

Clinical and Radiological Features of Childhood Onset Adult Moyamoya Disease: Implication for Hemorrhagic Stroke

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Abstract

Some of the pediatric moyamoya patients spend their childhood without diagnosed as moyamoya disease (MMD) because of their mild ischemic attacks and emerge again with ischemic or hemorrhagic stroke in their adulthood. This study was aimed to clarify the clinical characteristics of adult moyamoya patients with childhood onset and elucidate the impact of long disease period on their clinical features. Present study included 116 untreated hemispheres of 69 adult patients with MMD. They were divided into two groups: childhood onset group (26 hemispheres of 14 patients) and adult onset group (90 hemispheres of 55 patients). Clinical features were compared between the two groups. The incidence of hemorrhagic stroke was significantly higher in childhood onset group ($P = 0.0091$). Lenticulostriate and choroidal channels were more developed in childhood onset group ($P = 0.044$ and $P < 0.001$, respectively). Vault moyamoya was more frequently observed in childhood onset group ($P < 0.001$). The development of surgical collaterals through indirect bypass was more marked in childhood onset group ($P = 0.0019$). Multivariate analysis revealed that childhood onset and developed choroidal channels were significantly associated with the occurrence of hemorrhagic stroke (OR 4.31 [95% CI 1.21–15.4], $P = 0.025$ and OR 6.78 [95% CI 1.78–25.8], $P = 0.0050$, respectively). This study clearly shows that adult moyamoya patients with childhood onset have more developed spontaneous collaterals, which may, in turn, highly causes hemorrhagic stroke. Adult moyamoya patients with “childhood onset” should be recognized as a novel and important concept when elucidating the underlying mechanisms of hemorrhagic stroke in MMD.

Keywords: moyamoya disease, childhood onset, cerebral angiography, collateral channels, hemorrhagic stroke

Introduction

In moyamoya disease (MMD), the perforating arteries such as the lenticulostriate arteries (LSAs) are markedly dilated to supply collateral blood flow to the ischemic brain.^{1,2} They often abnormally anastomose with medullary arteries in periventricular areas, and supply collateral blood flow to cerebral cortex.¹ These fragile “moyamoya” vessels are well known to rupture and cause hemorrhagic stroke because of a long-standing hemodynamic stress onto them. A randomized clinical trial, Japan Adult

Moyamoya (JAM) Trial, has shown that direct or combined bypass can significantly reduce the risk of rebleeding in adult moyamoya patients with hemorrhagic stroke onset probably because of post-operative decline of hemodynamic stress onto the moyamoya vessels.

On the other hand, MMD characteristically leads to diverse symptoms such as transient ischemic attack (TIA), ischemic stroke, and hemorrhagic stroke. Most of the pediatric patients develop TIA, ischemic stroke, headache, or seizure and are usually diagnosed as MMD because of such symptoms. A certain subgroup of pediatric patients, however, is known to spend their childhood without diagnosed as MMD because of their mild attacks. In such cases, their attacks are known to gradually disappear when they are grown up. However, some of them emerge again with ischemic or hemorrhagic stroke in their

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adulthood. Much longer disease period may also have significant impact on their future life through a persistent hemodynamic stress on the moyamoya vessels. However, there are no reports evaluating whether adult moyamoya patients with childhood onset present specific clinical features when compared with those with adult onset or not. Therefore, present study was aimed to clarify demographic and radiological findings of adult moyamoya patients with childhood onset and elucidate the impact of long disease period on their clinical features.

Materials and Methods

This study was approved by an Institutional Review Board at our hospital and informed consent was obtained from each patient.

