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CLINICAL ARTICLE - VASCULAR

Contralateral progression and its risk factor in surgically treated unilateral adult moyamoya disease with a review of pertinent literature

Sang Chul Lee · Jin Sue Jeon · Jeong Eun Kim · Young Seob Chung · Jun Hyong Ahn · Won-Sang Cho · Young-Je Son · Jae Seung Bang · Hyun-Seung Kang · Chang Wan Oh

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Abstract
Background The fate of the contralateral unaffected side of the surgically treated unilateral moyamoya disease (MMD) in adults has not been well described due to the limited number of cases and the heterogeneous ages and treatment methods. The aim of this study was to evaluate the contralateral angiographic progression rate and its risk factors in homogeneous adult MMD patients who underwent surgical revascularization, with a review of pertinent literature.
Methods Forty-one surgically treated unilateral MMD patients were retrospectively evaluated. We reviewed medical and radiological records including data on gender, age, hypertension (HTN), smoking, familial MMD, presenting symptom, surgical method, Suzuki stage, and contralateral progression. Then, we conducted univariate and multivariate analyses to determine risk factors.
Results Six of the 41 cases (14.6 %) exhibited contralateral progression during the mean follow-up of 34 months. Four of those six patients (66.7 %) were asymptomatic. Additional revascularization surgery was performed in the two symptomatic patients. The presence of a contralateral angiographic abnormality on initial angiography was a statistically significant risk factor for progression (OR, 49.00; $p=0.04$). Younger age at diagnosis (32.7±7.8 years in progression group vs. 42.5± 10.3 years in non-progression group, $p=0.046$) was statistically significant in the univariate analysis, but age was not a significant factor in the multivariate analysis ($p=0.82$). Other variables, such as gender ($p=0.13$), HTN ($p=0.24$), smoking ($p=0.47$), and familial MMD ($p=0.20$), did not show statistical significance.
Conclusions The presence of a contralateral angiographic abnormality on initial angiography was a significant risk factor for progression in surgically treated unilateral adult MMD. Consequently, patients with contralateral abnormalities should be monitored closely.

Keywords Unilateral · Moyamoya disease · Adult · Progression · Risk factor

Introduction

Unilateral moyamoya disease (MMD) refers to unilateral progressive steno-occlusive disorder of the distal internal carotid artery (ICA) or proximal anterior cerebral artery (ACA) and the middle cerebral artery (MCA), with moyamoya vasculature observable in angiographic findings. The incidence of unilateral MMD has ranged up to 18 % in patients who underwent surgical revascularization [9]. However, the incidence and natural history of unilateral MMD in a general MMD population have not been fully described due to the limited number of published case reports. In particular, the fate of the contralateral unaffected side of the unilateral MMD after revascularization surgery in adults has not been well described in detail. Although the contralateral angiographic progression rate and progression-associated risk factors have been reported [3, 9, 13, 22], the small number of cases and the heterogeneous ages (mixed group of pediatric and adult cases) and treatment methods (mixed group of medical and surgical treatments) of those cases limit the

Sang Chul Lee and Young Seob Chung contributed equally to this work.

S. C. Lee · J. S. Jeon · J. E. Kim (✉) · Y. S. Chung · J. H. Ahn · W.-S. Cho · Y.-J. Son · J. S. Bang · H.-S. Kang · C. W. Oh
Department of Neurosurgery, Seoul National University College of Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, South Korea
e-mail: eunkim@snu.ac.kr

interpretation of the results. Considering the differences in the brain plasticity and clinical manifestation between pediatric and adult cases [13], and the variation in surgical and medical treatment modalities, the results of previous studies may not be applicable in surgically treated unilateral MMD in an adult population. Consequently, studies that focus on contralateral angiographic progression in surgically treated unilateral MMD in a large number of adults are needed to elucidate the natural course of the disease and to establish appropriate clinical treatment plans.

The retrospective analysis reported here was undertaken to reveal the angiographic progression rate and the risk factors associated with the unaffected contralateral side, in unilateral adult MMD patients who underwent surgical revascularization for hemodynamic insufficiency in the affected side. In this report, we have included a review of pertinent literature.

