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ORIGINAL ARTICLE

Hemodynamic contribution of transdural collateral flow in adult patients with moyamoya disease

Ji Man Hong[1] · Yoon Hee Hong[1] · Seong-Joon Lee[1] · Sung Eun Lee[1] · Jin Soo Lee[1] · Dong Hoon Shin[2]

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Abstract To evaluate the hemodynamic contributions of collateral flow in adult patients with moyamoya disease, neurological deterioration or fluctuation during admission, Suzuki grade, various collateral routes, lesion volume, cerebral blood flow (CBF), and their associations were analyzed. Thirty patients (60 cerebral hemispheres, mean age 45 ± 25 years, and 73.3 % female) who were diagnosed with moyamoya disease or syndrome were enrolled over 3 years. Moyamoya stages from each hemisphere were stratified according to the Suzuki's criteria through six-vessel angiography into internal carotid arteries (ICAs), external carotid arteries (ECAs), and vertebral arteries (VAs). Collateral routes were categorized into the circle of Willis, leptomeningeal, and transdural. The volume of ipsilateral infarction was analyzed by magnetic resonance imaging. CBF volume was measured using color-coded duplex sonography. Suzuki's grade was inversely correlated with flow volume of the ICAs ($p < 0.001$), whereas no association was found with that of the ECAs ($p = 0.445$) or VAs ($p = 0.096$). Among hemispheres with ≥ grade 3 ($n = 36$), patients with transdural ECA collateral flow had less neurological deterioration or fluctuation (0.0 vs. 30.8 %, $p = 0.047$), smaller lesion volume (2.4 ± 3.6 vs. 27.6 ± 59.3 mL, $p = 0.041$), lower ICA flow (88.4 ± 45.9 vs. 146.2 ± 121.7 mL/min, $p = 0.022$), higher ECA flow (205.7 ± 77.7 vs. 135.9 ± 52.7 mL/min, $p = 0.046$), and a higher ECA/ICA flow volume ratio (31.8 ± 92.8 vs. 1.7 ± 1.9, $p = 0.024$). Our results suggest that ICA flow volume is inversely correlated with Suzuki grade, and that transdural ECA collaterals appear to be an important detour in adult patients with advanced stage moyamoya disease, suggesting a protector against an impending ischemic attack.

Keywords Moyamoya disease · Cerebrovascular disease · Collateral flow · Leptomeningeal · Transdural

Introduction

Moyamoya disease (MMD) or syndrome (MMS) is a cerebrovascular condition associated with progressive stenosis or occlusion of the intracranial internal carotid arteries (ICAs) and their proximal branches [1]. The disease is associated with reduced blood flow through the major cerebral vessels leading to hemodynamic compensation and neovascularization of collateral routes, such as small vessels near the apex of the carotid, leptomeningeal anastomosis from the anterior and posterior circulation, and transdural anastomosis from the external carotid artery (ECA) [2–4]. Successful compensatory collateralization has been considered a defensive measure against ischemic and hemorrhagic stroke [5, 6].

Conventional criteria proposed by Suzuki et al. addressed the diagnosis and grading of MMD in terms of vascular morphology using cerebral angiography [4]. However, this morphological classification does not fully reflect the hemodynamic compromise and is not perfectly correlated

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✉ Ji Man Hong
dacda@hanmail.net

[1] Department of Neurology, School of Medicine, Ajou University, 5 San, Woncheon-dong, Yongtong-gu, Suwon-si, Kyunggi-do, Suwon 442-749, South Korea

[2] Department of Neurology, Gachon University Gil Medical Center, Incheon, South Korea

with clinical symptoms and impeding stroke risk [5, 7, 8]. As a consequence, a recent study suggested new criteria that include the status of the vasculature, brain lesions, and cerebrovascular reserves [5, 7–9].

We performed a multimodal investigation, including cerebral angiography, magnetic resonance imaging (MRI), and color-coded duplex sonography in adult patients with MMD to clarify hemodynamic compensation in terms of disease progression and its implications for the development of ischemic stroke. We then examined the significance of incorporating arterial collateral flow status into the conventional Suzuki grading system to better predict neurological deterioration or fluctuations during admission.

