerebral metabolic rate for oxygen significantly improved in younger adult patients without parenchymal lesions (P=0.0264; odds ratio, 0.88; 95% confidence interval, 0.79–0.99).

Conclusions—Cerebral oxygen metabolism is significantly depressed in ≈80% of the involved hemispheres of moyamoya disease and improves in pediatric and younger adult patients without parenchymal lesions after bypass surgery. Cerebral oxygen metabolism may be reversibly depressed in response to cerebral ischemia in them although the underlying mechanisms are still unclear. **(*Stroke*. 2014;45:2717-2721.)**

Key Words: brain ischemia ■ bypass surgery ■ moyamoya disease ■ positron emission tomography

Moyamoya disease is a unique cerebrovascular disorder characterized by progressive stenosis of the terminal portion of the internal carotid artery. The perforating arteries in the basal ganglia and thalamus markedly dilate and function as an important collateral circulation, called as moyamoya vessels.[1,2] The posterior cerebral arteries are also involved in a certain subgroup of patients. Therefore, cerebral hemodynamics is often impaired especially in the frontal lobe, leading to transient ischemic attack and cerebral infarction. Furthermore, the dilated, fragile moyamoya vessels often rupture and cause intracranial hemorrhage. Superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and indirect synangiosis are known to improve cerebral hemodynamics and are used to reduce the risk of subsequent cerebrovascular events and contribute to improve long-term outcome in patients with moyamoya disease, although the value of this approach has only been shown by clinical trial in adults to prevent intracerebral hemorrhage.[3–10]

Using single photon emission computed tomography and positron emission tomography (PET), many previous studies have shown that surgical revascularization improves the parameters of cerebral hemodynamics, including cerebral blood flow (CBF), cerebral blood volume (CBV), cerebrovascular reactivity to acetazolamide, and elevated oxygen extraction fraction (OEF) in moyamoya disease. These beneficial effects are prominent especially in the frontal lobe.[6,11–19] However, there are no studies that focused on surgical effects on cerebral oxygen metabolism in moyamoya disease, although some of previous studies just presented the data of cerebral metabolic rate for oxygen ($CMRO_2$). Therefore, this prospective study was aimed to evaluate the effect of surgical revascularization on cerebral oxygen metabolism in moyamoya disease, using ^{15}O-gas PET.

Patients and Methods

This prospective study included totally 42 patients who were admitted to our hospital between 2000 and 2011. All of them were diagnosed as

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moyamoya disease based on the guideline for the diagnosis of moyamoya disease set by the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of the Ministry of Health, Welfare, and Labor of Japan.[20] There were 12 children and 30 adults. There were 10 men and 32 women. Mean age was 11.7±3.9 and 45.8±11.7 years in pediatric and adult patients, respectively. In pediatric patients, clinical diagnosis included transient ischemic attack in 7, ischemic stroke in 2, headache in 2, and asymptomatic in 1. In adult patients, clinical diagnosis included transient ischemic attack in 15, ischemic stroke in 7, hemorrhagic stroke in 4, and asymptomatic in 4.

Radiological Examinations

MRI, cerebral angiography, and ^{15}O-gas PET were performed before and 3 to 4 months after surgery in all patients. T1-weighted images, T2-weighted images, and fluid attenuated inversion recovery images were obtained to locate ischemic and hemorrhagic lesions in the brain parenchyma. All patients were scanned with ECAT EXACT HR+ (Siemens) before and 3 to 4 months after surgery, as described previously.[21,22] Briefly, 1-minute inhalation of ^{15}O-CO (2 GBq/min) followed by 3-minute static scanning and 3-time arterial blood sampling were performed to measure CBV. After 15-minute inhalation of ^{15}O-O_2 (0.5 GBq/min), a steady-state O_2 image was scanned and 3-time arterial blood sampling was performed for 5 minutes to measure OEF and $CMRO_2$. Finally, to determine CBF, steady-state CO_2 image was scanned and 3-time arterial blood sampling was performed for 5 minutes after 15-minute inhalation of ^{15}O-CO_2 (0.5 GBq/min). Each PET parameter was obtained using 10-mm diameter circular regions of interest, which were placed on the frontal or temporal cortex without cerebral infarction.

Normal PET values were obtained from 10 adult volunteers: CBF, 44±4 mL/min per 100 g; $CMRO_2$, 3.3±0.6 mL/min per 100 g; CBV, 3.7±0.7 mL/100 g, and OEF, 0.40±0.05 (mean±SD).

