Table 1. Primary End Point in Subgroups

Stratification Variable	Allocation		*P* Interaction
	Nonsurgical (n=38)	Surgical (n=42)	
Hemorrhagic site			0.013
Anterior			
No. of participants	21	24	
Primary end point (no. [%])	3 (14.3)	5 (20.8)	
HR (95% CI)	1.00 (reference)	1.62 (0.39–6.79)	
Posterior			
No. of participants	17	18	
Primary end point (no. [%])	10 (58.8)	1 (5.6)	
HR (95% CI)	1.00 (reference)	0.07 (0.01–0.55)	
Age			0.705
≥42 y			
No. of participants	17	22	
Primary end point (no. [%])	6 (35.3)	4 (18.2)	
HR (95% CI)	1.00 (reference)	0.46 (0.13–1.64)	
<42 y			
No. of participants	21	20	
Primary end point (no. [%])	7 (33.3)	2 (10.0)	
HR (95% CI)	1.00 (reference)	0.30 (0.06–1.44)	
Sex			0.729
Female			
No. of participants	27	28	
Primary end point (no. [%])	10 (37.0)	4 (14.3)	
HR (95% CI)	1.00 (reference)	0.35 (0.11–1.13)	
Male			
No. of participants	11	14	
Primary end point (no. [%])	3 (27.3)	2 (14.3)	
HR (95% CI)	1.00 (reference)	0.51 (0.09–3.07)	
Hypertension			0.377
Yes			
No. of participants	8	8	
Primary end point (no. [%])	4 (50.0)	2 (25.0)	
HR (95% CI)	1.00 (reference)	0.44 (0.08–2.39)	
No			
No. of participants	30	34	
Primary end point (no. [%])	9 (30.0)	4 (11.8)	
HR (95% CI)	1.00 (reference)	0.38 (0.12–1.23)	
ICH w/o IVH			0.831
Yes			
No. of participants	8	14	
Primary end point (no. [%])	3 (37.5)	2 (14.3)	
HR (95% CI)	1.00 (reference)	0.34 (0.06–2.05)	
No			
No. of participants	30	28	
Primary end point (no. [%])	10 (33.3)	4 (14.3)	
HR (95% CI)	1.00 (reference)	0.41 (0.13–1.30)	

CI indicates confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage; and IVH, intraventricular hemorrhage.

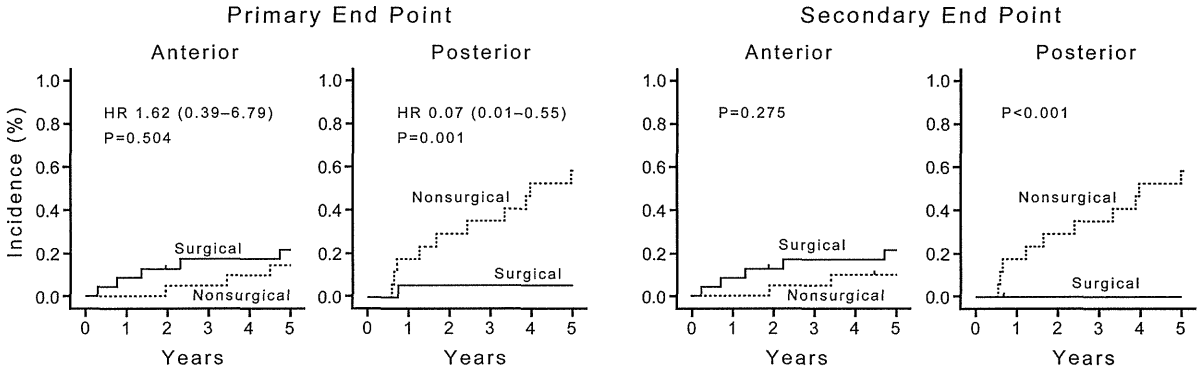

Figure 2. Kaplan–Meier estimates of the incidence of primary and secondary end points by hemorrhagic site. *P*=0.013 for interaction in the primary end point. Calculation of the hazard ratio (HR) and interaction *P* value was impossible for the secondary end point.

treatment effect) was focused on the hemorrhagic site subgroup because the sample size was insufficient to allow the assessment across all baseline subgroups. Effect modification was tested by Cox proportional hazards analyses incorporating the interaction term and was presented as a *P* value for interaction. We also analyzed effect modification for the other baseline variables: age (with the median as the cutoff point), sex, hypertension, and hemorrhage type.

Reproducibility of the classification as anterior or posterior hemorrhage was assessed by a panel assembled for this analysis, and agreement was expressed as the κ coefficient. Sensitivity analysis based on the panel classification was also performed. Two-sided values of $P<0.05$ were considered significant. All analyses were performed with IBM SPSS software, version 20 (IBM Software Group, Chicago, IL).

Results

Of the 80 patients enrolled in total, 42 were assigned to the surgical group and 38 to the nonsurgical group. Patient demographics for both the groups were comparable as described in the published article. As a result of stratified randomization, the numbers of patients with anterior or posterior hemorrhage were similar in the surgical and nonsurgical groups; the surgical group included 24 patients with anterior hemorrhage (57.1%) and 18 with posterior hemorrhage (42.9%), whereas the nonsurgical group included 21 patients with anterior hemorrhage (55.3%) and 17 with posterior hemorrhage (44.7%). The classifications of anterior and posterior hemorrhage showed almost perfect inter-rater agreement (κ=0.82; 95% confidence interval [CI], 0.70–0.95).

Surgical Effects by Hemorrhagic Site

The effect of bypass surgery on the event rate was varied by the hemorrhagic site. About the primary end point, the hazard ratio (HR) for the surgical group relative to the nonsurgical group was 0.07 (95% CI, 0.01–0.55) for the posterior group, whereas the ratio exceeded 1 in the anterior group (HR, 1.62; 95% CI, 0.39–6.79), with $P=0.013$ for interaction (Table 1; Figure 2); this indicates that significant effect modification was observed. About the secondary end point, the similar effect modification was apparent as shown in the Kaplan–Meier curves (Figure 2). Calculation of either the HR or the interaction *P* value was impossible for the secondary end point because the event rate was zero in the surgical group within the posterior hemorrhage strata. The HR was not substantially influenced by age, sex, presence of hypertension, or type of hemorrhage (Table 1). The results of the sensitivity analysis are shown in Table I in the online-only Data Supplement.

Analysis of the Nonsurgical Group

The analysis was then limited to the nonsurgical group, which comprised 38 patients (21 with anterior hemorrhage and 17

Table 2. Baseline Variables in Nonsurgical Group (n=38)

Variable	Anterior Hemorrhage (n=21)	Posterior Hemorrhage (n=17)	*P* Value*
Mean age±SD, y	41.4±11.9	41.3±13.0	0.980
Female (%)	14 (66.7)	13 (76.5)	0.508
Hypertension (%)	4 (19.0)	4 (23.5)	0.736
Diabetes mellitus (%)	2 (9.5)	0	0.191
Hyperlipidemia (%)	2 (9.5)	0	0.191
History of ischemic event (%)	6 (28.6)	4 (23.5)	0.726
History of hemorrhagic stroke (%)	1 (4.8)	3 (17.6)	0.198
Hemorrhagic type			
ICH w/o IVH	6 (28.6)	2 (11.8)	0.263
ICH w/ IVH	11 (52.4)	14 (82.4)	
Primary IVH	3 (14.3)	1 (5.9)	
SAH only	1 (4.8)	0	

ICH indicates intracerebral hemorrhage; IVH, intraventricular hemorrhage; and SAH, subarachnoid hemorrhage.
*t test or χ^2 test.