Patients

This prospective study included totally 74 adult patients who were admitted to our hospital between 2013 and 2018. All of them underwent cerebral angiography and were diagnosed as MMD according to the guideline for the diagnosis of MMD set by the Research Committee on Moyamoya Disease of the Ministry of Health, Welfare, and Labor of Japan.³⁾ They were categorized into bilateral type ($n = 54$) and unilateral type ($n = 20$). As a result, 128 hemispheres were judged as involved hemispheres. Of these, 12 hemispheres were excluded because they had already undergone surgical revascularization on initial admission. As a result, this study included 116 involved hemispheres of 69 adult patients with MMD. There were 24 males and 45 females. Mean age was 41.4 ± 10.9 years. Clinical diagnosis included TIA or ischemic stroke ($n = 44$), hemorrhagic stroke ($n = 16$), and asymptomatic ($n = 9$). Based on inquiry for each patient and their family, all patients were divided into childhood onset group and adult onset group. Childhood onset was defined as the presence of histories of repeated ischemic symptoms, seizures, or involuntary movements in their childhood (<18 years). The patients' demographic data including age, sex, and onset type in both groups were precisely analyzed.

Preoperative cerebral angiography

In this study, the findings on cerebral angiography were systemically evaluated. Thus, the following angiographical characteristics were compared in all involved hemispheres between two groups: Suzuki's angiographical stage, the angiographical grades of abnormal collateral channels, vault moyamoya, and posterior cerebral artery (PCA) involvement.

According to the method proposed by JAM Trial group,⁴⁾ the abnormal collateral channels were

categorized into three routes: lenticulostriate, thalamic, and choroidal channel. In this study, the degree of development of each collateral channel was classified into three grades (Grade 0–2) as reported elsewhere.⁴⁾

The degree of PCA involvement was also categorized into three grades as reported elsewhere.⁴⁾ We defined Grade 0 as no PCA stenosis, Grade 1 as a significant stenosis in the P2-P3 segments of PCA, and Grade 2 as the occlusion of PCA.

Surgical procedures

Superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis and indirect bypass, encephalo-duro-myo-arterio-pericranio synangiosis were performed onto the hemispheres with impaired cerebral hemodynamics in symptomatic patients.⁵⁾

Postoperative cerebral angiography

Cerebral angiography was performed 3–6 months after revascularization surgery because the collaterals through indirect bypass require several months for their development. The degree of development of indirect bypass was classified into three grades (Grade 0–2) according to the method described by Matsushima et al.⁶⁾ We defined Grade 0 when indirect bypass supplies blood flow to less than one-third of MCA area, Grade 1 when more than one-third and less than two-thirds of MCA area, and Grade 2 when more than two-thirds of MCA area.

Statistical analysis

Continuous data were expressed as mean \pm standard deviation (SD). The differences between two groups were analyzed using chi-square test, *t*-test as appropriate. Multiple logistic regression models were used to estimate the factors affecting postoperative development of indirect bypass and occurrence of hemorrhagic stroke. A forward stepwise logistic regression was used in model-building with the interrogated parameters, using $P < 0.20$ achieved by univariate analysis as the cutoff. Differences were considered statistically significant when the *P* value was < 0.05 .

Results

Demographic data

Based on the interview to the patients and their family, 26 hemispheres of 14 patients were categorized into childhood onset group and the remaining 90 hemispheres of 55 patients were categorized into adult onset group. All of childhood onset patients experienced TIA during their childhood. Demographic data in both groups are summarized in **Table 1**. The patients with childhood onset were significantly

Table 1 Characteristics and clinical presentation in childhood onset group and adult onset group

	Childhood onset group	Adult onset group	P value
Number of patients	14	55	
Number of hemispheres	26	90	
Age (mean \pm SD)	34.0 \pm 6.2	43.3 \pm 11.1	0.0002
Sex (male:female)	3:11	21:34	0.240
Onset type			0.0091
Ischemia	6	38	
Ischemic stroke	2	14	
TIA	4	24	
Intracranial hemorrhage	8	8	
Asymptomatic	0	9	

TIA: transient ischemic attack.

younger than those with adult onset, 34.0 \pm 6.2 and 43.3 \pm 11.1 years, respectively ($P < 0.001$). There was no gender difference between two groups ($P = 0.24$). The prevalence of hemorrhagic stroke was more often in childhood onset group than in adult onset group, 57.1% and 14.5%, respectively ($P = 0.0091$).