Surgical Treatment

All patients underwent STA-MCA anastomosis combined with indirect synangiosis, encephalo-duro-myo-arterio-pericranial synangiosis.[5] Briefly, large fronto-temporal craniotomy extending to the frontal area was made. The 1 or 2 branches of STA were anastomosed to the cortical branches of MCA. The pedicles of dura mater, temporal muscle, and frontal pericranium were used to cover the brain surface as the donor tissues of indirect bypass. Surgical revascularization was performed on 21 hemispheres in 12 pediatric patients and on 48 hemispheres in 30 adult patients. Therefore, totally 69 hemispheres were analyzed in this study. MRI, cerebral angiography, and PET were repeated 3 to 4 months after surgery to assess its effects on cerebral hemodynamics and metabolism in all patients.

Statistical Analysis

Data were expressed as percentages or mean±SD. Categorical variables were compared using a χ^2 test. Continuous variables were compared using paired t test and unpaired t test as appropriate. Differences were considered to be statistically significant if the P value was <0.05. Differences between pre- and postoperative values that were higher and lower than the 95% confidence interval (CI) were judged as increased and decreased, respectively. The differences within 95% CI were judged as unchanged. A multivariate logistic regression model was conducted to test the effects of surgical revascularization on hemodynamic and metabolic parameters on ^{15}O-gas PET. A forward stepwise model-building procedure was performed for the parameters, using P<0.10 achieved in univariate analysis. In the final multivariate analysis, the statistical level of significance was set at P<0.05.

Results

Clinical Results

There was no surgical mortality. Ischemic stroke developed in 3 (4.3%) of 69 operated hemispheres. None of operated patients experienced ischemic or hemorrhagic stroke after surgery during follow-up periods of mean 9.3 years.

On postoperative angiography, STA-MCA anastomosis and indirect synangiosis widely covered the operated hemispheres in all 69 hemispheres. Thus, postoperative external carotid angiography revealed that surgical collaterals opacified more than two thirds of the MCA territory in 50 hemispheres and between one thirds and two thirds of the MCA territory in 19. Basal moyamoya vessels disappeared or markedly diminished in all operated hemispheres.

PET Parameters in Pediatric Patients

Totally 21 hemispheres of 12 pediatric patients underwent surgical revascularization. Table 1 shows pre- and postoperative PET parameters in these 22 hemispheres. Before surgery, CBF was 36.5±8.2 mL/min per 100 g and $CMRO_2$ was 2.9±0.7 mL/min pre 100 g, being significantly lower than the control values obtained from adult volunteers (P<0.01). The differences would be much larger between pediatric patients and healthy children because it is well known that CBF and $CMRO_2$ are much higher in children than in adults.[12,17] $CMRO_2$ was decreased in 16 of 21 hemispheres (76%). Mean CBV value was 5.9±2.3 mL/100 g, being significantly higher than the control value (P<0.01). Although OEF was significantly elevated in 5 (22.7%) of 22 hemispheres, mean OEF value (0.43±0.10) did not differ from the control value.

As shown in Table 1, surgical revascularization significantly improved CBF, CBV, and $CMRO_2$ in the operated hemispheres. Thus, CBF significantly increased from 36.5±8.2 to 42.4±5.5 mL/min per 100 g after surgery (P<0.01; 95% CI, 3.0–8.7). CBV significantly decreased from 5.9±2.3 to 3.7±0.8 mL per 100 g (P<0.01; 95% CI, 0.7–3.8). Furthermore, $CMRO_2$ significantly increased from 2.9±0.7 to 3.5±0.5 mL/min per 100 g after surgery (P<0.01; 95% CI, 0.3–0.9). However, OEF did not show statistically significant change after surgery although significantly elevated OEF normalized in all 5 hemispheres. Thus, pre- and postoperative OEFs were 0.43±0.10 and 0.46±0.04, respectively.

PET Parameters in Adult Patients

Totally 48 hemispheres of 30 adult patients underwent surgical revascularization. Table 2 shows pre- and postoperative PET parameters in these 48 hemispheres. Before surgery, mean CBF value was 29.7±7.3 mL/min per 100 g and $CMRO_2$ was 2.4±0.6 mL/min per 100 g, being significantly lower than the control value (P<0.01). $CMRO_2$ was decreased in 38 of 48 hemispheres (79%). Mean CBV value was 5.3±2.0 mL/100 g,

Table 1. Pre- and Postoperative Parameters on ^{15}O-Gas Positron Emission Tomography in Pediatric Patients With Moyamoya Disease (n=21 Hemispheres)

	Preop.	Postop.	Significance, P Value
CBF, mL/min per 100 g	36.5±8.2	42.4±5.5	<0.05
CBV, mL/100 g	5.9±2.3	3.7±0.8	<0.01
$CMRO_2$, mL/min per 100 g	2.9±0.7	3.5±0.5	<0.05
OEF	0.43±0.1	0.46±0.4	NS

CBF indicates cerebral blood flow; CBV, cerebral blood volume; $CMRO_2$, cerebral metabolic rate for oxygen; and OEF, oxygen extraction fraction.