Methods

Patient selection

We retrospectively analyzed patients who were admitted to a stroke unit due to a transient ischemic attack and non-hemorrhagic stroke in a tertiary care stroke center between October 2009 and June 2012. Among them, we collected patients with cerebral vascular abnormalities suggesting MMD using conventional four-vessel angiography. Based on the guidelines for diagnosing MMD set by the Research Committee on moyamoya disease (Spontaneous Occlusion of the Circle of Willis) of the Ministry of Health and Welfare of Japan [1], patients were consecutively collected into our MMD database if they had (a) stenosis or occlusion at the terminal portion of the ICA and/or at the proximal portion of the anterior and/or the middle cerebral arteries (MCAs) and (b) abnormal vascular networks (moyamoya vessels) in the vicinity of the occlusive or stenotic lesions in the arterial phase. Comprehensive imaging analyses were decided in a consensus meeting of stroke neurologists blinded to the clinical course.

Inclusion criteria for this study were: (a) admission to the stroke unit within 48 h of symptom onset and (b) non-hemorrhagic stroke or transient ischemic attack diagnosed as MMD in cases of bilateral cerebrovascular changes without identifiable systemic condition(s) or moyamoya syndrome (MMS) in cases of a unilateral change with abnormal vascular networks or bilateral changes without abnormal vascular networks [1]. Exclusion criteria were (a) patients <16 years old; (b) patients with extra- or intracranial atherosclerotic stenosis (i.e., stenosis of mid to distal MCA and/or anterior cerebral artery); (c) patients with unilateral stenosis of proximal vessels around the Willis circle without an abnormal vascular network; and (d) patients who had not completed necessary studies, such as four-vessel cerebral angiography, brain MRI, and duplex sonography. Patients were evaluated according to an institutional protocol that included clinical manifestations and general demographics.

Hospital course

The National Institutes of Health Stroke Scale (NIHSS) score was analyzed independently from admission to the stroke unit to discharge by trained neurologists and stroke nurses to assess clinical progression. Neurological deterioration within 1 week was defined as an increase of ≥2 points on the NIHSS occurring >24 h after index stroke or symptom onset [10]. Neurological fluctuation was defined as a change in the NIHSS, either an increase followed by 2-point decrease in the NIHSS episodically or vice versa. Neurological deterioration or neurological fluctuation was determined as an "unstable course during admission". All patients underwent a vital sign check, routine blood tests, echocardiography and continuous electrocardiographic monitoring to evaluate the presence of atrial fibrillation.

Brain MRI and angiographic parameters

Brain MRI scanning (1.5-T, GE Medical, Milwaukee, WI, USA) was conducted with conventional T2-weighted MRI and diffusion weighted imaging (DWI) in the axial plane with a 5-mm slice thickness. We checked the status of ischemic lesions in all hemispheres: acute infarction on DWI, old infarction on T2 or fluid-attenuated inversion recovery images, or a combination of acute and old lesions. Whole lesion volume in each hemisphere with acute and old infarctions was measured by multiplying lesion area per slice by section thickness (slice thickness + interslice gap).

During the admission period, Patients underwent six-vessel cerebral angiography, including bilateral common carotid arteries (CCAs) (ICAs and ECAs) and vertebral arteries (VAs). All images, including computed tomography (CT) and conventional angiography, were reviewed, and the vascular stage was identified in monthly adjudicated meetings according to the Suzuki's original drawings (Supplemental Figure 1) [4]. The Suzuki's vascular grade was defined on the six-vessel angiography. Stage 1: narrowing of carotid fork (only the carotid fork stenosis is observed); stage 2: initiation of basal moyamoya (all the main cerebral arteries are dilated); stage 3: Intensification of moyamoya (remarkable moyamoya vessels on the vase of the brain, the detection of the middle and anterior cerebral arteries is observed); stage 4: minimization of moyamoya (the defection of the posterior cerebral artery is observed); stage 5: reduction of moyamoya (all the main cerebral arteries missing); stage 6: disappearance of moyamoya (cerebral blood flow supplied only form external carotid artery).