Materials and methods

Enrolled patients

This study was approved by the Institutional Review Board (IRB) at the participating institution (H-1305-628-491). A retrospective analysis was performed on data from patients who were diagnosed as MMD between 2001 and 2011 at a single institution. Six hundred sixty-seven patients over 18 years of age were diagnosed as adult MMD patients. The diagnostic criteria for adult MMD were the same as previously reported [10]. After excluding 610 (91.5 %) bilateral MMD patients, 57 (8.5 %) unilateral MMD patients were recruited. Unilateral MMD was considered to exhibit normal contralateral arterial findings or minimal abnormalities in the ACA, MCA, or terminal ICA [9]. Patients with a history of cranial irradiation and meningitis, patients with brain tumor, aneurysm, Down syndrome, neurofibromatosis type 1 (NF-1), autoimmune disease, and cases with unavailable data were excluded from the analysis [1, 16]. Among the 57 patients exhibiting unilateral MMD, 41 (72 %) underwent surgical treatment for hemodynamic impairment on the affected side and were included in our analysis. The reasons for exclusion (n =16) were: medical treatment (n =4, 25 %); unavailable data (n =4, 25 %); atherosclerotic steno-occlusive lesions (n =3, 18.75 %); concomitant aneurysm (n =3, 18.75 %); and prior history of surgery (n =2, 12.5 %).

Surgical revascularization

Unilateral MMD patients who met previously described criteria [10] were treated with a superficial temporal artery to middle cerebral artery (STA-MCA) bypass with encephalo-duro-galeo-synangiosis (EDGS) [14, 18] or encephalo-duro-arterio-synangiosis (EDAS) [11], performed by two neurosurgeons (J.E. Kim and H.S. Kang, respectively). The surgical indications of unilateral MMD were: symptomatic lesion, asymptomatic lesion with angiographic progression, and hemodynamic insufficiency shown by using single photon emission tomography (SPECT) with acetazolamide challenge. Patients without hemodynamic insufficiency did not receive surgical treatment [10]. Among the 41 surgically treated patients, STA-MCA bypass with EDGS was performed in 23 (56.1 %) patients and EDAS was performed in 18 (43.9 %) patients. Estimation of the observation period was based on the duration from the date of diagnosis to the date of last follow-up or to the date of confirmation of disease progression.

Collection of medical and radiological data

Medical data including gender, age, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, history of smoking, familial history of MMD, initial presenting symptoms, surgical treatment methods, radiologic data including Suzuki stage, and the presence of disease progression were obtained and analyzed. Patients' HTN, DM, dyslipidemia and smoking statuses were defined according to previously described criteria [23]. Initial presenting symptoms included transient ischemic attack (TIA), cerebral infarction and hemorrhage, such as intracranial hemorrhage (ICH), intraventricular hemorrhage (IVH) or subarachnoid hemorrhage (SAH). Radiological data were reviewed blindly by one neurosurgeon and one neuroradiologist. Any disagreement on the radiologic findings was reevaluated by a third reader. Follow-up radiologic tests were carried out with conventional transfemoral catheter angiography (TFCA) at 6 months and 5 years after the revascularization surgery, with time-of-flight (TOF) magnetic resonance angiography (MRA) every 12 months between the 6-month and 5-year TFCA and thereafter, with TOF-MRA whenever new neurologic symptoms and signs presented. Patients for whom progression was suspicious based on MRA underwent TFCA for confirmation. The presence of a contralateral angiographic abnormality on initial angiography indicated equivocal or mild M1, A1, and ICA stenosis [9]. The degree of stenosis (%) was determined by using the formula: [1− (stenotic vessel diameter/normal proximal artery diameter)] × 100 [6, 19]. Stenosis with degrees <30 % were classified as mild stenosis [24]. Time to disease progression was defined as the duration from initial angiography to the angiography that showed disease progression.

