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ORIGINAL ARTICLE - VASCULAR NEUROSURGERY - OTHER

Difference in periventricular anastomosis in child and adult moyamoya disease: a vascular morphology study

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Abstract

Backgrounds Periventricular anastomosis (PA), which is a novel term for extended collateral vessels in moyamoya disease (MMD), is reportedly associated with a high risk of intracranial hemorrhage in adult patients. The present study aimed to clarify the similarities and the differences in the development of PA between three MMD groups, classified by age at the time of diagnosis and clinical phenotype.

Methods This study included 232 hemispheres of 132 patients with MMD who underwent surgical revascularization. The subjects were classified into child ischemic (CI) group, adult ischemic (AI) group, and adult hemorrhagic (AH) group. We evaluated the lenticulostriate (LSA), thalamic (THA), choroidal (ChA), anterior choroidal (AChA), and posterior choroidal (PChA) anastomosis as well as the posterior cerebral artery (PCA) involvement. The PA scores and the sums of each grade of LSA, THA, and ChA anastomosis were also calculated in all of the cases.

Results In a multiple comparison test, the PA scores ($P < 0.01$), LSA ($P < 0.01$), and ChA anastomosis ($P = 0.013$) were more prominent in the CI than in the AI group. The PA scores ($P < 0.01$) and LSA ($P = 0.011$), ChA ($P < 0.01$), AChA ($P < 0.01$), and PChA anastomosis ($P = 0.016$) were more prominent in the AH group than in the AI group. The CI and AH groups showed similar characteristics except for PCA involvement. After multivariate adjustments using the AI group as a reference group, the PA scores and the positive rates of LSA and ChA anastomosis remained significantly higher in the CI and AH groups.

Conclusion The patterns of PA development in the CI and AH groups were similar in that they were more prominent than in the AI group. These findings may contribute to a better understanding of the progression of ischemic and hemorrhagic MMD.

Keywords Moyamoya disease · Periventricular anastomosis · Angiography · Vascular disease

Introduction

Moyamoya disease (MMD) is a unique cerebrovascular disorder characterized by chronic progressive occlusion of the terminal portion of the internal carotid artery and has a hazy network of basal perforating arteries [6, 18, 19]. Periventricular anastomosis (PA) is an unusual angiographic finding that indicates the development of collateral vessels connecting to the medullary arteries in the periventricular region, arising from the lenticulostriate artery (LSA), thalamic artery (THA), and choroidal artery (ChA) [2–4]. These abnormal collateral channels, especially the choroidal collaterals, have been considered as a main indicator of increased hemorrhagic risk in MMD [3, 4, 20].

Recent studies have demonstrated that the pattern of PA differs between child and adult MMD and also between adult ischemic-onset and adult hemorrhagic-onset MMD [1, 8]. However, to the best of our knowledge, there have been no multiple comparisons between the three different clinical subgroups, which are defined by both age and clinical presentation. We report the analysis of the angiographic findings in child ischemic (CI), adult ischemic (AI), and adult hemorrhagic (AH) MMD patients, focusing on the PA.

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Materials and methods

This observational cohort study was approved by the Ethics Committee of the National Cerebral and Cardiovascular Center (IRB approval no. M30-013).

Patient selection

This retrospective study included 232 hemispheres of 132 patients with MMD who had undergone surgical revascularization between March 2014 and March 2018. The patients were diagnosed as "definite MMD" or "unilateral MMD" according to the guidelines of the research committee on MMD established by the Japanese Ministry of Health and Welfare [6]. A unilateral evaluation was performed in 32 patients (30 patients with unilateral MMD and 2 patients with prior history of surgical revascularization). The subjects were divided into three groups according to their age at the time of diagnosis and the type of clinical presentation (ischemic or hemorrhagic). Ischemic presentations were defined as transient ischemic attacks (TIAs) or completed stroke. The affected hemispheres in the patients < 16 years old were included in the (1) CI group ($n = 79$). All of the pediatric patients had ischemic presentations. The affected hemispheres in patients ≥ 16 years old were divided into two groups according to the type of clinical presentation as (2) AI group ($n = 95$) and (3) AH group ($n = 58$). The patients' demographic data are summarized in Table 1. The mean ages (± standard deviation) in the AI and AH groups were 40.5 ± 12.0 years and 41.8 ± 10.8 years, respectively, with no significant difference ($P = 0.18$). The female percentage in the AH group was significantly higher than that in the CI group ($P = 0.002$).