Table 2. Pre- and Postoperative Parameters on ^{15}O-Gas Positron Emission Tomography in Adult Patients With Moyamoya Disease (n=48 Hemispheres)

	Preop.	Postop.	Significance, *P* Value
CBF, mL/min per 100 g			
CBV, mL/100 g	5.3±2.0	3.5±1.0	<0.01
$CMRO_2$, mL/min per 100 g	2.4±0.6	2.6±0.5	NS
OEF	0.45±0.1	0.40±0.5	NS

CBF indicates cerebral blood flow; CBV, cerebral blood volume; $CMRO_2$, cerebral metabolic rate for oxygen; and OEF, oxygen extraction fraction.

being significantly higher than the control value (P<0.05). Although OEF was significantly elevated in 7 (14.6%) of 48 hemispheres, mean OEF value (0.45±0.10) did not differ from the control value.

As shown in Table 2, surgical revascularization significantly improved CBF and CBV in adult patients. Thus, CBF significantly increased from 29.7±7.3 to 37.6±6.9 mL/min per 100 g after surgery (P<0.01; 95% CI, 5.2–10.6). CBV significantly decreased from 5.3±2.0 to 3.5±1.0 mL/100 g (P<0.01; 95% CI, 0.8–2.8). However, $CMRO_2$ did not significantly change after surgery. Thus, pre- and postoperative $CMRO_2$ were 2.4±0.6 and 2.6±0.5 mL/min per 100 g, respectively. OEF did not show statistically significant changes after surgery, although elevated OEF normalized in all 4 hemispheres. Thus, pre- and postoperative OEFs were 0.45±0.10 and 0.40±0.05, respectively.

Clinical Factors to Determine Postoperative Improvement of $CMRO_2$

In pediatric patients, $CMRO_2$ was significantly lower than the control value in 16 (76%) of 21 operated hemispheres. Of these, $CMRO_2$ significantly improved in all 8 hemispheres without ischemic or hemorrhagic lesions on MRI after surgery. However, $CMRO_2$ did not improve in other 8 hemispheres with parenchymal lesions on MRI.

In adult patients, $CMRO_2$ was significantly lower than the control value in 38 (79%) of 48 operated hemispheres. Of these, $CMRO_2$ significantly improved in 13 of 22 lesion-free hemispheres after surgery. Cerebral oxygen metabolism did not change in other 9 lesion-free hemispheres. However, $CMRO_2$ did not improve in the remaining 25 hemispheres with parenchymal lesions on MRI.

As the next step, therefore, statistical analysis was performed to determine clinical factors that were closely related to postoperative improvement of $CMRO_2$ in the lesion-free hemispheres of adult patients. The effects of various factors on postoperative improvement of $CMRO_2$ are shown in Table 3. There was no significant difference in postoperative $CMRO_2$ improvement between sexes (P=0.1078; χ^2 test). Patient's age was significantly lower in the hemispheres with postoperative $CMRO_2$ improvement than those without, 40.1±9.7 and 51.4±9.4 years, respectively (P=0.0126; unpaired t test). Onset type was not a significant predictor for postoperative $CMRO_2$ improvement (P=0.2007; χ^2 test). Similarly, the side of operated hemispheres did not predict it (P=0.4285; χ^2 test). Only patient's age, therefore, was included in the logistic regression analysis. As shown in Table 3, the model indicated

Table 3. Independent Predictors of Postoperative $CMRO_2$ Improvement Among 22 Hemispheres Without Parenchymal Lesions in Adult Patients With Moyamoya Disease

	Postoperative Change of $CMRO_2$				
	Improved (n=13)	Unchanged (n=9)	Univariate Analysis	Multivariate Analysis	OR (95% CI)
Sex					
Men	0	3	P=0.1078	...	...
Women	13	6	...	...	...
Age, y	40.1±9.7	51.4±9.4	P=0.0126	P=0.0264	0.88 (0.79–0.99)
Onset type					
TIA	9	8	P=0.2007	...	...
Ischemic stroke	0	1	...	...	...
Intracranial hemorrhage	2	0	...	...	...
Asymptomatic	2	0	...	...	...
Operated side					
Right	8	4	P=0.4285	...	...
Left	5	5	...	...	...

Continuous data are expressed as mean±SD. CI indicates confidence interval; $CMRO_2$, cerebral metabolic rate for oxygen; OR, odds ratio; and TIA, transient ischemic attack.

that patient's age is an independent factor as predictor of postoperative $CMRO_2$ improvement (odds ratio, 0.88; 95% CI, 0.79–0.99; P=0.0264).