Review of pertinent literature

Published reports concerning contralateral angiographic progression in unilateral MMD were reviewed. The MEDLINE database for the period January 1980 to December

2012 was searched by using the key words "unilateral moyamoya," "probable moyamoya," "progression," and "risk factors." Reports, excluding case reports, that include clear information about the presence of contralateral progression after surgery, risk factors such as gender, age at diagnosis, and contralateral abnormality presence on initial angiography, and treatment methods were reviewed for comparison with our observations.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous data are shown as the mean ± standard deviation (SD). Fisher's exact, chi-square, Student's *t* or Wilcoxon rank-sum tests were carried out to estimate categorical and continuous variables. Multivariate analysis using variables with $p \leq 0.2$ was performed to identify the risk factors for contralateral angiographic progression. In cases with separation, logistic regression with Firth's penalized likelihood procedure was conducted. *P*-values<0.05 were regarded as statistically significant. Statistical analyses were performed using SAS (version 9.2, SAS Institute Inc, Cary, NC, USA).

Results

Patient characteristics

Data from 41 surgically treated unilateral adult MMD patients were examined (Table 1). The mean follow-up duration was 50.1±28.0 months. Thirty-one of those patients were female (75.6 %). Mean age at diagnosis was 41.1±10.5 years. All patients included in this study were symptomatic. Thirty-one patients (75.6 %) presented with ischemic symptoms such as transient ischemic attack and cerebral infarction. Hemorrhage presentation was reported in five patients (12.2 %) (IVH, $n=3$; ICH with IVH, $n=1$; SAH, $n=1$). Twenty-six patients (63.4 %) underwent surgical treatment on right-side affected unilateral MMD. The distribution of' initial angiographic stages of unilateral MMD, also known as Suzuki stage, was: stage 3, $n=20$ (48.8 %); stage 4, $n=15$ (36.6 %); and stage 5, $n=6$ (14.6 %). Contralateral minimal abnormality on initial angiography, as previously described [9], occurred in 18 patients (43.9 %). The distribution of the initial abnormalities according to anatomical location was as follows: A1, $n=9$; M1, $n=3$; ICA, $n=1$; A1 and ICA, $n=3$; and A1 and M1, $n=2$. The presence of a single A1 narrowing ($n=9$, 50 %) was the most frequently detected among those 18 patients. Twenty-three cases (56.1 %) underwent STA-MCA bypass with EDGS and 18 cases (43.9 %) underwent EDAS. Regarding the risk factors for stroke, there were 12 patients with HTN and nine patients with a history of smoking. Familial MMD was present in two patients in this series.

Table 1 Clinical features of surgically treated unilateral moyamoya disease in adults included in this study ($n=41$)

Clinical parameters	Number (%)
Gender	
Male	10 (24.4 %)
Female	31 (75.6 %)
Age at diagnosis	41.1±10.5 years*
Follow-up duration	50.1±28.0 months*
Initial presentation	
Transient ischemic attack or infarct	31 (75.6 %)
Hemorrhage	5 (12.2 %)
Seizure	2 (4.9 %)
Headache/dizziness	3 (7.3 %)
Surgically treated side	
Right	36 (63.4 %)
Left	15 (36.6 %)
Suzuki stage prior to surgery	
Stage 3	20 (48.8 %)
Stage 4	15 (36.6 %)
Stage 5	6 (14.6 %)
Contralateral abnormality on initial angiography	18 (43.9 %)
A1	9
M1	3
ICA	1
A1 and ICA	3
A1 and M1	2
Surgical method	
Direct revascularization†	23 (56.1 %)
Indirect revascularization‡	18 (43.9 %)
Risk factors for stroke	
Hypertension	12 (29.3 %)
Hyperlipidemia	2 (4.9 %)
Smoking	9 (22.0 %)
Familial moyamoya disease	2 (4.9 %)

Continuous data are presented as mean ± SD

A1 A1 segment of anterior cerebral artery, *M1* M1 segment of middle cerebral artery, *ICA* internal carotid artery

†Superficial temporal artery–middle cerebral artery anastomosis with encephalo-duro-galeo-synangiosis

‡Encephalo-duro-arterio-synangiosis

Contralateral angiographic progression

Six patients (14.6 %) experienced contralateral angiographic progression during the mean follow-up of 34 months (range 7–63) (Table 2). All patients who showed contralateral progression presented initially with transient ischemic attack (TIA). Four patients (66.7 %) had right-side affected unilateral MMD. Two patients underwent revascularization surgery for repetitive symptomatic lesions of TIA and cerebral infarction.