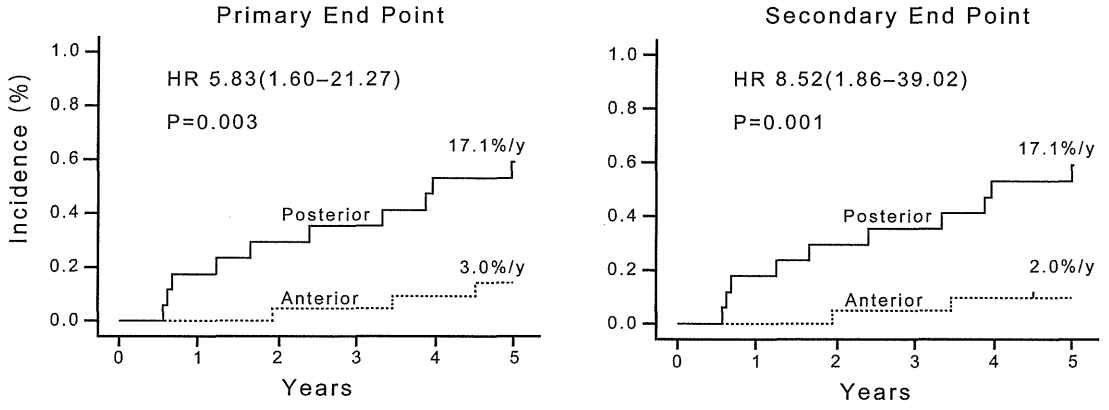

Figure 3. Kaplan–Meier estimates of incidence of primary and secondary end points within the nonsurgical group (n=38). HR indicates hazard ratio.

with posterior hemorrhage). Overall 5-year risk and annual incidence of rebleeding were 31.6% (12/38) and 7.6%, respectively. Baseline characteristics such as age, sex, coexisting disease, history of hemorrhagic or ischemic stroke, and type of hemorrhage were not significantly different between anterior and posterior groups (Table 2). The incidence rates for both the primary and secondary end points were significantly higher for the posterior group than for the anterior group (P=0.003 and 0.001 for log-rank test, respectively; Figure 3). The annual incidence rate for the primary end point was as high as 17.1% per year for the posterior group, as compared with 3.0% per year for the anterior group. The HR for posterior hemorrhage relative to anterior hemorrhage was 5.83 (95% CI, 1.60–21.27) for the primary end point and 8.52 (95% CI, 1.86–39.02) for the secondary end point. No other baseline factor was significantly associated with the incidence of end points in the univariate analysis (Table 3), and no further multivariate analysis was performed. The results of the sensitivity analysis are shown in Table II in the online-only Data Supplement.

Table 3. Univariate Analysis of Factors Associated With End Points in Nonsurgical Group (n=38)

Exposure Variable	Primary End Point HR (95% CI)	Secondary End Point HR (95% CI)
Hemorrhagic site		
Anterior	1.00 (reference)	1.00 (reference)
Posterior	5.83 (1.60–21.27)	8.52 (1.86–39.02)
Age (y; continuous variable)	1.02 (0.98–1.07)	1.03 (0.98–1.08)
Female	1.46 (0.40–5.31)	1.30 (0.35–4.80)
Hypertension	1.68 (0.52–5.47)	1.27 (0.34–4.70)
Diabetes mellitus	1.30 (0.17–9.99)	NA
Hyperlipidemia	1.30 (0.17–9.99)	NA
History of ischemic event	0.20 (0.03–1.57)	0.23 (0.03–1.76)
History of hemorrhagic stroke	0.65 (0.09–5.03)	0.71 (0.09–5.52)
Hemorrhagic type		
ICH w/o IVH	1.00 (reference)	1.00 (reference)
ICH w/ IVH	0.76 (0.20–2.88)	0.76 (0.20–2.88)
Primary IVH	0.65 (0.07–6.27)	0.66 (0.07–6.36)
SAH only	2.26 (0.23–21.91)	NA

CI indicates confidence interval; HR, hazard ratio; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; NA, not applicable; and SAH, subarachnoid hemorrhage.

Analysis of the Surgical Group

The Kaplan–Meier analysis within the surgical group revealed that the incidence rate for the secondary end points was significantly higher for the anterior group than for the posterior group (P=0.045), indicating a tendency opposite to that revealed in the analysis of the nonsurgical group.

Discussion

Rebleeding Risk by Hemorrhagic Site

Our results suggest that the posterior hemorrhage group is, by its nature, at higher risk of rebleeding than the anterior group. Previous observational studies have identified only a few risk factors associated with rebleeding, including age at onset and the presence of silent cerebral microbleeds,[10,11] and have rarely addressed the bleeding site in the manner of this study. Only Kobayashi et al[1] reported a higher incidence of rebleeding in patients with thalamic hemorrhage compared with those with basal ganglia hemorrhage, although their definition of hemorrhagic site differed from ours.

The high incidence of rebleeding in the posterior hemorrhage group can be explained by the vascular morphology of moyamoya disease, which has recently received more attention. As shown in the outstanding work of Morioka et al,[4] dilated and extended choroidal or thalamic perforating arteries seem more responsible for bleeding than do the tiny vessels that proliferate from the lenticulostriate artery, which have traditionally been denoted as moyamoya vessels and suspected as source of bleeding. In moyamoya disease, the anterior choroidal artery can form abnormal anastomoses of the medullary artery around the trigon of the lateral ventricle, where bleeding can occur.[12] The dilatation and extension of the perforators from the posterior communicating artery create a risk of bleeding in the thalamus.[4] Other thalamic perforators can also proliferate, especially when the posterior cerebral artery is occluded.[13] All bleeding from these fragile collaterals could be commonly classified as posterior hemorrhage; for this reason, the rebleeding risk of the posterior group might have been elevated.

However, the causes of anterior hemorrhage might be heterogeneous because, by definition, it includes hemorrhage of

unknown origin. The lenticulostriate arteries, possible sources of anterior hemorrhage, might suffer less hemodynamic stress than the choroidal or thalamic arteries as long as the terminal portion of the internal carotid artery has narrowed. These points of speculation should be confirmed through further analysis.

Surgical Effects by Hemorrhagic Site

Our results suggest that patients with posterior hemorrhage accrue greater surgical benefit than those with anterior hemorrhage. No previous study, to the best of our knowledge, has focused on the effect modification by hemorrhagic site. Our results seem valid because biases were minimized through the prospective design of the study and the determination to analyze a prespecified (versus post hoc) subgroup.

This result might reflect the different natures of the anterior and posterior hemorrhage groups, as discussed above. The abnormal collaterals formed by the thalamic or choroidal arteries, possible sources of posterior hemorrhage, can connect to the middle cerebral artery in the cortex via the medullary artery.[3,12] Direct bypass, introduced in the territory of the middle cerebral artery, might eliminate hemorrhagic stress on the collaterals by augmenting blood flow in that very area. Kuroda et al[7] reported the elimination of peripheral aneurysms after bypass surgery, all of which had formed in the thalamic or choroidal artery. A more recent report, revealing that the dilatation and extension of the choroidal and thalamic arteries was likely to diminish after bypass surgery,[14] also supports this speculation. The degree of preoperative perfusion impairment or postoperative improvement might differ between the anterior and posterior groups and should also be analyzed in further studies.

As shown in this analysis, higher rebleeding risk and greater surgical effects in the posterior hemorrhage group might, after careful interpretation, provide valuable information on the treatment of hemorrhagic moyamoya disease. Although the efficacy of bypass surgery was confirmed in the overall comparison of the JAM Trial,[2] identification of a more beneficial subgroup is required, considering the potential invasiveness of surgery. Patients with posterior hemorrhage might comprise a more optimal target group for bypass surgery. Further studies, along with the present result, might reveal optimal indications for bypass surgery in the future.

Limitations

This study has several limitations. First, although the JAM Trial is the only randomized controlled trial for moyamoya disease, the sample size was relatively small because of the low prevalence of the disease; this resulted in the wide CIs observed in the results. Second, a type I error could have contaminated the credibility of the subgroup results, even if multiple comparisons were carefully avoided by restricting the focus on the predetermined subgroup. Third, potential misclassification of the hemorrhagic site could have affected the results, although the results of the sensitivity analysis correspond closely to those of the primary analysis and seem to support the conclusion. Further prospective studies, as well as subgroup analyses from other observational studies, should confirm whether similar results are consistently observed.

Conclusions

This analysis of the JAM Trial supports our prespecified hypothesis about hemorrhagic moyamoya disease that both the outcome of nonsurgical treatment and effect of bypass surgery at preventing rebleeding vary with the initial bleeding site. Careful interpretation of the results suggests that patients with posterior hemorrhage are, by its nature, at higher risk and accrue greater benefit from bypass surgery than do those with anterior hemorrhage. Further studies might identify the optimal target group for bypass surgery in hemorrhagic moyamoya disease.

