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Cerebral hemodynamics and metabolism in adult moyamoya disease: Comparison of angiographic collateral circulation

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Purpose: The extent of the hemodynamic and metabolic impairments in adult patients with moyamoya disease is still controversial. The aim of the present study was to evaluate the hemodynamic and metabolic status in relation to the development of basal moyamoya vessels (BMVs). ***Methods:*** The cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), oxygen extraction fraction (OEF), and cerebral blood volume (CBV) were measured using PET in ten patients with ischemic adult moyamoya disease (mean age, 36.6 years) and six age-matched normal controls (mean age, 33.3 years). The cerebrovascular reserve (CVR) after acetazolamide (ACZ) loading was also estimated using iodine-123 *N*-isopropyl-*p*-iodo amphetamine single photon emission computed tomography (^{123}I-IMP SPECT). ***Results:*** Based on the angiographic findings, eleven cerebral hemispheres with well-developed BMV (extensive BMV hemispheres) and nine cerebral hemispheres with diminished BMV (diminished BMV hemispheres) were identified. The main routes of collateral circulation in extensive BMV hemispheres were BMVs and leptomeningeal anastomoses. On the other hand, in diminished BMV hemispheres, transdural anastomosis was predominant, and leptomeningeal anastomoses were less developed. In cortices distal to the occluded internal carotid artery, the extensive BMV hemispheres exhibited a significantly lower CBF, $CMRO_2$, CBF/CBV, and CVR ($p < 0.05$) and a significantly higher CBV and OEF than in diminished BMV hemispheres and controls ($p < 0.05$). Except for the CBF in the white matter, the mean hemodynamic and metabolic parameters of the diminished BMV hemispheres were not significantly different from those of the controls. ***Conclusion:*** The extensive development of basal moyamoya vessels is a sign of severe hemodynamic impairment in adult patients with ischemic moyamoya disease. The results may not apply to adults with hemorrhagic onset.

Key words: adult moyamoya disease, collateral circulation, PET, cerebral blood flow, cerebral metabolism

INTRODUCTION

MOYAMOYA DISEASE is a cerebrovascular disease characterized by the spontaneous and progressive occlusion of the terminal portion of the bilateral internal carotid arteries (ICA), proximal parts of the anterior cerebral artery (ACA), and the middle cerebral artery (MCA) with a spontaneously developed collateral vascular network.[1–3] Most pediatric patients demonstrate extensive development of basal moyamoya vessels and present with

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Table 1 Patient characteristics

Patient No.	Age y/Sex	Subtype	Major clinical symptoms	Duration from onset of disease	Infarct on MRI
1	31/F	TIA	Weakness of Rt limbs	22 y	Lt WM lacunar
2	37/F	TIA	Weakness of limbs	28 y	Negative
3	21/F	TIA	Syncope	3 mo	Lt WM lacunar
4	37/M	CI	Lt hemianopsia	3 mo	Rt occipital
5	42/F	AS	None	None	Negative
6	47/F	CI	Weakness of Lt limb	3 mo	Rt precentral area
7	29/F	CI	Lt hemianopsia	23 y	Rt parietooccipital
8	35/F	TIA	Weakness of Rt limbs, aphasia	1 mo	Lt LN lacunar
9	32/F	AS	Headache	8 y	BG-WM lacunar
10	50/M	CI	Rt hemianopsia	5 y	Lt occipital

TIA, transient ischemic attack; CI, cerebral infarction; AS, Asymptomatic: indicates asymptomatic carotid artery disease; BG, basal ganglia; WM, white matter; LN, lentiform nucleus; Lt, left; Rt, right.