Angiographic evaluation

The preoperative digital subtraction angiograms were retrospectively reviewed. The present study employed a PA grading system introduced in the supplementary study of the Japan Adult Moyamoya (JAM) trial with minor modification to evaluate the development of collateral vessels [1, 4].

Collateral vessels were categorized into LSA, THA, and ChA collaterals [3, 4]. Our only modification was that the ChA collaterals were dichotomized into anterior choroidal artery (AChA) and posterior choroidal artery (PChA) collaterals. The grade of ChA collateral was defined as a higher value of AChA collateral or PChA collateral. The grade of PChA collateral was also defined as a higher value of the lateral or medial PChA collateral.

The collateral vessel of each group was graded as 0, 1, or 2 [1]. Grade 0 was defined as the artery with no dilation and extension. Grade 1 was defined as the artery showing the intermediate findings between grades 0 and 2. The remarkably dilated and extended arteries were assessed as grade 2. The grading criteria and the typical images of grade 2 collaterals are shown in Fig. 1. "Positive LSA anastomosis" (grade 2 LSA collateral) was defined as LSAs connecting the medullary arteries near the frontal horn or body of the lateral ventricle beyond the pericallosal line. "Positive THA anastomosis" (grade 2 THA collateral) was defined as thalamotuberal or thalamo-perforating arteries connecting the medullary arteries beyond the medial PChA. "Positive ChA anastomosis" was defined when the AChA and/or PChA collateral had a grade of 2. Grade 2 AChA and lateral PChA collateral was defined as the choroidal arteries connecting the medullary arteries beyond the lateral wall of the body or the atrium of the lateral ventricle. Grade 2 medial PChA collateral was defined as the artery penetrating the corpus callosum and connecting to the pericallosal artery.

The PA score was calculated as the sum of each grade of LSA, THA, and ChA collateral for each patient, ranging from 0 to 6. Posterior cerebral artery (PCA) involvement was defined as the presence of occlusion or stenosis > 50% in the P1 to P3 segment of ipsilateral PCA [4].

All of the angiographic images were reviewed by three neurosurgeons (J.R., E.H., and J.C.T.) who were completely blinded to the patients' clinical information, and a consensus was reached by all three raters. The senior neurosurgeon (J.C.T.) had experience in PA judgment as a member of the image-determination committee in the supplementary studies of the JAM trial [1, 4].

Statistical analyses

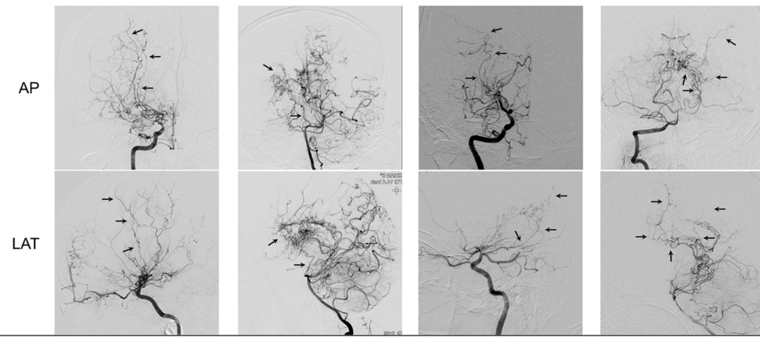
The Kruskal-Wallis test and the chi-squared test were conducted to evaluate the differences in the PA scores and the proportion of each grade 2 collateral among the three groups. If a significant difference was found using the Kruskal-Wallis test and chi-squared test, we performed a post hoc multiple comparison (Mann-Whitney test and chi-squared test) with the Bonferroni correction. Statistical significance was set at $P < 0.05$, except for when the Bonferroni correction was used for multiple comparisons, in which case statistical significance was set at $P < 0.0167$. The multiple logistic regression models were used to adjust for age and sex. All of the statistical analyses were performed using SPSS 24.0 software (SPSS Inc., Chicago, IL, USA).

