Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

Persistent Periventricular Anastomosis Associated With Rebleeding After Bypass Surgery for Hemorrhagic Moyamoya Disease

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BACKGROUND: Although bypass surgery can reduce rebleeding risk in hemorrhagic moyamoya disease, the risk remaining after surgery is not negligible. We hypothesized that the postoperative persistence of periventricular anastomosis (PA), a fragile periventricular collateral manifestation, is associated with rebleeding.

METHODS: This retrospective cohort study included patients with moyamoya disease who underwent direct bypass at 2 institutions after hemorrhagic presentation. Either presence or absence of PA after surgery was radiologically determined by grading of each subtype, lenticulostriate, thalamic, or choroidal anastomosis, 3–6 months after surgery. The time interval between the surgery and the rebleeding event or last visit was calculated.

RESULTS: Of 116 eligible patients comprising 232 hemispheres, 172 hemispheres underwent surgery. Rebleeding occurred in 16 hemispheres of 15 patients (2.0% per person-year) during the median follow-up period of 6.3 years. The hemisphere-based annual rebleeding rate was 2.0% in the PA-positive hemispheres as compared with 0.46% in the PA-negative hemispheres. The adjusted hazard ratio of rebleeding for positive PA relative to negative PA was 4.11 (95% CI, 1.07–15.82). Among subtypes of PA, lenticulostriate anastomosis was the most likely to persist after surgery (34 of 62 anastomoses) and to cause rebleeding (8 of 16 hemispheres).

CONCLUSION: The persistence of PA, especially that of lenticulostriate anastomosis, might be associated with rebleeding after surgery. This suggests the importance of assessing and optimally managing PA for improving long-term outcomes.

Key Words: cerebral revascularization ■ cohort study ■ moyamoya disease ■ periventricular anastomosis

Moyamoya disease (MMD) is characterized by progressive stenosis of the terminal portion of the internal carotid artery with abnormal collateral vessels typical of the disease.[1–4] Intracranial hemorrhage accounts for approximately half of the manifestations in Japanese adult patients.[5,6] Several studies, including a randomized controlled trial and systematic reviews, have suggested the preventive effect

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Nonstandard Abbreviations and Acronyms

ChA	choroidal anastomosis
LSA	lenticulostriate anastomosis
MMD	moyamoya disease
PA	periventricular anastomosis
THA	thalamic anastomosis.

CLINICAL PERSPECTIVE

What Is New?

- This study is the first to reveal the association between persistent periventricular anastomosis, especially lenticulostriate anastomosis, and rebleeding after direct bypass surgery for hemorrhagic moyamoya disease.

What Are the Clinical Implications?

- Our results suggest the importance of postoperative assessment of periventricular anastomosis with precise imaging modalities.
- Further studies aiming at the effective reduction of periventricular anastomosis through establishing an optimal surgical strategy could help improve long-term outcomes in hemorrhagic moyamoya disease.

of bypass surgery against rebleeding in hemorrhagic MMD.[7–11] Relatively high rebleeding rates have been reported, however, even in surgically treated patients.

Although hemorrhage can be related to peripheral pseudoaneurysms in abnormal collateral,[1,5] it can also occur by the rupture of periventricular collaterals without aneurysms. Periventricular anastomosis (PA), the term describing such fragile collaterals, is defined as pathological anastomoses between the perforating or choroidal arteries and medullary arteries in the periventricular area that serves as a collateral to the cortex via the retrograde flow in the medullary artery.[12–14 15] PA is classified into three subtypes: lenticulostriate anastomosis (LSA), thalamic anastomosis (THA), and choroidal anastomosis (ChA). ChA is a strong predictor for bleeding[16–19] and is considered to carry the highest risk of bleeding among subtypes of PA.

PA can be reduced after bypass surgery through the normalized direction of the flow in the medullary artery.[20–23] Although such reduction might explain the effectiveness of bypass surgery against bleeding, the mechanism of rebleeding after bypass surgery remains unclear. We hypothesized that the persistence of PA after surgery is associated with rebleeding in hemorrhagic MMD. The objective of the present study was to test this hypothesis and to clarify the mechanism of rebleeding by investigating the rebleeding site, rebleeding source, and the factors associated with rebleeding. Addressing these issues might contribute to the stratification of rebleeding risk after surgery and the improvement of long-term outcomes in hemorrhagic MMD.