Table 2 Clinical features of surgically treated unilateral moyamoya disease in adults who showed progression on the contralateral side ($n=6$)

Case number	Gender/age	Initial			Contralateral progression		
		Symptom	Side	Surgery	Symptom	Suzuki stage	Interval (months)
1	M/37	TIA	Left	Direct	None	None to 3	63
2	F/32	TIA	Right	Direct	TIA	None to 3	22
3	F/38	TIA	Right	Direct	None	None to 2	7
4	M/24	TIA	Left	Indirect	Infarction	None to 3	9
5	F/23	TIA	Right	Direct	None	None to 3	45
6	M/42	TIA	Right	Direct	None	None to 2	58

M male, *F* female, *TIA* transient ischemic attack, *direct* superficial temporal artery–middle cerebral artery anastomosis with encephalo-duro-galeo-synangiosis, *indirect* encephalo-duro-arterio-synangiosis

One of those patients (case number 2) underwent an STA-MCA bypass with EDGS and the other patient (case number 4) underwent EDAS. The remaining four patients did not undergo revascularization surgery due to hemodynamically stable asymptomatic lesions. Angiographic change, as assessed by change in Suzuki stage, was: none to Suzuki stage 3 in four patients, and none to stage 2 in two patients.

Predictors of contralateral angiographic progression

Among the risk factors included in the univariate and multivariate analyses, the only statistically significant factor associated with prediction of contralateral progression in surgically treated unilateral adult MMD patients was the presence of contralateral minimal abnormality on initial angiography (odds ratio [OR], 49.00; 95 % confidence interval [CI], 1.13 to >999.99; $p=0.04$) (Table 3). Mean age at diagnosis was a significant factor for progression (32.7±7.8 years in progression group vs. 42.5±10.3 years in non-progression group) in the univariate analysis ($p=0.046$), but it was insignificant in the multivariate analysis (OR, 0.99; 95 % CI, 0.89–1.10; $p=0.82$). Patients under 40 years were more prevalent in the progression group ($n=5$, 83.3 %), but the difference between the two groups was not significant. Moreover, there were insignificant differences between the two groups in the other variables analyzed, i.e., gender ($p=0.13$ in univariate analysis, $p=0.09$ in multivariate analysis), HTN ($p=0.24$ in univariate analysis), smoking history ($p=0.47$ in univariate analysis), familial history of MMD ($p=0.20$ in univariate analysis, $p=0.24$ in multivariate analysis) and surgical methods ($p=0.21$ in univariate analysis).

Review of pertinent literature

Eight published studies were reviewed (Table 4). The number of unilateral adult MMD patients included in those studies ranged from 4 to 14. Mean age at diagnosis ranged from 26.8 to 43.5 years. The progression rates of the contralateral side ranged from 0 to 50 % in the studies' adult MMD populations. The time to progression ranged from 8 to 96 months. In those studies, the risk factors for contralateral progression were female gender [13] and the presence of contralateral abnormality on initial angiography [9].

Case illustrations

Case number 1 in Table 2

A 37-year-old man presented with transient right-side weakness and motor dysphasia. Left carotid angiography revealed nearly total distal ICA occlusion with leptomeningeal collateral flow from the posterior cerebral artery (PCA) to MCA and ACA without evidence of bilateral MMD. Mild stenoses of the M1 (arrow) and A1 on the right side were observed (Fig. 1a, b). Diamox-challenged single photon emission computed tomography (D-SPECT) showed reductions of cerebral blood flow (CBF) and vascular reserve capacity in the left cerebral hemisphere (data not shown). The patient underwent STA-MCA bypass with EDGS on the left side. Follow-up right carotid angiography performed 63 months later showed marked proximal MCA occlusion with dilatation of the lenticulostriate arteries (Fig. 1c). Follow-up D-SPECT showed mild decreases of CBF and vascular reserve capacity on the left hemisphere without evidence of decreases of CBF and vascular reserve capacity on the right hemisphere (data not shown). The patient remained asymptomatic and was scheduled for periodic check-up.