Table 1 Clinical characteristics of 132 patients with moyamoya disease

	CI group	AI group	AH group
No. of patients (hemispheres)	44 (79)	55 (95)	33 (58)
Age (mean ± SD)	8.7 ± 3.3	40.8 ± 11.7	42.6 ± 10.0
Female (%)	22 (50.0%)	36 (65.5%)	28 (84.8%)

**AH* adult hemorrhagic, *AI* adult ischemic, *CI* child ischemic

	LSA	THA	AChA	PChA
Grade 0	No dilation and extention	No dilation and extention	No dilation and extention	No dilation and extention
Grade 1	Dilatation and/or extension below the level of the pericallosal artery	Dilatation and/or extension below the level of the MPChA	Dilatation and/or extension below the level of the lateral ventricle	Dilatation and/or extension below the level of the pericallosal artery (MPChA) and the lateral ventricle (LPChA)
Grade 2	Dilation and extension beyond the level of the pericallosal artery	Dilation and extension beyond the level of the MPChA	Dilation and extension beyond the level of lateral ventricle	Dilation and extension to the pericallosal artery (MPChA) and beyond lateral ventricle (LPChA)



PA Score	A sum of LSA grade, THA grade and ChA grade (ChA grade, a higher value of between AChA grade and PChA grade)

Fig. 1 The periventricular anastomosis grading system for evaluating each type of collateral vessels. This system is a minor modified version of the method described by Funaki et al. Typical angiographic findings of LSA, THA, AChA, and PChA anastomosis were included. The anteroposterior and lateral views are shown in the upper and lower rows, respectively. The solid arrows in the images indicate the running course of each anastomosis. *AChA, anterior choroidal artery; ChA, choroidal artery; LSA, lenticulostriate artery; LPChA, lateral posterior choroidal artery; MPChA, medial posterior choroidal artery; PChA, posterior choroidal artery; THA, thalamic artery

Results

Angiographic evaluation

Table 2 and Figs. 2 and 3 show the angiographic features in each group.

Table 2 Angiographic findings in child ischemic (CI), adult ischemic (AI), and adult hemorrhagic (AH) groups

Collateral vessels	Grade	CI group	AI group	AH group
LSA	0/1	47 (59.5%)	74 (77.9%)	34 (58.6%)
	2	32 (40.5%)	21 (22.1%)	24 (41.4%)
THA	0/1	64 (81.0%)	87 (91.6%)	52 (89.7%)
	2	15 (19.0%)	8 (8.4%)	6 (10.3%)
ChA	0/1	30 (38.0%)	54 (56.8%)	16 (27.6%)
	2	49 (62.0%)	41 (43.2%)	42 (72.4%)
AChA	0/1	38 (48.1%)	61 (64.2%)	24 (41.4%)
	2	41 (51.9%)	34 (35.8%)	34 (58.6%)
PChA	0/1	58 (73.4%)	81 (85.3%)	40 (69.0%)
	2	21 (26.6%)	14 (14.7%)	18 (31.0%)
PA score (mean, SD)		3.50 ± 1.69	2.83 ± 1.38	3.67 ± 1.23
PCA involvement		7 (8.9%)	13 (13.7%)	14 (24.1%)

**AChA* anterior choroidal artery, *ChA* choroidal artery, *LSA* lenticulostriate artery, *PA* periventricular anastomosis, *PCA* posterior cerebral artery, *PChA* posterior choroidal artery, *THA* thalamic artery

