Development of Hemorrhage-prone Anastomoses in Asymptomatic Moyamoya Disease—A Comparative Study with Japan Adult Moyamoya Trial

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Objective: Present study was aimed to precisely evaluate the angio-architectures in patients with asymptomatic moyamoya disease (MMD) by comparing with those with hemorrhagic stroke. *Methods*: This study used the data set of cerebral angiography in Asymptomatic Moyamoya Registry (AMORE) Study and Japan Adult Moyamoya (JAM) Trial at enrollment. The development of 3 subtypes of collateral vessels, including lenticulostriate, thalamic, and choroidal anastomosis, was evaluated on cerebral angiography. Suzuki's angiographical stage and posterior cerebral artery (PCA) involvement were also assessed. These findings were compared between asymptomatic (AMORE) and hemorrhagic (JAM) groups. *Results*: This study included 55 hemispheres of 35 patients in asymptomatic group and 75 hemispheres of 75 patients in hemorrhagic group. In asymptomatic group, thalamic anastomosis was less developed than in hemorrhagic group (P = .011), but there were no significant differences in the development of lenticulostriate and choroidal anastomosis between the 2 groups (P = .077 and P = .26, respectively). Suzuki's stage was more progressed and the prevalence of PCA involvement was significantly higher in hemorrhagic group than in asymptomatic group (P = .0033 and P = .016, respectively). *Conclusions*: This study reveals no significant differences in the development of choroidal anastomoses between asymptomatic and hemorrhagic-onset MMD. On the other hand, disease stage and PCA involvement were less advanced in asymptomatic MMD than in hemorrhagic-onset MMD. These findings strongly suggest a certain subgroup of asymptomatic patients with MMD is at potential risk for hemorrhagic stroke.

Key Words: Asymptomatic moyamoya disease—collateral vessels—cerebral angiography—hemorrhagic stroke

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Introduction

Moyamoya disease (MMD) is a unique cerebrovascular disorder characterized by progressive stenosis of the terminal portion of the internal carotid artery . The perforating arteries in the basal ganglia and thalamus markedly dilate and function as an important collateral circulation, called as "moyamoya" vessels. Cerebral hemodynamics is often impaired especially in the frontal lobe, leading to transient ischemic attack (TIA) and cerebral infarction. Furthermore, the dilated, fragile moyamoya vessels often rupture and cause intracranial hemorrhage.[1,2] Since before, surgical revascularization is well known to improve cerebral hemodynamics and reduce the risk of subsequent ischemic events such as TIA and ischemic stroke. Recent randomized clinical trial, Japan Adult Moyamoya (JAM) Trial, has also shown that direct or combined bypass can significantly reduce the risk of rebleeding in patients who developed hemorrhagic stroke due to MMD.[3] Subgroup analysis has clarified that patients with posterior hemorrhage are at higher risk of rebleeding and accrue greater benefit from surgery than those with anterior hemorrhage.[4] Furthermore, JAM Trial Investigators (2017) have reported that choroidal anastomosis and PCA involvement are closely related to posterior hemorrhage. Their topographical analysis also revealed good correspondence between the bleeding points and anatomical distribution of choroidal anastomosis.[5]

On the other hand, recent widespread use of MR examination has identified much more patients with asymptomatic MMD than thought before. However, pathophysiology and long-term outcome of asymptomatic MMD is still undetermined. In early 2000's, the first multicenter, nation-wide survey in Japan was conducted to evaluate the prognosis in asymptomatic patients and revealed that the annual risk of stroke was 3.2%. More importantly, the incidence of hemorrhagic stroke was much higher than that of ischemic stroke.[6] However, this study was designed as a historical prospective study, and the sample size was too small (n = 34) to reach any conclusion. Therefore, a multicenter prospective cohort study, Asymptomatic Moyamoya Registry (AMORE) Study has been conducted to clarify the long-term prognosis of asymptomatic patients with MMD since January 2012. Totally 109 patients with asymptomatic MMD have been enrolled during 4 years and medically followed-up for at least 5 years to determine their incidence and predictor of any adverse events including stroke.[7]

Based on these observations, this study was aimed to clarify the angio-architectures in asymptomatic MMD by comparing with those in hemorrhagic hemispheres, because a recent series of subanalyses in JAM Trial have clarified that MMD-specific anastomoses can be categorized according to their risk for subsequent intracranial hemorrhage in MMD. The results would be valuable to stratify the patients with asymptomatic MMD and predict their long-term outcome.

