TABLE 1. Cross tabulation, sensitivity, specificity, and intra- and interrater agreement for each type of periventricular anastomosis

Type of PA	Hemorrhage		p Value	Sensitivity	Specificity	κ (95% CI)	
	Yes	No				Intrarater Agreement	Interrater Agreement
Lenticulostriate							
Yes	9	22	0.02	0.50	0.79	0.85 (0.65–1.00)	0.93 (0.79–1.00)
No	9	82					
Thalamic							
Yes	16	50	<0.01	0.89	0.52	0.58 (0.28–0.88)	0.58 (0.28–0.88)
No	2	54					
Choroidal							
Yes	13	43	0.02	0.72	0.59	0.70 (0.46–0.94)	0.54 (0.28–0.80)
No	5	61					

PA = periventricular anastomosis.

0.58 for both intra- and interrater agreement). Good intra- and interrater reliability was observed for ratings of the periventricular anastomosis score (κ_w = 0.65 [95% CI 0.43–0.86] for intrarater agreement and 0.70 [95% CI 0.49–0.90] for interrater agreement).

For every type of periventricular anastomosis, the prevalence of hemorrhage was significantly higher in patients with anastomosis than in those without (p = 0.02 for the lenticulostriate type, p < 0.01 for the thalamic type, and p = 0.02 for the choroidal type; Table 1). The estimated sensitivity and specificity for differentiating hemorrhage were 0.50 and 0.79 for the lenticulostriate type, 0.89 and 0.52 for the thalamic type, and 0.72 and 0.59 for the choroidal type, respectively.

Association Between Periventricular Anastomosis and Hemorrhage

Table 2 summarizes the baseline characteristics of patients with and without hemorrhagic presentation. Age and periventricular anastomosis score were significantly higher in patients with hemorrhagic presentation than in those without. No significant differences in other factors—sex, concurrent disorders, hypertension, diabetes mellitus, unilateral disease, and severe hemodynamic compromise—were seen between the two groups.

TABLE 2. Baseline characteristics of patients with and without hemorrhage

Variable	Hemorrhage		p Value
	Yes (n = 18)	No (n = 104)	
Median age (IQR)	37.5 (24.5–43.25)	24 (8.25–41.75)	0.02
Female (%)	10 (55.6)	64 (61.5)	0.80
Associated disorders (%)	0	7 (6.7)	0.59
Hypertension (%)	3 (16.7)	16 (15.4)	1.00
Diabetes mellitus (%)	0	3 (2.9)	1.00
Unilateral disease (%)	4 (22.2)	20 (19.2)	0.75
Severe hemodynamic compromise (%)	9 (50.0)	62 (60.2)	0.45
Median PA score (IQR)	2 (1.75–3)	1 (0–2)	<0.01

IQR = interquartile range.

As shown in Fig. 2, the prevalence of hemorrhagic presentation increased along with the periventricular anastomosis score: 2.8% for Score 0, 8.8% for Score 1, 18.9% for Score 2, and 46.7% for Score 3 (p < 0.01 for trend). The cutoff score determined by the receiver operating characteristic curve was 2. The sensitivity and specificity for differentiating hemorrhagic presentation at the cutoff were 0.78 and 0.63, respectively (area under the curve 0.77).

Both the age variable and periventricular anastomosis score, statistically significant variables in the univariate analysis, were incorporated into the logistic regression model. Age was significantly associated with hemorrhagic presentation (OR 1.05 [95% CI 1.01–1.09]). Multivariate ORs of hemorrhage for the 2 highest periventricular anastomosis score groups relative to the lowest score group (Score 0) exceeded 1 and were statistically significant (OR for Score 2, 8.92 [95% CI 1.40–175.04]; OR for Score 3,

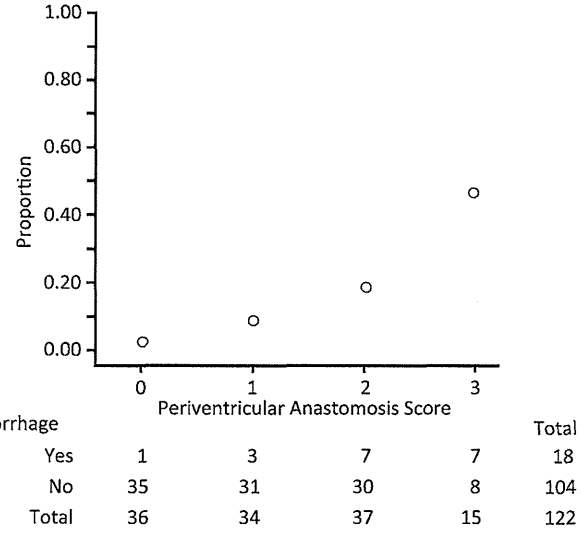

FIG. 2. Prevalence of hemorrhage relative to periventricular anastomosis score. p < 0.01 for trend.

TABLE 3. Multivariate odds ratio for hemorrhage according to periventricular score (adjusted for age)

PA Score	Coefficient	Multivariate OR (95% CI)
0	0	1.00 (reference)
1	1.18	3.26 (0.38–68.8)
2	2.19	8.92 (1.40–175.04)
3	3.66	38.84 (5.46–811.48)
Every 1-point increase	1.22	3.38 (1.84–7.00)

38.84 [95% CI 5.46–811.48]) (Table 3 and Fig. 3). The multivariate OR for score 1 relative to score 0 also exceeds 1, although it was not statistically significant (OR 3.26 [95% CI 0.38–68.8]). As the relationship between periventricular anastomosis score and estimated coefficient was approximately linear, the score was incorporated with the age variable into the logistic regression model as an interval variable. Multivariate OR for every 1-point increase in the score was 3.38 (95% CI 1.84–7.00), which was statistically significant (Table 3).

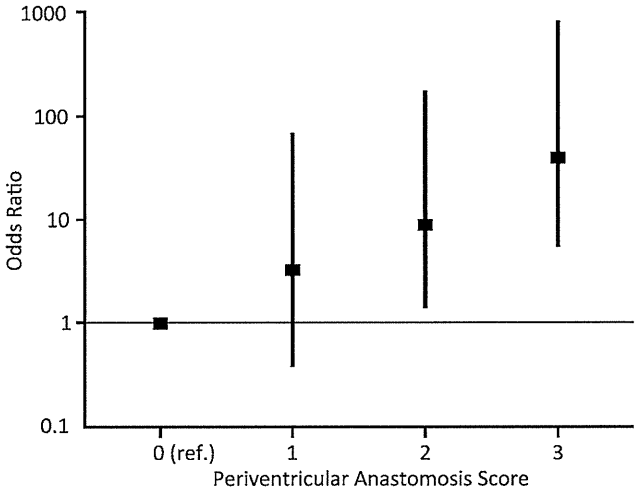

FIG. 3. Multivariate OR for hemorrhage *(squares)* and 95% CI *(bars)* according to periventricular anastomosis score. Logarithmic scale for y axis. ref. = reference.

Discussion

Our results suggest that periventricular anastomosis is independently associated with hemorrhagic presentation in moyamoya disease. These results are in line with widely accepted speculation that abnormal fragile collaterals typical of moyamoya disease cause hemorrhage. Several examples of cerebral microbleeds suggest the presence of a certain vascular pathology in the periventricular area. The results of a meta-analysis by Qin et al. revealed that periventricular white matter was the most common site where microbleeds associated with moyamoya disease were detected.[18] Kazumata et al. demonstrated that cerebral microbleeds observed in the periventricular area were more likely to be associated with hemorrhage from moyamoya disease than those in other locations.[11] Sun et al. documented in the cohort study that microbleeds in the deep periventricular white matter were an independent predictor for subsequent intraventricular hemorrhage.[20] Periventricular anastomosis might sufficiently explain these phenomena, given that the anastomosis might be related to hemorrhage.

A traditional theory of vascular supply in the periventricular area might be the key to understanding the development of periventricular anastomosis. Van den Bergh hypothesized 2 terminal arteries in the periventricular area, the ventriculofugal subependymal artery and ventriculopetal medullary artery.[23,24] These arteries form no anastomosis in the normal brain,[3,23] as the border zone between these arteries is believed to be the cause of periventricular ischemia. Long-standing cortical ischemia in moyamoya disease, however, might induce an abnormal connection between these arteries and result in periventricular anastomosis.[14] This speculation might be supported by the fact that proangiogenic factors are overexpressed in the intracranial arteries and cerebrospinal fluid in patients with moyamoya disease.[8,21,25]

Several mechanisms of periventricular anastomosis causing hemorrhage can be hypothesized. First, the dilated perforating or choroidal arteries proximal to the anastomoses, serving as collaterals to the cortex, might be subject to long-standing hemodynamic stress contributing to risk of rupture. This speculation is consistent with histopathology of vascular networks in moyamoya disease, in which ruptured perforating arteries become extremely dilated.[26] Second, anastomotic sites in the periventricular collateral might be especially fragile because of histologically abnormal connection between vessels. This speculation might be supported by our previous finding that microbleeds were frequently seen at the exact site of the anastomoses.[5] Third, microaneurysms, another possible bleeding source in moyamoya disease,[26] might grow at the site of anastomoses because of the characteristic inflection points that typically form in the collateral at these sites.