METHODS

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Patients and Setting

The present multicentered cohort study was approved by the ethics committee of Kyoto University Hospital and the National Cerebral and Cardiovascular Center (R3267) and was designed according to the Strengthening the Reporting of Observational Studies in Epidemiology statement. All participants gave opt-out consent in accordance with the ethical standards of the institutional and national research committees. We retrospectively recorded the data of the patients who fulfilled the following inclusion criteria and who had been admitted to either Kyoto University Hospital between 2009 and 2021 or the National Cerebral and Cardiovascular Center between 2003 and 2021 because treatment strategies were almost the same between the 2 hospitals during these periods. The study included patients who had been diagnosed with MMD according to the diagnostic criteria,[3] who had exhibited symptomatic hemorrhagic stroke, and who had undergone direct bypass surgery (superficial temporal artery [STA]-middle cerebral artery [MCA] anastomosis) after the hemorrhagic event at the aforementioned 2 hospitals. The data of patients who had initially been admitted to either hospital or who had been followed at another hospital were recorded at the latter. The present study excluded patients who had manifested subarachnoid hemorrhage at onset due to the rupture of the saccular aneurysm on the circle of Willis, had suffered from symptomatic intracranial hemorrhage immediately after surgery due to hyperperfusion syndrome, or had exhibited "questionable (Q)" hemispheres.[16] The patients for whom both magnetic resonance angiography (MRA) and digital subtraction angiography (DSA) had been lost, or those in whom the rebleeding side could not be determined due to unavailable radiographies, were also excluded from

the analysis. The present study excluded hemispheres that did not require bypass surgery because of normal hemisphere, and so forth, hemispheres that exhibited "Q" appearance, and patients who had a history of craniotomy at another hospital.

Surgical Management

Bypass surgery was indicated for the patients who fulfilled the eligibility criteria of the Japan Adult Moyamoya Trial.[7] As our institutions had participated in the trial, eligible patients who were admitted up to 2009 were randomized into either bypass surgery or best medical treatment. We recommended bilateral surgery for those with bilateral MMD according to the trial; however, surgery was not indicated for the nonhemorrhagic hemisphere with normal appearance and so on. Our original procedures of STA-MCA anastomosis have been reported previously.[24] Encephalomyosynangiosis was added only for pediatric patients. STA-MCA "double" anastomosis, during which both frontal and parietal branches of the STA are harvested, was considered if the procedures were feasible in terms of the development of both donor and recipient arteries. STA-MCA double anastomosis was also considered if the multiple PAs outflowed to various cortical areas. Antiplatelet agents were administered during the perioperative period according to the surgeons' preference.

Imaging Schedule and Follow-Up

Patients routinely underwent magnetic resonance imaging (MRI) including MRA, single-photon emission tomography, and DSA before and 3–6 months after surgery. All patients were encouraged to visit and undergo MRI annually thereafter. The outcome of each patient at the last visit was recorded between January 2023 and July 2024. If patients suffered from hemorrhagic stroke during follow-up, the aforementioned imaging modalities were also acquired if possible.

Outcome

The primary outcome was rebleeding-free survival, defined as the period from the date of the first surgery to the date of rebleeding. The rebleeding event was defined as any symptomatic rebleeding attack that occurred within 14 days after surgery. The side (right/left) and location of bleeding (anterior/posterior)[25] were recorded based on computed tomography (CT) or MRI acquired immediately after surgery. The subtype of PA responsible for rebleeding was determined by MRIs in the chronic phase if available.[26] If MRIs in the chronic phase were not available due to the patient's condition, the responsible PA was determined by CT images by a consensus of 2 expert raters (E.H. and T.F.). Patients who had had no rebleeding attacks until the last visit or who were lost to follow-up were treated as being censored at the last visit.

Risk Factors

We focused on the postoperative persistence of Grade-2 PA as a risk factor for rebleeding. It was determined by DSA and the sliding-thin-slab maximum-intensity-projection coronal MRA acquired at 3–6 months after surgery. The diagnosis and grading of each subtype of PA with DSA and MRI were described in detail elsewhere.[12,15,19] Two expert raters (E.H. and T.F.), who were blinded to other clinical statuses, rated each subtype of PA (LSA, THA, or ChA) as Grade 0, 1, or 2 by consensus. The variable of persistent Grade-2 PA was rated as "positive" when at least 1 subtype of PA was Grade 2. Persistent Grade-2 PA was rated as "negative" when all subtypes of PA were non-Grade 2.

We also recorded the following factors as potential confounders: age; sex; comorbidities including hypertension, diabetes, dyslipidemia, and smoking; use of antiplatelet agent; location of initial hemorrhage (anterior versus posterior); number of bleeding events before surgery; Suzuki stage[27]; hemodynamic stage assessed with single-photon emission tomography (Stage 0–2);[28] bypass procedure (single versus double anastomosis); Matsushima angiographic grade of revascularization area[29]; and presence or absence of posterior cerebral artery involvement.[30] According to a previous study,[17] the hazard ratio for positive Grade-2 PA relative to negative Grade-2 PA was adjusted with age, diagnosis of hypertension, and posterior cerebral artery involvement. "The number of operations," indicating whether a unilateral hemisphere or bilateral hemispheres underwent surgery, was also added to the adjustment factors.