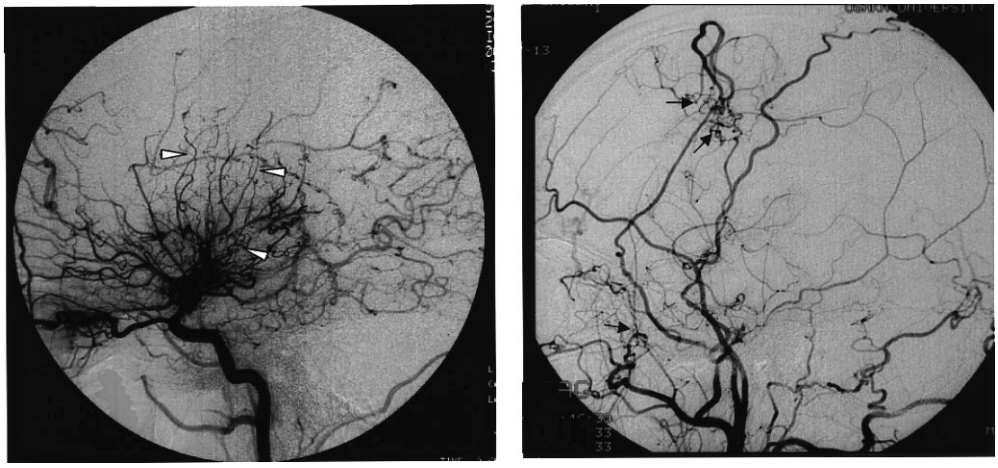

Fig. 1 Representative findings of the cerebral angiography in moyamoya disease. Left panel: Typical angiographic image of extensive basal moyamoya vessels development type. Nether middle-nor anterior cerebral arteries are visible, and moyamoya vessels with retrograde filling of long-penetrating medullary arteries developed (*white arrowhead*). Right panel: Typical angiographic image of diminished basal moyamoya vessels type. Branches of the internal carotid artery and basal moyamoya vessels are not seen. Transdural anastomosis (*arrow*) developed instead.

ischemic events.[4] Previous studies have indicated a decrease in cerebral blood flow (CBF) and CBF in response to carbon dioxide inhalation.[5–7] Compensating mechanisms, such as an increase in cerebral blood volume (CBV) and the oxygen extraction fraction (OEF) have been found in the territory of the occluded arteries.[7] Cerebral oxygen metabolism was maintained in the normal range.[8,9]

In contrast, the severity of the hemodynamic and metabolic impairments in adult patients remains controversial. Kuwabara et al. found no significant reduction in CBF or the cerebral metabolic rate of oxygen ($CMRO_2$) in four adult patients. Misery perfusion was not detected either.[8] Taki et al. found a decrease in the CBF/CBV ratio, an index of perfusion pressure, in nine adult patients.[9] In both of these studies, the $CMRO_2$ did not decrease in the cortical gray matter, basal ganglia, or white matter. On the other hand, Morimoto et al. found a decrease in the cortical CBF and $CMRO_2$ and an increase in the CBV and OEF in five patients who later underwent superficial temporal artery to middle cerebral artery (STA-MCA) bypass surgery.[10] The discrepancies among these studies may be caused partly by a selection bias in the patients, the severity of the primary steno-occlusive ICA lesion, or the development of collateral circulation.

The aim of the present study was to clarify the extent of the hemodynamic and metabolic impairments in adult patients with ischemic moyamoya disease by examining collateral circulation using cerebral angiography. Patients with well-developed basal moyamoya vessels (BMVs) were compared with those with diminished basal moyamoya vessels.

PATIENTS AND METHODS

All the patients were seen at the Osaka University Medical School Hospital between March 2000 and April 2003. Eighteen consecutive patients diagnosed as having moyamoya disease were selected. Pediatric patients, patients with a cerebral infarction measuring more than 3 cm in diameter in the ICA territory (based on magnetic resonance imaging [MRI] images), patients with intracerebral hemorrhage and patients with a history of head surgery were excluded from the study. Patients were also excluded if they had experienced a clinical stroke event within one month prior to the start of the study.