† Values expressed as number (%) of patients, unless otherwise indicated

PA scores

The mean PA scores in the CI, AI, and AH groups were 3.5 ± 1.7, 2.8 ± 1.3, and 3.6 ± 1.2, respectively. The PA scores were significantly different among the three groups ($P = 0.001$, Kruskal-Wallis test). The PA scores of the CI and AH groups were significantly higher than those of the AI group (CI to AI, $P = 0.002$; AI to AH, $P = 0.0001$; Mann-Whitney test with Bonferroni correction). No difference was observed between the CI and AH groups ($P = 0.99$).

LSA anastomosis, THA anastomosis, and ChA anastomosis

Positive LSA anastomosis accounted for 40.5% in the CI group, 22.1% in the AI group, and 41.4% in the AH group, showing significant differences among the three groups ($P = 0.01$). The proportions of positive LSA anastomosis in the CI and AH groups were more prominent than those in the AI group (CI to AI, $P = 0.009$; AI to AH, $P = 0.011$; chi-squared test with Bonferroni correction). No difference was observed between the CI and AH groups ($P = 0.92$). Positive THA anastomosis accounted for 19.0% in the CI group, 8.4% in the AI group, and 10.3% in the AH group, with no significant difference across the three groups. Positive ChA anastomosis accounted for 62.0% in the CI group, 43.2% in the AI group, and 72.4% in the AH group, showing significant differences among the three groups ($P < 0.01$). The proportion of positive ChA anastomosis in the CI and AH groups was more prominent than that in the AI group (CI group to AI, $P =$

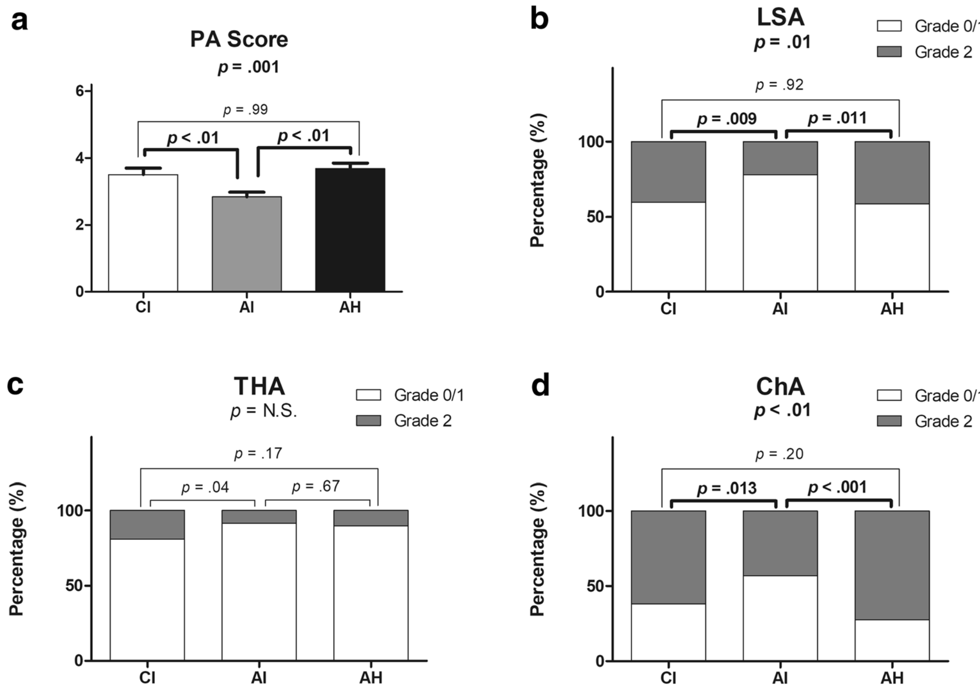


Fig. 2 Periventricular anastomosis (PA) scores and rates of the positive (grade 2) PA anastomosis in child ischemic (CI), adult ischemic (AI), and adult hemorrhagic (AH) groups. **a** PA scores. **b**, **c**, and **d** Rates of positive LSA, THA, and ChA anastomosis, respectively. The PA scores and the positive rates of LSA and ChA anastomosis in the CI and AH groups were significantly higher than those in the AI group. The *P* value on top of the bar graph signifies the overall difference among the three groups (significant, $P < 0.05$), whereas the other three *P* values indicate the results of multiple comparison tests (significant, $P < 0.016$). The bold characters and lines indicate statistically significant values