In our results, intra- and interrater reliability of the identification of periventricular anastomosis was generally acceptable, and intra- and interrater reliability of the scoring for periventricular anastomosis was good. This suggests that an MRA-based scoring system for abnormal collaterals could become a feasible scale for estimating bleeding risk. Morioka et al. proposed an angiography-based grading system for "moyamoya vessels" and collaterals from the posterior communicating and choroidal arteries.[17] The reproducibility of such an angiographic grading system, however, has not been assessed. Our results are consistent with their primary finding that "dilatation and branch extension of the posterior communicating and choroidal arteries"—probably representing thalamic and choroidal periventricular anastomosis in our definition—was associated with hemorrhage. On the other hand, our finding that the lenticulostriate type was also significantly associated with hemorrhage is inconsistent with their result, in which "moyamoya vessels" were less likely to be related to hemorrhage. The subtypes of periventricular anastomosis might vary in terms of hemorrhage risk. Further studies are necessary to verify or refine scoring of periventricular anastomosis.

Hemorrhage is a devastating manifestation of moyamoya disease,[13] and risk estimates for hemorrhage might be a relevant issue. Periventricular anastomosis might serve as an indicator of hemorrhage risk. The results of a randomized controlled trial for hemorrhagic moyamoya disease suggest that direct bypass can prevent rebleeding.[16] Shrinkage of abnormal collaterals through elimination of hemodynamic stress is a rationale for the effectiveness of bypass surgery.[9,10] Periventricular anastomosis might also be used to evaluate the effectiveness of bypass surgery.

Limitations

As the present study incorporates a cross-sectional design, any causal relationship between the periventricular anastomosis and hemorrhage in moyamoya disease remains tentative. The score-dependent increase in the prevalence of the hemorrhagic presentation observed in this study supports the possibility of a causal relationship. However, the hypothesis that periventricular anastomosis can predict hemorrhage, introduced in the present results, should be tested in further prospective studies.

Although 3-T MRA appears effective at revealing abnormal collaterals in moyamoya disease,[6] the limited resolution hinders detection of very tiny arteries. The direction of blood flow in the collateral vessels was also not taken into account. Further validation studies comparing MRA with a reference standard such as conventional angiography are required.

Conclusions

The results of the present study suggest that the periventricular anastomosis score based on MRA has good interrater reliability. The results also suggest that periventricular anastomosis is associated with hemorrhagic presentation at onset in moyamoya disease. Further prospective studies are needed to determine whether periventricular anastomosis might be useful for estimating hemorrhage risk in moyamoya disease.

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Disclosures

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

Conception and design: Funaki. Acquisition of data: Funaki, Morimoto. Analysis and interpretation of data: Funaki, Drafting the article: Funaki, Fushimi. Critically revising the article: Takahashi, Yoshida, Mineharu. Reviewed submitted version of manuscript: Takahashi, Yoshida, Takagi, Fushimi, Kikuchi, Mineharu, Okada, Morimoto, Miyamoto. Approved the final version of the manuscript on behalf of all authors: Funaki. Statistical analysis: Funaki. Study supervision: Takahashi.

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ORIGINAL ARTICLE doi: 10.2176/nmc.oa.2014-0360
Neurol Med Chir (Tokyo) 55, 204–209, 2015 Online February 20, 2015

Visualization of Periventricular Collaterals in Moyamoya Disease with Flow-sensitive Black-blood Magnetic Resonance Angiography: Preliminary Experience

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Abstract

Fragile abnormal collaterals in moyamoya disease, known as "moyamoya vessels," have rarely been defined. While flow-sensitive black-blood magnetic resonance angiography (FSBB-MRA) is a promising technique for visualizing perforating arteries, as of this writing no other reports exist regarding its application to moyamoya disease. Six adults with moyamoya disease underwent FSBB-MRA. It depicted abnormal collaterals as extended lenticulostriate, thalamic perforating, or choroidal arteries, which were all connected to the medullary or insular artery in the periventricular area and supplied the cortex. This preliminary case series illustrates the potential for FSBB-MRA to reveal abnormal moyamoya vessels, which could be reasonably defined as periventricular collaterals.

Key words: moyamoya disease, periventricular anastomosis, black-blood magnetic resonance angiography

Introduction

Intracranial hemorrhage is a devastating symptom of moyamoya disease.[1)] Fragile abnormal vascular collaterals, known as "moyamoya vessels," are suspected as a source of bleeding.[1,2)] Although such collaterals are generally assumed to arise from dilated lenticulostriate arteries,[3,4)] the angiographical extension of dilated thalamic perforators or choroidal arteries is also known to involve bleeding.[5)] A pioneering study implied that all these types of collaterals arising from the lenticulostriate, thalamic perforating, and choroidal arteries clustered around the periventricular subependymal area to connect to the medullary arteries and were frequently associated with cerebral microbleeds.[6)] However, morphological details of the connection of such collaterals have not been sufficiently documented. Furthermore, because numerous overlapping vessels can obscure the view, angiography often fails to reveal these details.

Flow-sensitive black-blood magnetic resonance angiography (FSBB-MRA) is a recently introduced noninvasive black-blood imaging technique for visualizing perforating arteries.[7,8)] High-resolution 3-tesla FSBB-MRA can reveal tiny parenchymal arteries as well as cisternal and ventricular arteries in the coronal view of the brain. As of this writing, no previous report has addressed the use of FSBB-MRA in visualization of abnormal collateral vessels in moyamoya disease. Noninvasive detection of such collaterals might gain clinical significance in light of risk estimates of bleeding in moyamoya disease. In the present preliminary case series, this innovative imaging technique was applied to six patients with moyamoya disease to facilitate visualization and analysis of the morphological characteristics of periventricular collaterals.

Received October 14, 2014; Accepted November 26, 2014

Materials and Methods

I. Patients

Six adult patients (male 4, female 2) with moyamoya disease were included in the present study (Table 1). The age of these patients ranged from 34 years to 44 years. The mode of manifestation was intracranial hemorrhage in five patients and transient ischemic attack in one patient. All patients underwent magnetic resonance (MR) imaging including

Table 1 Summary of patients

Case	Age/Sex	Manifestation mode	Location of hemorrhage	Initial symptoms	Suzuki stage, R/L	Number of periventricular anastomoses (R/L)
1	43F	ICH	left temporal lobe	headache, speech disturbance	1/3	2 (1/1)
2	37M	ICH with IVH	right thalamus	headache, nausea	5/5	5 (3/2)
3	47M	ICH	left temporal lobe	hemiparesis, motor aphasia	4/4	3 (2/1)
4	37M	ICH	left insula and lateral part of thalamus	hemiparesis	0/3	3 (0/3)
5	34M	IVH	lateral ventricle	consciousness disturbance	5/5	5 (2/3)
6	44F	TIA	–	transient motor weakness	4/4	1 (1/0)

ICH: intracerebral hemorrhage, IVH: intraventricular hemorrhage, TIA: transient ischemic attack.

FSBB-MRA, routine clinical 3-tesla MR imaging including susceptibility-weighted imaging (SWI), and conventional cerebral angiography during the same admission period. All patients provided written informed consent to the FSBB-MRA.

II. Imaging technique

A 3-tesla research MR scanner (Vantage; Toshiba Medical Systems Corporation, Otawara, Tochigi) with a 32-channel head coil was used to obtain FSBB images. These images were scanned as coronal sections with the following parameters: repetition time (TR)/ echo time (TE), 35/13 ms; flip angle, 15°; acquisition matrix size, 384 × 384; and field of view (FOV), 192 × 192 mm in 1 axial 3D slab of 80 sections (0.8 mm thickness); and a parallel imaging factor of 2. The imaging field extended from the anterior horn to the atrium. A motion-probing gradient of b = 0.3 s/mm^2 was applied to dephase arterial blood flow in three directions. Total scan time was 8 m 31 s. In addition to source images with 0.8 mm thickness, minimum-intensity projection images were also generated as 2.5-mm thick and 10-mm thick slabs of overlapping volumes. Both minimum-intensity projection images and source images were assessed by a neuroradiologist and a neurosurgeon.

During the same admission period, all patients underwent MR imaging including FSBB-MRA, routine clinical 3-tesla MR imaging including susceptibility-weighted imaging (SWI) to detect the evidence of bleeding, and conventional cerebral angiography.