Statistical Analysis

We had estimated the sample size at 65 patients with $\alpha = 0.05$ and $1 - \beta = 0.8$ under the following assumptions: the ratio of negative to positive PA was 4; and the prevalence of rebleeding was 40% in the PA-positive group as compared with 10% in the negative group for 7.5 years. We used the estimated number of cases calculated above as a reference for collecting patient data. Summary statistics were constructed using frequencies and proportions for categorical data. For continuous variables, the mean and SD were obtained when a distribution of normality was observed, and the median and interquartile range when a distribution of normality was not observed. The *t*-test, Wilcoxon rank-sum test, chi-square test, or Fisher's exact test was used as appropriate for comparison between the 2 groups.

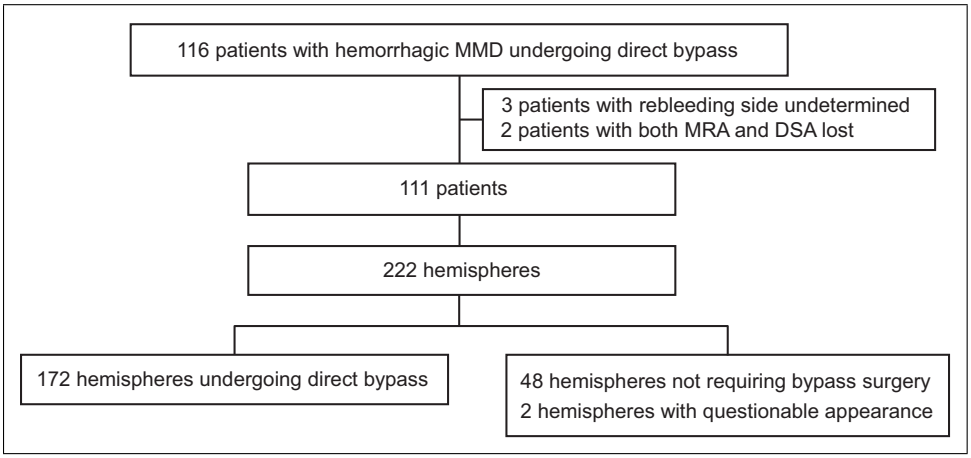

Figure 1. Study profile. DSA indicates digital subtraction angiography; MMD, moyamoya disease; and MRA, magnetic resonance angiography.

Because each patient had 2 hemispheres and bleeding events can occur in each hemisphere, we focused on a hemisphere-by-hemisphere analysis. To evaluate the effect of postoperative Grade-2 PA persistence on recurrence-free survival, we estimated rebleeding-free survival using the Kaplan–Meier method. Furthermore, the Wei, Lin, Weissfeld method based on the marginal Cox model was used to account for the correlation between hemispheres, and the results were expressed as hazard ratios and 95% CIs (CIs. In addition, to explore the effects of each subtype of PA, rebleeding-free survival time was estimated for each subtype of PA using the Kaplan–Meier method, and the log-rank test was used to compare each group according to Grade-2 or non-Grade 2 anastomosis. McNemar's test was used to assess the postoperative change in the proportion of Grade-2 anastomoses.

RESULTS

The study profile is summarized in Figure 1. A total of 116 patients who underwent direct bypass for hemorrhagic MMD met the criteria of the present study. Seventy-seven patients were treated at the National Cerebral and Cardiovascular Center, and 39 at Kyoto University Hospital. Of these, 3 patients including 6 hemispheres in which the rebleeding side was undetermined due to unavailable radiographies, and 2 patients including 4 hemispheres in which both MRA and DSA were deficient, were excluded from the analysis. Of the 111 patients with 222 hemispheres, 48 did not require bypass surgery due to normal hemispheres, and so forth, and 2 hemispheres had a "Q" appearance. Consequently, 172 hemispheres remained as those that underwent direct bypass.

Outcome

Rebleeding occurred in 15 (12.8%) of 116 patients during the median follow-up period of 6.3 years (interquartile range, 3.1–9.3 years). One patient experienced a rebleeding event in each hemisphere, and a total of 16 rebleeding events occurring in 16 hemispheres were counted. The annual rebleeding rate was 2.0% per person-year. Rebleeding occurred at a mean of 3.9 (SD, ±4.1) years after surgery. The median modified Rankin Scale score at the last follow-up was higher in the rebleeding group than in the non-rebleeding group (median [interquartile range], 4 [2–5] versus 0 [0–1], $P<0.001$).

The rebleeding side was not determined in 3 of 16 rebleeding events as mentioned. The remaining 13 rebleeding events occurring in 13 hemispheres were included in a hemisphere-by-hemisphere analysis. During the follow-up 4 patients died: 2 patients died after rebleeding, and 2 patients by causes unrelated to MMD. The latter patients were treated as being censored.

Demographics of Patients and Hemispheres

Table 1 summarizes the demographics of the 111 patients included in the analysis. No differences in patient-based factors, including age, comorbidities, location of initial hemorrhage, use of antiplatelet agents, and number of rebleeding events before surgery, were observed between the bleeding and nonbleeding groups.