0.013; AI to AH, $P < 0.001$). No difference was observed between the CI and AH groups ($P = 0.20$).

AChA anastomosis, PChA anastomosis, and PCA involvement

In the subgroup analysis of the ChA collaterals, positive AChA anastomosis accounted for 51.9% in the CI group, 35.8% in the AI group, and 58.6% in the AH group, showing significant differences among the three groups ($P = 0.013$). The proportion of AChA anastomosis in the AH group was more prominent than that in the AI group ($P = 0.006$). Positive PChA anastomosis accounted for 26.6% in the CI group, 14.7% in the AI group, and 31.0% in the AH group, with statistically significant differences among the three groups ($P = 0.04$). The proportion of PChA anastomosis in the AH

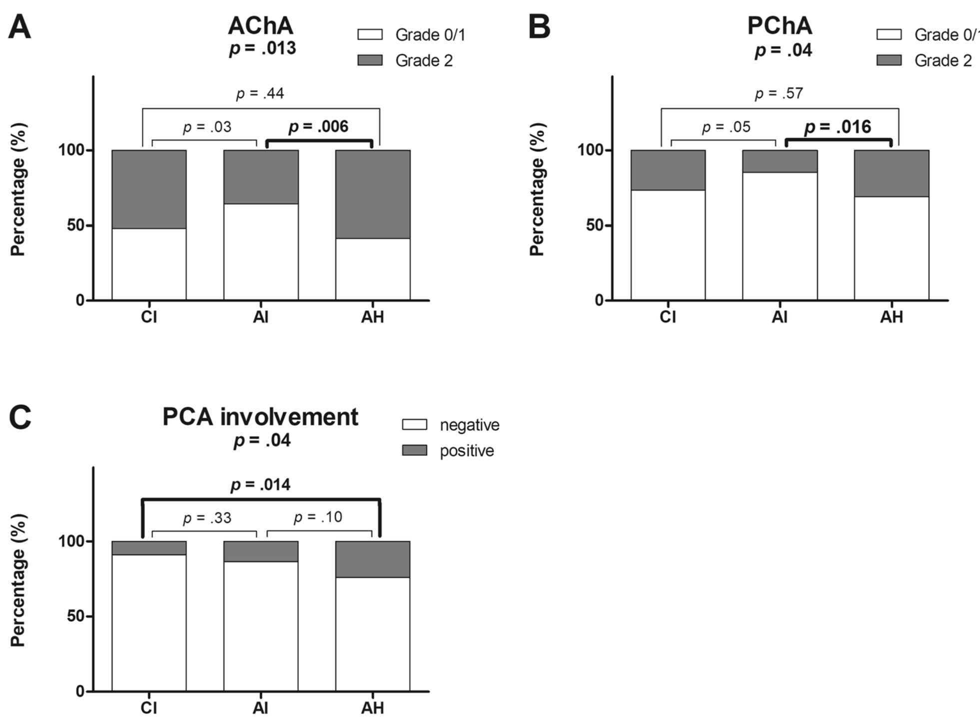


Fig. 3 AChA anastomosis, PChA anastomosis, and PCA involvement in the three groups. **a** and **b** Positive rates of AChA and PChA anastomosis, respectively. **c** Positive rate of the PCA involvement. The positive rates of AChA and PChA anastomosis in the AH group were significantly higher than those in the AI group. PCA involvement was the only difference between the CI and AH groups in this study

group was more prominent than that in the AI group ($P = 0.016$). In both subgroup analyses, no difference was observed between the CI and AH groups. The positive findings of PCA involvement accounted for 8.9% in the CI group, 13.7% in the AI group, and 24.1% in the AH group, with significant differences among the three groups ($P = 0.04$). The PCA involvement in the AH group was more prevalent than that in the CI group ($P = 0.014$). This was the only angiographic difference between the CI group and the AH group.