III. Analysis

Both a neurosurgeon (Takeshi Funaki) and a neuroradiologist (Yasutaka Fushimi) carefully compared the results of the arterial-phase angiography and FSBB-MRA for each patient. Periventricular anastomosis, the finding of interest in the present study, was defined as that between the perforating and medullary arteries or between the choroidal and medullary arteries, which was located around the periventricular area. Any topographical relationship between periventricular anastomoses and SWI-visible lesions was assessed on a workstation integrated into the image-archiving and communication system.

Results

Periventricular anastomoses were observed in FSBB-MRA images obtained from all six patients (Table 1). The morphologies of the periventricular anastomoses revealed in the FSBB-MRA images exactly coincided with those revealed in the arterial phase of angiography, confirming that FSBB-MRA truly depicted arteries. A total of 19 periventricular anastomoses were identified with FSBB-MRA. An SWI-visible lesion was identified at the exact sites of 11 anastomoses (57.9%).

Representative cases

Case 1: A 43-year-old female with moyamoya disease suffered from left temporal lobe hemorrhage. Left internal carotid artery angiography (Fig. 1a, b) revealed the medullary arteries derived from a lenticulostriate artery, suggesting an anastomosis between the lenticulostriate and medullary arteries around the periventricular area. FSBB-MRA more clearly revealed an anastomosis between these arteries at the lateral corner of the frontal horn of the ventricle with exact correspondence to angiography (Fig. 1c). Note that the medullary arteries have the largest caliber in the cortical area and smallest in their periventricular portion, indicating that the arteries originally arose from the cortical arteries. Blood flow was directed "ventriculofugally" toward

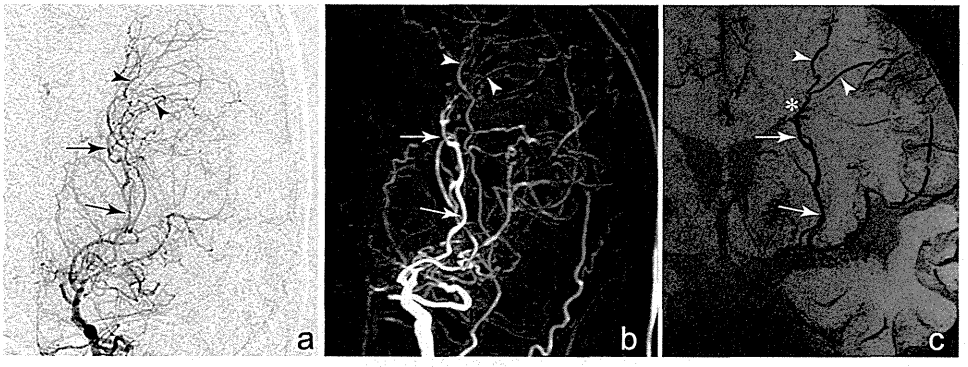

Fig. 1 Periventricular anastomosis originating from the lenticulostriate artery (Case 1). a: Anterior-posterior view of conventional angiography of the left internal carotid artery showing the medullary arteries (*arrowheads*) branching from a lenticulostriate artery (*arrows*). b: The same view of a maximum-intensity projection image reconstructed with 3-dimensional rotation angiography. c: Flow-sensitive black-blood magnetic resonance angiography revealing an anastomosis (*asterisk*) between the medullary arteries (*arrowheads*) and the lenticulostriate artery (*arrows*) at the lateral corner of the frontal horn of the ventricle.

the cortical area in the medullary arteries; it thus travels opposite to the original direction of flow in the medullary artery. In this patient, FSBB-MRA of the contralateral side revealed a very similar finding.

Case 2: A 37-year-old male with moyamoya disease suffered from right thalamic hemorrhage. Meticulous reading of left carotid artery angiography might identify a tortuous perforating artery originating from the thalamotuberal artery and connecting to the medullary arteries, but numerous overlapping vessels obscure the view (Fig. 2a). FSBB-MRA more clearly revealed the thalamotuberal artery, which coursed around the periventricular area of the third ventricle and then abnormally extended laterally beyond the thalamus and connected to the medullary artery (Fig. 2b). Note that a microbleed was revealed at the inflexion point of the collaterals, the site supposed to be the first anastomotic site, located beneath the ependymal layer of the third ventricle. In this patient, FSBB-MRA of the contralateral side revealed a very similar finding, where the evidence of thalamic hemorrhage was observed.

Case 3: A 47-year-old male with moyamoya disease suffered from left temporal lobe hemorrhage. Right vertebral artery angiography showed the probable thalamogeniculate artery connecting to the insular artery and subsequently to the middle cerebral artery, revealing a somewhat arbitrary spatial relationship (Fig. 3a). FSBB-MRA more clearly demonstrated the anastomosis between the thalamogeniculate artery and the insular artery, a type of medullary artery originally derived from the middle cerebral artery (Fig. 3b). The anastomosis was located at the inferolateral margin of the thalamus near the inferior horn of the lateral ventricle. SWI revealed a microbleed at the exact

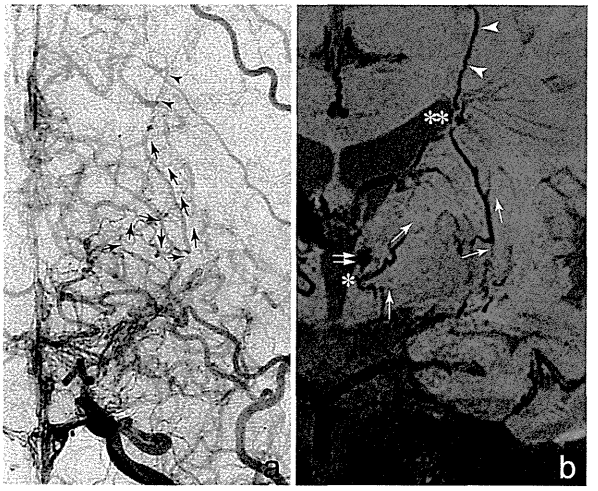

Fig. 2 Periventricular anastomosis originating from the thalamotuberal artery (Case 2). a: Anterior-posterior view of left common carotid artery angiography showing a tortuous thalamotuberal artery (*arrows*) connecting to the medullary arteries (*arrowheads*). b: Flow-sensitive black-blood magnetic resonance angiography demonstrating the arteries more clearly. Anastomotic sites are supposed to be located both beneath the ependyma of the third ventricle (*asterisk*) and at the lateral corner of the lateral ventricle (*double asterisk*). The evidence of bleeding is observed at the first anastomotic site (*double arrow*).

point of the anastomosis (Fig. 3c). In this patient, FSBB-MRA of the contralateral side revealed a similar finding, where the evidence of temporal lobe hemorrhage was observed.

Case 4: A 37-year-old male with moyamoya disease suffered from hemorrhage extending through the lateral part of the thalamus and insula in the left

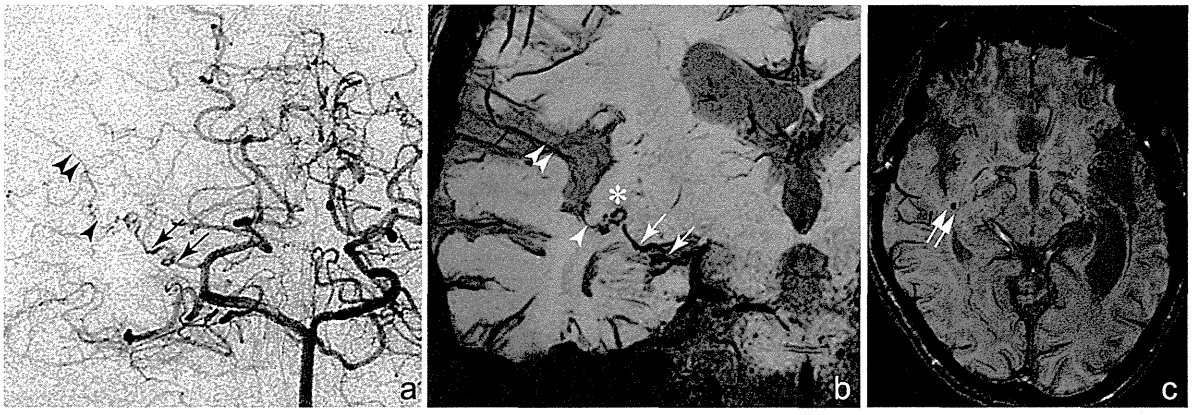

Fig. 3 Periventricular anastomosis originating in the thalamogeniculate artery (Case 3). a: Anterior-posterior view of vertebral artery angiography showing the thalamogeniculate artery (*arrows*), which connects to the insular artery (*arrowhead*) and subsequently to the middle cerebral artery (*double arrowhead*), revealing a somewhat arbitrary spatial relationship. b: Flow-sensitive black-blood magnetic resonance angiography more clearly demonstrating the anastomosis (*asterisk*) between the thalamogeniculate artery (*arrows*) and the insular artery (*arrowhead*), which is located at the temporal stem. c: Susceptibility-weighted imaging revealing a microbleed at the exact site of the anastomosis (*double arrow*).

hemisphere. Left internal carotid artery angiography showed an abnormal extension of the dilated choroidal artery (Fig. 4a, b). FSBB-MRA more clearly revealed anastomosis between the choroidal artery and the medullary artery beneath the lateral wall of the atrium of the lateral ventricle (Fig. 4c), with exact correspondence to the anterior-posterior view from the angiography. The evidence of a microbleed can be observed at the exact point of the anastomosis (Fig. 4c, d). In this patient, the anastomosis between the thalamogeniculate and insular arteries was also observed in the lateral part of the left thalamus, where the evidence of hematoma was observed.