Primary collateral flow via the fetal variant posterior communicating artery (PcoA) or hyperplastic PcoA was

designated based on a previous computed tomography angiography method [11]. The routes of arterial collaterals, including leptomeningeal and transdural collaterals from the ECAs were also investigated. Leptomeningeal collateral pathways from the posterior circulation were considered if there was any retrograde filling of MCA territory on a VA angiogram [8, 12]. A transdural collateral from the ECAs was designated as any intracranial filling of blood flow on an ECA angiogram. This study was approved by the Institutional Review Board of Ajou University Hospital.

Cerebral blood flow volume parameters

The patients were placed in a supine position during a 10-min rest period and extracranial arteries on both sides were explored with a 7.0-MHz linear array transducer and 5-MHz pulsed Doppler of a color-coded ultrasound system (LOGIQ S6; GE Medical, Yokogawa, Japan). Their measurements were taken 1–2 cm above the carotid bulb in the ECA and ICA, in the C4–C5 intertransverse segment of the VA, and 1.5–2 cm below the carotid blub in the CCA. Luminal diameter of the vessels was measured using a color-coded image of the vessel, and angle-corrected time-averaged flow velocity was determined as the integral of the mean flow velocities of the sample volume over at least four complete cardiac cycles. Hemispheric cerebral blood flow (CBF) volume was determined as the sum of the ICA and VA flow volumes on the same side. Total CBF volume was defined as the sum of each hemispheric volume [11, 13]. All parameters were measured by a well-trained ultrasonographer and an expert physician who were blinded to the imaging findings.

Statistical analysis

Pearson's correlation analysis was conducted between Suzuki grade and each of the hemodynamic parameters obtained by duplex sonography to investigate the association between Suzuki grade and collateralization. Correlation analyses between Suzuki grade and MRI lesion volume were done using Spearman's rank correlation analysis because the lesion volumes were not normally distributed ($p < 0.001$ by Kolmogorov–Smirnov test). The MRI lesion patterns in relation to angiographic severity were analyzed using the χ^2 test. A receiver operating characteristics (ROC) curve analysis with a subsequent analysis of area under the curve was applied to identify the performance of each arterial collateral pathway for predicting the clinical course. A p value <0.05 was considered significant. All statistical analyses were performed using SPSS ver.18 for Windows software (SPSS Inc., Chicago, IL, USA).

Results

General characteristics and clinical presentation

Among the 2731 patients who were admitted with ischemic stroke, 75 consecutive patients were recruited for our MMD database through screening CT or MR angiography. Among them, 45 patients were excluded according to the protocol. Reasons for exclusion were: admitted ≥48 h after stroke onset ($n = 13$), pediatric MMD patients ($n = 10$), hemorrhagic stroke ($n = 8$), only unilateral intracranial or extracranial stenosis without basal moyamoya vessels ($n = 7$), incomplete work-up ($n = 5$), and other stroke etiologies ($n = 2$). Table 1 shows the demographics of the 30 patients (22 females and eight males; mean age, 44.6 ± 12.7 years) included in the study. Among them, 22 patients were diagnosed with MMD and eight were diagnosed with MMS. Seven patients had unilateral involvement and 23 patients had bilateral involvement of their hemispheres. The Suzuki grade distribution in the 60 hemispheres was: normal in seven hemispheres; grade 1 in four; grade 2 in twelve; grade 3 in seventeen; grade 4 in thirteen; and grade 5 in seven hemispheres. Among the 30 patients, 5 patients experienced neurological deterioration or fluctuation, and among the 60 hemispheres, this type of unstable clinical course was seen in 8 hemispheres (2 unilateral, 3 bilateral hemispheric symptoms).

Angiographic grading, clinical presentation, and collaterals

Two authors (JMH and YHH) used Suzuki's diagrams (Supplemental Figure 1) to come to an inter-rater consensus with high agreement ($k = 0.937$, $p < 0.001$). Suzuki grade was correlated with ipsilateral lesion volume on MRI (Spearman's rank correlation: $p < 0.001$, $\rho = 0.516$). All comparisons were performed according to the dichotomized stage groups, comparing the lower stage (Suzuki <3) and higher stage (Suzuki ≥3) groups (Table 2). The higher stage group was more likely to have an unstable clinical course compared to that in the lower stage group (22.2 vs. 0.0 %, $p = 0.013$). The higher stage group also had variable lesion patterns on MRI, including acute lesions only, old lesions only, and acute and old lesions ($p = 0.026$). In addition, whole lesion volume was larger in the higher stage than that in the lower stage group (27.6 ± 59.3 vs. 2.4 ± 3.6 mL, $p = 0.041$). Leptomeningeal collaterals from the posterior circulation was observed more frequently in the lower stage group than those on the higher stage group (75 vs. 25 %), and ECA collaterals were present only in higher stage hemispheres (27.8 %), as expected based on the conventional Suzuki grading system (Table 2).