Methods

The study was approved by the ethical committees of all participating centers and was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR, ID: C000000166, 2005 for JAM Trial and C000006640, 2012 for AMORE Study).

Participants and Setting

In this cross-sectional study, angiographic data of asymptomatic MMD were obtained from the data set available at the time of enrollment in AMORE Study. The AMORE study is a prospective multicenter, nation-wide observational study conducted by the Research Committee on MMD in Japan to clarify the epidemiology, pathophysiology, and prognosis in patients with asymptomatic MMD. Patients were enrolled from 20 centers between January 2012 and December 2015, if they met the following criteria: age 20-70 years; bilateral or unilateral MMD on cerebral angiography or MR angiography; no episodes suggestive of TIA, ischemic stroke, and hemorrhagic stroke; possible to conservatively follow-up; and independent in daily life (modified Rankin scale 0 or 1). Exclusion criteria included previous episodes suggestive of TIA, ischemic stroke, and hemorrhagic stroke, and quasi-MMD. All patients provided written informed consent when included in this study. Clinical information at enrollment included patient's age, gender, the clue of diagnosis, past history, family history of MMD, modified Rankin scale, medicine, the frequency, location, and severity of headache, laboratory data, blood pressure, MR imaging (T2-weighted images, T2*-weighted images, and fluid-attenuated inversion recovery images), 3-dimensional time-of-flight MR angiography or cerebral angiography, and single photon emission computed tomography/positron emission tomography data. As aforementioned, the AMORE study is an ongoing study now, therefore only the data obtained at enrollment, including cerebral angiography, were used in the present study.[7]

On the other hand, angiographic data of patients with hemorrhagic-onset MMD was derived from the data set available at the time of enrollment in the JAM Trial. Detailed information on the participants and setting of the JAM Trial has been presented elsewhere.[3] Patients with MMD were enrolled from 22 centers if they had experienced intracranial hemorrhage within 12 months before randomization, were 16-65 years old, were independent in daily life (modified Rankin Scale Score 0-2), had completed acute-phase treatment at least 1 month before randomization, and had been free from ischemic/hemorrhagic attack for at least 1 month. Patients with

ruptured aneurysms on the circle of Willis were excluded. In both AMORE Study and JAM Trial, MMD was diagnosed according to the guidelines proposed in 1997.[3]

Radiological Evaluation

The Image Determination Committee, which included 5 members (M.F., T.F., J.C.T, S.K., S.M.), recorded the presence or absence of each type of collaterals in each hemisphere according to the criteria outlined below. All 5 members of the Image Determination Committee attended the discussion on the angiographic findings in all cases, and the angiographic grades in each collateral type, Suzuki's disease stage, and PCA involvement were ultimately decided after they got unanimous in their approval of the particular grade.

Abnormal Collateral Vessels (Moyamoya)

The development of abnormal collateral vessels in the basal and periventricular regions was also analyzed according to classification system introduced in our previous study (Table 1).[5] Briefly, collateral vessels were classified into 3 types: lenticulostriate anastomosis, thalamic anastomosis, and choroidal anastomosis.

Lenticulostriate Anastomosis

Lenticulostriate anastomosis is anatomically defined as an anastomosis between the lenticulostriate artery (LSA) and the medial end of the medullary artery, serving as a supply route to the cortex.[5] We defined Grade 0 as no dilatation and no extension of LSAs, Grade 1 as dilation and extension of LSAs below the level of the pericallosal artery, and Grade 2 as dilation and extension of LSAs beyond the level of the pericallosal artery in the lateral view. Grade 2 was ultimately considered to be a positive angiographic indicator of lenticulostriate anastomosis (Fig 1A).