Radiological data

As shown in **Fig. 1A**, there was no significant difference in Suzuki's angiographical stage between two groups ($P = 0.32$). On the other hand, the development of lenticulostriate channel was more advanced in childhood onset group than in adult onset group ($P = 0.044$, **Fig. 1B**), although such difference was not observed in thalamic channel ($P = 0.094$, **Fig. 1C**). Development of choroidal channel was also more prominent in childhood onset group than in adult onset group ($P < 0.001$, **Fig. 1D**). As shown in **Fig. 2A**, there was no significant difference in the involvement of the PCA between two groups ($P = 0.099$). The prevalence of vault moyamoya was significantly higher in childhood onset group than in adult onset group, 88.5% and 27.8%, respectively ($P < 0.001$, **Fig. 2B**).

Combined bypass surgery was performed in 23/26 hemispheres and 57/90 hemispheres in childhood onset group and adult onset group, respectively. Of these, cerebral angiography was performed in 21/23 and 47/57 hemispheres after surgery in childhood onset group and adult onset group, respectively. The results on postoperative external carotid angiography are shown in **Fig. 2C**. In childhood onset group, the development of surgical collaterals through indirect bypass was judged as Grade 0 in 1 hemisphere (4.8%), Grade 1 in 2 (9.5%), and Grade 2 in 18 (85.7%). In adult onset group, however, it was judged as Grade 0 in 10 hemispheres (25.0%), Grade 1 in 18 (38.3%), and Grade 2 in 19 (40.4%),

showing significant difference between two groups ($P = 0.0019$). As the next step, the predictors for Grade-1 and Grade-2 development of surgical collaterals through indirect bypass were analyzed. As shown in **Table 2**, univariate analysis identified Grade-2 choroidal channel and presence of vault moyamoya as the candidates to predict it. However, multivariate analysis with multiple logistic regression model revealed no significant predictors for it.

Clinical factors affecting hemorrhagic stroke

As shown in **Table 3**, univariate analysis demonstrated that childhood onset, Grade-2 thalamic channel, and Grade-2 choroidal channel were significantly associated with the occurrence of hemorrhagic stroke. Then, multivariate analysis with multiple logistic regression model revealed that childhood onset (OR 4.31 [95%CI 1.4], $P = 0.025$) and Grade-2 choroidal channel significantly predicted it (OR 6.78 [95% CI 1.8], $P = 0.005$; **Table 3**).

Discussion

This is the first study that denotes clinical features of adult moyamoya patients with childhood onset. As a result, they experienced cerebrovascular events when 10-year younger than those without (mean 34.0 and 43.3 years, respectively). Considering the fact adult MMD has a peak of the population around 40 years,^{7,8)} the difference is not small. In addition, they are at fourfold higher risk for hemorrhagic stroke than those without. These findings strongly suggest that adult moyamoya patients with childhood onset may more readily develop cerebrovascular events than those without. Of these, TIA or ischemic stroke may more early occur through additional cerebral ischemia due to disease progression.