Table 1 General demographics, presence of cerebral lesions, and angiographic grading according to laterality

Case	Age/sex	Clinical manifestations (L/R)	MRI lesion (L/R)	Suzuki's grading (L/R)	Initial NIHSS	Maximum NIHSS	Unstable clinical course	Hospital stay, day	mRS at 3-month
1	56/F	Aphasia/none	Yes/no	4/4	9	9	Yes	17	1
2	31/F	Headache with facial palsy and dysarthria/headache with weakness	Yes/no	2/1	0	0	No	7	1
3	38/F	Headache	Yes/yes	4/3	0	0	No	7	0
4	44/F	Headache and weakness	No/no	2/3	0	0	No	9	1
5	46/F	Weakness with dysarthria	Yes/yes	4/1	2	2	No	9	0
6	40/F	Weakness/none	No/no	3/0	0	0	No	10	0
7	43/M	None/weakness	No/no	0/3	1	1	No	7	0
8	52/F	Weakness/none	Yes/no	4/2	1	1	No	9	0
9	72/F	Weakness/weakness	Yes/no	4/4	0	3	Yes	18	3
10	64/M	Headache	Yes/no	4/4	0	0	No	4	0
11	43/F	Headache	No/no	0/4	0	0	No	4	0
12	36/F	Headache	No/no	2/0	0	0	No	4	0
13	24/F	Aphasia/none	Yes/no	3/2	3	3	No	18	0
14	61/F	Weakness and seizure/none	No/no	2/0	0	0	No	9	1
15	33/M	Headache/headache with weakness	Yes/yes	2/3	4	4	No	9	1
16	48/F	Weakness and seizure/none	Yes/yes	3/3	2	2	No	8	0
17	42/M	Aphasia/none	Yes/no	5/0	0	5	Yes	33	2
18	59/F	Aphasia/dysarthria	Yes/yes	3/3	8	8	No	11	0
19	36/F	Aphasia and chorea/none	Yes/yes	5/5	0	0	No	6	1
20	47/F	Dizziness and dysarthria	Yes/yes	3/3	0	0	No	4	0
21	46/F	Weakness/none	Yes/no	2/2	0	0	No	4	0
22	57/F	Weakness/none	Yes/no	3/1	2	2	No	11	0
23	47/M	Weakness/dysarthria with facial palsy	No/yes	2/4	0	0	No	6	0
24	48/M	None/weakness	Yes/yes	4/3	1	8	Yes	24	2
25	27/M	Syncope	No/no	1/3	0	0	No	5	0
26	39/F	None/weakness	Yes/yes	5/5	0	0	No	17	0
27	40/M	None/weakness	No/yes	0/2	0	0	No	11	0
28	66/F	Seizure	Yes/no	3/5	0	0	No	5	0
29	41/F	None/weakness	No/yes	2/4	0	0	No	6	1
30	21/M	Aphasia/none	Yes/no	5/3	9	12	Yes	24	3

L left, *R* right, *NIHSS* National Institute of Health Stroke Scale, *mRS* modified Rankin Scale; Unstable clinical course is a deterioration or fluctuation of at least 2 points of NIHSS scores

Angiographic grading and cerebral blood flow volume parameters

Suzuki grade was inversely correlated with ICA flow volume ($r = -0.547$, $p < 0.001$) and hemispheric flow volume ($r = -0.417$, $p = 0.001$). However, ECA flow volume ($r = 0.100$, $p = 0.445$) and VA flow volume ($r = 0.130$, $p = 0.322$) were not associated with Suzuki grade. The ECA-to-ICA ($r = 0.218, p = 0.094$) and VA-to-ICA volume ratios ($r = 0.217, p = 0.096$) were not correlated with Suzuki grade (Table 2). The changes in ICA, ECA, and VA flow volumes according to the Suzuki grade are shown in Fig. 1.