Table 2 summarizes the demographics of the 172 hemispheres that underwent surgery. The proportion of positive persistent Grade-2 PA was higher in the rebleeding group than in the nonrebleeding group (76.9% versus 38.4%, $P = 0.007$). Regarding the

Table 1. Demographics of 111 Patients Included in the Analysis

		Rebleeding		
	Total	**Yes**	**No**	***P* value**
No. of patients	111	12	99	NA
Female, n (%)	86 (77.5)	9 (75.0)	77 (77.8)	0.73
Mean age at onset, y±SD	41.6±13.6	43.8±11.8	41.3±13.8	0.55
Comorbidity, n (%)				
Hypertension	13 (11.7)	1 (8.3)	12 (12.1)	1.00
Diabetes	3 (2.7)	0 (0)	3 (3.0)	1.00
Dyslipidemia	9 (8.1)	1 (8.3)	8 (8.1)	1.00
Smoker	6 (5.4)	0 (0)	6 (6.1)	1.00
Use of antiplatelet agent*, n (%)	10 (9.4)	1 (8.3)	9 (9.6)	1.00
Location of initial hemorrhage†, n (%)				0.81
Anterior	51 (46.8)	6 (50.0)	45 (46.4)	
Posterior	58 (53.2)	6 (50.0)	52 (51.6)	
Number of bleedings before surgery‡				0.12
1	98 (89.1)	9 (75.0)	89 (90.8)	
2	12 (10.9)	3 (25.0)	9 (9.2)	

*Data were missing in 5 patients.
†Data were missing in 2 patients.
‡Data were missing in 1 patient.

Table 2. Demographics of 172 Hemispheres

		Rebleeding		
	Total	**Yes**	**No**	***P* value**
No. of hemispheres	172	13	159	NA
Right	86	7	79	
Left	86	6	80	
Persistent Grade-2 PA, n (%)				0.007
Positive*	71 (41.3)	10 (76.9)	61 (38.4)	
Negative	101 (58.7)	3 (23.1)	98 (61.6)	
Type of PA, n (%)				
Lenticulostriate, Grade 2†	38 (22.1)	8 (61.5)	30 (18.9)	0.002
Thalamic, Grade 2†	5 (2.91)	1 (7.7)	4 (2.5)	0.33
Choroidal, Grade 2†	45 (26.2)	7 (53.9)	38 (23.9)	0.042
Median Suzuki stage (IQR)	3 (3–4)	3 (3–4)	3 (3–4)	0.96
SPECT stage‡, n (%)				0.21
0 (negative hemodynamic failure)	11 (6.7)	2 (15.4)	9 (5.9)	
1+2 (positive hemodynamic failure)	154 (93.3)	11 (84.6)	143 (94.1)	
Bypass procedure, n (%)				0.52
Single anastomosis	123 (71.5)	8 (61.5)	115 (72.3)	
Double anastomosis	49 (28.5)	5 (38.5)	44 (27.7)	
Revascularization area¶, n (%)				0.92
<1/3 of MCA territory	27 (18.5)	2 (18.2)	25 (18.5)	
1/3–3/2 of MCA territory	56 (38.4)	5 (45.5)	51 (37.8)	
>2/3 of MCA territory	63 (43.2)	4 (36.4)	59 (43.7)	
PCA involvement, n (%)				1.00
Positive	24 (13.9)	2 (15.4)	22 (13.8)	
Negative	148 (86.1)	11 (84.6)	137 (86.2)	

IQR indicates interquartile range; MCA, middle cerebral artery; PA, periventricular anastomosis; PCA, posterior cerebral artery; and SPECT, single-photon emission tomography.
*At least one type of PA was rated as Grade 2.
†vs non-Grade 2.
‡Data were missing in 7 hemispheres.
¶Data were missing in 26 hemispheres.