Thalamic Anastomosis

This type of collateral is defined as an anastomosis between thalamic perforators and the medial end of the medullary artery or the insular artery, serving as a supply route to the cortex.[5] The thalamotuberal artery arising from the posterior communicating artery and thalamoperforating artery arising from the posterior cerebral artery are the origins of such an anastomosis. We defined Grade 0 as no dilatation and no extension of thalamic perforators, Grade 1 as dilation and extension of thalamic perforators below the level of the medial posterior choroidal artery, and Grade 2 as dilation and extension of thalamic perforators beyond the level of the medial posterior choroidal artery. Grade 2 was ultimately considered to be a positive angiographic indicator of thalamic anastomosis (Fig 1B and C).

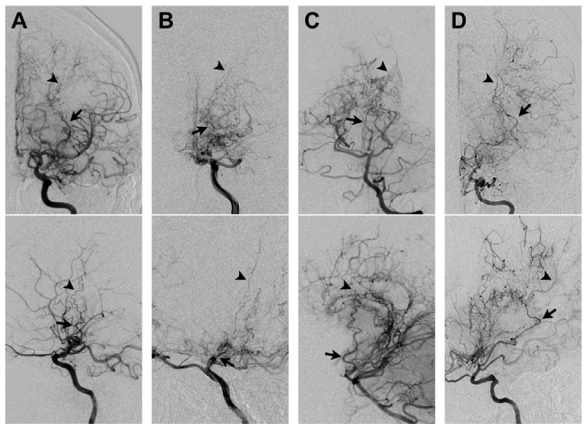

Figure 1. *Representative findings of Grade 2 in the lenticulostriate (A), thalamic (B and C), and choroidal anastomosis (D). Anteroposterior and lateral views are shown in the upper and lower panel, respectively. The perforating or choroidal arteries are indicated by arrows, and the medullary arteries are indicated by arrowheads. Each anastomosis was categorized into 3 grades based on the degree of development* (see the text).

Choroidal Anastomosis

This type of collateral is typically defined as an anastomosis between the choroidal artery and the medial end of the medullary artery.[5] Both the anterior and lateral posterior choroidal arteries can serve as the origin of such an anastomosis. A positive angiographic (lateral view) indicator of choroidal anastomosis is extreme dilation and extension of the choroidal artery with sudden deviation from the shape of the lateral ventricle at its peripheral portion to connect to the medullary artery.[5] In the anteroposterior view, this collateral is similar to lenticulostriate anastomosis in that it has a typical sharp inflection

Table 1. *Demographic data of asymptomatic and hemorhagic moyamoya disease patient*

Variable	Asymptomatic group	Hemorrhagic group	*P* value
No. of patients	35	75	
No. of hemispheres	55	75	
Mean age ± SD, y	44.5 ± 9.9	41.9 ± 11.4	.18
Female sex	26 (74.3%)	51 (68.0%)	.50
Hypertention	15 (42.9%)	15 (20.0%)	.012
Diabetes mellitus	4 (11.4%)	3 (4.0%)	.14
Hyperlipidemia	6 (17.1%)	4 (5.3%)	.045

laterally.[5] Another positive indicator is the extreme extension of the anterior choroidal or lateral posterior choroidal artery beyond the atrium of the lateral ventricle to reach the body of the lateral ventricle. Regarding the medial posterior choroidal artery, the anastomosis is considered positive when the artery connects to the pericallosal artery by penetrating the corpus callosum. We defined Grade 0 as no dilatation and no extension of the choroidal artery, Grade 1 as dilation and extension of the choroidal artery below the shape of the lateral ventricle, and Grade 2 as dilation and extension of the choroidal artery beyond the shape of the lateral ventricle. Grade 2 was ultimately considered to be a positive angiographic indicator of choroidal anastomosis (Fig 1D).

Disease Stage

Using cerebral angiography, each involved hemisphere was graded into 6 stages according to Suzuki's angiographical staging.[1]

PCA Involvement

The degree of PCA involvement was categorized into 3 grades on the basis of the findings of cerebral angiography. We defined Grade 0 as no steno-occlusive change in PCA, Grade 1 as the presence of stenosis greater than 50% in the P1−P3 segments of the PCA with decreased delineation of the cortical arteries, and Grade 2 as occlusion of the PCA.[5]

Statistical Analysis

Continuous data were expressed as mean ± standard deviation. The differences in development of abnormal collateral vessels, Suzuki's angiographical stage, and degree of PCA involvement between patients enrolled in AMORE Study and in JAM Trial were assessed using chi-square test. Multiple logistic regression models were used to adjust for age and sex. As for comparison of the baseline characteristics, unpaired *t* test was used. Differences were considered statistically significant when the *P* value was $<.05$.