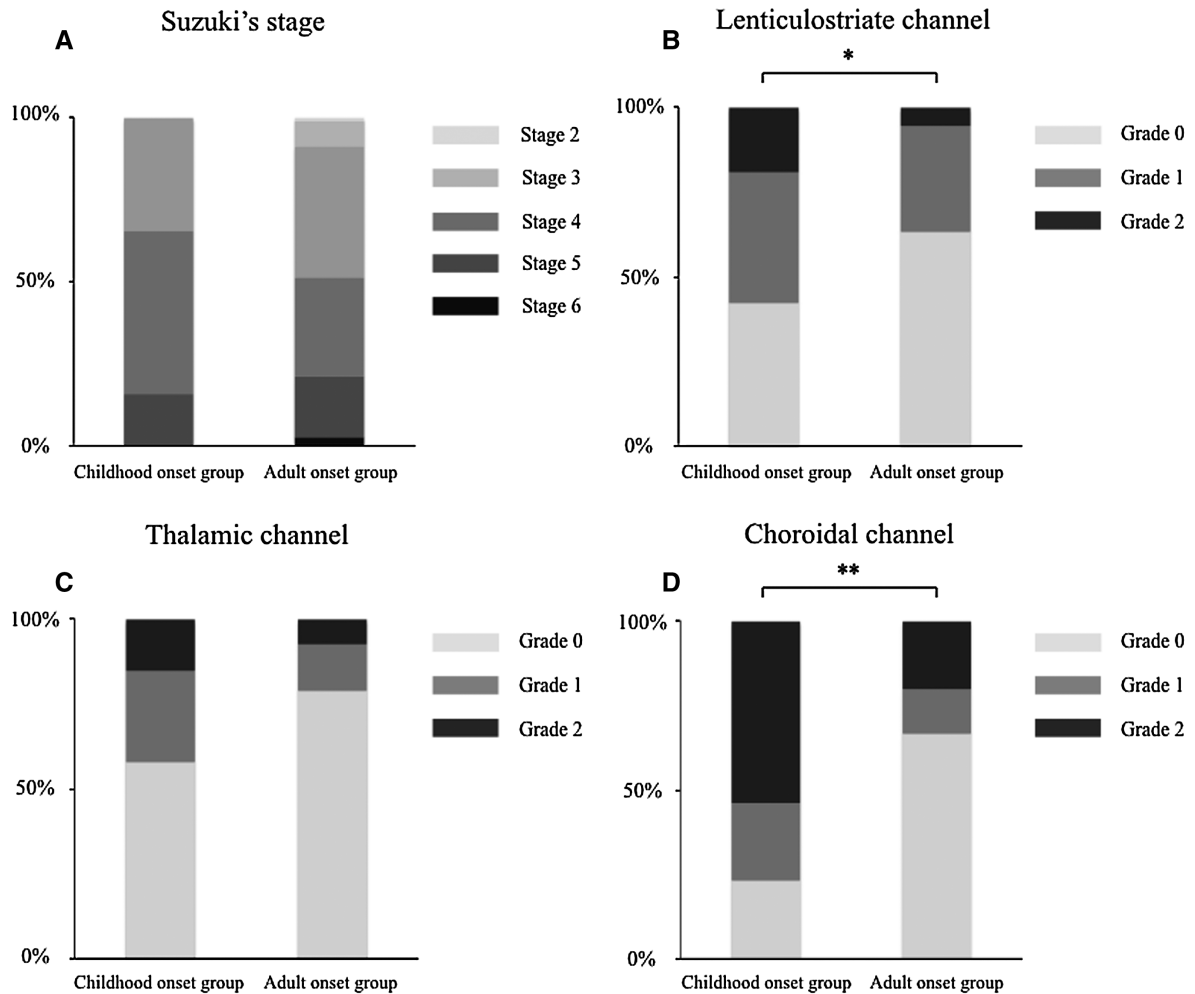


Fig. 1 The bar graph demonstrates the Suzuki's angiographical stage and the development of collateral channels in the childhood onset group and the adult onset group. The degree of development of collateral channels is categorized into three grades (see the text). * $P < 0.05$, ** $P < 0.01$. (A) There is no significant difference between the two groups ($P = 0.32$, chi-square test). (B) Lenticulostriate channel is more developed in the childhood onset group than in the adult onset group ($P = 0.044$, chi-square test). (C) There is no significant difference in thalamic channel between the two groups ($P = 0.094$). (D) Choroidal channel is remarkably developed in the childhood onset group than in the adult onset group ($P < 0.001$).

Long-standing hemodynamic stress onto the fragile moyamoya vessels since childhood may lead to more prevalent hemorrhagic stroke in younger age.