Appendix

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Acknowledgments

We are grateful to Drs Ichiro Tsuji and Yasutake Tomata of the Department of Public Health, Tohoku University Graduate School of Medicine for performing statistical analyses.

Sources of Funding

The Japan Adult Moyamoya Trial has been funded since 1999 by a grant from the Japanese Ministry of Health, Labour and Welfare as a major project of the Research Committee on Spontaneous Occlusion of the Circle of Willis (moyamoya disease).

Disclosures

None.

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Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Significance of the Hemorrhagic Site for Recurrent Bleeding: Prespecified Analysis in the Japan Adult Moyamoya Trial

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Stroke. 2016;47:37-43; originally published online December 8, 2015;
doi: 10.1161/STROKEAHA.115.010819
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

ONLINE SUPPLEMENT

Significance of the hemorrhagic site for recurrent bleeding: A prespecified analysis in the Japan Adult Moyamoya Trial

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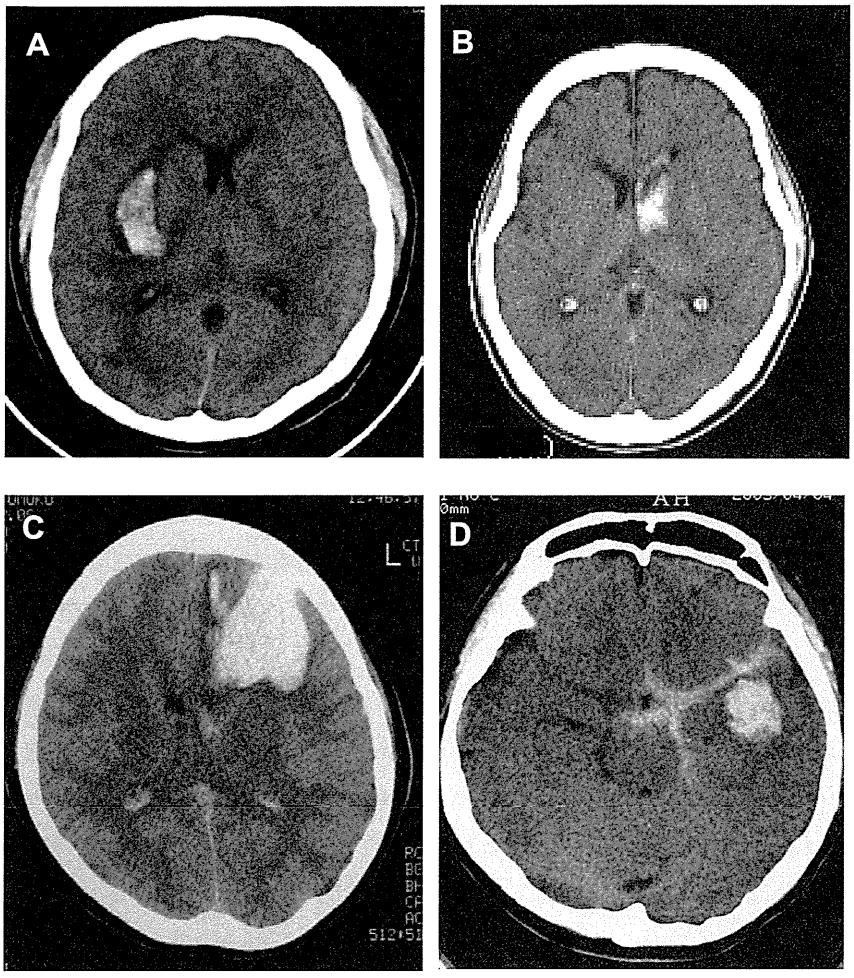
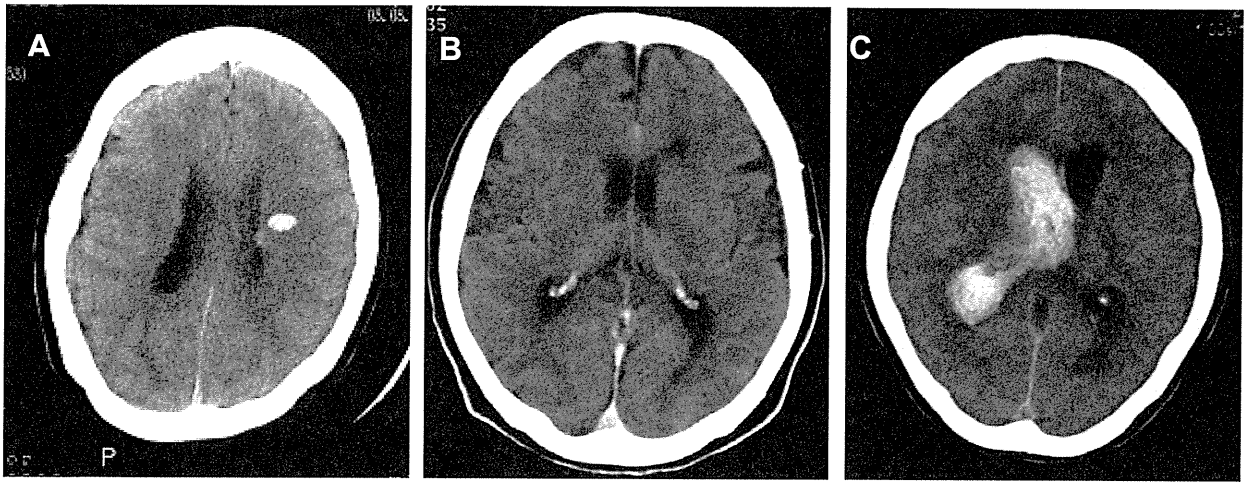
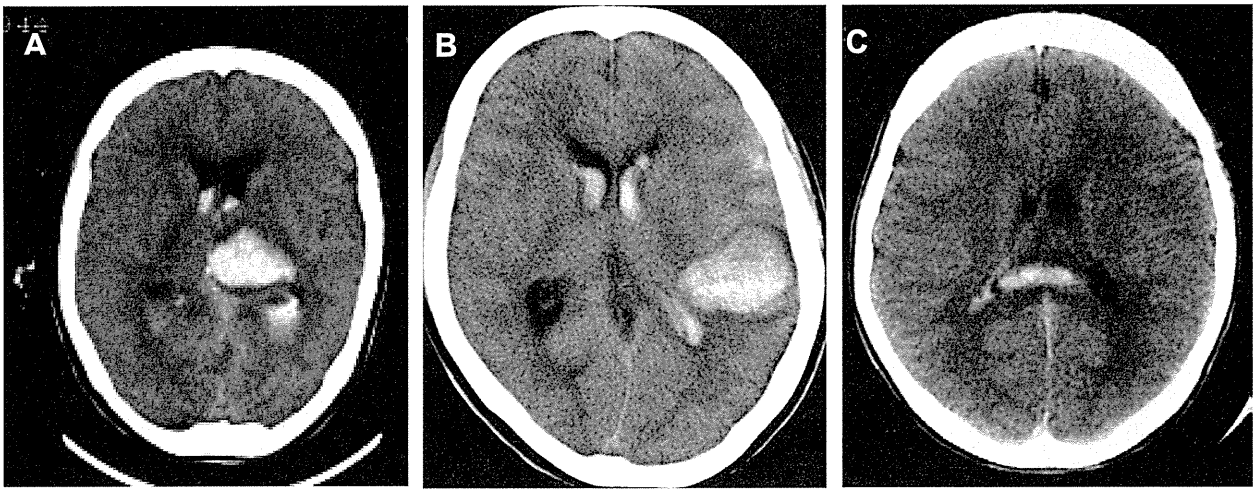