Results

Cerebral angiography was performed at enrollment into AMORE Study in 35 (32.1%) of 109 patients with asymptomatic MMD. Of these, 15 patients were classified into unilateral type and 20 were classified into bilateral type. Therefore, totally 55 hemispheres of 35 patients were included in this study as asymptomatic group. On the other hand, totally 80 hemorrhagic-onset patients were enrolled in the JAM Trial as reported elsewhere.[3] Of these, 4 were excluded from the present analysis because their hemispheres in which their hemorrhage occurred could not be determined; specifically, in 3 of these patients the hemorrhage occurred on the midline and in the remaining patient the diffusely distributed intraventricular hemorrhage occurred in the bilateral ventricles. Another patient was excluded because the original angiography study of that patient had been lost. Therefore, 75 hemorrhagic hemispheres of 75 patients were included in this study as hemorrhagic group. Taken together, 55 hemispheres in 35 asymptomatic patients and 75 hemorrhagic hemispheres in 75 hemorrhagic-onset patients were included in this comparative analysis.

Demographic Data

All patients included in this study were older than 18 years. Their mean age was 44.5 ± 9.9 and 41.9 ± 11.4 years in asymptomatic and hemorrhagic group, respectively. The ratio of female patients was 74.3% (26/35) and 68.0% (51/75) in asymptomatic and hemorrhagic group, respectively. There were no significant differences in age and gender between 2 groups ($P = .18$ and $P = .50$, respectively). As shown in Table 1, the prevalence of patients with hypertension and hyperlipidemia were significantly higher in asynptomatic group than in hemorrhagic group ($P = .012$ and .045, respectively). There were no significant difference in that of patients with diabetes mellitus between 2 groups ($P = .14$).

Abnormal Collateral Vessels (Moyamoya)

As shown in Fig 2A, lenticulostriate anastomosis in asymptomatic hemispheres was judged as Grade 0 in 5 hemispheres (9.1%), Grade 1 in n = 42 (76.4%), and Grade 2 in 8 (14.5%). On the other hand, lenticulostriate anastomosis in hemorrhagic hemispheres was judged as Grade 0 in 11 hemispheres (14.7%), Grade 1 in 43 (57.3%), and Grade 2 in 21 (28.0%). There was no significant difference in the development of lenticulostriate anastomosis between asymptomatic and hemorrhagic group ($P = .077$). In univariate analysis, the odds ratio of Grade 2 lenticulostriate anastomosis showed no significant difference between 2 groups ($P = .069$). Even after age/sex adjustments, there was no significant difference between them ($P = .10$, Table 2).

As shown in Fig 2B, thalamic anastomosis in asymptomatic hemispheres was judged as Grade 0 in 37 hemispheres (67.3%), Grade 1 in 11 (20.0%), and Grade 2 in 7 (12.7%). On the other hand, thalamic anastomosis in hemorrhagic hemispheres was judged as Grade 0 in 31 hemispheres (41.3%), Grade 1 in 22 (29.3%), and Grade 2 in 22 (29.3%). Therefore, the development of thalamic anastomosis was significantly more pronounced in hemorrhagic group than in asymptomatic group ($P = .011$). In univariate analysis, the odds ratio of Grade 2 thalamic anastomosis was significantly higher in hemorrhagic group than in asymptomatic group ($P = .028$). After age/sex adjustments, it remained significantly higher in hemorrhagic group ($P = .039$, Table 2).