Radiological analysis supports this speculation. Thus, lenticulostriate and choroidal anastomoses more prominently developed in adult moyamoya patients with childhood onset than those without, although there was no significant difference in Suzuki's disease stage between them. Recent studies have clearly demonstrated that the so-called moyamoya vessels are very closely related to the occurrence of hemorrhagic stroke, although they are working as important collateral routes to prevent ischemic stroke. The rupture of lenticulostriate channel causes anterior-type hemorrhage in the putamen and caudate

head, while the rupture of thalamic and choroidal channels leads to posterior-type hemorrhage in the thalamus and periventricular white matter in the trigon.^{4,9-11)} In fact, this study clearly demonstrated that childhood onset and Grade-2 choroidal channel were independent predictors for hemorrhagic stroke in adult moyamoya patients, using multivariate analysis. Their odds ratio was 4.31 and 6.78, respectively (Table 3). Recently, JAM Trial Investigators have demonstrated that adult moyamoya patients with hemorrhagic onset had significantly more prominent extension and dilation of thalamic ($P = 0.043$) and choroidal channel ($P < 0.001$) than those with ischemic onset.¹²⁾ Likewise, we have reported that the thalamic and choroidal channels more distinctly

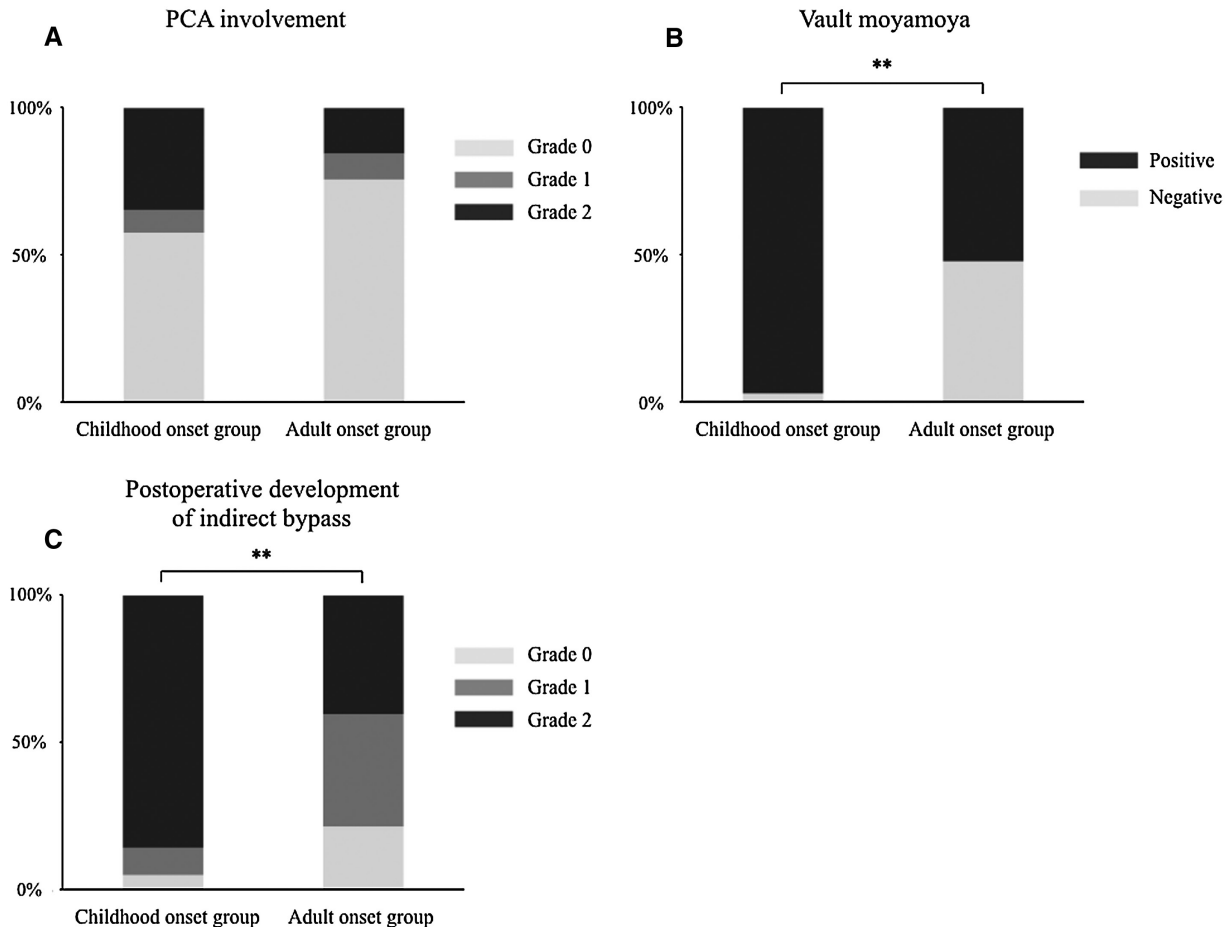


Fig. 2 The bar graphs demonstrate the degree of PCA involvement, prevalence of vault moyamoya, and the degree of postoperative development of indirect bypass in the childhood onset group and the adult onset group. The degree of PCA involvement and postoperative development of indirect bypass are categorized into three grades (see the text). ** $P < 0.01$. (A) There is no significant difference in degree of PCA involvement between the two groups ($P = 0.099$, chi-square test). (B) The proportion of presence of vault moyamoya is much higher in the childhood onset group than in the adult onset group ($P < 0.001$). (C) Indirect bypass is more developed in the childhood onset group than in the adult onset group ($P = 0.0019$). PCA: posterior cerebral artery.

developed in hemorrhagic-onset hemispheres than in ischemic-onset hemispheres.²⁾ Based on these observations, therefore, adult patients with childhood onset should be recognized as a novel clinical entity that have distinct features such as younger stroke onset and higher incidence of hemorrhagic stroke probably because of the rupture of choroidal channel, and should be separated from those without when considering treatment strategies.