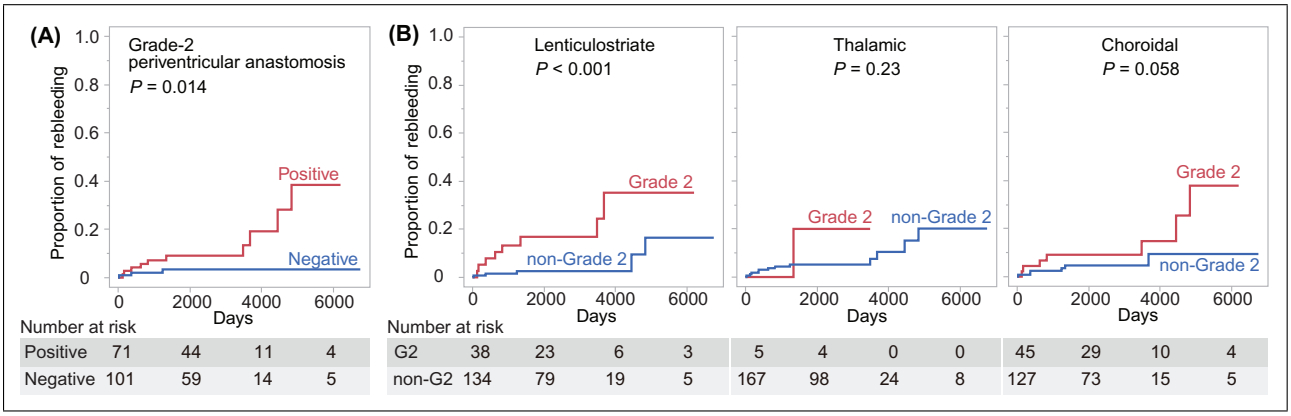

Figure 2. Kaplan–Meier curve for rebleeding (172 hemispheres). A, Comparison between positive and negative Grade-2 periventricular anastomosis. **B**, Comparison between Grade-2 and non-Grade-2 for each type of anastomosis. G2 indicates Grade 2.

subtype of PA, Grade-2 LSA and ChA were more common in the rebleeding group than in the nonrebleeding group (Grade-2 LSA, 61.5% versus 18.9%, $P = 0.002$; ChA, 53.9% versus 23.9%, $P = 0.042$). No differences in Grade-2 THA, preoperative Suzuki stage, single-photon emission tomography stage, bypass procedure, revascularization area, or presence of posterior cerebral artery involvement were observed between the 2 groups.

Rebleeding Risk and Predictors

Survival curves for the positive or negative Grade-2 PA in the 172 hemispheres that underwent surgery are shown in Figure 2A. The annual rebleeding rate was 2.0% in the PA-positive hemispheres as compared with 0.46% in the negative hemispheres; the 5-year rebleeding risk was 9.1% in the PA-positive hemispheres as compared with 3.4% in the negative hemispheres (log-rank test, $P = 0.014$). Multivariate analysis using the Wei, Lin, Weissfeld model revealed that persistent Grade-2 PA was an independent predictor for rebleeding (hazard ratio, 4.11 [95% CI, 1.07–15.82], Table 3).

Survival curves for each subtype of PA in the 172 hemispheres are shown in Figure 2B. The annual rebleeding rate in the hemispheres with Grade 2 LSA was 3.1% as compared with 0.56% in the hemispheres without (log-rank test, $P = 0.014$). Regarding THA and ChA, no differences in the annual rebleeding rate were observed between the Grade-2 and non-Grade-2 hemispheres (THA, 3.2%/y versus 1.1%/y, log-rank test: $P = 0.23$; ChA, 2.1%/y versus 0.73%/y, log-rank test: $P = 0.058$). No differences in the proportion of Grade-2 LSA were observed between the choroidal-Grade-2 and choroidal-non-Grade-2 groups (28.9% versus 19.7%, $P = 0.20$).

Details of Rebleeding Events

Table 4 summarizes radiographic data on 16 rebleeding events occurring in 15 patients. Among the 13 rebleeding events in which both the rebleeding side and site could be determined, 10 (76.9%) occurred in the hemisphere ipsilateral to the initial bleeding, and 3 (23.1%) occurred in that contralateral to the initial bleeding. LSA was determined to be responsible for rebleeding in 8 of 16 events (50.0%), and ChA was in 5 (31.3%). No rebleeding attributable to THA was observed. The putamen was the most common site of bleeding after surgery in the rebleeding cases (5 of 16 events, 31.3%), followed by the atrium of the lateral ventricle (4 of 16 events, 25%). CT images of all rebleeding cases are shown in the Figure S1−S3.

Change in Periventricular Anastomosis After Surgery

The changes in each subtype of PA after surgery were analyzed for 155 hemispheres in which both preoperative and postoperative images were available (Table 5). The proportion of Grade-2 LSA, Grade-2 THA, and Grade-2 ChA significantly decreased after surgery (40.0% versus 22.6%, $P<0.001$; 12.3% versus 3.2%, $P<0.001$; 65.8% versus 25.8%, $P<0.001$; respectively). The reduction, defined as the postoperative change from Grade 2 to non-Grade 2, occurred in 28 (45.2%) of 62 Grade-2 LSAs, 14 (73.7%) of 19 THAs, and 63 (61.8%) of 102 ChAs; that is, LSA is the most likely to persist after surgery (34/62, or 54.8%).