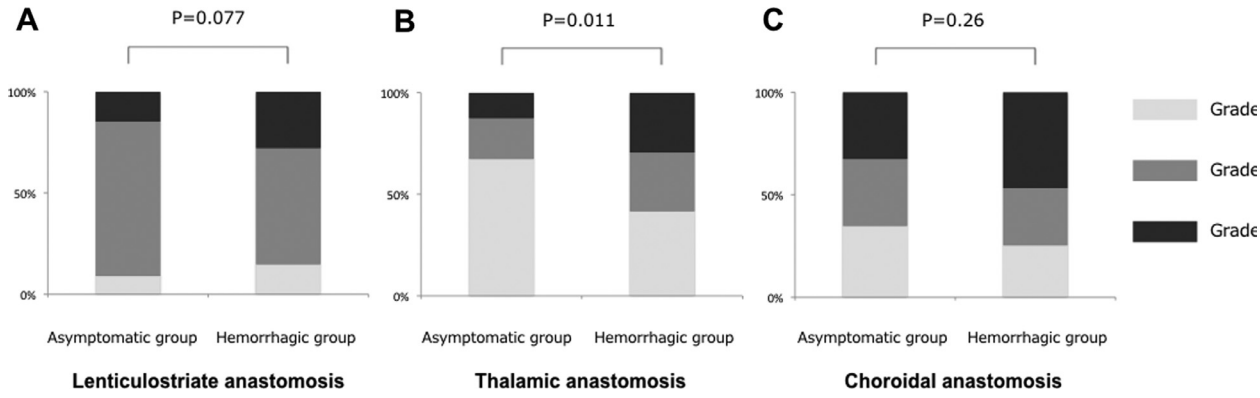

Figure 2. *The bar graphs demonstrate the development of lenticulostriate (A), thalamic (B), and choroidal anastomosis (C) in asymptomatic and hemorrhagic groups. There are no significant differences in development of lenticulostriate and choroidal anastomosis between asymptomatic and hemorrhagic groups* (P = *.077 and* P= *.26, respectively, A and C). On the other hand, the development of thalamic anastomosis is more pronounced in hemorrhagic group than that in asymptomatic group* (P = *.011, B).*

As shown in Fig 2C, choroidal anastomosis in asymptomatic hemispheres was judged as Grade 0 in 19 hemispheres (34.5%), Grade 1 in 18 (32.7%), and Grade 2 in 18 (32.7%). On the other hand, choroidal anastomosis in hemorrhagic hemispheres was judged as Grade 0 in 19 hemispheres (25.3%), Grade 1 in 21 (28.0%), and Grade 2 in 35 (46.7%). There was no significant difference in the development of choroidal anastomosis between asymptomatic and hemorrhagic group (P = .26). In univariate analysis, the odds ratio of Grade 2 choroidal anastomosis showed no significant difference between 2 groups (P = .11). Even after age/sex adjustments, there was no significant difference between them (P = .11, Table 2).

Disease Stage

As shown in Fig 3A, Suzuki's angiographical stage in asymptomatic hemispheres was judged as Stage 1 in 1 hemisphere (1.8%), Stage 2 in 9 (16.4%), Stage 3 in 23 (41.8%), Stage 4 in 19 (34.5%), Stage 5 in 2 (3.6%), and Stage 6 in 1 (1.8%). In hemorrhagic group, however, Suzuki's angiographical stage in hemorrhagic hemispheres was judged as Stage 2 in 2 hemispheres (6.4%), Stage 3 in 22 (29.3%), Stage 4 in 35 (46.7%), and Stage 5 in 16 (21.3%). There was a significant difference in Suzuki's angiographical stage between 2 groups (P = .0033). In univariate analysis, the odds ratio of advanced Suzuki's stage (stage 4-6) was significantly higher in hemorrhagic group than in asymptomatic group (P = .0015). After age/sex adjustments, it remained significantly higher in hemorrhagic group (P = .0011, Table 3). Thus, the disease stage was more advanced in hemorrhagic group than in asymptomatic group.