Generally, the development of moyamoya vessels is closely linked to Suzuki's disease stage, but the degree of lenticulostriate and choroidal channel development was different between adult moyamoya patients with childhood onset and those without, although there was no significant difference in disease stage between two groups. The mechanisms are still unclear, but following explanation may be possible:

Thus, previous studies have shown that cerebral blood flow (CBF) is much higher in children than in adults, probably because of higher metabolic demand in children for brain growth.¹³⁻¹⁵⁾ Kennedy and Sokoloff found that CBF in 3- to 11-year-old children was about 1.8 times of healthy young adults.¹³⁾ Ogawa et al. (1987) demonstrated that CBF in children younger than 5 years old was about twice in adults, and decreased thereafter until adulthood.^{16,17)} In adult moyamoya patients with childhood onset, therefore, higher demand of CBF in childhood may aggressively induce the development of moyamoya vessels to protect the brain by compensating cerebral ischemia, which in turn carries the higher risk for hemorrhagic stroke in their adulthood. In this study, very similar phenomenon could be observed in vault moyamoya, which is one of the alternative collateral

Table 2 Univariate and multivariate ORs for postoperative development of indirect bypass

	Development of indirect bypass		Univariate analysis			Multivariate analysis		
	Yes	No	OR	95% CI	P value	OR	95% CI	P value
Number of hemispheres	57	11						
Mean age	39.1 ± 1.6	9.5 ± 3.6	1.00	0.95–1.06	0.90			
Female sex	45 (78.9)	6 (54.5)	3.13	0.81–12.0	0.097	2.80	0.62–12.7	0.18
Hemorrhagic onset	13 (22.8)	2 (18.2)	1.47	0.28–7.60	1.00			
Childhood onset group	20 (35.1)	1 (9.1)	5.41	0.64–45.3	0.15	1.38	0.097–19.7	0.81
Suzuki's angiographical stage (≥4)	31 (54.3)	4 (36.3)	0.48	0.13–1.82	0.33			
Lenticulostriate channel (Grade 2)	7 (12.3)	0	NA	NA	NA			
Thalamic channel (Grade 2)	9 (15.8)	0	NA	NA	NA			
Choroidal channel (Grade 2)	26 (45.6)	1 (9.1)	8.39	1.01–69.9	0.04	6.14	0.65–57.9	0.11
PCA involvement (Grade 1 and 2)	20 (35.1)	1 (9.1)	5.41	0.64–45.3	0.15	2.93	0.31–27.9	0.35
Vault moyamoya	30 (52.6)	2 (18.2)	5.00	0.99–25.2	0.05	2.86	0.37–22.0	0.31