Illustrative Case

An 8-year-old girl suddenly developed transient motor aphasia and was admitted to our hospital. Neurological examinations on admission revealed no definite abnormality. MRI showed no abnormality in the brain parenchyma, but cerebral angiography demonstrated severe stenosis of the left carotid forks associated with moyamoya vessels. Preoperative ^{15}O-gas PET revealed decreased CBF and increased CBV in the territory of the left internal carotid artery. Marked reduction of $CMRO_2$ was also observed in the left cerebral hemisphere. She underwent STA-MCA anastomosis and indirect synangiosis on the left side. Postoperative course was uneventful. Cerebral angiography performed 4 months after surgery showed good development of surgical collaterals over the operated hemispheres. Follow-up ^{15}O-gas PET revealed that hemodynamic and metabolic parameters significantly improved after surgery. Especially, $CMRO_2$ dramatically increased in the left cerebral hemisphere (Figure).

Discussion

This study clearly shows that cerebral oxygen metabolism is significantly depressed in ≈80% of involved hemispheres in both pediatric (16/21; 76%) and adult moyamoya disease (38/48; 79%). Furthermore, effective surgical revascularization significantly improves it in a certain subgroup of patients, including pediatric or younger adult patients without parenchymal lesions. This is the first report that focuses on the effects of surgical revascularization on cerebral oxygen metabolism in moyamoya disease.[6,11–19]

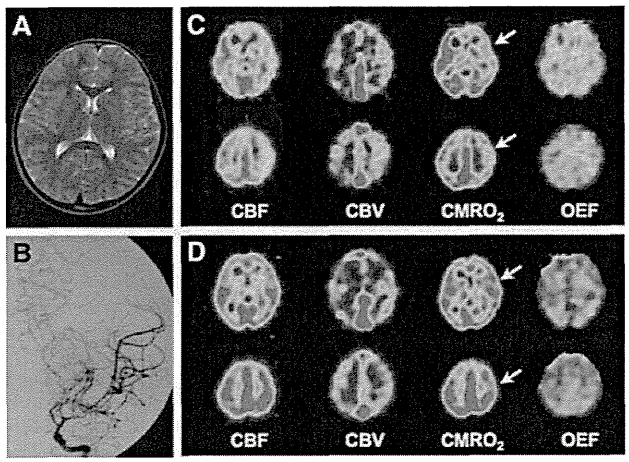

Figure. Radiological findings of a 8-year-old girl who developed transient motor aphasia. **A**, Preoperative T2-weighted MRI revealed no parenchymal lesion in the brain. **B**, Preoperative left internal carotid angiography revealed a marked stenosis of the left carotid fork and the development of basal moyamoya vessels. **C**, Preoperative positron emission tomographic (PET) scans showed cerebral blood flow (CBF) decrease, cerebral blood volume (CBV) increase, cerebral metabolic rate for oxygen ($CMRO_2$) decrease, and oxygen extraction fraction (OEF) elevation in the left cerebral hemisphere. Note a marked reduction of $CMRO_2$ in the left cerebral hemisphere (arrows). **D**, Postoperative PET scans performed 4 months after surgery revealed a normalization of all of 4 PET parameters. Note a normalization of $CMRO_2$ in the left cerebral hemisphere (arrows).

Previously, several investigators have analyzed PET parameters, including $CMRO_2$, in moyamoya disease. Thus, Taki et al[15,23] found CBV increase and CBF/CBV decrease in both pediatric and adult patients with moyamoya disease, but OEF was not significantly increased. Ikezaki et al[11] reported CBF decrease, CBV increase, and OEF elevation in 13 pediatric patients without parenchymal lesions. In their study, a mean value of $CMRO_2$ was similar to that in the controls. Shirane et al[17] also reported pronounced ischemia in pediatric moyamoya disease but found no differences in OEF between pediatric patients and healthy children, because of $CMRO_2$ reduction in the frontal and parietal cortex. Morimoto et al[18] reported CBF decrease, $CMRO_2$ decrease, and OEF elevation in the MCA territory of 5 patients with moyamoya disease. Piao et al[19] also reported similar results. Therefore, the value of $CMRO_2$ may largely depend on the patient's age and their clinical conditions.

However, there are only few studies that shed light on the effects of surgical revascularization on cerebral oxygen metabolism. Thus, Morimoto et al measured PET parameters in 5 patients with moyamoya disease before and after surgery. As a result, $CMRO_2$ value changed from 2.8±0.6 to 3.4±0.7 mL/min per 100 g after surgery. Although there was no significant difference between them probably because of small sample size, $CMRO_2$ markedly improved in 2 of these 5 patients.