A total of ten patients with moyamoya disease (two males, eight females; mean ± SD age, 36.6 ± 9.1 years, range 21 to 50 years) were finally enrolled in the study. All patients had undergone a digital subtraction angiography (DSA) and MRI examination. Four patients had transient ischemic attacks (TIAs), one patient suffered from headache, one patient had asymptomatic carotid artery disease, and four patients had minor cerebral infarctions. Table 1 shows the clinical features and MRI findings of these ten patients. All patients were clinically diagnosed as definite cases of moyamoya disease based on the *Criteria for the Diagnosis of Moyamoya Disease* (Ministry of Health and Welfare of Japan, 1996).[11] We evaluated the angiographic findings of all 20 hemispheres in the ten patients. The hemispheres were divided into two groups according to the extent of BMV development, extensive BMV with retrograde filling of long-penetrating medullary arteries (extensive BMV group; n = 11 hemispheres), and poor BMV with no retrograde filling of the medullary arteries (diminished BMV group; n = 9 hemispheres) (Fig. 1). Furthermore, the development of leptomeningeal collateral circulation was evaluated using the classification system established by Mugikura et al.[12] The development of leptomeningeal anastomosis was classified into four grades: good, cortical branches in all three (frontal, parietal, and temporal) lobes opacified; moderate, cortical branches in two lobes opacified; poor, cortical branches in one lobe opacified; none, no collateral circulation. Six age-matched normal volunteers (two males and four females, 33.3 ± 6.6 years, range 26 to 43 years) were recruited as a control group. All subjects underwent both PET and iodine-123 *N*-isopropyl-*p*-iodo amphetamine single photon emission computed tomography (^{123}I-IMP SPECT) examinations. A detailed explanation of the purpose of the study and all the procedures used in the study was given prior to the enrollment of the subjects in the study. Written informed consent was obtained from all the subjects. The study was approved by the Ethical Committee of Osaka University.

SPECT Imaging

We used the split-dose ^{123}I-IMP SPECT method.[13] A high-performance, four-head rotating gamma camera (Gamma View SPECT 2000H, Hitachi Medical Co., Tokyo, Japan) was used to perform the SPECT imaging. This gamma camera was equipped with a low-energy, general purpose, parallel-hole collimator with a spatial resolution of 13.0 mm full-width-at-half-maximum (FWHM). Subjects were asked to lie supine on the

Table 2 Development of basal moyamoya vessels and collateral circulation on angiography

	patient No.	side	site of ICA occlusion	leptomeningeal*	transdural
extensive BMV	1	Rt	cavernous	moderate	+
	1	Lt	lacerum	poor	+
	2	Rt	communicating	moderate	+
	2	Lt	communicating	moderate	+
	3	Rt	cavernous	good	–
	3	Lt	cavernous	good	+
	4	Rt	clinoid	poor	+
	4	Lt	ophthalmic	poor	+
	5	Rt	communicating	good	–
	6	Rt	ophthalmic	good	+
	10	Lt	clinoid	good	+
diminished BMV	5	Lt	communicating	none	–
	6	Lt	ophthalmic	none	+
	7	Rt	cavernous	poor	++
	7	Lt	ophthalmic	moderate	++
	8	Rt	communicating	moderate	++
	8	Lt	communicating	moderate	++
	9	Rt	ophthalmic	good	+
	9	Lt	communicating	poor	++
	10	Rt	clinoid	good	+

BMV, basal moyamoya vessels; ICA, internal carotid artery; Lt, left; Rt, right; +, indicates thin collateral; ++, indicates rich collateral; –, none; *, classification of Mugikura et al.