Discussion

I. Periventricular anastomosis as a concept defining fragile collateral networks in moyamoya disease

In the present case series, all patients have a type of anastomosis between the perforating and medullary arteries or between the choroidal and medullary arteries. These types of anastomoses probably serve as a collateral to the cortex and compensate for the decrease in cerebral blood flow attributable to occlusion of the internal carotid artery. Such collaterals, although the subject of limited interest, have been denoted variously in previous reports as "anastomosis between the perforating branch and medullary artery,"[9] "abnormal vessel network/medullary artery anastomosis,"[4] or "lenticulostriate-medullary artery anastomosis."[3] Most of these collaterals, however, have barely been identified through meticulous angiographic observation and thus have rarely been

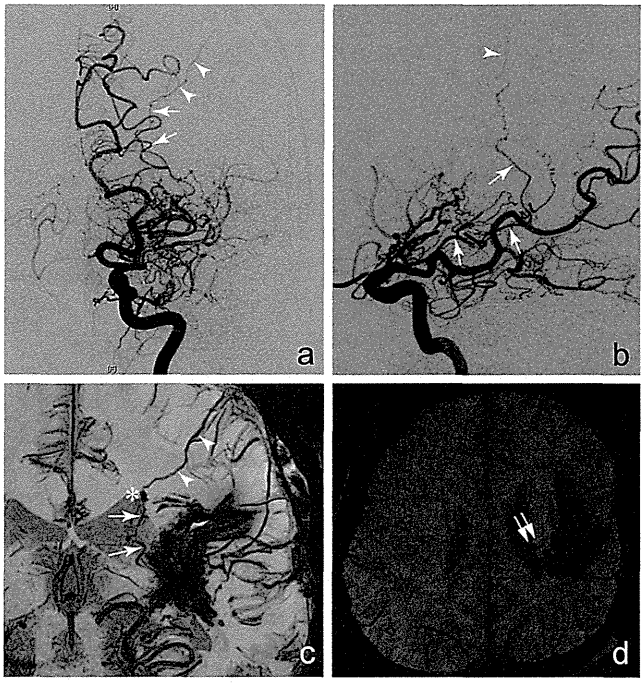

Fig. 4 Periventricular anastomosis originating in the anterior choroidal artery (Case 4). a, b: Anterior-posterior (a) and lateral (b) views of left internal carotid artery angiography showing dilated anterior choroidal artery (*arrows*) connecting to the medullary artery (*arrowhead*). c: Flow-sensitive black-blood magnetic resonance angiography revealing anastomosis (*asterisk*) between the choroidal artery (*arrows*) and the medullary artery (*arrowheads*) located beneath the lateral wall of the atrium. d: Susceptibility-weighted imaging showing the microbleed (*double arrow*) coincident with periventricular anastomosis.

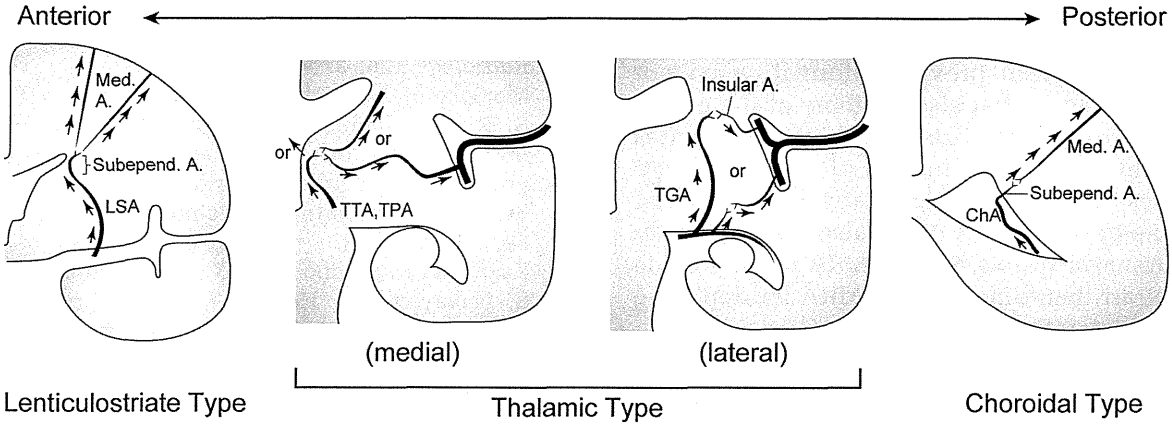

Fig. 5 Schematic illustrations showing a coronal plane of the left cerebral hemisphere and three types of periventricular anastomoses. A.: artery, ChA: choroidal artery, LSA: lenticulostriate artery, Med.: medullary, subepend.: subependymal, TGA: thalamogeniculate artery, TPA: thalamoperforating artery, TTA: thalamotuberal artery.

systemized. Furthermore, these reports focused only on perforating arteries such as lenticulostriate arteries as sources of collaterals. Morioka et al. stressed that abnormal extension or branching of the dilated choroidal artery also served as important collaterals possibly associated with bleeding.[5] Although they did not clearly define the abnormal branches from the choroidal artery, we assumed from observation suggests that the medullary artery represents such branches.

All collaterals described in the present cases share one feature: all anastomosis sites were located in the periventricular area, that is, at the lateral corner of the anterior body of the lateral ventricle (Fig. 1), beneath the ependyma of the third ventricle (Fig. 2), superior to the inferior horn of the lateral ventricle (Fig. 3), and beneath the lateral wall of the atrium of the lateral ventricle (Fig. 4). It might thus be reasonable to classify all these types of anastomoses under one identifier as, say, periventricular anastomosis (Fig. 5).

These anastomoses cluster in the periventricular area possibly because of the presence of the subependymal artery,[10,11] an anatomically hypothesized artery beneath the ependyma and originally described as the ventriculofugal (or centrifugal) artery.[12,13] The subependymal artery might intervene between the perforating and medullary arteries or between the choroidal and medullary arteries in a specific pathological condition such as moyamoya disease. As shown in Fig. 5, periventricular anastomoses can be reasonably classified into three types: lenticulostriate, thalamic, and choroidal. These classifications differ only slightly from those proposed by Kazumata et al.[6] The thalamic type could be subclassified into medial and lateral types according to the location of the anastomosis. The medial thalamic type could also include the connection between the perforating artery and the medial posterior choroidal artery in the roof of the third ventricle, which was not observed in the present series. It might also be acceptable to include in the choroidal classification the possible connection between the medial posterior choroidal artery and pericallosal artery through the corpus callosum, a condition not observed in the present series.

The distribution of periventricular anastomoses corresponds closely to common bleeding sites in moyamoya disease; that is, the basal ganglia, thalamus, temporal stem, and periventricular areas of the entire lateral and third ventricles.[6] This evidence could support the hypothesis that periventricular anastomosis is a surrogate marker for bleeding, a consideration that should be tested in further studies.

II. Clinical importance of FSBB-MRA

FSBB-MRA is a high-resolution black-blood imaging method adequate for visualizing small perforating arteries in the general population and in patients with lacunar infarction.[7] The imaging methods can more sensitively visualize the perforating arteries than time-of-flight MRA.[8] In FSBB-MRA, the signal from rapidly flowing blood in the arteries is attenuated through the application of a very weak motion-probing gradient for signal dephasing, while the signal from slow-moving components, such as the flow in the veins, is much less affected. FSBB-MRA might have two benefits for detecting periventricular anastomoses. First, minimum-intensity projection coronal images with adequate slab thickness noninvasively facilitate visualization of periventricular anastomosis without any effect from numerous vessels overlapping and obscuring the view. Partial volume effect is avoid-

able by simultaneous reading of thin slice source images. Second, unlike conventional angiography, black-blood MRA can provide information on not only the tiny arteries but also anatomy of the parenchymal structure. Visualization of both anatomies seems essential to the evaluation of periventricular anastomoses. Although a recent study illustrated that 3-tesla time-of-flight MRA could also noninvasively depict moyamoya vessels,[14] FSBB-MRA might provide better contrast than time-of-flight MRA for depicting both the collaterals and parenchyma.