Hemodynamic contribution by transdural collaterals

In the higher stage hemispheres (Suzuki grade ≥ 3), comparison of variables between the transdural and no transdural groups was performed to investigate the hemodynamic contribution of transdural collaterals (Table 3). Hemispheres with transdural collaterals ($n = 10$) had significantly smaller infarction volumes on MRI (27.6 ± 59.3 vs. 2.4 ± 3.6 mL, $p = 0.041$) than those without transdural collaterals ($n = 26$), and none of the patients with transdural collaterals had an unstable clinical course.

Table 2 Lesion patterns and hemodynamic contributors according to hemispheric Suzuki grading [lower stages (0–2) vs. higher stages (≥3)]

Characteristic	Lower stage on hemisphere ($n = 24$)	Higher stage on hemisphere ($n = 36$)	p
General			
Age, years	42.3 ± 10.8	46.1 ± 13.8	0.254
Sex, female	18 (75.0)	26 (72.2)	0.812
Unstable clinical course	0 (0.0)	8 (22.2)	0.013
Lesion pattern			0.026
No lesion	18 (75.0)	10 (27.8)	
Acute lesion only	4 (16.7)	7 (19.4)	
Old lesion only	2 (8.3)	12 (33.3)	
Acute and old combined lesions	0 (0.0)	7 (19.4)	
Whole lesion volume, cm^3	1.37 ± 5.60	20.57 ± 51.41	0.033
Collateral flow routes			
Leptomeningeal	18 (75.0)	9 (25.0)	<0.001
pCoM hyperplasia	3 (12.5)	9 (25.0)	0.196
Transdural	0 (0.0)	10 (27.8)	0.005
Flow volume (ml/min)			
ICA	252 ± 84	131 ± 109	<0.001
ECA	158 ± 58	152 ± 69	0.715
VA	113 ± 56	119 ± 78	0.749
ECA/ICA flow volume ratio	0.70 ± 0.38	9.73 ± 69	<0.001

pCoM posterior communicating artery

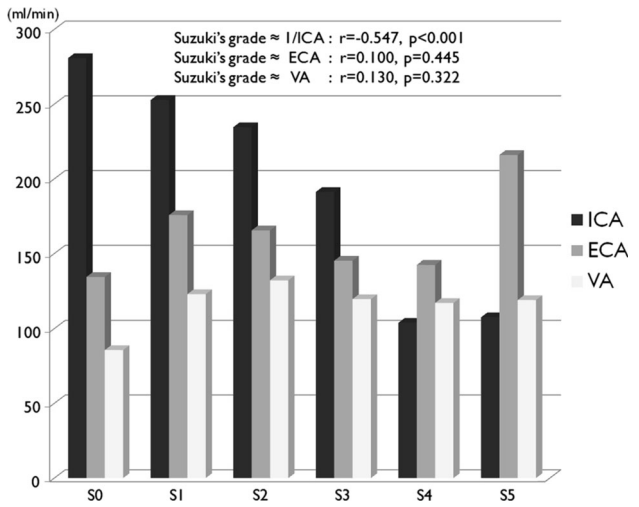

Fig. 1 Relationships between Suzuki grade and cerebral flow volumes in internal carotid arteries (ICAs), external carotid arteries (ECAs), and vertebral arteries (VA) on the duplex sonographic studies. ICA flow volume gradually decreased but significantly associated with a progression of Suzuki stage, whereas ECA and VA flow volume was not associated with the Suzuki staging

Patients with transdural collaterals had a lower ICA flow volume (88.4 ± 45.9 vs. 146.2 ± 121.7 mL/min, $p = 0.022$) and a higher ECA flow volume (205.7 ± 77.7 vs. 135.9 ± 52.7 mL/min, $p = 0.046$) than those without transdural collaterals. No difference in VA flow volume was detected between the two groups. Patients with transdural collaterals had a higher prevalence (60.0 vs. 11.5 %, $p = 0.003$) of an ECA-to-ICA flow volume ratio >2 compared to those without transdural collaterals (31.78 ± 92.83 vs. 1.67 ± 1.94, $p = 0.024$) (Table 3).