Based on the concept of incomplete infarction, postoperative improvement of $CMRO_2$ in a certain subgroup of patients with moyamoya disease is peculiar.[22,24–26] Indeed, both CBF and CBV significantly improved after surgery. OEF also normalized in all of the hemispheres that had the elevated values before surgery. These findings strongly suggest that surgical revascularization significantly improved cerebral perfusion pressure, resolving hemodynamic compromise in the operated hemispheres. Simultaneously, $CMRO_2$ significantly improved pediatric or younger adult patients without parenchymal lesions. These findings are different from the above-written concepts and strongly indicate that oxygen metabolism was depressed before surgery because of the reasons apart from irreversible tissue damage. Therefore, it is most likely that cerebral oxygen metabolism was reversibly depressed because of persistent ischemia before surgery and that postoperative improvement of $CMRO_2$ was closely related to those of cerebral hemodynamics.

It is unclear through which mechanisms cerebral oxygen metabolism is reversibly depressed in a certain subgroup of patients with moyamoya disease. Previous studies, however, have reported that cerebral oxygen metabolism significantly improved after STA-MCA anastomosis even in some patients with occlusive carotid artery diseases.[27–30] Thus, Grubb et al[27] found that $CMRO_2$ significantly improved after surgery in 3 of 9 patients after bypass surgery. Samson et al[28] also reported a parallel improvement of CBF and $CMRO_2$ after bypass surgery and suggested that long-standing hemodynamic failure may induce a state of metabolic depression that is still potentially reversible, although the underlying mechanism is undetermined. Furthermore, some investigators have also reported that both $CMRO_2$ and neurological functions significantly improved after STA-MCA anastomosis in a certain subgroup of patients.[29,30] Although these findings are indeed anecdotal and are not widely accepted, the present results strongly suggest the possibility that the lesion-free brains of younger humans may have potential ability to downregulate their oxygen metabolism and to protect itself against chronic hypoxia or ischemia by reducing its metabolic demand than adult's one. Indeed, newborn mammals are much more resistant to hypoxia than adults. Child's brain may retain their defensive mechanism to suppress metabolic demand against ischemia/hypoxia to some degree. In other words, the brain in pediatric moyamoya disease may be in the condition of reversible brain hibernation.[31] Experimental studies would be warranted to assess the hypothesis in near future.

Ischemic or hemorrhagic stroke often causes irreversible brain damage in moyamoya disease. According to the present results, cerebral oxygen metabolism irreversibly decreases once parenchymal lesions develop. Therefore, early diagnosis and appropriate treatment would be essential to improve cerebral oxygen metabolism especially in pediatric or younger adult patients with moyamoya disease. Previous study has proven that good intellectual outcome can be expected in pediatric patients who do not have completed stroke and surgical revascularization that widely covers the frontal lobe.[32] Therefore, postoperative reversal of depressed oxygen metabolism may contribute to improve their intellectual prognosis.

Conclusions

Cerebral oxygen metabolism is significantly depressed in ≈80% of the involved hemispheres of moyamoya disease and improves in pediatric and younger adult patients without parenchymal lesions after STA-MCA anastomosis and indirect synangiosis. Pre- and postoperative PET measurements strongly suggest that their cerebral oxygen metabolism was reversibly depressed in response to cerebral ischemia, although the underlying mechanisms are still unclear.

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Disclosures

None.

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Effects of Surgical Revascularization on Cerebral Oxygen Metabolism in Patients With Moyamoya Disease: An 15O-Gas Positron Emission Tomographic Study

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CLINICAL ARTICLE - VASCULAR

Surgical anatomy and preservation of the middle meningeal artery during bypass surgery for moyamoya disease

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Abstract
Background The middle meningeal artery (MMA) is known to function as one of the important collateral routes in moyamoya disease. However, the anterior branch frequently courses within the lesser wing of the sphenoid bone and can easily be damaged during craniotomy for bypass surgery. This prospective study aimed to study the surgical anatomy of the MMA and to establish the technique to preserve it during bypass surgery for moyamoya disease.
Methods Twenty-two patients with moyamoya disease underwent STA-MCA anastomosis combined with indirect bypass on 27 sides. The anatomical relationship between the anterior branch of the MMA and lesser wing was classified into three types: the bridge, monorail, and tunnel types. During surgery, the lesser wing was carefully resected with a rongeur or high-speed diamond drill to preserve the anterior branch of the MMA.
Results The anterior branch of the MMA was classified into the bridge type in 5 sides (18.5 %), monorail type in 10 sides (37.0 %), and tunnel type in 12 sides (44.5 %). Patient age was closely related to the anatomical findings (χ^2 test, p=0.0168). Careful resection of the lesser wing with a rongeur could preserve bridge- and monorail-type MMAs (100 and 71.4 %, respectively). However, drilling out of the lesser wing under a surgical microscope was essential to preserve the tunnel-type MMA. Intraoperative indocyanine green videoangiography was useful to confirm patency during surgery.
Conclusions It is essential to understand the surgical anatomy of the MMA around the pterion in order to preserve its anterior branch during bypass surgery for moyamoya disease.