In conclusion, this preliminary case series illustrates the potential of FSBB-MRA to reveal abnormal collaterals in moyamoya disease, or moyamoya vessels, characterized as those arising from the lenticulostriate, thalamic perforating, or choroidal arteries and connecting to the medial end of the medullary or insular artery in the periventricular area. The concept of periventricular anastomosis, an alternative definition of moyamoya vessels, might facilitate future optimal grading and classification of moyamoya vessels. The detection of periventricular anastomoses with FSBB-MRA could generate risk estimates of bleeding in moyamoya disease, and larger studies are required.

Acknowledgments

This work was supported by JSPS KAKENHI Grant Number 25461815 and a sponsored research program, "Researches for improvement of MR visualization (No. 150100700014)" provided to Professor Kaori Togashi, Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, by Toshiba Medical Systems Corporation, Japan. The authors also thank Ms. Kyoko Takakura for her technical assistance regarding MRI.

Conflicts of Interest Disclosure

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

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REVIEW ARTICLE doi: 10.2176/nmc.ra.2014-0326

Neurol Med Chir (Tokyo) 55, 199–203, 2015 Online February 20, 2015

Cognitive Dysfunction Survey of the Japanese Patients with Moyamoya Disease (COSMO-JAPAN Study): Study Protocol

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Abstract

Moyamoya disease is a cerebrovascular occlusive disease characterized by progressive stenosis or by occlusion at the terminal portion of the bilateral internal carotid arteries. The unusual vascular network (moyamoya vessels) at the base of the brain with this disease as collateral channels is developed in this disease. Social independence because of cognitive impairment has recently been recognized as an important unsolved social issue with adult moyamoya disease. The patients with cognitive impairment have difficulty in proving their status because the standard neuroradiological and neuropsychological methods to define cognitive impairment with moyamoya disease are not determined. These patients with cognitive impairment should be supported by social welfare as psychologically handicapped persons. Thus Cognitive Dysfunction Survey of the Japanese Patients with Moyamoya Disease (COSMO-JAPAN study) is planned. In this study, we want to establish a standard finding of the cognitive impairment in patients with moyamoya disease.

Key words: moyamoya disease, cognitive dysfunction, [^{123}I]iomazenil-single photon emission computed tomography, neuropsychological study

Introduction

Moyamoya disease is a cerebrovascular occlusive disease characterized by progressive stenosis or by occlusion at the distal ends of bilateral internal carotid arteries.[1] The unusual vascular network (moyamoya vessels) at the base of the brain of individuals with this disease is considered to represent collateral channels formed as a result of progressive brain ischemic changes.[1–3] The etiology of the disease is undefined. The findings that the incidence of the disease is highest in East Asian people and that the condition is frequently familial, suggest the involvement of a genetic factor in its pathogenesis.[1] Extracranial-intracranial bypass surgery has been established as an effective neurosurgical intervention that increases cerebral blood flow (CBF) and prevents from ischemic attacks.[4,5] However, difficulty with social independence accompanied by cognitive impairment has recently been recognized as an important unsolved social issue faced by patients with adult moyamoya disease.[6–8] These patients are physically independent in daily life, but economically dependent. It is very difficult for them to obtain vocational skills because of cognitive impairment. These patients with cognitive impairment should be supported by social welfare as psychologically handicapped persons. They have difficulty in proving their status because the standard neuroradiological and neuropsychological methods to define cognitive impairment with moyamoya disease are not determined. Generally, cognitive impairment has been described as a neuropsychological disorder occurring after strokes that shows as disturbances in memory, attention, performance, and social behavioral disturbances mainly in pediatric cases.[9,10] However, recent reports have focused on adult cases with neurocognitive impairment even without neuroradiological evidence of major stroke.[8,11,12] Nakagawara et al.[8] indicated that even if infarction has not yet occurred, brain dysfunction was associated with persistent hemodynamic compromise in the medial frontal lobes that can be visualized using [^{123}I]iomazenil (IMZ)-single photon emission computed tomography (SPECT). This technique has the potential to become a tool for diagnosing cognitive impairment in adult moyamoya patients who do not show major abnormalities on computed

Received October 19, 2014; Accepted December 10, 2014

tomography (CT) scans or magnetic resonance imaging (MRI). In addition, a common methodology for neuropsychological evaluation of these patients is yet to be determined.[6,12,13] In this study, we want to establish the standard finding of the cognitive impairment in patients with moyamoya disease.

Materials and Methods

I. Methods/design

This is a prospective multicenter trial planning to analyze 60 patients with moyamoya disease. The study was approved by the Regional Ethical Review Board at Kyoto University (reference number: E-1754), and all patients will provide written informed consent before inclusion in the trial.

II. Inclusion and exclusion criteria

Inclusion criteria are as follows:

1. Male or female aged above 18 years under 60 years
2. Diagnosed as moyamoya disease or unilateral moyamoya disease on assessment by the neuroradiological committee[14]
3. Without intracranial hemorrhage including intracerebral hemorrhage, intraventricular hemorrhage, and subarachnoid hemorrhage
4. Without a large structural lesions (less than 1 cortical artery region) on neuroradiological studies
5. No neurological disorder influencing neuropsychological assessment, e.g., aphasia, hemianopsia, and agnosia
6. Modified Rankin scale ranging from 0 to 3
7. Without serious cognitive dysfunction assessed by subjective, objective symptoms, or daily life situation
8. Confirmation of informed consent

Exclusion criteria are as follows:

1. Quasi-moyamoya disease
2. Impossible to perform MRI
3. Assessment as unsuitable for this study

These criteria are also described in Table 1.

Table 1 Inclusion and exclusion criteria

Inclusion criteria
1. Male or female aged above 18 years under 60 years
2. Diagnosed as moyamoya disease or unilateral moyamoya disease on assessment by the neuroradiological committee
3. Without intracranial hemorrhage including intracerebral hemorrhage, intraventricular hemorrhage, and subarachnoid hemorrhage
4. Without a large structural lesions (less than 1 cortical artery region) on neuroradiological studies
5. No neurological disorder influencing neuropsychological assessment, e.g., aphasia, hemianopsia, and agnosia
6. Modified Rankin scale ranging from 0 to 3
7. Without serious cognitive dysfunction assessed by subjective, objective symptoms, or daily life situation
8. Confirmation of informed consent
Exclusion criteria
1. Quasi-moyamoya disease
2. Impossible to perform MRI
3. Assessment as unsuitable for this study

MRI: magnetic resonance imaging.

III. Background data

As background data of the patients, including in this study institute, sex, age, history of education, history of jobs, familial history, reason for diagnosis, modified Rankin scale, medication, and neurological deficits are recorded. In addition, blood sample is collected.

IV. SPECT

Brain N-isopropyl-p-^{123}I-iodoamphetamine (^{123}I-IMP) SPECT using QSPECT/dual table autoradiographic (ARG) method with three-dimensional stereotactic surface projection (3D-SSP) is performed to calculate the regional cerebral blood flow. To assess the regional cerebral vascular reserve, Diamox challenge SPECT is performed. The procedure for QSPECT/dual table ARG is described elsewhere in more detail.[15,16] The data is analyzed by the SEE-JET (stereotactic extraction estimation based on the Japan EC-IC bypass trial study) program.[17]

^{123}I-IMZ-SPECT using QSPECT method with 3D-SSP is performed to assess cortical neuronal loss. Cortical neuron loss is analyzed using the SEE method (level 3: gyrus level) for 3D-SSP Z-score maps as previously reported.[8]

V. MRI

MRI scans are also performed in all subjects. The scans are acquired on a 1.5 T or a 3 T scanner using a three-dimensional (3D) sagittal magnetization-prepared rapid gradient-echo imaging sequence, which is specially adjusted for the Japanese Alzheimer's disease Neuroimaging Initiative (J-ADNI) 1/2 protocols. T_1 structural sequences [3D MPRAGE on Siemens (Erlangen, Germany) and Philips Healthcare (Best, the Netherlands), 3D IR-SPGR on GE], FLAIR, T_2WI (Dual Echo), T_2*WI and TOF-MRA images are obtained in this study.[18]

VI. Neuropsychological assessment

Basic cognitive ability is evaluated using the

Table 2 Neuroradiological and neuropsychological study

Neuroradiological study
SPECT
^{123}I-IMP SPECT
^{123}I-IMZ-SPECT
MRI
MPRAGE/IR-SPGR
FLAIR
T_2WI (Dual Echo)
T_2*WI
TOF-MRA
Neuropsychological study
WAIS-III
WMS-R
FAB
WCST
Stroop test
Word-fluency
TMT A/B
BDI II
STAI
FrSBe
WHOQOL26

Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) to assess intelligence, the Wechsler Memory Scale-Revised (WMS-R) to assess memory,[19,20] and supplemental subtests for each task. Several frontal-functioning tests are also administered to detect specific neuropsychological deficits associated with adult moyamoya disease that co-occurs with difficulty in social independence. The Frontal Assessment Battery (FAB) tests general frontal cognitive ability. The Trail Making Test Part A (TMT-A) assesses speed of information processing,[21,22] and the Trail Making Test Part B (TMT-B) and the Wisconsin Card Sorting Test (WCST) assess executive ability.[5,18] Stroop test, Word-fluency test, and Frontal Systems Behavior Scale (FrSBe) are also used for frontal lobe function.[22–24] The Beck Depression Inventory—Second Edition (BDI II) and State-Trait Anxiety Inventory (STAI) assess depressive state.[26,27] In addition, WHOQOL26 assesses the quality of life. The item of neuroradiological and neuropsychological study is summarized in Table 2.[28]

Discussion

Patients with moyamoya disease often suffer higher cognitive impairments such as memory, attention, and social behavioral disturbances.[11–13] Such cognitive impairments may occur in patients with medial frontal lobe damage including the anterior cingulate cortex. However, confirmatory diagnosis of higher cognitive dysfunction in patients with moyamoya disease without obvious brain damages on CT or MRI imaging has not been established and could become a social issue.[8]

In general, higher brain dysfunction associated with adult moyamoya disease could be detected by both neuropsychological findings and obvious medial frontal lobe damage detected by CT or MRI.[11–13] In addition, hemodynamic ischemia in this region is analyzed by SPECT at rest and after Diamox challenge.[15,16] More recently, loss of frontal cortical neuron could be estimated by functional neuroimaging using SPECT, because central benzodiazepine receptor mapping using ^{123}I-IMZ is available for clinical use.[8] IMZ is a specific radioactive tracer for the central benzodiazepine receptor that may be useful as a marker of cortical neuron loss. Recent work using IMZ-SPECT has demonstrated the association between cortical neuron loss in bilateral frontal medial cortices and cognitive dysfunction.[8]

Neuropsychological analysis in patients with brain damage played an important role in the history of developing the research of brain function.[13,19–22,29] Among brain dysfunction, higher cognitive dysfunction has been underestimated in the neurosurgical field. This dysfunction is often due to frontal lobe dysfunction. An extensive focus on frontal lobe function has not yet been taken by previous research regarding moyamoya disease. CBF and IMZ studies have shown that antero-medial frontal cortices fed by anterior circulation develop blood insufficiencies.[8,30] For this reason, several neuropsychological test batteries to evaluate frontal lobe functioning in relation to hemodynamic compromise were employed for our preliminary study. Based on this preliminary study, we developed this study and adopted several tasks to examine the frontal lobe functions.[11] To date, this is the first nation-wide survey of patients with moyamoya disease focusing on the neuroradiological and neuropsychological analysis in association with higher cognitive dysfunction. Patients with cognitive impairment should be supported by social welfare as psychologically handicapped persons.

The data obtained from the results of the study will play an important role in clarifying higher cognitive dysfunction in patients with moyamoya disease.

Conflicts of Interest Disclosure

All authors have no conflicts of interest in this manuscript.

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Acta Neurochir (2014) 156:551–559
DOI 10.1007/s00701-013-1975-7

CLINICAL ARTICLE - VASCULAR

Incidence of late cerebrovascular events after direct bypass among children with moyamoya disease: a descriptive longitudinal study at a single center

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Received: 27 June 2013 / Accepted: 4 December 2013 / Published online: 22 December 2013

Abstract
Background The potential for late cerebrovascular events following surgical revascularization presents a challenge in the treatment of pediatric moyamoya disease. Limited information is available on the incidence of such events after direct bypass. The objective of this descriptive study was to examine the incidence of late cerebrovascular events after direct bypass for pediatric moyamoya disease.
Methods The study cohort comprised consecutive patients with moyamoya disease who had undergone direct bypass at less than 18 years of age in the authors' institute between 1978 and 2003. They were prospectively followed until the end of the study period or, if applicable, the time of death.
Results Fifty-six of 58 enrolled patients (96.6 %) were followed for a mean period of 18.1 years. Four patients experienced late cerebrovascular events, comprising one stroke and three hemorrhages, an average of 13 years after surgery, one of whom experienced a fatal second hemorrhage. The only late ischemic stroke in the cohort occurred after a severe head injury and emergent craniotomy. The incidence of late cerebrovascular events was 0.41 % per year (95 % confidence interval, 0.15–1.08); 10-year, 20-year, and 30-year cumulative incidences were 1.8 %, 7.3 %, and 13.1 %, respectively.
Conclusions Despite the efficacy of surgical revascularization, pediatric patients remain at risk of future cerebrovascular events, especially hemorrhage, after reaching adulthood and thus require careful long-term follow-up.

Keywords Moyamoya disease · Pediatrics · Cerebral revascularization · Cohort study · Stroke · Hemorrhage

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Introduction

Moyamoya disease is characterized by progressive spontaneous stenosis or occlusion of the terminal portion of the bilateral internal carotid arteries and development of abnormal collateral vessels at the base of the brain. Epidemiological studies have shown that the age distribution of disease onset has two peaks: childhood and the 40s [1, 20, 37]. In childhood, ischemic symptoms such as transient ischemic attack and stroke are the main initial manifestations. In adult patients, intracranial hemorrhage is as common as ischemic symptoms and often results in serious sequelae [1, 38]. Although numerous follow-up studies have supported the evidence that revascularization surgery is effective at preventing ischemic symptoms in pediatric patients with moyamoya disease [3, 8, 16, 21, 24, 27, 29, 31, 32, 36], more recent studies have reported that the slight risk of late cerebrovascular events, including both ischemic stroke and hemorrhage, remains even after revascularization surgery [8, 12, 27, 31]. Considering the bimodal age distribution of disease onset, a late cerebrovascular event is likely to occur after pediatric patients reach

adulthood and thus is a future potential problem for them. Estimation of the incidence of a late cerebrovascular event is essential for planning the follow-up of pediatric patients. However, only a few studies have focused on this issue, and long-term prospective studies are rare. Furthermore, in those studies addressing the issue of a late cerebrovascular event, surgical revascularization generally takes the form of indirect bypass such as encephalo-duro-arterio-synangiosis; consequently, there is a lack of information on late cerebrovascular events following direct bypass surgery, such as superficial temporal artery (STA) to middle cerebral artery (MCA) bypass.

In this study, we prospectively followed a cohort comprising consecutive patients with moyamoya disease, all of whom had undergone direct bypass in childhood. The objective of the study was to examine the incidence and features of late cerebrovascular events after direct bypass for pediatric moyamoya disease.

Methods

The study protocols for the present study were reviewed and approved by the ethics committee of the Kyoto University Graduate School of Medicine.

Inclusion criteria

This study includes consecutive pediatric patients surgically treated mainly by the senior author at Kyoto University Hospital and its satellite hospital between April 1978 and March 2003. The inclusion criteria were as follows:

1. Japanese patients under 18 years of age at first admission for moyamoya disease
2. Diagnosed with moyamoya disease following angiography according to the criteria proposed by the Research Committee on Moyamoya Disease in Japan [5, 30]
3. Had undergone direct bypass in this institute
4. Children with a typical occlusive finding at the terminal portion of the unilateral internal carotid artery alone were also included [30]

Patients from outside Japan were excluded from the present study because of racial differences and difficulties with follow-up. Also excluded were children with autoimmune disease, meningitis, brain tumor, Down syndrome, neurofibromatosis type 1, or a history of head irradiation. Since 1978, we have been employing a direct bypass method comprising STA-MCA bypass as a first-line treatment for pediatric moyamoya disease [16]. For patients under 10 years of age, encephalo-myo-synangiosis (EMS) [14], an additional indirect bypass procedure using the pedicle flap of the temporalis muscle was combined with STA-MCA bypass. All but two surgeries were performed by the senior author: in the earliest case, the first two surgeries were performed by another surgeon and the subsequent ones by the senior author. Patients with involvement of the bilateral internal carotid artery underwent STA-MCA bypass first on the more symptomatic or hemodynamically impaired hemisphere and then on the contralateral hemisphere. The second revascularization was performed no earlier than 4 weeks after the first revascularization because patients require the time for recovery from unstable cerebral hemodynamics including hyperperfusion, which can occur shortly after direct bypass [15, 35]. Angiography was performed 3 months after the second revascularization to assess bypass patency. If examinations 3 months after the second revascularization suggested insufficient hemodynamic improvement in the anterior or posterior cerebral artery territories, additional direct revascularizations to these areas were considered.