A ROC analysis was performed for Suzuki grade alone and for Suzuki grade combined with the status of each arterial collateral route to determine the usefulness of arterial collaterals for predicting the clinical course. Figure 2 shows that the area under the curve values was highest for Suzuki grade combined with status of the transdural ECA collaterals (0.904), regardless of combining with leptomeningeal (0.779) or direct PcoA collaterals (0.845). More than half of the patients with higher stage hemispheres (60 %) had an ECA-to-ICA volume ratio >2.

Discussion

Our study findings show that modified Suzuki's staging (incorporating hemodynamic status) is needed to predict the clinical deterioration after admission through emergency room in patients with various acute symptoms. This kind of clinical deterioration is especially more common in patients with a higher Suzuki stage hemisphere (≥stage 3) and without transdural collateral flow. In addition, ECA-to-ICA flow ratio with a bedside ultrasonogram can

Table 3 Characteristics and hemodynamic contributors according to the presence of transdural collateral circulation in higher stage hemispheres

Characteristic	No transdural collateral hemisphere ($n = 26$)	Transdural collateral hemisphere ($n = 10$)	p
Suzuki's grading			0.048
3	11 (42.3)	0	
4	12 (46.2)	8 (80.0)	
5	3 (11.5)	2 (20.0)	
Unstable clinical course	8 (30.8)	0 (0.0)	0.047
Lesion patterns			0.296
No lesion	7 (26.9)	3 (30.0)	
Acute lesion only	7 (26.9)	0 (0.0)	
Old lesion only	8 (30.8)	4 (40.0)	
Acute and old lesion combined	4 (15.4)	3 (30.0)	
Whole lesion volume, mL ($n = 32$)	27.56 ± 59.27	2.40 ± 3.63	0.041
Flow volume (ml/min)			
ICA	146.2 ± 121.7	88.4 ± 45.9	0.022
ECA	135.9 ± 52.7	205.7 ± 77.7	0.046
VA	117.4 ± 79.9	116.4 ± 75.8	0.972
ECA/ICA flow volume ratio	1.67 ± 1.94	31.78 ± 92.83	0.024
ECA/ICA flow volume ratio ≥2	3 (11.5)	6 (60.0)	0.003

pCoM posterior communicating artery, *ICA* internal carotid artery, *ECA* external carotid artery, *VA* vertebral artery

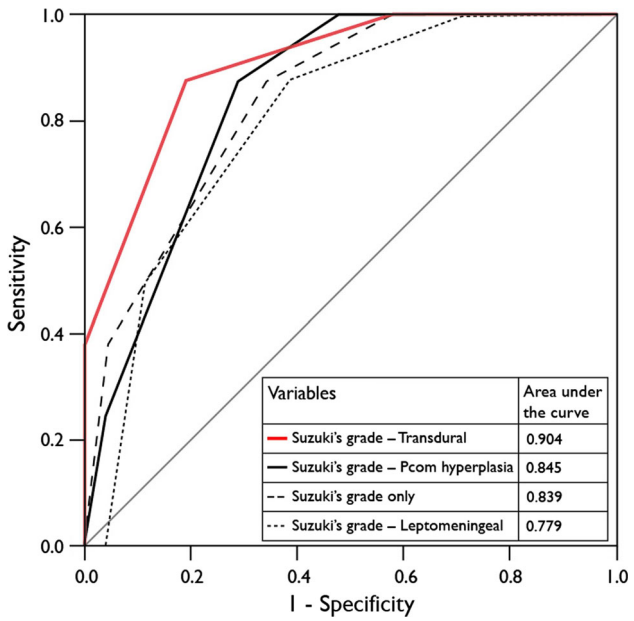

Fig. 2 Receiver operating characteristics (ROC) curves for predicting an unstable neurological course according to various models incorporating Suzuki staging with various collateral routes. The model incorporating Suzuki grade and transdural collaterals had the largest area (0.904) under the ROC curve for an unstable neurological course during hospitalization

be helpful to easily recognize such important transdural collateral detours.