Keywords Moyamoya disease · Bypass surgery · Middle meningeal artery · Sphenoid bone

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Introduction

Moyamoya disease is an uncommon cerebrovascular disease characterized by progressive occlusion of the terminal portion of the internal carotid artery and its main branches within the circle of Willis. This occlusion results in the formation of a fine vascular network (moyamoya vessels) at the base of the brain [1, 2]. Clinical features of moyamoya disease differ substantially between children and adults. Most pediatric patients with moyamoya disease develop a transient ischemic attack (TIA) or cerebral infarction, whereas about half of adult patients develop intracranial bleeding, and the other half develop TIA or cerebral infarction [1]. Nowadays, it is well known that surgical revascularization improves the cerebral hemodynamics and prevents further ischemic and hemorrhagic stroke [3–7]. Surgical procedures for moyamoya disease can be classified into three categories: direct bypass, indirect bypass, and combined bypass. Direct bypass procedures are represented by superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis. Direct bypass is useful to improve the cerebral hemodynamics and resolve ischemic attacks immediately after surgery. The frequency of postoperative ischemic stroke is lower after direct or combined bypass than it is after indirect bypass. Surgical procedures for indirect bypass are characteristic for moyamoya disease. Indirect bypass surgery that induces spontaneous angiogenesis between

the brain surface and vascularized donor tissues is technically simple to do and has been widely used. The superficial temporal artery (STA), dura mater, temporal muscle, and galeal tissue have been used as the pediculate donor tissues [1]. The middle meningeal artery (MMA) can provide important collateral flow through the dura mater. Especially, its anterior (frontal) branch provides collateral blood flow to the anterior cerebral artery (ACA) territory through the falx [8, 9].

On the other hand, the MMA enters the floor of the middle cranial fossa through the foramen spinosum, passes laterally on to the temporal bone and curves anteriorly over the great wing of the sphenoid. Thereafter, it is divided into an anterior and posterior branch at a variable point [10, 11]. It is well known that the course of the anterior branch of the MMA around the pterion is not simple [11]. Ma et al. (2012) precisely analyzed the bone structure around the pterion and found that the vascular marking of the MMA consisted of a groove in 30 %, a complete canal in 49 %, and a disrupted or partial canal in the remainder [12]. Shimizu et al. (2008) also reported that the MMA pierced the tunnel located on the temporal side of the lesser wing of the sphenoid bone in about 75 % of adults [13]. However, no study has precisely analyzed the relationship between the MMA and pterion from the surgical point of view, although conventional frontotemporal craniotomy may easily damage the MMA during bypass surgery for moyamoya disease. To avoid this problem, the authors modified the craniotomy technique, but could not always preserve the MMA [4, 9]. This study, therefore, aimed to precisely analyze the anatomical relationship between the MMA and sphenoid bone and to develop a surgical technique to preserve the MMA during bypass surgery for moyamoya disease.

Methods

Patients

This prospective study included a total of 22 patients who underwent surgical revascularization for moyamoya disease between April 2012 and March 2014 at Toyama University Hospital and its affiliated hospital. All of them were diagnosed with moyamoya disease based on the guideline for the diagnosis of moyamoya disease set by the Research Committee on Moyamoya Disease (spontaneous occlusion of the circle of Willis) of the Ministry of Health, Welfare and Labor of Japan [14]. There were 9 children and 13 adults, 8 males and 14 females. Mean age was 12.8±5.0 and 40.4±11.9 years in pediatric and adult patients, respectively. In pediatric patients, clinical presentation included TIAs in five, ischemic stroke in two, and headache in two. In adult patients, clinical presentation included TIAs in four, ischemic stroke in three, and hemorrhagic stroke in six (Table 1). All patients provided informed consent, and their identity was protected.

Radiological examinations

Using a 1.5-T MR apparatus, time-of-flight (TOF) MR angiography was performed in all patients before surgery. The anatomical relationship between the anterior branch of the MMA and lesser wing of the sphenoid bone was precisely analyzed on the raw images of TOF-MR angiography. Plain CT scans were also performed to visualize the bony groove or tunnel around the pterion in all patients.

Cerebral angiography and/or MR angiography was employed to evaluate the blood flow in the anterior branch of the MMA in all patients at 3 to 4 months after surgery.