Using the AI group as a reference group, the data of PA scores and the positive rates of LSA and ChA anastomosis were entered in the multiple regression model (Table 3). "Sex-adjusted" and "age- and sex-adjusted" analyses were performed to compare those variables between the AI and CI groups and between the AI and AH groups, respectively. After the sex adjustment, the PA scores ($P = 0.005$), LSA ($P = 0.01$), and positive rates of ChA anastomosis ($P = 0.01$) remained significantly higher in the CI group. After the age and sex adjustments, the PA scores ($P < 0.001$) and the positive rates of LSA ($P = 0.008$) and ChA anastomosis ($P < 0.001$) also remained significantly higher in the AH group.

Discussion

PA is a new concept that indicates abnormal extended collateral vessels in MMD, as described in previous studies [2, 3, 21]. Intraventricular hemorrhage is a common manifestation of hemorrhagic MMD, and cerebral microbleeds in the periventricular area are closely associated with the hemorrhagic event in MMD [11, 16, 17]. Funaki et al. showed a good topographical correspondence between the bleeding points associated with ChA anastomosis and the distribution of ChA anastomosis and indicated that ChA anastomosis is a strong risk factor for rebleeding [4, 5]. In a recent comparative study between child and adult MMD, the development of PChA and THA and the decrease of LSA were observed in adult MMD [7]. Yamamoto et al. suggested that the collateral vessels longitudinally shift from the anterior to the posterior component during disease progression and aging [23]. However, there have been no multiple comparison studies between the subgroups, which are divided by both age at the time of diagnosis and clinical presentation. To the best of our knowledge, this study is the first analysis to reveal the difference of PA development among three different groups, namely, CI, AI, and AH.

Considering the similarity in the symptoms of the CI and AI groups, we originally suspected that a similar pattern of PA would be observed in the CI and AI groups and that PA would be more prominent in the AH group. Contrary to our initial expectation, the present study demonstrated that PA scores and LSA and ChA anastomosis are similarly prominent in the CI and AH groups, while they are less prominent in the AI group. Moreover, we found no differences in the subtypes of PA between the CI and AH groups.

The angiographic results in the AI group were partially consistent with findings in previous reports [12, 19]. The number of so-called moyamoya vessels was higher in child MMD (≤ 20 years) than in adult MMD (> 20 years) [22]. Hori et al. showed that LSA anastomosis was less prominent in adult patients than in pediatric patients. Considerably less development of LSA and ChA anastomosis in the AI group may suggest further involvement of the proximal middle cerebral artery and the distal internal carotid artery. Yamashita et al. speculated that the stenosis and obstruction process in moyamoya vessels may also be related to an ischemic event [24].

The question remains as to why the CI and AH groups show different clinical presentations despite similar findings of PA. Suzuki grade 4 was observed more frequently in adult MMD than in child MMD [9]. The proportion of advanced Suzuki grade (stages 4–6) was significantly higher in the adult hemorrhagic-onset group than that in the adult ischemic-onset group [1]. These findings may indicate that the patients in the AH group experienced a more prolonged duration of illness than those in the CI group. As PA serves as a main collateral pathway to compensate for the reduced cerebral perfusion,

Table 3 Adjusted odds ratio of periventricular anastomosis (PA) score, positive rates of the lenticulostriate artery (LSA), and choroidal artery (ChA) anastomosis