Hemodynamic changes according to disease progression

Our results show that blood flow in the ICA and total blood flow in each hemisphere were inversely correlated with Suzuki grade, which is consistent with the findings of recent four-vessel angiography and transcranial Doppler studies [7, 14]. In contrast, our results of blood flow from the posterior circulation and the ECAs varied according to the angiographic stage. This hemodynamic compensation seemed to vary based on the progression of MMD. Nevertheless, higher graded patients (Suzuki grades 3–5) without transdural collateral flow were at risk for an impending stroke. Therefore, our clinical and radiological findings suggest that a higher Suzuki grade indicates intracranial shrinkage from anterior circulation, which is more vulnerable to impending ischemia [14], depending on tissue perfusion status from posterior or extracranial collateral compensation (Fig. 3). This point seems to correspond well with Suzuki's classical perspectives, even in adult patients with MMD (Supplementary Figure 1).

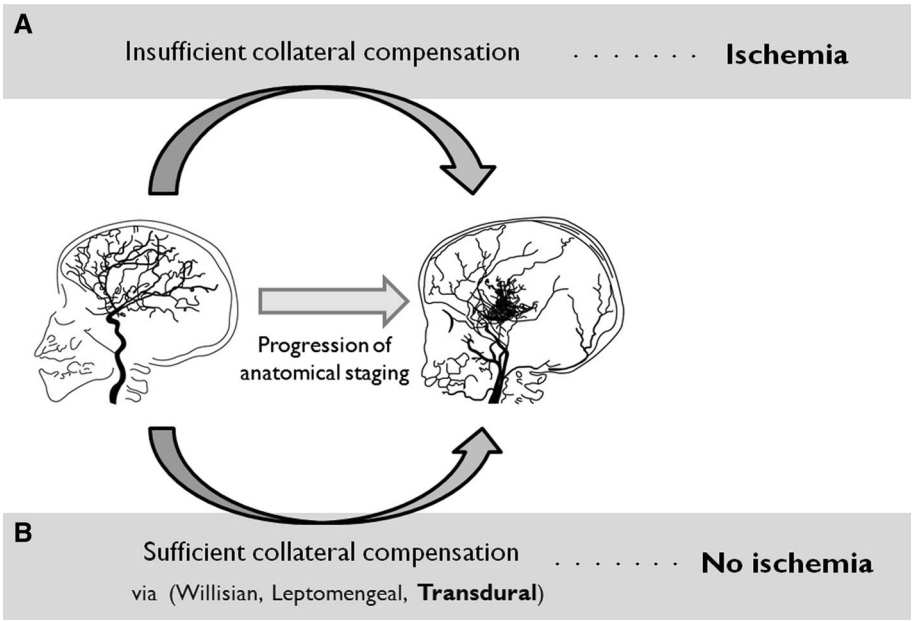

Fig. 3 A possible hemodynamic compromise according to the progression of Suzuki stage: either **a** insufficient compensation or **b** sufficient collateral compensation. Development of a transdural collateral route may be the most important detour against impending ischemia in adult patients with advanced stage (≥3 of the Suzuki stage) of moyamoya disease

Various collateral routes and the clinical impact of transdural collaterals

We found a significant difference in the development of collaterals between the lower and higher stage Suzuki groups. The main route for the lower stage group was leptomeningeal collaterals, whereas it was transdural collaterals in the higher stage group. Noticeably, no neurological deterioration or fluctuation episodes were detected during admission in patients with transdural collaterals, suggesting that these cerebral detours can prevent ischemic insults. Our results also suggest that this detour may be a mainstay for maintaining cerebral perfusion against ischemic damage in higher staged patients [12].

Cerebral collateral circulation refers to the ancillary web of vascular channels that stabilize CBF when principal conduits are not working [15]. This anatomical network is divided into primary collaterals and secondary collaterals, in which the latter develop when the primary collaterals are insufficient [15]. Moreover, the inefficiency of intracerebral leptomeningeal collaterals from the posterior circulation can be explained by PCA involvement in higher stage hemispheres. The degree of leptomeningeal collaterals from the PCA decreases in the advanced angiographic stage, as the steno-occlusive lesion extends to the PCA [2, 7, 16].