Case number 2 in Table 2

A 32-year-old female presented with transient left-sided weakness. Right carotid angiography revealed a total proximal MCA occlusion with basal cerebral moyamoya vessels with mild narrowing of the proximal MCA and anterior temporal artery on the left side (Fig. 2a, b).

Table 3 Predictors of contralateral progression in surgically treated adult unilateral moyamoya disease (MMD)

Variables	Progression ($n=6$)	Non-progression ($n=35$)	Univariate analysis	Multivariate analysis	Odds ratio (95 % CI)
Female	3 (50 %)	28 (80 %)	$p=0.13$	$p=0.09$	0.13 (0.01–1.37)
Age (years)	32.7±7.8	42.5±10.3	$p=0.046$*	$p=0.82$	0.99 (0.89–1.10)
<40	5 (83.3 %)	15 (42.9 %)	$p=0.09$		
≥40	1 (16.7 %)	20 (57.1 %)			
Contralateral abnormality			$p=0.04$ *	$p=0.04$ *	49.00 (1.13–>999.99)
Yes	6 (100 %)	12 (34.3 %)			
No	0 (0 %)	23 (65.7 %)			
Surgical methods			$p=0.21$		
Direct†	5 (83.3 %)	18 (51.4 %)			
Indirect‡	1 (16.7 %)	17 (48.6 %)			
Hypertension	3 (50 %)	9 (25.7 %)	$p=0.24$		
Smoking	2 (33.3 %)	7 (20 %)	$p=0.47$		
Familial MMD	1 (1.7 %)	1 (2.9 %)	$p=0.20$	$p=0.24$	9.09 (0.23–361.78)

Penalized likelihood method was used for analysis

†Superficial temporal artery–middle cerebral artery anastomosis with encephalo-duro-galeo-synangiosis

‡Encephalo-duro-arterio-synangiosis

* $p<0.05$ is significant

D-SPECT showed marked reduction of vascular reserve capacity in the right MCA territory (data not shown). The patient underwent an STA-MCA bypass with EDGS on the right side. Follow-up left carotid angiography performed 22 months later disclosed marked proximal MCA occlusion with prominent basal moyamoya vessels (Fig. 2c). In addition, follow-up D-SPECT showed decreased vascular reserve capacity on the left hemisphere (data not shown). The patient experienced transient motor weakness on the right extremity with dysphasia. The patient underwent an STA-MCA bypass with EDGS on the left side. The post-operative course was uneventful.

Discussion

Treatment strategies for the contralateral unaffected side of unilateral adult MMD patients following revascularization surgery in the affected side are not well defined, due to the limited amount of information available on the angiographic contralateral side progression rate and its associated risk factors in a large cohort. Although previous studies have addressed the incidence and risk factors of such progression [2–4, 9, 13, 22], most of those studies were carried out in small cohorts that were heterogeneous in terms of age (mixed pediatric and adult groups) and treatment methods (mixed

Table 4 Summary of results of previous studies concerning contralateral angiographic progression in surgically treated unilateral moyamoya disease in adults

Author, year	Total patients (adults)	Male/female of adults	Mean (range) age, years	Progression (rate)	Follow-up interval, month (range)	Risk factor
Kawano, [8] 1994	32 (14)	NA	35.3 (19–63)	5 (35.7 %)	33.6 (12–72)	NA
Houkin, [5] 1996	10 (6)	3/3	40.3	0	–	NA
Hirotsune, [4] 1997	17 (4)	0/4	32.5	0	–	NA
Kuroda, [13] 2005	11 (11)	NA	43.5	4 (36.4 %)	20 (18–96)	Female gender
Hallemeier, [2] 2006	12 (12)	6/6	NA	0	–	NA
Kelly, [9] 2006	18 (13)	4/9	36.8 (21–52)	5 (38.5 %)	12.4 (8–22)	Contralateral abnormality*
Smith, [22] 2008	33 (4)	1/3	26.8	2(50 %)	NA	NA
Hayashi, [3] 2010	9 (8)	2/6	42.6 (23–65)	0	–	NA
Present series, 2013	41 (41)	10/31	41.1 (21–64)	6 (14.6 %)	34 (7–63)	Contralateral abnormality*