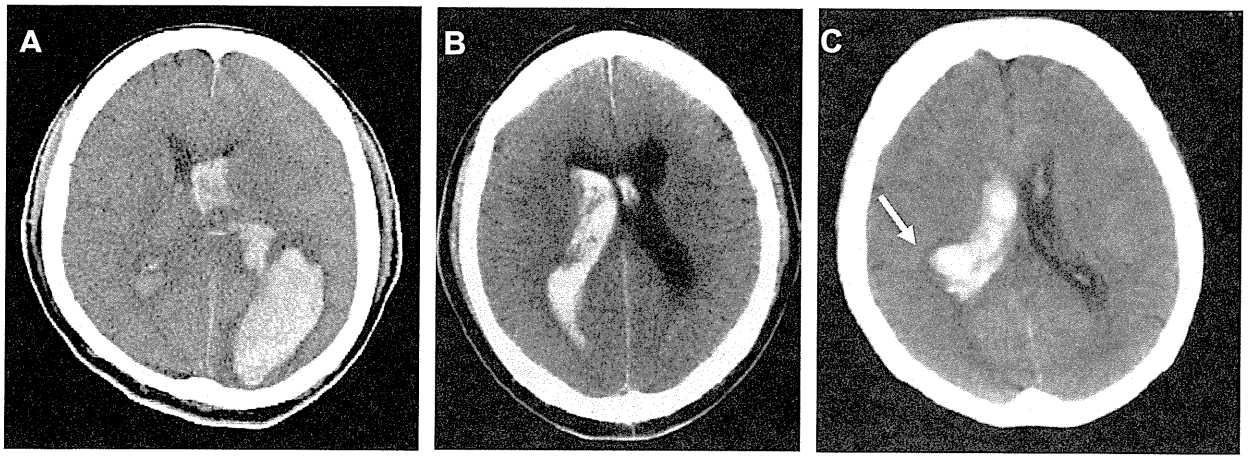
Supplemental Figure I. Representative CT images of anterior hemorrhage. A: Putaminal hemorrhage. B: Hemorrhage in the caudate head. C: Hemorrhage in the frontal lobe. D: Hemorrhage in the anterior half of the temporal lobe.



Supplemental Figure II. Representative CT images of anterior hemorrhage (cont'd). A: Hemorrhage in the subependymal area of anterior part of the lateral ventricle. B: Subarachnoid hemorrhage in the anterior half of the cistern. C: Primary intraventricular hemorrhage, diffusely distributed with unknown origin.



Supplemental Figure III. Representative CT images of posterior hemorrhage. A: Thalamic hemorrhage. B: Hemorrhage in the posterior half of the temporal lobe. C: Hemorrhage in the posterior half of the corpus callosum.



Supplemental Figure IV. Representative CT images of posterior hemorrhage (cont'd). A: Hemorrhage in the parietal and occipital lobes. B: Primary intraventricular hemorrhage (posterior distribution). C: Hemorrhage in the subependymal area of the posterior part of the lateral ventricle (arrow).

Supplemental Table I. Surgical effects by hemorrhage site (sensitivity analysis based on panel classification)

	Allocation		
	Nonsurgical (n = 38)	Surgical (n = 42)	P-interaction
Primary end point			
Anterior			
No. of participants	21	25	
Primary end point [no. (%)]	4 (19.1)	4 (16.0)	
HR (95% CI)	1.00 (reference)	0.93 (0.23, 3.71)	0.100
Posterior			
No. of participants	17	17	
Primary end point [no. (%)]	9 (52.9)	2 (11.8)	
HR (95% CI)	1.00 (reference)	0.17 (0.04, 0.77)	
Secondary end point			
Anterior			
No. of participants	21	25	
Primary end point [no. (%)]	3 (14.3)	4 (16.0)	
HR (95% CI)	1.00 (reference)	1.23 (0.28, 5.51)	0.038
Posterior			
No. of participants	17	17	
Primary end point [no. (%)]	9 (52.9)	1 (5.9)	
HR (95% CI)	1.00 (reference)	0.08 (0.01, 0.65)	

HR: Hazard ratio; 95%CI: 95% confidence interval

Supplemental Table II. Analysis of nonsurgical group (n = 38; sensitivity analysis based on panel classification)

	Primary end point			Secondary end point		
	Incidence	HR	(95%CI)	Incidence	HR	(95%CI)
Hemorrhage site						
Anterior	4%/y	1.00	(reference)	3%/y	1.00	(reference)
Posterior	15.4%/y	3.92	(1.20, 12.80)	15.4%/y	5.10	(1.38, 18.91)

HR: hazard ratio; CI: confidence interval

ORIGINAL ARTICLE doi: 10.2176/nmc.oa.2015-0044

Neurol Med Chir (Tokyo) 55, 796–804, 2015 Online September 15, 2015

Specific Shrinkage of Carotid Forks in Moyamoya Disease: A Novel Key Finding for Diagnosis

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Abstract

This study was aimed to analyze the outer diameter of the involved arteries in moyamoya disease, using three-dimensional (3D) constructive interference in steady state (CISS) and direct surgical inspection. Radiological evaluation was performed in 64 patients with moyamoya disease. As the controls, six patients with severe middle cerebral artery (MCA) stenosis and 17 healthy subjects were also recruited. On 3D-CISS, the outer diameter was quantified in the supraclinoid portion of internal carotid artery (C1), the horizontal portions of MCA (M1) and anterior cerebral artery (A1), and basilar artery. The involved carotid fork was directly observed during surgery in another series of three adult patients with moyamoya disease. In 53 adult patients with moyamoya disease, the outer diameters of C1, M1, and A1 segments were 2.3 ± 0.7 mm, 1.3 ± 0.5 mm, and 1.0 ± 0.4 mm in the involved side (n = 91), being significantly smaller than the control (n = 17), severe M1 stenosis (n = 6), and non-involved side in moyamoya disease (n = 15, P < 0.01). There were significant correlations between Suzuki's angiographical stage and the outer diameters of C1, M1, and A1 (P < 0.001). The laterality ratio of C1 and M1 was significantly smaller in unilateral moyamoya disease (n = 20) than the controls and severe MCA stenosis (P < 0.01). Direct observations revealed a marked decrease in the outer diameter of the carotid fork (n = 3). These findings strongly suggest specific shrinkage of the involved arteries in moyamoya disease, which may provide essential information to distinguish moyamoya disease from other intracranial arterial stenosis and shed light on the etiology and novel diagnosis cue of moyamoya disease.

Key words: moyamoya disease, three-dimensional constructive interference in steady state, carotid fork, outer diameter, diagnosis

Introduction

Moyamoya disease is an uncommon cerebrovascular disorder that is characterized by progressive occlusion of the supraclinoid internal carotid artery (ICA) and its main branches within the circle of Willis. This occlusion results in the dilation of perforating arteries at the base of brain (moyamoya vessels). Histopathological findings in the carotid terminations include fibrocellular thickening of the intima, an irregular undulation (waving) of the internal elastic lamina, and attenuation of the media, all of which have been believed to initiate the luminal stenosis in moyamoya disease for these four decades.[1–3] In fact, the diagnosis of moyamoya disease has been based on the radiological information of intraluminal stenosis in the carotid fork.[4] The concept is quite similar to diagnosis process in atherosclerotic arterial stenosis.

Even now, however, it is not rare to experience the difficulty to distinguish moyamoya disease from intracranial arterial stenosis in a certain population of patients. Furthermore, our recent knowledge on susceptibility gene for moyamoya disease has embossed unclear border between moyamoya disease and intracranial arterial stenosis.[5] These issues may result from previous diagnostic concept on the basis of radiological information

Received February 16, 2015; Accepted May 12, 2015

of intraluminal stenosis. In this study, therefore, the outer diameter of the involved arteries was precisely analyzed on three-dimensional constructive interference in steady state (3D-CISS) images and was also directly inspected during surgery in patients with moyamoya disease.

Materials and Methods

I. Patients

In this prospective study, the outer diameter of the intracranial arteries around the circle of Willis was determined in 64 patients with moyamoya disease, using 3D-CISS. All of them were diagnosed as moyamoya disease based on the guideline for the diagnosis of moyamoya disease set by the Research Committee on Moyamoya Disease of the Ministry of Health, Welfare, and Labor of Japan. There were 11 children and 53 adults. There were 27 males and 37 females. Mean age was 9.8 ± 4.1 years and 44.6 ± 14.5 years in pediatric and adult patients, respectively. In pediatric patients, clinical diagnosis included transient ischemic attack (TIA) in seven and ischemic stroke in four. In adult patients, clinical diagnosis included TIA in 22, ischemic stroke in 18, intracranial hemorrhage in 10, and asymptomatic in 3. Of these 64 patients, 44 were defined as bilateral type and other 20 were defined as unilateral type.