	AI group (reference)	CI group	Sex adjusted*			AH group	Age and sex adjusted†		
			OR	95% CI	*P*		OR	95% CI	*P*
PA score	2.83 ± 1.38	3.50 ± 1.69	1.33	1.09–1.63	0.005	3.67 ± 1.23	1.74	1.30–2.34	< 0.001
LSA positive	21 (22.8%)	32 (40.5%)	2.39	1.23–4.67	0.01	24 (41.4%)	2.74	1.38–5.79	0.008
ChA positive	41 (43.2%)	49 (62.0%)	2.15	1.17–3.95	0.01	58 (72.4%)	4.18	1.98–8.81	< 0.001

* Sex-adjusted model was used to compare the variables between the AI and the CI groups

† Age- and sex-adjusted model was used to compare the variables between the AI and the AH groups

AI adult ischemic, *CI* child ischemic, *AH* adult hemorrhagic, *OR* odds ratio, *95% CI* 95% confidence interval long-standing hemodynamic burden on the fragile PA may predispose to rupture.

Furthermore, we recently found that PCA involvement was higher in the AH group than in the CI group and that both AchA and PChA anastomosis were higher in the AH group than in the AI group. PCA involvement is a main surrogate marker for posterior hemorrhage in MMD [4]. The hemodynamic insufficiency induced by PCA involvement may also cause PA to develop from the PCA (i.e., PChA). Additional studies are required to evaluate the relationship between PCA involvement and the development of ChA anastomosis.

Recently, the ring finger 213 (RNF213) gene, located on 17q25, has been identified as the susceptibility gene for MMD [10, 15]. The RNF213 homozygous c.14576G > A variant carriers demonstrated earlier age at onset, more frequent occurrence of infarctions at initial presentation, and PCA involvement [14]. However, neither the exact roles of RNF213 nor its relationship to angiographic features has been clarified. Further studies are needed to elucidate the pathogenic effect of RNF213 mutation on the development of PA in MMD.

The present study has several limitations. First, it was a retrospective study. Second, there might be some selection bias because the subjects were recruited only from among MMD patients with surgical revascularization. Third, the definition of the age of child and adult might be controversial. This study adopted the definition of adult (≥ 16 years old) according to the criteria of the JAM trial that focused on adult hemorrhagic MMD. Fourth, the reliability of the PA grading system may have influenced the results. As consensus was achieved on the image determination [3], the result of interrater reliability was not evaluated. In some cases, distinguishing a lateral PChA from an AChA was difficult because of the complex microanatomy of the collateral network. However, compared with the study period of the JAM trial [13], this study reviewed more recent, better-quality angiographic images and achieved reliable results by a thorough investigation conducted by our three raters.

Conclusion

The present study demonstrated the similarities and the differences in PA among the CI, AI, and AH groups. The PA in the CI group was prominent in a manner similar to that in the AH group, whereas the PA in the AI group was less prominent. These findings may provide additional insights into the development of PA and a better understanding of the progression of MMD.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This observational cohort study was approved by the Ethics Committee of the National Cerebral and Cardiovascular Center (IRB approval no. M30-013).

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Comments

This is interesting and valuable study concerning periventricular ?anastomosis in Moyamoya disease (MMD). The greatest characteristic of MMD its multiplicity. One patient may present ischemic ?complications, while another presents hemorrhagic complications. Moreover, one patient may develop symptoms during childhood while another does so during adulthood. Periventricular anastomosis (PA) has been a focus of attention recently in hemorrhagic MMD. The authors compared the pattern of PA development between child ischemic, adult ischemic, and adult hemorrhagic groups. The child ischemic and adult hemorrhagic groups revealed similar pattern of PA development and showed more prominent PA development than adult ischemic group. This result can be a clue of understanding complex pathophysiology underlying multiplicity of MMD. Regardless of similar PA development in child ischemic and adult hemorrhagic groups, there was a difference of symptoms between two groups. Aging of vessels (atherosclerosis) may relate to the discrepancy in addition to the difference of duration of illness.

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