PCA Involvement

In asymptomatic group, the PCA involvement score included Grade 0 in 49 hemispheres (89.1%), Grade 1 in 3 (5.5%), and Grade 2 in 3 (5.5%). In hemorrhagic group, however, the PCA involvement score included Grade 0 in 51 hemispheres (68.0%), Grade 1 in 8 (10.7%), and Grade 2 in 16 (21.3%). The prevalence of PCA involvement was significantly higher in hemorrhagic group than in asymptomatic group (P = .016). In univariate analysis, the odds

Table 2. *Univariate and multivariate-adjusted ORs for Grade 2 abnormal collateral vessels*

	Grade ≤ 1		Grade 2		Crude			Age/sex adjusted		
	No.	%	No.	%	OR	95% CI	*P* value	OR	95% CI	*P* value
Lenticulostriate anastomosis										
Asymptomatic group	47	85.4%	8	14.5%	1.00	Reference		1.00	Reference	
Hemorrhagic group	54	72.0%	21	28.0%	2.28	.93-5.64	.069	2.18	.86-5.54	.10
Thalamic anastomosis										
Asymptomatic group	48	87.3%	7	12.7%	1.00	Reference		1.00	Reference	
Hemorrhagic group	53	70.6%	22	29.3%	2.79	1.09-7.11	.028	2.75	1.05-7.16	.039
Choroidal anastomosis										
Asymptomatic group	37	67.3%	18	32.7%	1.00	Reference		1.00	Reference	
Hemorrhagic group	40	53.3%	35	46.7%	1.80	.87-3.71	.11	1.84	.88-3.87	.11

Abbreviations: CI, confidence interval; OR, odds ratio.

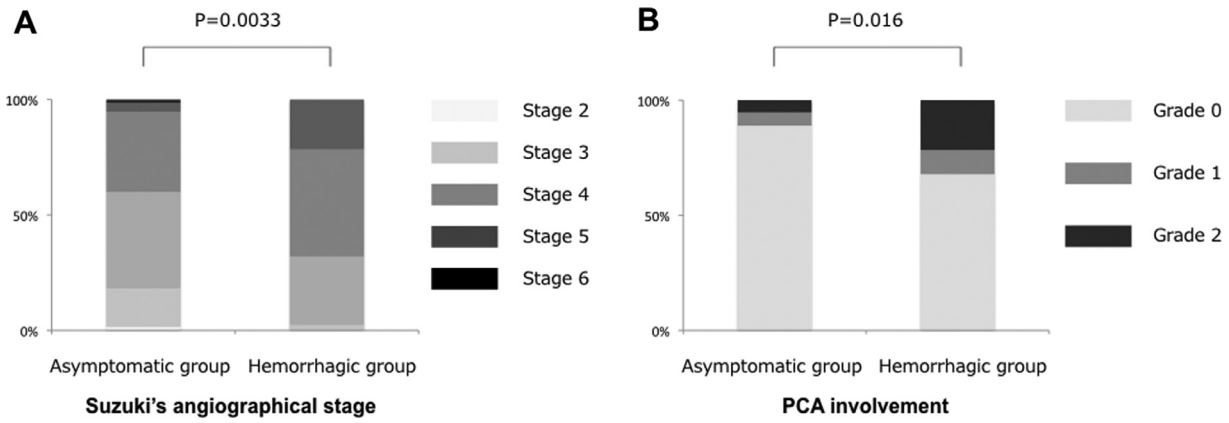

Figure 3. *The bar graphs show the Suzuki's angiographical stage (A) and degree of PCA involvement (B) in asymptomatic and hemorrhagic groups. Suzuki's angiographical stage was more advanced in hemorrhagic group than in asymptomatic group* (P= .0033). *On the other hand, the prevalence of PCA involvement was significantly higher in hemorrhagic group than in asymptomatic group* (P= .016).

ratio of PCA involvement (Grade 1-2) was significantly higher in hemorrhagic group than in asymptomatic group (P = .0048). After age/sex adjustments, it remained significantly higher in hemorrhagic group (P = .0027, Table 4).