*Contralateral abnormality on initial angiography

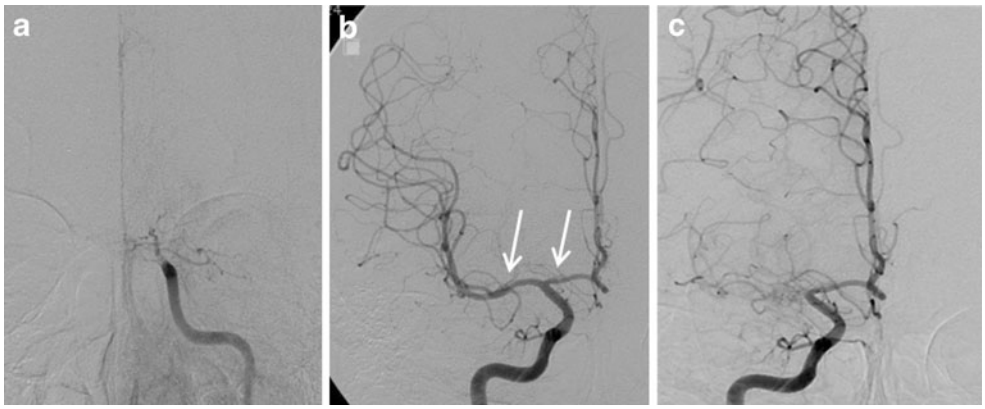

Fig. 1 A 37-year-old man presented with transient ischemic attack. **a**–**b** Preoperative conventional angiography revealed nearly total occlusion of the left distal internal carotid artery as well as mild stenoses of the M1 segment of the middle cerebral artery (MCA) and the A1 segment of anterior cerebral artery (ACA) (*arrows*) on the right side. The patient underwent a superficial temporal artery to middle cerebral artery bypass with encephalo-duro-galeo-synangiosis on the left side. **c** Follow-up right carotid angiography performed 63 months later revealed marked proximal MCA occlusion with dilatation of the lenticulostriate arteries. The patient remained asymptomatic and was scheduled for periodic check-ups

medical and surgical groups). Accordingly, it may be inappropriate to apply the results of those studies to a surgically treated unilateral adult MMD population.

As there are differences in brain plasticity and clinical characteristics between pediatric and adult MMD patients [13], age at diagnosis could affect study results. Kawano et al. [8] and Smith et al. [22] reported high progression rates [66.7 % (4/15 patients) and 50 % (2/4 patients), respectively] in adult patients with mean ages of 35.3 years and 26.8 years, respectively. In contrast, Houkinet al. [5] and Hayashi et al. [3] reported no progression in adult patients with mean ages of 40.3 years and 42.6 years, respectively. Accordingly, age at diagnosis may affect contralateral angiographic progression. In this study, we included unilateral adult MMD patients aged over 18 years. Although younger age at diagnosis was a significant factor for progression in our univariate analysis results ($p=0.046$), the relationship was not significant in our multivariate analysis results ($p=0.82$). Regarding pediatric MMD, Smith et al. [22] reported that a younger age at diagnosis was associated with a rapid contralateral progression (age <7 years, progression 0.9 years vs. age ≥7 years, progression 3.1 years). Park et al. [17] reported a similar relationship between age and progression (age <8 years, progression 14.18 months vs. age ≥8 years, 22.38 months). However, the absence of further statistical analysis and the presence of a pediatric population mixed with adults [22] are limitations on those associations. Yeon et al. [26] reported that age <9 years was the only statistically significant risk factor for contralateral angiographic progression among patients under the age of 17 years.