Values are presented as the number of hemispheres (%). CI: confidence interval, NA: not applicable, OR: odds ratio, PCA: posterior cerebral artery.

Table 3 Univariate and multivariate ORs for intracranial hemorrhage

	Intracranial hemorrhage	Other onset type	Univariate analysis			Multivariate analysis		
			OR	95% CI	P value	OR	95% CI	P value
Number of hemispheres	18	98						
Mean age	40.8 ± 11.6	41.2 ± 11.1	1.00	0.95–1.04	0.89			
Female sex	14 (77.8)	63 (64.3)	1.94	0.59–6.36	0.42			
Childhood onset	10 (55.6)	16 (16.3)	6.41	2.19–18.7	<0.001	4.31	1.21–15.4	0.025
Suzuki's angiographical stage (≥4)	10 (55.6)	53 (54.1)	1.06	0.39–2.92	1.00			
Lenticulostriate channel (Grade 2)	3 (16.7)	7 (7.1)	2.60	0.60–11.2	0.19	0.99	0.15–6.66	0.99
Thalamic channel (Grade 2)	5 (27.8)	6 (6.1)	5.90	1.57–22.1	0.013	2.55	0.40–16.5	0.33
Choroidal channel (Grade 2)	13 (72.2)	19 (19.4)	10.8	3.43–34.0	<0.0001	6.78	1.78–25.8	0.005
PCA involvement (Grade 1 and 2)	7 (38.9)	20 (20.4)	2.48	0.85–7.22	0.13	0.63	0.13–2.98	0.56

Values are presented as the number of hemispheres (%). CI: confidence interval, OR: odds ratio, PCA: posterior cerebral artery.

routes in MMD.¹⁸⁾ Vault moyamoya is known as pathognomonic in MMD and its spontaneous angiogenesis from the STA and middle meningeal artery to the MCA and anterior cerebral artery, called as IC-EC conversion.¹⁹⁾ It is well known that vault moyamoya starts to develop in the advanced stage (Stages 5 and 6). However, there was a large difference in the prevalence of vault moyamoya between the two groups, although Suzuki's disease stage did not differ between them. Higher CBF demand in childhood may play an important role in the development of vault moyamoya in adult moyamoya patients with childhood onset.

This is the first study showing that surgical collaterals through indirect bypass more often

develop in childhood onset group than in adult onset group (P = 0.0019). Previous studies have shown that surgical collaterals through indirect bypass in almost all pediatric patients, but in only 67.9–77.6% of adult patients.^{20,21)} There was no clinical and radiological factors to favor it in this study and the underlying mechanisms are still unknown. However, adult moyamoya patients with childhood onset may specifically have some biological features that favor spontaneous angiogenesis, as described above.

Taken together, this study characterizes specific clinical and radiological features of adult moyamoya patients with childhood onset. The findings should be taken into considerations when treating them.

However, their sample size was rather small to reach final results in this study. However, their population is still unclear, and thus, future cooperative study with larger cohort would be warranted.

Conclusion

This study clearly shows that adult moyamoya patients with childhood onset have distinct clinical and radiological features such as more advanced development of spontaneous collaterals, which may, in turn, highly causes hemorrhagic stroke probably because of their longer disease period and a higher blood flow demand in their childhood. Therefore, adult moyamoya patients with “childhood onset” should be recognized as a novel and important concept when elucidating the underlying mechanisms of hemorrhagic stroke in adult MMD.

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Conflicts of Interest Disclosure

None.

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