To compare with radiological findings in moyamoya disease, this study also included six patients with severe (> 80%) stenosis of the horizontal portion of middle cerebral artery (MCA; M1). There were five males and one female. Mean age was 62.0 ± 15.7 years. Furthermore, this study included totally 17 healthy controls without any history of cerebrovascular disorders. There were 13 males and 4 females. Mean age was 57.5 ± 13.3 years.

In another series of three adult patients with moyamoya disease, the carotid fork was directly observed under surgical microscope during clipping surgery for the aneurysms originated from the internal carotid artery-anterior choroidal artery junction, anterior communicating artery, and basilar artery (BA)-superior cerebellar artery junction.

II. Radiological examinations

Magnetic resonance (MR) imaging, MR angiography, and cerebral angiography were performed in all 64 patients with moyamoya disease. Disease stage was classified into six stages according to Suzuki's angiographic stage.[3] MR imaging was performed on a clinical 1.5T or 3T MR imaging unit (Magnetom Avanto or Verio, Siemens AG, Erlangen, Germany) using a standard 12-channel head coil. T_1-weighted images, T_2-weighted images, T_2*-weighted images, fluid attenuated inversion recovery (FLAIR) images, and diffusion-weighted images were obtained to locate ischemic and hemorrhagic lesions in the brain parenchyma. In this study, 3D-CISS images were obtained in the evaluation of the outer diameter of the intracranial arteries. Parameters for the 3D-CISS at 1.5T were as follows: repetition time (TR), 9.94 ms; echo time (TE), 4.97 ms; flip angle, 70°; matrix size, 256 × 256; slice thickness, 0.7 mm; field of view (FOV), 160 mm; voxel size, 0.6 × 0.5 × 0.7 mm; number of excitations (NEX), one: scan time, 4 min 16 sec. Parameters for the 3D-CISS at 3T were as follows: TR, 6.59 ms; TE, 2.77 ms; flip angle, 40°; matrix size, 307 × 307; slice thickness, 0.6 mm; FOV, 160 mm; voxel size, 0.5 × 0.4 × 0.6 mm; NEX, one: scan time, 4 min 24 sec.

The outer diameter of involved arteries was measured at the site where the outer diameter was smallest in the involved arteries. As a result, the outer diameter was quantified at the C1 just proximal to the bifurcation and at the M1 and A1 around 3–5 mm distal to the origins in a majority of cases with moyamoya disease.

III. Statistical analysis

Data were expressed as mean ± standard deviation (SD). Continuous variables were compared among more than three groups, using one-factor analysis of variance (ANOVA) followed by Tukey's post hoc test. Differences were considered statistically significant if the P value was < 0.05.

Results

I. Outer diameter of involved arteries in adult moyamoya disease

Using 3D-CISS, the outer diameter of involved arteries was quantified in patients with moyamoya disease, and was compared with those in the controls and patients with severe M1 stenosis. For this purpose, the data in 11 pediatric patients were excluded, because no control data in healthy children were obtained in this study. As a result, the data in 106 sides of 53 adult patients were analyzed. Of these 106 sides, 91 were involved and other 15 were not involved (stage 0).

Fig. 1 demonstrates representative findings on 3D-CISS in a patient with severe M1 stenosis and that with moyamoya disease. The results are summarized in Table 1. The outer diameter of C1, M1, A1, and BA in the controls was 3.8 ± 0.5 mm, 3.0 ± 0.3 mm, 2.0 ± 0.3 mm, and 3.4 ± 0.5 mm, respectively. There were no significant differences in their outer

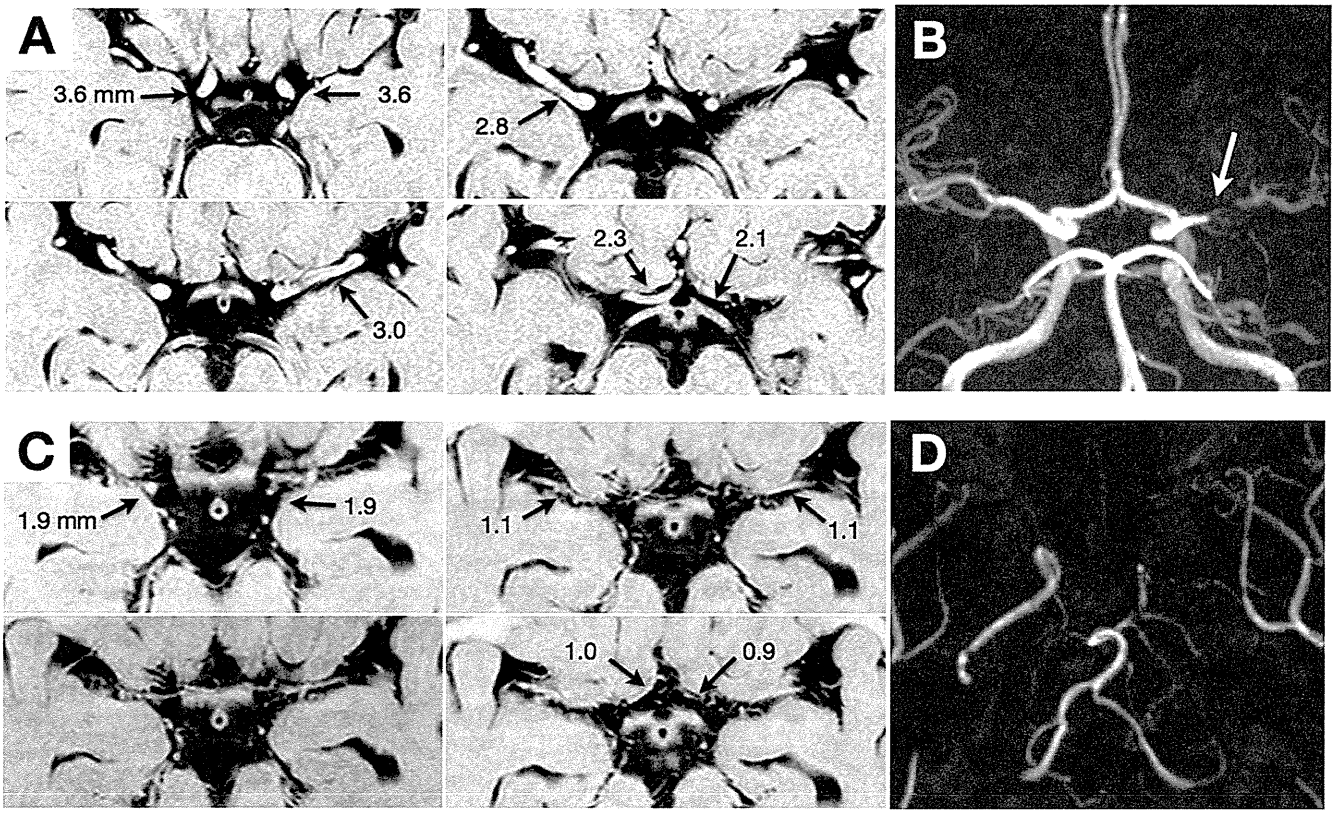

Fig. 1 Representative three-dimensional constructive interference in steady state (A, C) and magnetic resonance (MR) angiography findings (B, D) of a 41-year-old male with severe stenosis of the left middle cerebral artery (A, B) and a 36-year-old female with bilateral moyamoya disease (C, D). A: The outer diameter of the bilateral C1, M1, and A1 is printed. B: MR angiography shows severe stenosis of the left M1 (*arrow*). C: The outer diameter of the bilateral C1, M1, and A1 is printed. D: On MR angiography, the internal carotid arteries are occluded on both sides, being graded as stage 5.