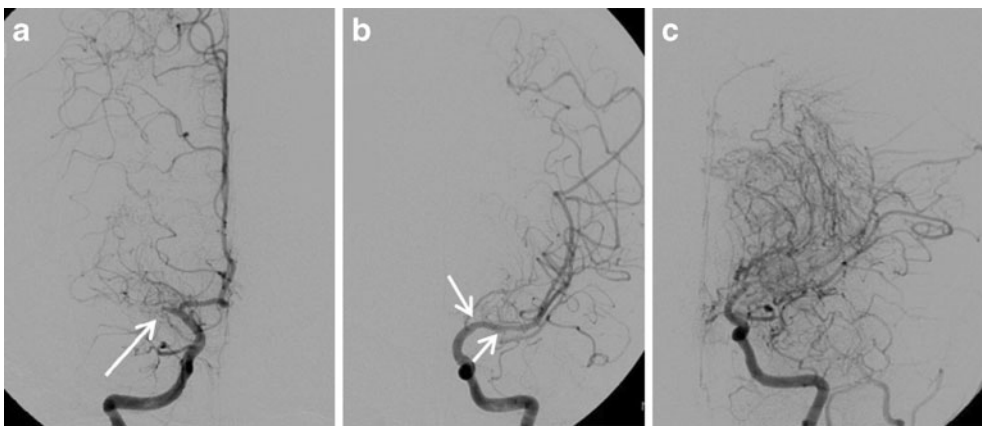

Fig. 2 A 32-year-old female presented with transient left-sided weakness. **a**–**b** Preoperative conventional angiography revealed total occlusion of the right proximal middle cerebral artery (MCA) with basal cerebral moyamoya vessels (*arrow*), as well as mild narrowing of the left proximal MCA and anterior temporal artery (*arrows*). D-SPECT showed a marked reduction of vascular reserve capacity in the right MCA territory. The patient underwent an STA-MCA bypass with encephalo-duro-galeo-synangiosis (EDGS) on the right side. **c** Follow-up left carotid angiography obtained 22 months later revealed marked proximal MCA occlusion with prominent basal moyamoya vessels. Follow-up D-SPECT revealed decreased vascular reserve capacity on the left side. The patient was symptomatic and underwent an STA-MCA bypass with EDGS on the left side. The post-operative course was uneventful

Female gender and the presence of contralateral abnormality on initial angiography have been suggested as risk factors for progression. Kuroda et al. [13] reported female gender as a potential risk factor for disease progression. They observed four instances of angiographic progression among 11 unilateral adult MMD cases and all four were female. However, other studies have not reported an association between gender and contralateral angiographic progression [2, 22]. In our series, three female patients (50 %) showed contralateral side progression, but the incidence was not significantly different from that in male patients ($p=0.13$).

The presence of contralateral abnormality on initial angiography has also been suggested as a risk factor. In the report by Kelly et al. [9], equivocal or mild angiographic change on initial angiography was the only significant risk factor for progression. In particular, they reported that change in the contralateral side A1 segment of the ACA was associated with disease progression. In our series, 18 patients (43.9 %) showed contralateral abnormality on initial angiography. Among them, six patients (33.3 %) experienced contralateral angiographic progression during follow-up. The presence of contralateral minimal abnormality at the time of diagnosis was the only significant risk factor in our cohort (OR, 24.44; $p=0.04$).

Mean time to progression on the contralateral side in unilateral adult MMD populations has varied among studies (Table 4). Kelly et al. [9] and Kuroda et al. [13] reported mean time to progression as 14.3 months (range 8–22) and 20 months (range 18–96), respectively. However, a longer time to progression (33.6 months, range 12–72) has also been observed [8]. In our cohort, the mean progression time was 34 months (range 7–63) in the six patients who showed contralateral angiographic progression (Table 2). Two of those patients (33.3 %) were symptomatic; one patient with TIA (case number 2) 22 months after operation, and one patient with cerebral infarction (case number 4) 9 months after operation. Both underwent revascularization surgery for progressive and symptomatic lesions. Asymptomatic progression on the contralateral side was noted in the remaining four patients. None of those patients underwent revascularization surgery because all were hemodynamically stable. In our study, a 14.6 % progression rate was detected, suggesting that periodic follow-up radiographic examinations are needed, especially in patients with the significant risk factor of contralateral abnormality presence on initial angiography.