Illustrative Case

A 44-year-old patient (Case 1 in Table 4) manifested intracerebral hemorrhage in the left temporal lobe at onset (Figure 3A). An emergency hematoma removal was performed, and motor apraxia and incomplete

Table 3. Multiple-Adjusted HR for Rebleeding Using the WLW Model (Hemisphere-by-Hemisphere analysis)

	Crude		Multivariate adjustment	
	HR	95% CI	HR	95% CI
Persistent Grade-2 PA				
Positive	4.21	1.14–15.52	4.11	1.07–15.82
Negative	1.00	Reference	1.00	Reference
Age (every 1-year increase)	1.03	0.99–1.06	1.02	0.98–1.07
Diagnosis of hypertension				
Positive	0.52	0.06–4.44	0.48	0.05–4.72
Negative	1.00	Reference	1.00	Reference
PCA involvement				
Positive	1.20	0.27–5.38	0.92	0.18–4.63
Negative	1.00	Reference	1.00	Reference
Number of operation(s)				
2 (bilateral)	1.15	0.34–3.85	1.16	0.32–4.13
1 (unilateral)	1.00	Reference	1.00	Reference

HR indicates hazard ratio; PA, periventricular anastomosis; PCA, posterior cerebral artery; and WLW, Wei, Lin, Weissfeld.

Table 4. Radiographic Data on 16 Rebleeding Events in 15 Patients

Case No.	Age, y	Sex	Rebleeding side against initial bleeding	Time to rebleeding, y	Rebleeding site	mRS score
Rebleeding attributable to lenticulostriate anastomosis (8 events)						
1	44	F	Ipsilateral	10.1	Putamen	4
2	45	F	Ipsilateral	1.0	Putamen	4
3	38	F	Contralateral	0.5	Caudate	2
4	52	F	Ipsilateral	0.4	Putamen	4
5	42	F	Ipsilateral	9.5	Putamen	6
6	60	F	Ipsilateral	1.7	Frontal lobe	5
7 (left hemisphere)	48	F	Ipsilateral	1.0	Anterior horn	5
7 (right hemisphere)	48	F	Contralateral	3.7	Putamen	5
Rebleeding attributable to choroidal anastomosis (5 events)						
8	66	F	Ipsilateral	0.1	Atrium	4
9	39	F	Ipsilateral	2.3	Atrium	5
10	29	M	Ipsilateral	13.2	Atrium	2
11	39	M	Contralateral	3.4	Atrium	2
12	24	M	Ipsilateral	12.2	Temporal lobe	1
Rebleeding side and site not determined (3 events)						
13	56	F	Not determined	1.3	Not determined	5
14	46	F	Not determined	4.0	Not determined	0
15	47	M	Not determined	2.1	Not determined	6

mRS indicates modified Rankin Scale.

right-sided hemiparesis remained with modified Rankin Scale score of 2. The patient underwent left STA-MCA anastomosis aiming at preventing hemorrhage. The patient developed rebleeding in the left putamen 10.1 years after bypass surgery (Figure 3B). MRA prior to the rebleeding had revealed persistent Grade-2 LSA running toward both the medial and lateral hemispheric surfaces despite good patency of the bypass (Figure 3C). The LSA corresponded to the rebleeding site and was determined as the responsible vessel (Figure 3D).

DISCUSSION

Our results revealed the association between persistent PA and rebleeding after direct bypass surgery for hemorrhagic MMD. The persistence of LSA was the most

Table 5. Postoperative Change in Periventricular Anastomosis (155 Hemispheres)

	Before surgery (n = 155)	After surgery (n = 155)	*P* value*	Reduction of Grade 2 anastomosis	
				Yes	No
LSA, n (%)			<0.001	28 (45.2)	34 (54.8)
Grade 2	62 (40.0)	35 (22.6)			
non-Grade 2	93 (60.0)	120 (77.4)			
THA, n (%)			<0.001	14 (73.7)	5 (26.3)
Grade 2	19 (12.3)	5 (3.2)			
non-Grade 2	136 (87.7)	150 (96.8)			
ChA, n (%)			<0.001	63 (61.8)	39 (38.2)
Grade 2	102 (65.8)	40 (25.8)			
non-Grade 2	53 (34.2)	115 (74.2)			

ChA indicates choroidal anastomosis; LSA, lenticulostriate anastomosis; and THA, thalamic anastomosis.
*McNemar's test.