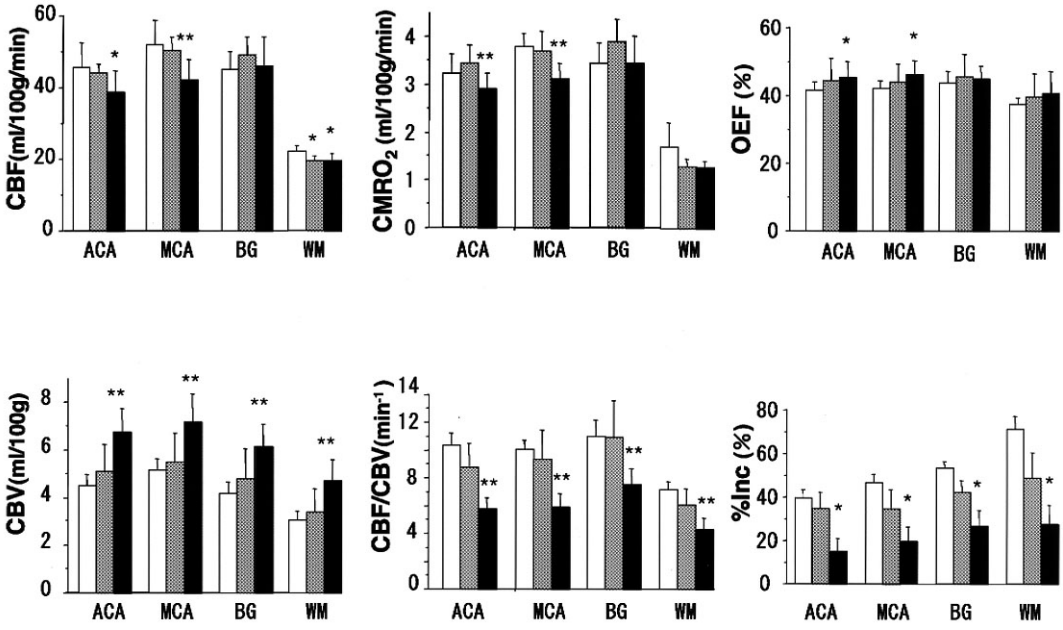

Fig. 2 Comparison of regional cerebral blood flow (CBF), regional cerebral metabolic rate of oxygen ($CMRO_2$), regional oxygen extraction fraction (OEF), regional cerebral blood volume (CBV), regional cerebral blood flow over cerebral blood volume (CBF/CBV), cerebrovascular reserve (CVR) by the angiographic types. Data are show as means plus SD. Open column, hatched column, and closed column indicate normal control, diminished basal moyamoya vessel (BMV) group, and extensive BMV group, respectively. MCA, middle cerebral artery territory; ACA, anterior cerebral artery territory; BG, basal ganglia; WM, white matter; *, $p < 0.05$ vs. normal control; **, $p < 0.05$ vs. normal control and diminished BMV group.

scanner bed with their eyes closed in a dimly lit and quiet room. The subject's head was immobilized using a head holder. A built-in light beam was adjusted to the subject's orbito-meatal (OM) line so that the system would reconstruct images parallel to the OM line. The acquisition started with the intravenous injection of 111 MBq of ^{123}I-IMP (Perfusamine^{TM}, Nihon Medi-Physics Co., Ltd., Nishinomiya, Japan). Nine minutes later, 1 g of acetazolamide (ACZ) (Diamox^{TM}, Lederle Ltd., Tokyo, Japan) was slowly administrated intravenously. At 27 minutes after the first injection, an additional 111 MBq of ^{123}I-IMP was injected. Data were collected in a continuous rotating mode in reciprocal directions at 20 seconds per revolution for 66 minutes from 96 directions. The transaxial images were reconstructed using a filtered back projection algorithm and a Butterworth prefilter. Resting and vasodilated perfusion images were obtained using the subtraction technique. Data were formatted as a 3-dimensional (3D) dataset with 64 × 64 × 64 cubic voxels, 4 mm per voxel side.

PET Imaging

A Headtome V/SET 2400W system (Shimadzu Co., Ltd., Kyoto, Japan) was used for the PET imaging. Prior to the emission scan, a Ge-68/Ga-68 transmission scan was performed for 10 minutes for attenuation correction. All scans were performed at a resolution of 3.7 mm FWHM in the transaxial direction and at 5 mm in the axial direction. Images were reconstructed using an ordered subset expectation maximization algorithm (12 iterations with 4 ordered subsets). The subject's head was fixed in place with a head holder and was positioned using light beams to obtain transaxial slices parallel to the OM line. Data were formatted as a 3D dataset with 63 slices (3.17 mm thick) in 128 × 128 matrices. CBF, $CMRO_2$, OEF and CBV were measured using the conventional O-15 gas steady-state method.

Data Analysis

The SPECT and PET data were analyzed using an image analyzing software system (Dr. View Pro 5.0, Asahi Kasei Joho System Ltd., Tokyo, Japan). The SPECT and PET image data sets were displayed side by side, and regions of interest (ROIs) were drawn at corresponding positions in both images.[14] Multiple circular ROIs (20 mm in diameter) were placed in the cortical ribbon, basal ganglia, and white matter. ROIs in multiple slices from the basal ganglia level to the centrum semiovale level were linked together into four areas: the ACA territory, MCA territory, basal ganglia territory, and white matter.

The cerebrovascular reserve (CVR) was calculated from the SPECT data using the following equation: CVR

= (ACZ challenge count – resting count) × 100 /resting count.

All data were expressed as the mean ± 1SD. Differences in the mean values of the groups were analyzed using a one-way ANOVA followed by Bonferroni's multiple comparison. Differences were considered to be significant when the statistical p value was under 0.05.