Table 1 Outer diameters of intracranial arteries in normal controls, M1 stenosis, and "adult" moyamoya disease on three-dimensional constructive interference in steady state

		Age (yr)	N	C1 (mm)	M1 (mm)	A1 (mm)	BA (mm)
Control		57.5 ± 13.3	17	3.8 ± 0.5	3.0 ± 0.3	2.0 ± 0.3	3.4 ± 0.5
M1 stenosis	Ipsilateral	62.0 ± 15.7	6	3.8 ± 0.8	2.7 ± 0.4	1.8 ± 0.2	3.6 ± 0.4
	Contralateral		6	3.9 ± 0.4	2.7 ± 0.3	2.1 ± 0.6	3.7 ± 0.4
Moyamoya	Stage 0	45.4 ± 11.2	15	3.6 ± 0.6	2.7 ± 0.5	1.6 ± 0.5	2.9 ± 0.6
	Stage 1–6	44.5 ± 15.1	91	2.3 ± 0.7**	1.3 ± 0.5**	1.0 ± 0.4**	3.1 ± 0.6
	Stage 1	49	1	2.7	2.1	1.1	3.2
	Stage 2	56.0 ± 10.4	3	2.8 ± 0.3**	2.3 ± 0.4	1.6 ± 0.2	3.3 ± 0.2
	Stage 3	34.3 ± 10.5	34	2.4 ± 0.6	1.4 ± 0.4**	1.1 ± 0.4**	2.9 ± 0.6
	Stage 4	47.2 ± 14.3	18	2.7 ± 0.7	1.3 ± 0.4	1.0 ± 0.6	3.2 ± 0.6
	Stage 5	50.0 ± 13.7	26	1.9 ± 0.5§§	1.1 ± 0.4	0.9 ± 0.3	3.3 ± 0.5
	Stage 6	57.7 ± 16.0	9	1.6 ± 0.4	1.2 ± 0.4	0.8 ± 0.3##	3.3 ± 0.6

*: $P < 0.05$, **: $P < 0.01$ vs. control and stage 0, §§: $P < 0.01$ vs. stage 2, ##: $P < 0.01$ vs. stage 3, One-factor analysis of variance (ANOVA) followed by Tukey's post hoc test, BA: basilar artery.

diameter between the control, severe M1 stenosis, and non-involved side in moyamoya disease. On the other hand, the outer diameter of C1, M1, A1, and BA in the involved sides of moyamoya disease was 2.3 ± 0.7 mm, 1.3 ± 0.5 mm, 1.0 ± 0.4 mm, and 3.1 ± 0.6 mm, respectively. The values of C1, M1, and A1 were significantly smaller in moyamoya disease than the controls and patients with severe M1 stenosis ($P < 0.01$).

Based on Suzuki's angiographical stage, totally 106 sides of 53 adult patients with moyamoya disease were classified into stage 0 in 15 sides, stage 1 in 1, stage 2 in 3, stage 3 in 34, stage 4 in 18, stage 5 in 26, and stage 6 in 9 (Table 1). The outer diameter of C1 was 2.8 ± 0.3 mm in stage 2, being significantly smaller than those in stage 0 and the control ($P < 0.01$). The value was 1.9 ± 0.5 mm in stage 5, being significantly smaller than that in stage 2 ($P < 0.01$). The outer diameter of M1 was 2.7 ± 0.5 mm in stage 0. The value was 1.4 ± 0.4 mm in stage 3, being significantly smaller than those in stage 0 and the control ($P < 0.01$). The outer diameter of A1 was 1.6 ± 0.5 mm in stage 0. The value was 1.1 ± 0.4 mm in stage 3, being significantly smaller than those in stage 0 and the control ($P < 0.01$). The A1 portion had further smaller outer diameter in stage 6 (0.8 ± 0.3 mm, $P < 0.01$). There were no significant differences in the outer diameter of BA among six stage groups. As shown in Fig. 2, there were significant correlations between Suzuki's angiographical stage and the outer diameters of C1 ($P < 0.001$, $r^2 = 0.424$), M1 ($P < 0.001$, $r^2 = 0.485$), and A1 ($P < 0.001$, $r^2 = 0.203$).

II. Laterality of involved arteries in unilateral moyamoya disease

As the next step, the ipsilateral-to-contralateral ratio of the outer diameter of involved arteries was calculated in 20 patients with unilateral moyamoya disease, because the intracranial arteries in the non-involved side (stage 0) could be used as the inner references. Both pediatric (n = 5) and adult patients (n = 15) were included in this analysis, because the ratio may be constant over patients' age. In the controls (n = 17), the ratio of C1, M1, and A1 was 0.99 ± 0.07, 0.98 ± 0.04, and 1.00 ± 0.14, respectively. In patients with severe M1 stenosis (n = 6), the ratio of C1, M1, and A1 was 1.01 ± 0.09, 1.06 ± 0.06, and 0.95 ± 0.27, respectively. The data did not differ between them.

The disease stage in 20 patients with unilateral moyamoya disease was defined as stage 3 in 13 patients, stage 4 in 6, and stage 6 in 1. Fig. 3 demonstrates representative 3D-CISS findings in

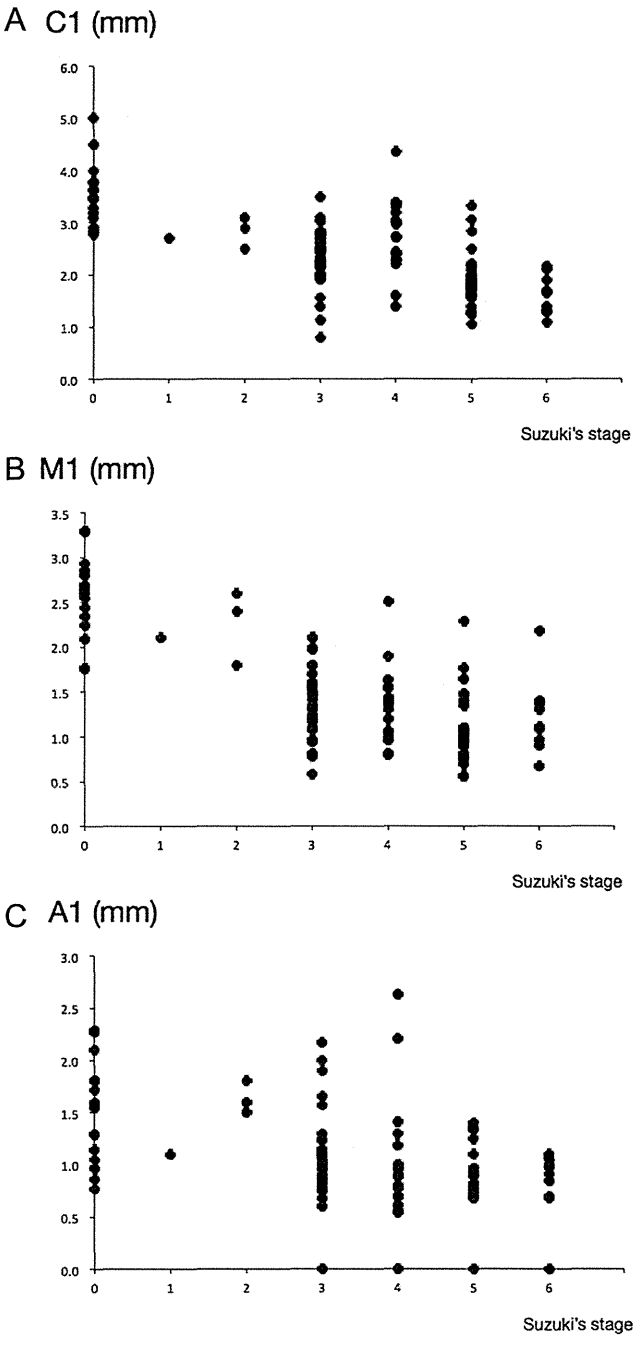

Fig. 2 Plotted graphs show the relationship between Suzuki's angiographical stage and the outer diameter of the C1 (A), M1 (B), and A1 (C) on three-dimensional constructive interference in steady state, respectively.

unilateral moyamoya disease. In patients with unilateral moyamoya disease, the ratio of C1, M1, and A1 was 0.68 ± 0.13, 0.54 ± 0.15, and 0.83 ± 0.34, respectively. Therefore, they had significantly lower ratio of C1 and M1 than the controls and patients with severe M1 stenosis ($P < 0.001$; Fig. 4).