Discussion

Previously, some investigators pointed out the differences in the development of abnormal collateral vessels between ischemic- and hemorrhagic-onset MMD. Irikura et al (1996) assessed the findings on cerebral angiography in 9 ischemic- and 10 hemorrhagic-onset patients, and found that the choroidal arteries more remarkably developed in hemorrhagic-onset patients.[8] Morioka et al (2003) reported that the extension and dilation of choroidal and/or thalamic perforating arteries could predict bleeding.[9] Liu et al (2011) also reviewed the findings on cerebral angiography in 79 ischemic- and 64 hemorrhagic-onset hemispheres, and reported that the extension and dilation of the anterior choroidal artery and posterior communicating artery significantly correlated with the occurrence of hemorrhagic events.[10] Very recently, Yamamoto et al (2018) reported that the posterior communicating artery, anterior choroidal artery, and posterior choroidal artery more distinctly developed in hemorrhagic-onset hemispheres than in ischemic-onset hemispheres.[11] Furthermore, JAM Trial Investigators conducted a case-control study to compare the development of abnormal collateral vessels between 103 ischemic- and 75 hemorrhagic hemispheres. As the results, the hemorrhagic-onset patients had significantly more prominent extension and dilation of thalamic (P = .043) and choroidal anastomosis (P < .001), but not of lenticulostriate anastomosis (P = .387) than ischemic-onset patients.[12] These observations correlate very well with the findings that thalamic and choroidal anastomoses play an important role as the source of hemorrhage, and strongly suggest that angio-architectures of abnormal vascular network at the base of brain may distinctly differ between ischemic- and hemorrhagic-type MMD.[13,14]

On the other hand, this is the first study to denote the differences in the development of abnormal collateral vessels at the base of brain between hemorrhagic-onset and asymptomatic MMD. As aforementioned, the significance of this study is considered very high because of several reasons. First, the long-term outcome of asymptomatic MMD is still obscure, although a prospective, multicenter cohort study (AMORE) is now conducted. Second, previous small-volume study demonstrated that annual risk of any stroke was not so low, 3.2%. Especially, hemorrhagic stroke developed in 3 (75%) of 4 patients who experienced any stroke during follow-up periods.[15] The present study reveals a significant difference in the angio-architectures between asymptomatic MMD and hemorrhagic-onset

Table 3. *Comparison of Suzuki's angiographical stage between asymptomatic and hemorrhagic groups*

	Suzuki's stage									
	Stage < 4		Stage ≥ 4		Crude			Age/sex adjusted		
	No.	%	No.	%	OR	95% CI	*P* value	OR	95% CI	*P* value
Asymptomatic group	33	60.0%	22	40.0%	1.00	Reference		1.00	Reference	
Hemorrhagic group	24	32.0%	51	68.0%	3.19	1.54-6.58	.0015	3.55	1.66-7.60	.0011

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 4. *Univariate and multivariate-adjusted ORs for PCA involvement*

	PCA involvement									
	Grade 0		Grade ≥ 1		Crude			Age/sex adjusted		
	No.	%	No.	%	OR	95% CI	*P* value	OR	95% CI	*P* value
Asymptomatic group	49	89.1%	6	10.9%	1.00	Reference		1.00	Reference	
Hemorrhagic group	51	68.0%	24	32.0%	3.84	1.45-10.2	.0048	4.78	1.72-13.3	.0027

Abbreviations: CI, confidence interval; OR, odds ratio; PCA, posterior cerebral artery.

MMD. However, the difference pattern is very unique, being different from that between hemorrhagic- and ischemic-onset MMD. Thus, the development of thalamic anastomosis is less prominent in asymptomatic patients than in hemorrhagic-onset patients (P = .011), but there are no significant differences in the development of lenticulostriate and choroidal anastomoses between them. Especially, the fact that choroidal anastomosis significantly develops in a subgroup of asymptomatic MMD patients is very striking, because this anastomosis is considered as a "dangerous" anastomosis for posterior hemorrhage in MMD nowadays. When combining the data from this study and our recent study,[12] the prevalence of Grade-2 choroidal anastomosis was 46.7% in hemorrhagic-onset MMD, 32.7% in asymptomatic MMD, and 16.5% in ischemic-onset MMD. According to the reports from JAM Trial group, there was no significant differences in the development of periventricular collaterals between hemorrhagic and nonhemorrhagic hemispheres in hemorrhagic group. For example, the prevalence of Grade 2 choroidal channel was 41.7% in nonhemorrhagic side of nonsurgical cohort and 47% in hemorrhagic side of whole cohort. Surprisingly, the prevalence of Grade-2 choroidal anastomosis in asymptomatic MMD is comparable to that in hemorrhagic-onset MMD and is much higher than that in ischemic-onset MMD. In other words, at least a certain subgroup of MMD patients potentially have well-developed choroidal anastomosis before their onset and are possibly at higher risk for hemorrhagic stroke. The fact strongly suggests that asymptomatic MMD is neither a "silent" nor "stable" disorder, and may readily cause stroke, especially hemorrhagic stroke. Final results of AMORE Study are warranted.