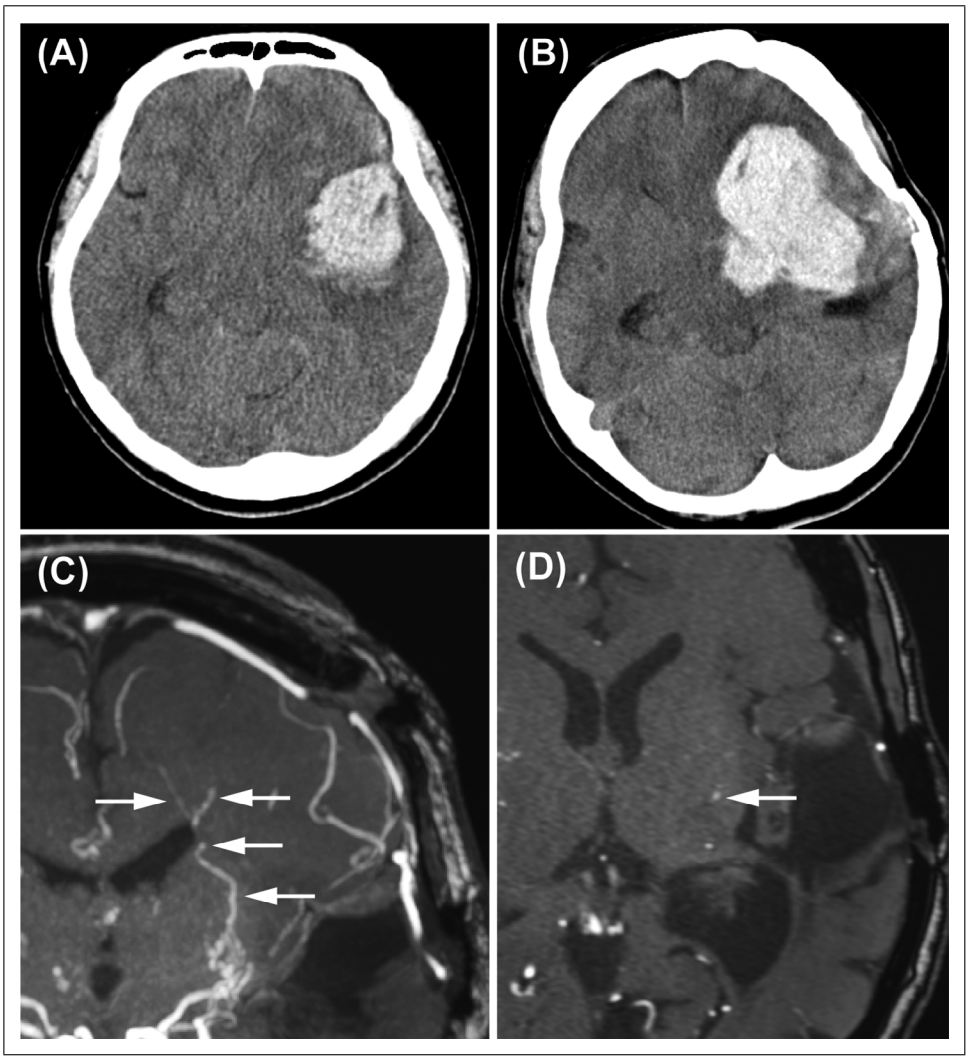

Figure 3. Illustrative case exhibiting rebleeding. A, CT showing hemorrhage at onset. **B**, CT showing rebleeding. **C**, Sliding-thin-slab maximum-intensity-projection coronal MRA acquired prior to rebleeding. Note that lenticulostriate anastomosis (arrows) runs toward both medial and lateral surfaces. **D**, Original axial image of MRA acquired prior to rebleeding. Note that lenticulostriate anastomosis (arrow) corresponds to the site of rebleeding. CT indicates computed tomography; and MRA, magnetic resonance angiography.

strongly associated with rebleeding among subtypes of PA. LSA was the most likely to persist after surgery and was the most commonly responsible for rebleeding.

The overall rebleeding rate after bypass surgery in our series (2.0% per person-year) is comparable with that in the literature (Jiang et al, 1.87% per person-year; Miyamoto et al, 2.7% per person-year; Zhang et al, 2.4% per person-year).[7,11,31] According to the JAM (Japan Adult Moyamoya) Trial, the preventive effect of direct bypass against rebleeding has been suggested to be under the rebleeding rate of 2.7% per person-year in the surgical group.[7] As the annual rebleeding rate in our study is slightly lower than that in the trial, our results seem acceptable in terms of the preventive effect against rebleeding.

Our results are in line with those of previous studies, in which an association between PA and hemorrhage was suggested.[12,32] As the overall PA was associated with rebleeding, the interpretation that any subtype of PA can be a risk factor for rebleeding might be reasonable. Furthermore, our study might be the first to suggest the effect of LSA on bleeding in a longitudinal analysis. This finding might be related to the fact that the basal ganglia are a common bleeding site in MMD (22%–56% of all hemorrhages in MMD).[7,33,34] A recent study has also suggested the significance of LSA through demonstrating poor outcomes associated with anterior type hemorrhage.[35]

Although our results suggest the effect of overall PAs, our negative result regarding ChA seems inconsistent in part with those in recent studies, most of which have suggested a strong association between ChA and bleeding. An analysis of the nonsurgical cohort in the JAM Trial revealed a higher rebleeding risk in the ChA-positive group as compared with the negative group (13.1% versus 1.3% per year).[17] A multicenter cohort study for asymptomatic MMD also revealed that Grade-2 ChA carried a higher risk of de novo bleeding (3.2% per hemisphere-year) than non-Grade-2 ChA did.[16] Two possible reasons for this difference are considered. First, our sample size might be insufficient for the subgroup analysis focusing on each subtype of PA. Second, some ChAs in our series, even if rated as Grade 2 after surgery, might have been partially reduced by bypass. A careful interpretation of our result for ChA might be required because ChA was the second most common rebleeding source (Table 4). In some cases, the bleeding source was different between initial and subsequent bleeding events, and this should also be carefully interpreted.