Treatment strategies for the non-affected side in unilateral MMD cases remain unresolved. For pediatric MMD patients, in particular those under 2 years old, single bilateral revascularization surgery has been recommended due to the high prevalence of subsequent lesion progression in the contralateral normal side [15]. Seol et al. [21] and Kim et al. [12] treated unilateral MMD by using EDAS with bifrontal encephalo-galeo-synangiosis (ribbon EGS), due to hemodynamic compromise in the ACA territory in the contralateral side. However, we only observed six cases of progression (14.6 %) in 41 surgically treated unilateral adult MMD patients. Consequently, single-session bilateral revascularization is not warranted in unilateral adult MMD cases.

Concerns remain regarding the possible effect on contralateral progression by surgical revascularization and the possible inclusion of atherosclerotic steno-occlusive disease in our cohort. The occurrence of surgical revascularization could be related to contralateral progression, and such a relationship could be examined by undertaking comparative analysis of surgical and medical treatment groups. In our series, we had only four cases of medically treated unilateral MMD with radiologic evidence of hemodynamic insufficiency (data not shown). That small sample was because surgical treatment was initially considered in the presence of symptomatic lesions or asymptomatic lesions with angiographic progression accompanied by hemodynamic insufficiency [10]. Neither the presence of contralateral angiographic abnormality on initial angiography nor contralateral progression in the follow-up angiography was noted in patients who received medical treatment. Therefore, a difference in contralateral angiographic progression according to treatment modalities requires further study.

Our data has shown a relatively low contralateral progression rate (14.6 %). Since MMV can also develop as a secondary collateral circulation in patients with atherosclerotic steno-occlusive diseases [23], inclusion of atherosclerotic steno-occlusive disease may have contributed to the low progression rate in the study. Differentiation of MMD from atherosclerotic steno-occlusive disease can be carried out, provided there is accurate detection of MMV, and by using clues for distinguishing MMD from atherosclerotic disease. Although atherosclerotic lesions can be accompanied by MMV, MMV is more likely to develop in patients with unilateral MMD. The existing MR criteria for diagnosing MMD include the presence of an abnormal vascular network in basal ganglia on MRA or more than two flow voids in basal ganglia on MRI [1]. However, low signal intensity on 3T MRI, which is currently widely used, might make it difficult to identify flow voids because low signal intensity of basal ganglia can result because of their iron-rich content [20, 25]. Sawada et al. [20] reported that cisternal MMV visualized in the sylvian valley on T2W1 or MRA results in higher detection accuracy than that from using previous MR criteria. On that basis, more accurate MMV detection can be achieved. Clues from radiologic tests can also help to distinguish MMD from atherosclerotic steno-occlusive diseases. Kaku et al. [7] reported that decreased outer diameters of ICA and the M1 segment of MCA, obtained through three-dimensional (3D) constructive interference in steady-state (CISS) MR imaging, could be a clue to identifying MMD based on the rationale of

differential pathogenesis for arterial narrowing between the two diseases. For MMD, constrictive remodeling of the affected arteries may contribute to luminal narrowing, which is different from that in atherosclerotic disease. Accordingly, 3D CISS MRI could be helpful when identifying homogeneous unilateral MMD in an adult population. Further study of contralateral progression in unilateral MMD based on the use of new MR technologies is required.

Our study has several distinctive characteristics. First, we only included data on surgically treated unilateral MMD adult patients. Second, among the available published studies, our study has the largest sample size (41 unilateral adult MMD cases). Third, all patients who underwent a surgical procedure were followed with diligence. Accordingly, we suggest that our study provides an accurate analysis of contralateral angiographic progression as a risk factor in adult MMD.

Limitations

There are some limitations in this study. First, this retrospective study was conducted in a single institute. Second, medically treated patients who did not undergo surgery were excluded from this study. Thus, it may not be appropriate to apply our results to patients who had medical treatment without surgery.

Conclusions

The presence of contralateral angiographic abnormality on initial angiography is a statistically significant risk factor for contralateral angiographic progression in unilateral adult MMD patients who have undergone revascularization surgery for hemodynamic insufficiency in the affected side. Consequently, patients with the presence of contralateral abnormality on initial angiography should be monitored diligently.

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Conflicts of interest None.

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