Protocol

Data including age at symptom onset, primary clinical manifestations (categorized as completed ischemic stroke, transient ischemic attack, intracranial hemorrhage, or epilepsy), and angiographical findings, translated later into a four-stage system [26], were collected upon first admission. A completed ischemic stroke was defined as a neurological symptom exceeding 24 h in duration and the presence of a corresponding ischemic lesion revealed through neuroradiological modalities. Patients were followed by the outpatient neurosurgical clinic until the end of the study period or until the time of death, if applicable. The final status of each patient was determined between January 2011 and April 2013 through regular follow-up at the outpatient clinic or through a telephone interview and mailed questionnaire if the patient did not visit the hospital during that period.

A late cerebrovascular event, an outcome of the present study, was defined as all ischemic and hemorrhagic strokes with neurological symptoms occurring more than 30 days after surgery and confirmed thorough neuroradiological modalities. Hemorrhages included intraventricular, parenchymal, and subarachnoid types. All patients had been encouraged to visit our hospital promptly if experiencing weakness in an extremity, sensation abnormality, speech disturbance, hemianopsia, or severe headache with vomiting. In such cases, an emergent radiological assessment including computed tomography and magnetic resonance imaging was performed to determine whether the patient was experiencing a cerebrovascular event.

Single photon emission tomography (SPECT) was performed between 2011 and 2013 in some patients who had provided their informed consent. Regional cerebral blood flow (rCBF) was quantitatively measured with iodine-123-

labelled N-isopropyl-p-iodoamphetamine (IMP) [10]. A region of interest was automatically set in each vascular territory.

Statistical analysis

The person-years method was used to calculate the incidence of late cerebrovascular event. The incidence was calculated by dividing the number of patients experiencing the outcome by person-years counted until the end of the study period or occurrence of the outcome. The Poisson distribution was used to calculate 95 % confidence intervals (95 % CIs) of the incidence. The Kaplan-Meier method was used to estimate the cumulative incidence. The rCBF values among three vascular territories were compared with the Kruskal–Wallis test [19]. Statistical analyses were performed with JMP 9 software (SAS Institute, Cary, NC, USA).

Results

A total of 58 patients met the criteria, all of whom gave informed consent and were enrolled in this study. The sex and age distributions at disease onset are summarized in Table 1. The overall female-to-male ratio was 1.4, and the peak age at onset was 6 years (mean, 6.4; range, 0–15; 95% CI, 5.5–7.3). Transient ischemic attack was the most common primary manifestation (75.9 %), followed by completed stroke (17.2 %) and epilepsy (5.2 %). No patients presented with intracranial hemorrhage at disease onset. Angiographical stages in anterior circulation assessed on admission were 1 in 7 (12.1 %) cases, 2 in 27 (46.6 %) cases, 3 in 22 (37.9 %) cases, and 4 in 2 (3.4 %) cases; those in posterior circulation were 1 in 36 (65.5 %) cases, 2 in 6 (10.9 %), and 3 in 13 (23.6 %) cases. A total of 114 bypass surgeries were performed. Additional revascularization to the anterior or posterior cerebral artery territories was performed in five (8.6 %) patients, of which three underwent direct bypass using another branch of the STA or the occipital artery and two underwent omental transplantation [17]. The patency of all bypasses was confirmed by postoperative angiography.

Table 1 Age distribution at disease onset and at end of follow-up

Age in years	At disease onset		At end of follow-up	
	Female	Male	Female	Male
0–4	13	6	0	0
5–9	15	13	0	0
10–14	5	5	1	0
15–19	1	0	6	2
20–24	0	0	6	8
25–29	0	0	9	6
30–34	0	0	7	5
35–39	0	0	2	0
40–44	0	0	0	1
45–50	0	0	2	0
Deceased	–	–	0	1
Lost to follow-up	–	–	1	1

The mean follow-up period was 18.1 years (range, 9–33.7; 95 % CI, 16.5–19.7). Age distribution at the end of the study is shown in Table 1; mean age at the end of the study was 26.5 years (range, 13–45; 95 % CI, 24.6–28.4). The outcome at the end of the study was not available in two patients, for a follow-up rate of 96.6 % (56/58). These two patients had been followed for 21 and 23 months after surgery, respectively, before they stopped visiting our hospital. Their postoperative courses were uneventful and had experienced no new neurological symptoms as of the last day of follow-up. We were unable to contact them at the end of the study because they had relocated.

Four of the 56 followed patients (7.1 %) experienced at least one late cerebrovascular event during observation period (Table 2). The mean interval between the initial surgery and the late cerebrovascular event was 13.0 years. One experienced an ischemic stroke after a head injury at 8 years of age. Three experienced an intracranial hemorrhage at a mean age of 26 years (range, 24–29), an average of 16.8 years (range, 13.9–20.9) after surgery. One of the patients experienced a second hemorrhage, which resulted in a fatal outcome. In all patients with late-onset hemorrhage, the bypasses were still patent at the time of the hemorrhagic event.

Until the end of the study, 986.6 person-years of follow-up (577.8 person-years for females and 408.8 person-years for males) were counted. The incidence of overall late cerebrovascular events calculated by the person-years method was 4/986.6 or 0.41 % per year (95 % CI, 0.15–1.08). The incidences of late ischemic and hemorrhagic events were 1/1004.7 or 0.10 % per year (95 % CI, 0.01–0.71) and 3/995.4 or 0.30 % per year (95 % CI, 0.10–0.93), respectively. According to the Kaplan-Meier method, the 10-year, 20-year, and 30-year cumulative incidences of late cerebrovascular events were 1.8 %, 7.3 %, and 13.1 %, respectively (Fig. 1).

The follow-up SPECT was obtained in 11 patients, and rCBF was measured in 22 hemispheres. The median rCBF (interquartile range) in the anterior, middle, and posterior cerebral artery territories were 40.5 (37.3–47.7), 38.9 (34.3–47.9), and 38.6 (34.5–47.6) ml/100 g/min, respectively. No statistically significant differences in rCBF were found among vascular territories (p=0.580).

Illustrative cases

Case 1 (late ischemic stroke) This patient had been experiencing transient motor weakness in the extremities triggered by hyperventilation since he was 3 years of age and was admitted

Table 2 Summary of patients experiencing late cerebrovascular events

Case	Age at onset in years, Sex	Primary manifestation	Age at OP in years	Type of late cerebrovascular event	Age at late cerebrovascular events in years	Time elapsed between OP and first late cerebrovascular event in years	mRS at end of follow-up
1	3 M	TIA	6	Ischemic stroke[a]	8	2.75	2
2	6 F	TIA	10	Thalamic hemorrhage	25	13.9	2
3	7 F	TIA	9	Intraventricular hemorrhage	24	15.5	0
4	4 M	TIA	8	Intraventricular hemorrhage	29 and 33	19.9	6

TIA transient ischemic attack, *OP* operation, *mRS* modified Rankin Scale

[a] The stroke occurred after a severe head injury and emergent craniotomy

to our hospital. At 6 years of age he was diagnosed with moyamoya disease (Fig. 2a–c) and underwent STA-MCA bypasses with EMS in both hemispheres. Postoperative angiography revealed good patency of bypasses (Fig. 2d). Although his symptoms disappeared after surgery, he experienced an acute subdural hematoma due to a traffic accident at 8 years of age (Fig. 2e) and underwent an emergent craniotomy at another hospital. Four days after surgery an infarction developed in the affected side of the frontal cortex (Fig. 2f), although the bypasses appeared to have remained patent in magnetic resonance angiography after surgery. He was discharged to home with a mild cognitive disturbance.

Case 2 (late hemorrhage) This patient had presented with transient right-side motor weakness experienced frequently since 6 years of age and was admitted to our hospital at 10 years of age. She was diagnosed with moyamoya disease. Angiography on admission revealed occlusion of the bilateral internal carotid arteries and posterior cerebral arteries with extensive development of abnormal collateral vessels known as moyamoya vessels (Fig. 3a, b). She underwent STA-MCA bypasses with EMS in both hemispheres. The transient ischemic attacks disappeared after surgery and administration of aspirin was ceased. Fourteen years after surgery, she was admitted to our hospital with left thalamic hemorrhage at 24 years of age (Fig. 3c). Angiography revealed that moyamoya vessels in the anterior circulation had decreased with good patency of the bypasses, while those in the posterior circulation had remained (Fig. 3d–f). No apparent decrease in CBF was detected in the posterior cerebral artery territory. She was discharged and is working as a homemaker with dysesthesia of the left side and mild memory disturbance.