It is completely unclear why the development of these pathognomonic anastomoses largely differs among asymptomatic, ischemic-type, and hemorrhagic-type MMD. However, very recent study has demonstrated the interethnic difference of collateral angio-architectures in MMD. Thus, the development of choroidal anastomosis was significantly more remarkable in Japanese than in European Caucasians. Ageing diminished lenticulostriate anastomosis and advanced thalamic and choroidal anastomoses in Japanese, but not in European Caucasians.[16] The finding correlates very well with the lower incidence of hemorrhagic stroke in Caucasians, and strongly suggests that some variations in biological features among the patients with MMD may determine the development of collaterals and onset type. Further clinical researches would shed the light on this issue.

In this study, disease stage was significantly less advanced in asymptomatic patients than in hemorrhagic-onset patients on Suzuki's angiographical score (P = .0033). Likewise, when combining the data from this study and our recent study,[12] the prevalence of advanced disease stage (Stage 4-6) was 68% in hemorrhagic-onset MMD, 52.4% in ischemic-onset MMD, and 39.9% in asymptomatic MMD. The fact strongly suggests that the disease period may be shorter in asymptomatic MMD than in the others and asymptomatic MMD has the potential risk of disease progression. It is well known that occlusive arterial lesions in adult MMD progress in both anterior and posterior circulation, in both symptomatic and asymptomatic patients, and in both bilateral and unilateral types.[6] Disease progression is closely related to the onset of ischemic stroke in asymptomatic MMD.[15] Disease progression also diminishes lenticulostriate anastomosis and accelerates the development of thalamic and choroidal anastomoses, which play an important role in the onset of hemorrhagic stroke in MMD.[11] Therefore, the disease stage may further advance in asymptomatic MMD, indicating the importance to repeat MR examinations with a constant interval. In addition, this study clearly showed that the prevalence of PCA involvement was significantly lower in asymptomatic patients than in hemorrhagic-onset patients (P = .016). PCA involvement is linked to disease progression, and readily causes TIA and/or ischemic stroke not only in the territory of PCA but also in the territory of anterior circulation, because the PCA is an important route of spontaneous collaterals to anterior circulation in MMD.[17-20] PCA involvement is also known as an independent factor for posterior hemorrhage, probably because cerebral ischemia in the posterior half of brain induces the development of thalamic and choroidal anastomosis to provide blood flow to the parietal and posterior temporal lobes.[5] Taken together, disease progression and PCA involvement may occur in patients with asymptomatic MMD, and even if 2 phenomena occur simultaneously or separately, they may possibly lead to the onset of either ischemic or hemorrhagic stroke. Therefore, it would be essential to serially

monitor their disease status in order to predict the occurrence of stroke in patients with asymptomatic MMD. Noninvasive examinations such as MR angiography should be recommended because they can be repeated at outpatient clinic.[21]

There are some limitations in this study. First, we recruited the angiographical data of asymptomatic MMD patients from AMORE Study. In this study, 109 subjects were enrolled, but cerebral angiography was performed in 35 patients (32.1%). Therefore, the sample size is a little bit small, when compared with the data from JAM Trial (n = 80). Further studies with larger cohort would be warranted to confirm the present results. Second, AMORE Study is an on-going study, and the potential risk of periventricular collaterals in asymptomatic MMD patients is still undetermined. Third, the present findings were derived from angiographical data of adult MMD patients. Therefore, these should not be applied to pediatric MMD patients.

Conclusions

This study reveals no significant differences in the development of choroidal anastomoses between asymptomatic and hemorrhagic-onset MMD. On the other hand, disease stage and PCA involvement were less advanced in asymptomatic MMD than in hemorrhagic-onset MMD. These findings strongly suggest a certain subgroup of asymptomatic patients with MMD is at potential risk for hemorrhagic stroke.

Declaration of Competing Interest

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

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