Surgical treatment

Surgical revascularization was performed on a total of 27 sides, including 11 and 16 hemispheres in 9 pediatric and 13 adult patients, respectively. All patients underwent superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis combined with indirect synangiosis, encephalo-duro-myo-arterio-pericranial synangiosis (EDMAPS) [4]. As shown in Fig. 1, the frontal and parietal branches of the STA were dissected from the scalp under a surgical microscope (Fig. 1a). The temporal muscle and frontal pericranium were dissected as the vascularized flaps for the indirect bypass (Fig. 1b). To perform large frontotemporal craniotomy, five burr holes were made (Fig. 1c). The burr hole at the center of craniotomy site was made rostral to the pterion to preserve the anterior branch of the MMA, because it is known to pierce the bony tunnel of the middle meningeal groove just beneath the junction of the sphenoparietal, sphenosquamosal, and squamosal sutures [13]. A heart-shaped craniotomy was performed, preserving the lesser wing of the sphenoid bone (Fig. 1d). Then, the lesser wing was carefully resected, preserving the anterior branch of the MMA, using a rongeur or high-speed drill (*see below*).

The dura was incised and rolled back, preserving the main branches of the MMA. One or two branches of the STA were anastomosed to the cortical branches of the MCA in an end-to-side fashion with 10-0 or 11-0 nylon threads. The clamping time of the recipient was approximately 20 to 30 min. Furthermore, the anastomosed STA grafts were attached onto the brain surface as long as possible, which can induce indirect angiogenesis between them. The dural flaps were turned into the epiarachnoid space (Fig. 1f). Then, the brain surface was covered, using the temporal muscle and frontal pericranium (Fig. 1g).

The patency of the anterior branch of the MMA was confirmed in all patients, using indocyanine green (ICG)

Table 1 Characteristics of the patients with moyamoya disease

Patient no.	Age/sex	Onset type	Operation	MMA		
				Type	Drill	Preservation
1	4/F	CI	Right STA-MCA (S)+EDMAPS	Bridge	−	+
2	47/F	CI	Right STA-MCA (D)+EDMAPS	Tunnel	−	−
3	39/M	ICH, IVH	Right STA-MCA (S)+EDMAPS	Tunnel	−	−
4	31/F	IVH	Right STA-MCA (S)+EDMAPS	Tunnel	−	−
	31/F	IVH	Left STA-MCA (S)+EDMAPS	Tunnel	−	−
5	14/M	TIA	Left STA-MCA (S)+EDMAPS	Bridge	−	+
6	10/M	CI	Left STA-MCA (D)+EDMAPS	Monorail	−	−
	10/M	CI	Right STA-MCA (D)+EDMAPS	Tunnel	+	+
7	42/F	CI	Left STA-MCA (D)+EDMAPS	Tunnel	+	+
8	12/F	TIA	Left STA-MCA (S)+EDMAPS	Monorail	−	+
9	26/M	TIA	Right STA-MCA (S)+EDMAPS	Monorail	−	+
	26/M	TIA	Left STA-MCA (S)+EDMAPS	Bridge	−	+
10	27/F	TIA	Left STA-MCA (S)+EDMAPS	Monorail	−	−
11	51/M	CI	Left STA-MCA (D)+EDMAPS	Monorail	+	+
12	38/F	TIA	Left STA-MCA (S)+EDMAPS	Tunnel	−	−
13	15/F	TIA	Left STA-MCA (D)+EDMAPS	Monorail	−	+
14	46/F	SAH	Left STA-MCA (D)+EDMAPS	Tunnel	+	+
15	16/M	headache	Right STA-MCA (D)+EDMAPS	Tunnel	+	+
16	45/F	ICH	Right STA-MCA (D)+EDMAPS	Monorail	−	+
17	28/F	TIA	Left STA-MCA (S)+EDMAPS	Monorail	−	+
	29/F	TIA	Right STA-MCA (S)+EDMAPS	Tunnel	+	+
18	69/F	ICH, IVH	Right STA-MCA (D)+EDMAPS	Tunnel	+	+
19	49/F	ICH	Right STA-MCA (S)+EDMAPS	Bridge	−	+
20	18/M	TIA	Left STA-MCA (S)+EDMAPS	Tunnel	+	+
	18/M	TIA	Right STA-MCA (S)+EDMAPS	Monorail	+	+
21	7/M	headache	Left STA-MCA (D)+EDMAPS	Bridge	−	+
22	19/F	TIA	Left STA-MCA (D)+EDMAPS	Monorail	+	+

MMA=middle meningeal artery; *CI*=cerebral infarction; *ICH*=intracerebral hemorrhage; *IVH*=intraventricular hemorrhage; *TIA*=transient ischemic attack; *SAH*=subarachnoid hemorrhage; *STA*=superficial temporal artery; *MCA*=middle cerebral artery; *S*=single; *D*=double; *EDMAPS*=encephalo-duro-myo-arterio-pericranial synangiosis

videoangiography during surgery and/or postoperative cerebral angiography.