Case 4 (late hemorrhage) This patient had presented with transient right side motor weakness when crying since 4 years of age and admitted to our hospital at 8 years of age. He was diagnosed with moyamoya disease and underwent STA-MCA bypasses with EMS in both hemispheres. Although he remained symptom-free for more than 10 years, he was admitted to our hospital with an intraventricular hemorrhage at 29 years of age (Fig. 4a). Angiography confirmed good patency of the bypasses but revealed abnormal dilated collaterals and peripheral microaneurysms in the posterior choroidal artery (Fig. 4b–d). He was treated conservatively and had recovered well without any neurological deficit. Additional revascularization was not indicated because the bypasses had broadly spanned the hemispheres. Direct treatment of the peripheral microaneurysms, such as endovascular embolization, was abandoned because of technical difficulty and the patient's objection. He was closely followed at our clinic; however, he experienced a second intraventricular hemorrhage at 33 years of age (Fig. 4e), which resulted in a fatal outcome.

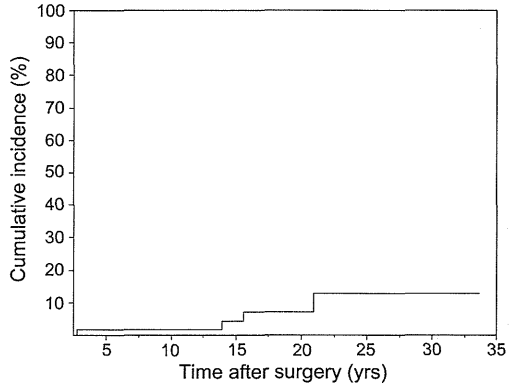

Fig. 1 Cumulative incidence of late cerebrovascular events

Discussion

Our results estimated the incidence of late cerebrovascular events as 0.41 % per year, which is far higher than the overall incidence of stroke in the general population in Japan [33]. This result coincides with those of recent long-term follow-up studies. We found two articles on pediatric moyamoya disease meeting the criteria of a mean follow-up period exceeding 10 years, a cohort of at least ten patients, and a follow-up rate exceeding 80 % [12, 27]. One addressed long-term follow-up after indirect bypass [27], while the other addressed patients

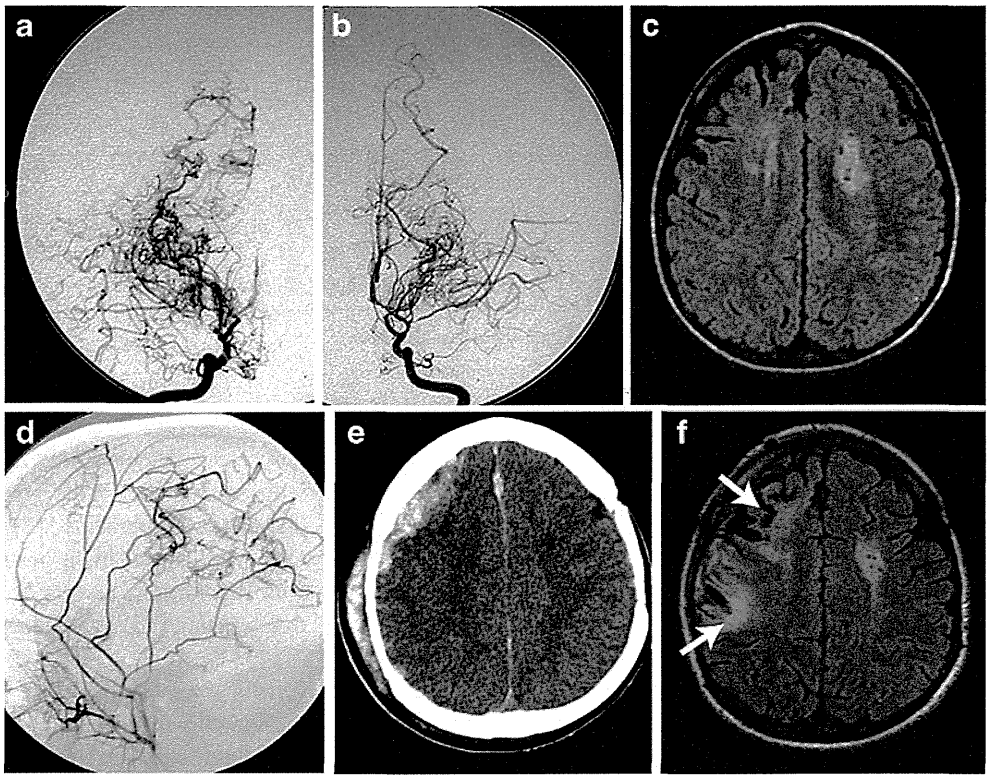

Fig. 2 Case 1. **a**, **b** Angiography before bypass surgery; right (**a**) and left (**b**) internal carotid angiography demonstrating occlusion at the terminal portion of the internal carotid artery with development of moyamoya vessels; **c** magnetic resonance imaging (MRI) before bypass surgery demonstrating subcortical infarction in the bilateral frontal lobe; **d** right external carotid angiography after bypass surgery revealing good patency of the bypass; **e** computed tomography performed at another hospital immediately after a head injury from a traffic accident, demonstrating acute subdural hematoma; **f** MRI after emergent craniotomy demonstrating newly-developed infarction in the frontal cortex (*arrows*)

treated either conservatively or with mainly indirect bypass [12]. The calculated incidences of late cerebrovascular events in these reports ranged between 0.24 and 0.85 % per year (Table 3).

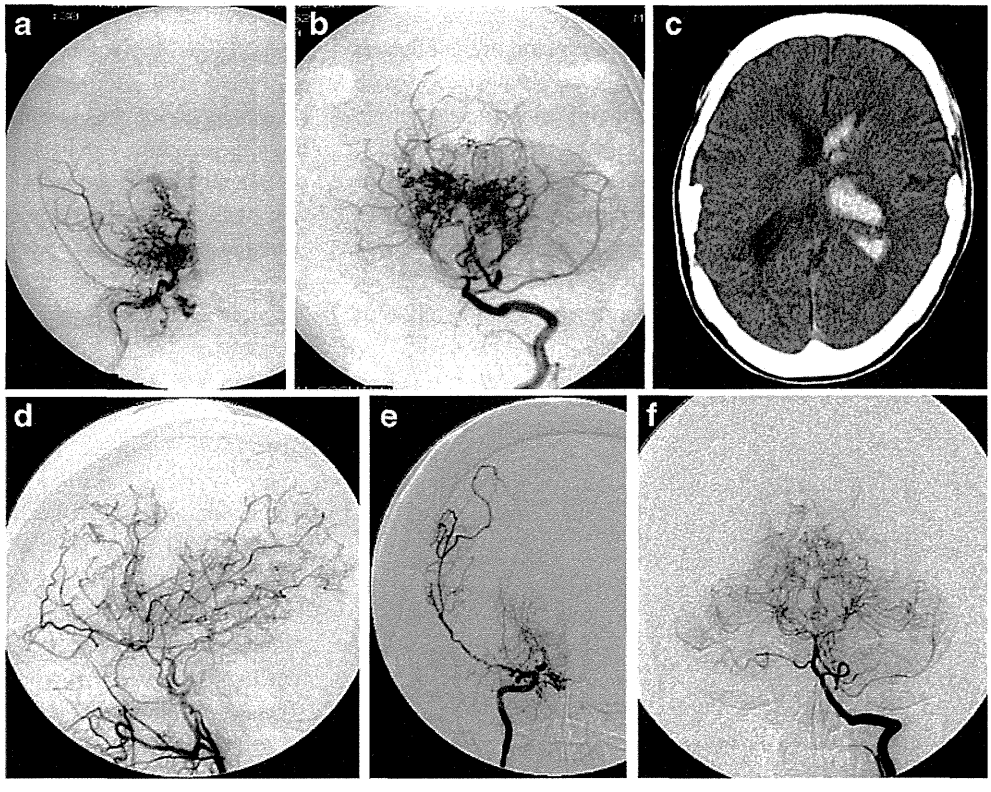

Fig. 3 Case 2. **a**, **b** Angiography before bypass surgery; **a** right internal carotid angiography demonstrating occlusion at the terminal portion of the internal carotid artery with development of moyamoya vessels; **b** left vertebral angiography demonstrating occlusion of the bilateral posterior cerebral artery with development of moyamoya vessels; **c** computed tomography showing left thalamic hemorrhage occurring 14 years after surgery; **d**–**f** angiography after thalamic hemorrhage; **d** right external carotid angiography revealing good patency of the bypass; **e** right internal carotid angiography revealing a marked decrease in moyamoya vessels in the anterior circulation; **f** left vertebral angiography revealing remaining moyamoya vessels in the posterior circulation