A unique finding of our study is that the bleeding risk of LSA was suggested in the surgical cohort. This might indicate that the impact of LSA could be enhanced especially after surgery. Anatomic features of LSA might explain the mechanism of the rebleeding after surgery. LSA is more likely to give off branches that run toward the medial hemispheric surface than ChA and THA are.[36] This feature might increase the risk of rebleeding from persistent LSA even after successful bypass surgery predominantly perfusing the lateral surface of the brain. Wang et al also reported that collateral channels giving off the medial branch carried a high risk of rebleeding.[32] Our results add novel information to several pioneering studies, which have identified risk factors for rebleeding after surgery, such as age, hemorrhage location, and number of episodes of bleeding.[25,37] Larger studies for elucidating the clinical features of LSA are required.

From the perspective of clinical practice, postoperative assessment of PA with precise imaging modalities is essential for risk stratification because persistent PA might be a possible underlying mechanism of rebleeding after surgery. Considering the relatively high rebleeding risk observed in the group with persistent Grade-2 PA (9.1% per 5 years), careful long-term follow-up is recommended especially when Grade-2 PA remains even after bypass surgery. A recent study suggested the feasibility of bypass surgery that targets PA to enhance the preventive effect against bleeding,[38] and selection of the craniotomy site and recipient artery according to the PA might be important during direct bypass for hemorrhagic MMD. LSA commonly outflows to the lateral surface of the frontal lobe and less commonly to the medial surface.[36] Bypass with a large craniotomy targeting the lateral surface of the frontal lobe might be effective if LSA is predominantly developed and responsible for hemorrhage.[21] In case intractable medial branches of LSA persist, additional direct bypass of the anterior cerebral artery territory after conventional STA–MCA anastomosis might be considered.[39,40] For hemispheres with both LSA and ChA, STA–MCA double anastomosis targeting both the frontal and parietal lobes might be required because targeting only the frontal lobe might result in persistence of ChA, which commonly outflows to the cortex posterior to the central sulcus.[20,38] Further studies aiming at the effective reduction of LSA through establishing an optimal surgical strategy could help improve long-term outcomes in hemorrhagic MMD.

Treatment options remain controversial, however, when ruptured aneurysms appear at PA, especially at ChA. Sato et al reported that aneurysmal formation at PA was associated with future hemorrhagic strokes and a worse prognosis.[41] Wiedmann et al reported that ruptured choroidal collateral artery aneurysms carried a high risk of rebleeding in conservative treatment and were efficiently obliterated with endovascular treatment.[42] On the other hand, Kuroda et al reported that ruptured peripheral artery aneurysms arising from dilated collateral vessels disappeared after

bypass surgery.[43] As our study was a retrospective one including many early cases, we could not sufficiently investigate the existence or absence of aneurysmal formation at PA. Rescue endovascular treatment might be considered for patients with persistent aneurysms at ChA even after successful bypass surgery; this should be addressed in further studies.

Our study has several limitations. First, the study included patients who had been followed for over 10 years, and missing data attributable to the loss of old records were inevitable. However, both MRA and DSA had been lost in only 2 patients, and so the effect on our main results is likely to be minimal. Second, the data were retrospectively collected at 2 hospitals, which could limit the generalizability of our results. Third, the sample size might be insufficient for the subgroup analysis as discussed previously; whether LSA carries the risk of bleeding remains to be solved through larger studies. Fourth, the present study was a retrospective one; prospective studies are required to confirm the results.

CONCLUSIONS

The present results support our hypothesis that the persistence of PA is associated with rebleeding after direct bypass for hemorrhagic MMD. Although LSA might be the most strongly associated with rebleeding among the subtypes of PA, this should be validated by larger studies. Our results suggest the importance of postoperative assessment of PA with precise imaging modalities. Further studies addressing the optimal management of PA might help improve long-term outcomes in hemorrhagic MMD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Figure S1. CT images of the rebleeding attributable to lenticulostriate anastomosis. **A**: Case 1. **B**: Case 2. **C**: Case 3. **D**: Case 4. **E**: Case 5. **F**: Case 6. The arrow indicates the bleeding point.

Figure S2. CT images of the rebleeding attributable to lenticulostriate anastomosis (cont'd). **A** and **B**: Case 7 (left hemisphere). **C**: Case 8 (right hemisphere). The arrow indicates the bleeding point.

Figure S3. CT images of the rebleeding attributable to choroidal anastomosis. **A**: Case 8. **B**: Case 9. **C**: Case 10. **D**: Case 11. **E**: Case 12. The arrows indicate the bleeding point.

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