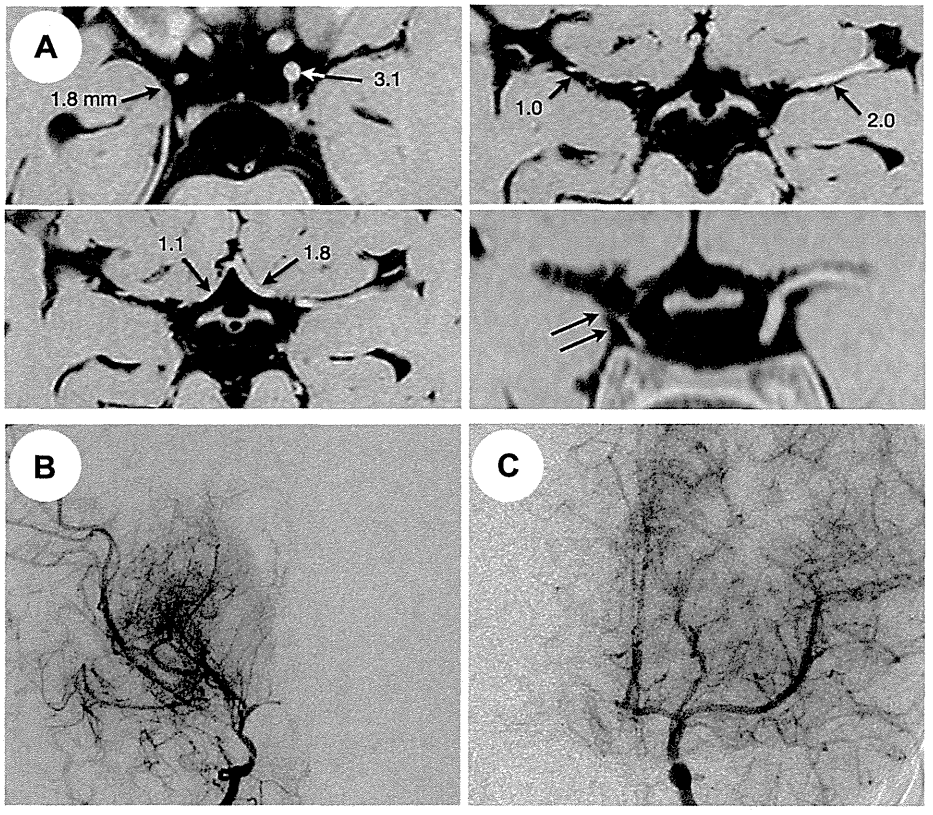

Fig. 3 Representative three-dimensional constructive interference in steady state (A) and magnetic resonance angiography findings (B, C) of a 4-year-old girl with unilateral moyamoya disease. A: The outer diameter of the bilateral C1, M1, and A1 is printed. Note the marked shrinkage of the right carotid fork on a coronal image (*double arrows*). B: Right carotid angiogram shows severe stenosis of the carotid fork and marked development of basal moyamoya vessels, being graded as stage 3. C: Left carotid angiogram shows no definite abnormality (stage 0).

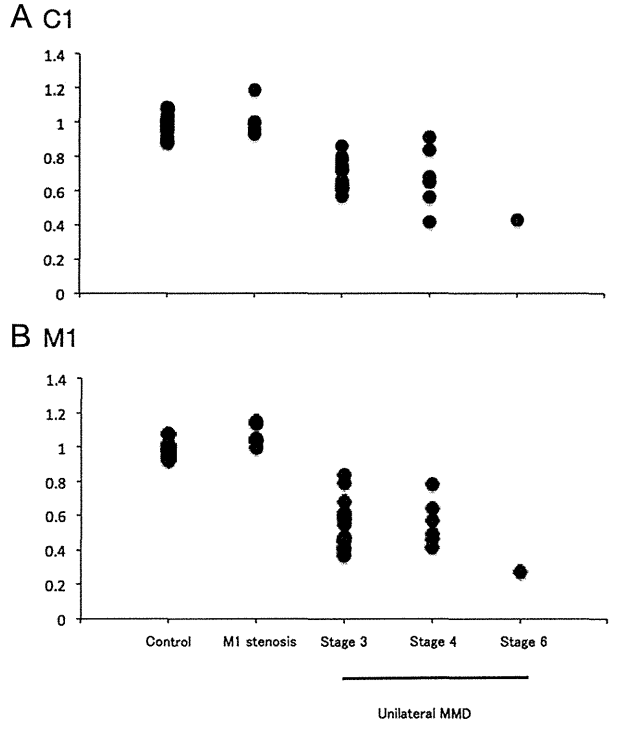

Fig. 4 Plotted graphs show the ipsilateral to contralateral ratio of the outer diameter of the C1 (A) and M1 (B) in normal controls, severe M1 stenosis, and unilateral moyamoya disease. In unilateral moyamoya disease, the data are shown according to Suzuki's angiographical stage.

III. Direct observation of carotid fork in adult moyamoya disease

The carotid fork was directly observed during surgery in three adult patients (Fig. 5). Two of them were male and another was female. Their age was 48 years, 65 years, and 29 years, respectively. In all three patients, the C1, proximal M1, and A1 segments were white-colored, and their outer diameter was much smaller than usual on visual inspection. However, the distal portion of M1 segment had normal red color and larger outer diameter than its proximal portion (Fig. 5). The outer diameter of the C1, proximal M1, and A1 segments was semi-quantitatively determined as the ratio to that of the anterior choroidal artery in each case. As a result, the ratio in the C1, M1, and A1 segment was 1.50 ± 0.25, 1.13 ± 0.38, and 0.87 ± 0.29, respectively. According to Lang (2001), the intracranial ICA and anterior choroidal artery had an average diameter of 3.26 (2.2–4.3) mm and 0.77 (0.4–1.25) mm, respectively.[6] Therefore, the diameter ratio of ICA to anterior choroidal artery can be calculated as 4.23. As a result, the mean value of 1.50 in our series would be much lower than normal controls. Likewise, the average diameter of M1 and A1 segments is 2.7 mm and 2.1 mm in the normal subjects.[6] Their diameter ratio to anterior choroidal artery can be calculated as 3.51 and

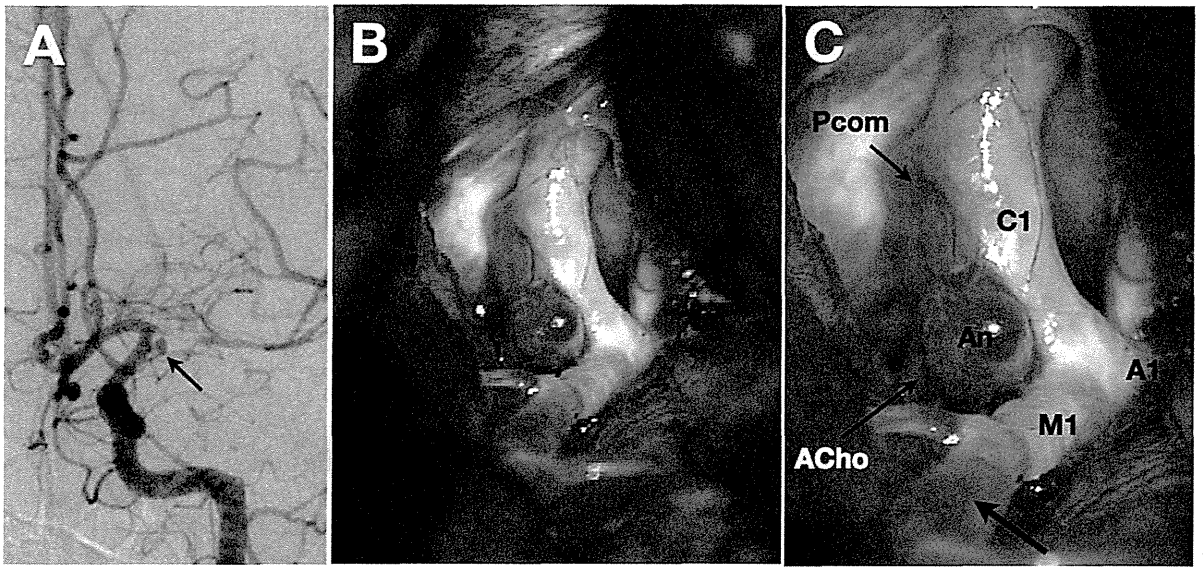

Fig. 5 Radiological and intraoperative findings of a 29-year-old female with moyamoya disease. A: Left carotid angiography reveals a stenosis in the left carotid fork and dilated moyamoya vessels. The horizontal portion of the left middle cerebral artery is severely stenotic. Note the saccular aneurysm (An) arising from the internal carotid artery-anterior choroidal artery junction (*arrow*). B, C: Direct inspection during surgery reveals that the left supraclinoid portion of internal carotid artery (C1) is severely constricted and white-colored, compared with the posterior communicating artery (Pcom) and anterior choroidal artery (ACho). The horizontal portions of middle (M1) and anterior cerebral arteries (A1) look very similar. Note that the distal segment of M1 has the normal red-colored appearance (C, *arrow*).