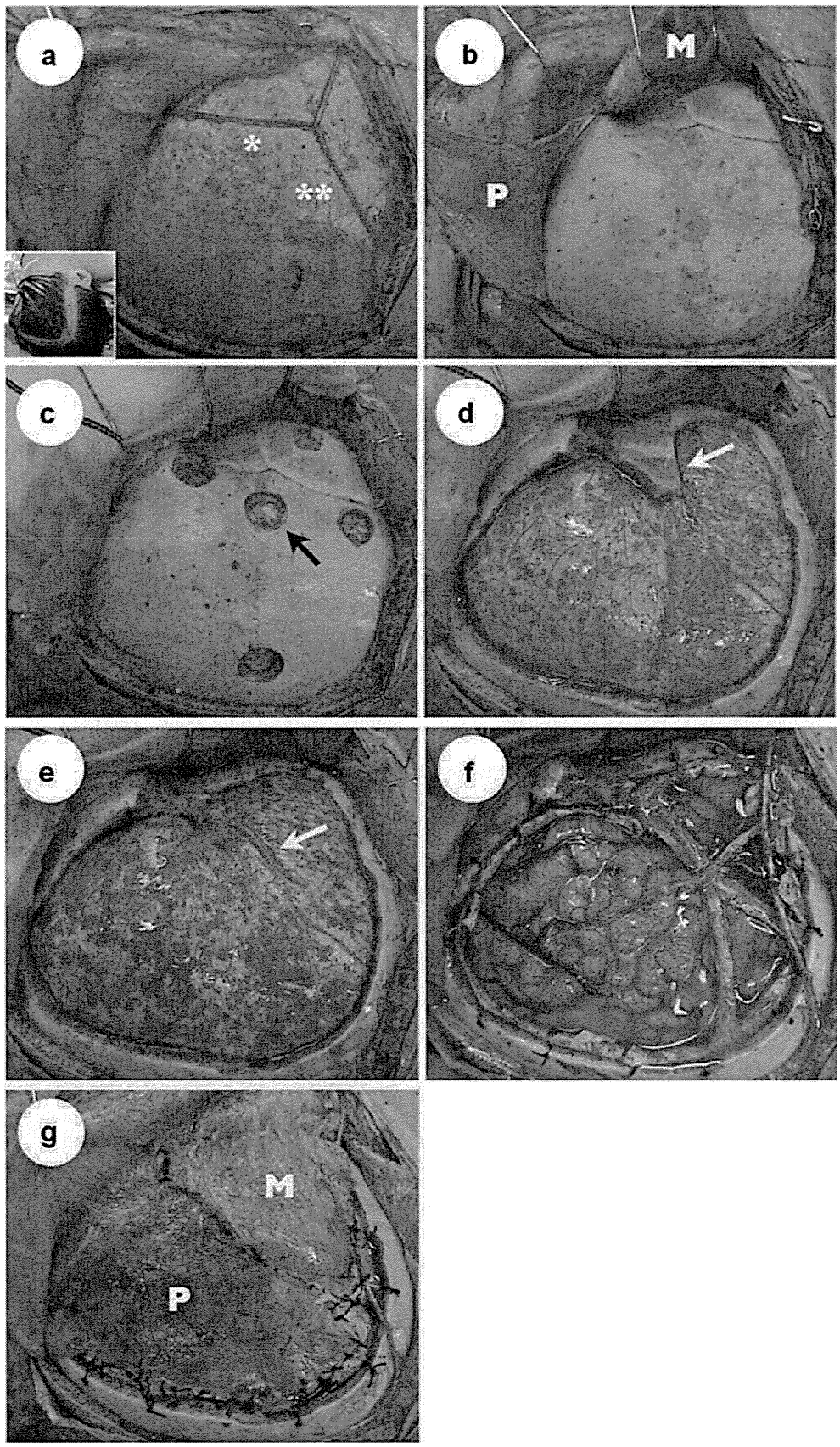
Surgical anatomy of the MMA

In this study, the anatomical relationship between the anterior branch of the MMA and lesser wing of the sphenoid bone was classified into three types: the bridge, monorail, and tunnel types (Fig. 2). In the bridge type, the anterior branch of the MMA runs within the shallow groove in the medial surface of the bone, which looks like a bridge over a river. In the monorail type, the anterior branch of the MMA runs within the deep groove in the medial surface of the bone, which looks like a monorail vehicle over a rail. In the tunnel type, the anterior branch of the MMA is completely enclosed within the bony canal in the lesser wing of the sphenoid bone, which looks like a tunnel. The bony tunnel is usually complete, but is deformed in some cases.

Results

Based on intraoperative observations, the anterior branch of the MMA was classified as the bridge type in 5 sides (18.5 %), monorail type in 10 sides (37.0 %), and tunnel type in 12 sides (44.5 %). The findings correlated very well with preoperative CT and MR angiography in all patients (Fig. 2).

Patient age was closely related to the anatomical relationship between the anterior branch of the MMA and lesser wing of the sphenoid bone (Fig. 3). There was a significant difference between them when the patients were divided into two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