A perfusion MRI study reported that intracerebral anastomoses may not provide adequate blood supply to the cerebral cortices in adult patients with MMD, even if they are fully developed [17]. Okada et al. showed that a direct extracranial–intracranial anastomosis improves CBF in adult patients with MMD and decreases hemorrhage risk by reducing the number of basal moyamoya vessels [18]. These observations suggest that the transdural collateral channel is an alternative route for supplying blood in place of intracerebral collaterals [17]. Recent studies also point out the significant role of the ipsilateral ECA to cerebral perfusion in patients with an occlusion or severe stenosis of the ICA [19–21].

Individual variations in collateral patterns and the clinical implications

Unlike pediatric patients with MMD, the collateral development patterns in adult patients with MMD are less predictable [4, 17, 22]. Moreover, inconsistencies have been reported for the primary and secondary collateral pathways in adult patients with MMD. In addition to different methodologies between studies, individual variability in the circle of Willis in adult patients is a large obstacle to claim collateral flow compensation [11, 23, 24].

Given the pathophysiological consideration of collaterals for protecting against ischemic stroke, specific individual patterns should be considered when determining disease severity in patients with MMD. However, the current morphological criteria focus primarily on the degree of ICA stenosis and the extent of basal moyamoya vessels [4] and do not incorporate individual variation with hemodynamic status or its clinical impact.

Czabanka et al. proposed a new grading system for adult patients with MMD [9]. This new grading system incorporates angiographic severity, MRI lesion pattern, and cerebrovascular reserve capacity using xenon-CT technology. As a result, this system is superior to each single parameter for predicting clinical manifestations. In our study, compared to using Suzuki grade alone, use of Suzuki

grade and collateral flow was able to predict the risk for impending ischemic stroke and neurological deterioration better. Therefore, our study results are in agreement with the study by Czabanka et al. which emphasize the significance of collaterals in evaluating patients with MMD.

Hemodynamic compromise and transdural collaterals using duplex sonography

The ECA collateral flow can be a pivotal detour for decreased ICA flow in patients with advanced stage MMD because a new infarction and neurological deterioration occurred mostly in our patients with higher stage hemispheres without transdural collaterals.

We used neck duplex sonography to measure the hemodynamic parameters in patients. Despite that it is operator dependent and has poor spatial resolution, recent advances of color coding, angle correction, and spectral time-averaging have uncovered a new measurement to analyze volumetric flow more accurately. In this study, a decrease in ICA flow volume and ECA-to-ICA flow volume ratio >2 described the existence of ipsilateral transdural collateral flow (60 %). Moreover, serial follow-ups using this method as a screening tool are practically feasible to predict the progression of ICA stenosis or moyamoya severity [25].

Limitations

Our study had some limitations. First, well-designed prospective studies with a large number of adult patients with MMD are needed for a balanced interpretation because our study was retrospective with a relatively small population. Second, our findings should not be generalized to all adult patients with MMD because we did not include the patients who presented with intracranial hemorrhage (ICH). Further studies are needed to validate our findings in other populations of patients with MMD and to evaluate the impact of collaterals in patients with ICH. Finally, a careful interpretation of our data is needed because ultrasonography parameters can be influenced by different examiners or by individual conditions (e.g., diurnal variation or caffeine intake). Nevertheless, the ECA/ICA flow volume ratio could be a valuable screening index to detect transdural collaterals using this bedside procedure.

Conclusions

We observed that ICA flow and total blood flow decreased according to the progression of MMD in adult patients, and that ischemic stroke occurred primarily in patients with higher Suzuki stage hemispheres, which was largely dependent on transdural ECA collaterals. Therefore, our observations support that investigating and considering ECA collateral status is necessary for risk stratification in higher stage group, and the ECA-to-ICA volume ratio is a useful index for the existence of these externally directed collaterals. Use of a multimodal approach, including non-invasive sonographic modalities to investigate CBF and the presence of transdural collateral flow may be helpful when predicting the clinical course in patients presenting with acute ischemic symptoms associated with MMD.

Compliance with ethical standards

Conflict of interest None of the authors have a competing interest.

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