2.73, being much higher than 1.13 and 0.87 in our series, respectively.

Discussion

Based on radiological and surgical observations, this study clearly shows that the involved arteries decrease their outer diameter in both bilateral and unilateral moyamoya disease. When disease stage progresses, they further decrease their outer diameter in bilateral moyamoya disease. In unilateral moyamoya disease, however, the ratio of the ipsi- to contralateral side did not differ among the disease stage probably because of limited number of samples. The findings are pathognomonic in moyamoya disease. Direct surgical observations support these radiological findings. Previously, there were several studies to evaluate the outer diameter of the involved arteries in moyamoya disease. Using 3D-CISS, Kaku et al. (2012) reported that the outer diameter of ICA and M1 segment is significantly smaller in moyamoya disease than in the control and in M1 stenosis or occlusion. However, they did not evaluate the relationship between their outer diameters and Suzuki's angiographical stage. Their study also included a significant number of pediatric patients when measuring the outer diameter on 3D-CISS, which may underestimate the values in moyamoya disease because the vessel size is smaller in children than in adults.[7] Kim et al. (2013) compared the outer diameter of M1 in 12 patients with moyamoya disease and 20 patients with intracranial atherosclerotic disease, and reported that the outer diameter was significantly smaller in the former than in the latter.[8] Ryoo et al. (2014) also found the shrinkage of M1 segment in 23 patients with moyamoya disease, but concluded that the outer diameter did not differ between stage 1–3 and stage 4–6.[9] Therefore, this is the first study that precisely analyzes the relationship between disease stage and the outer diameter of the involved arteries in a significant number of adult patients with moyamoya disease.

Furthermore, this is the first report to support the 3D-CISS findings by directly observing the carotid fork during surgery in adult patients with moyamoya disease. Surprisingly, the C1, proximal M1, and A1 segments were markedly constricted and white-colored, confirming our preliminary findings.[2] The diameter ratio of these segments to anterior choroidal artery was clearly smaller in moyamoya disease than in the normal subjects.[6] The finding is extremely notable, even thinking about the fact that the anterior choroidal artery is abnormally dilated to supply collateral blood flow in moyamoya

disease. Therefore, the carotid fork is considered abnormally constricted in moyamoya disease. Sample size in this study (n = 3) may be quite small, but it would continue to remain difficult to survey it in larger cohort, because it is quite rare to directly operate on the intracranial aneurysms associated with moyamoya disease nowadays.

Only few histopathological studies have previously paid attention to their outer diameter in moyamoya disease.[10,11] As aforementioned, histopathological findings in the involved arteries include fibrocellular thickening of the intima, an irregular undulation (waving) of the internal elastic lamina, and attenuation of the media, which are very specific for moyamoya disease. As with atherosclerosis, intimal thickening may contribute to luminal stenosis. Recent study has suggested that the circulating endothelial progenitor cells may contribute to intimal thickening in moyamoya disease.[12] On the other hand, attenuation of the media may induce the decrease in arterial wall volume and be related to the narrowing of their outer diameter in moyamoya disease. Takagi et al. (2006) found caspase-3-induced apoptosis in the media of MCA obtained from patients with moyamoya disease.[13] However, few studies have previously discussed the pathophysiological significance of irregular waving of the internal elastic lamina in moyamoya disease. Considering the shrinkage of involved arteries, this unusual phenomenon may be one of important manifestations to decode the unsolved etiology in moyamoya disease. Very interestingly, Uchida et al. (2011) produced a model of coronary artery spasm in the beagles and found that the internal elastic lamina are markedly folded like the "bellows of an old-fashioned camera," suggesting that this phenomenon may play an essential role in coronary artery spasm which causes the narrowing of outer diameter.[14] Histological findings in coronary spasm are very similar to those in moyamoya disease. Taken together, we tentatively propose the hypothesis that both luminal stenosis and outer diameter narrowing may simultaneously develop in the carotid forks and initiate moyamoya disease. Folding of the elastic lamina may play a key role in the outer diameter narrowing through the mechanisms similar to spasm (Fig. 6). The scheme is quite different from the phenomenon of "positive" remodeling that can be

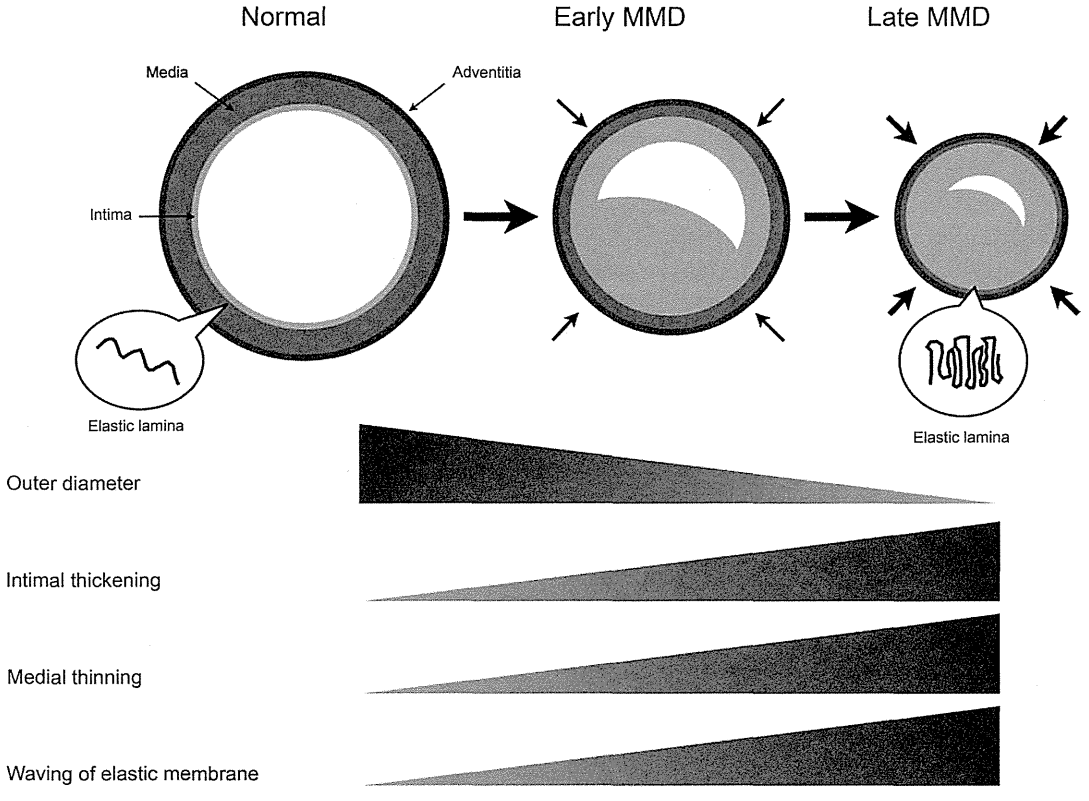

Fig. 6 The diagram shows a novel hypothesis of moyamoya disease development. As pointed out previously, the intimal thickening causes luminal stenosis in the carotid fork. At the same time, however, the carotid fork starts to decrease the outer diameter. These changes gradually progress the disease stage. Both the medial thinning and the waving of elastic lamina may be closely related to the shrinkage of carotid fork. MMD: moyamoya disease.