RESULTS

Table 2 presents the individual findings of cerebral angiography. The main routes of collateral circulation in extensive BMV hemispheres were BMVs and leptomeningeal anastomoses. On the other hand, in diminished BMV hemispheres, transdural anastomosis was predominant, while leptomeningeal anastomoses were less developed. The feeders of those transdural anastomoses in the ACA territory were the anterior falx artery and middle meningeal artery, and those in the MCA territory were the middle meningeal artery. In three diminished BMV hemispheres (Pt No. 5, 6, 9), the left ACA or MCA periphery was filled by developed basal thin channels. Of these three hemispheres, one (Pt No. 5) had neither leptomeningeal nor transdural anastomoses.

Figure 2 shows the CBF, $CMRO_2$, OEF, CBV, CBF/CBV, and CVR as measured using PET and SPECT. In the extensive BMV group, the CBF and $CMRO_2$ in the ACA territory and the MCA territory were significantly lower than those in the other groups. The regional OEF in the ACA territory and the MCA territory was significantly higher in the extensive BMV group than in the normal controls.

No significant differences in the CBF, $CMRO_2$, or the OEF in the basal ganglia or white matter were seen among the groups, except for the CBF in the white matter.

Large differences in the CBV and the CBF/CBV were seen among the groups. In all the regions examined, the extensive BMV group showed a significantly higher CBV and a lower CBF/CBV than the other groups. The CVR was significantly lower in the extensive BMV group than in the normal controls in all the regions examined.

In contrast, no significant differences in any of the PET measurements were seen between the normal control group and the diminished BMV group, except for the CBF in the white matter.

DISCUSSION

The present study on the hemodynamic and metabolic impairments in adult patients with ischemic moyamoya disease shows that the hemodynamic status of hemispheres with extensive BMV is different from that of hemispheres with diminished BMV. Transdural, rather than intracerebral, collaterals were effective for maintaining cerebral circulation in the territory of the occluded ICA.

In contrast to pediatric patients, adult patients with moyamoya disease often develop intracerebral hemorrhage. To evaluate the hemodynamics in adult ischemic moyamoya disease, the present study excluded patients with hemorrhagic episode because the hemodynamics in hemorrhagic cases might be different from those in ischemic cases. In some previous papers, it was reported that CBF and CVR were not impaired in moyamoya patients with hemorrhagic onset. From this point of view, the results of this study may not apply to adult hemorrhagic moyamoya disease.

BMV, leptomeningeal anastomosis between the PCA and anterior circulation, and transdural anastomosis between the extracranial and intracranial vessels are the main routes of collateral circulation in patients with moyamoya disease. Mugikura et al. reported that leptomeningeal collaterals developed most when prominent BMVs are present. In the advanced angiographic stage, the degree of leptomeningeal collaterals from the PCA decreases as the steno-occlusive lesion extends to the PCA.[12] The transdural anastomoses, represented by ethmoid moyamoya and vault moyamoya vessels, develop later in the advanced angiographic stage.[15,16]

In the present study, we classified the patients into two subgroups: patients with extensive BMVs and retrograde filling of long-penetrating medullary arteries and patients with poor BMVs and no retrograde filling of long-penetrating medullary arteries. The former group corresponded to stage III and the latter to stage IV (minimization of moyamoya vessels) and stage V (reduction of moyamoya vessels) in Suzuki's angiographic classification.[2]

The most important finding of the present study was that the patients with extensive BMV hemispheres exhibited impaired perfusion and metabolism in the cortices whereas patients with diminished BMV hemispheres did not. The exception was the white matter area in the diminished BMV group. The mean CBF in the area was significantly more reduced than that in the normal control group. This may be explained by the fact that patients in the diminished BMV group had multiple lacunar infarctions as revealed by MRI.

Our results suggested that intracerebral anastomoses may not provide an adequate blood supply to the cerebral cortices, even if they are fully developed. Diminished BMVs were associated with well-developed transdural anastomoses in our patients. Based on these findings, we speculate that transdural collateral channels are more efficient in supplying blood, than intracerebral anastomoses, but develop gradually when BMV is minimized in adult patients with moyamoya disease. From this point of view, the formation of BMVs may be accelerated by persistent cortical ischemia. This speculation is supported by some previous reports[10,17–19] describing that STA-MCA anastomosis improved CBF in adult patients with moyamoya disease. It was also reported that STA-MCA anastomosis reduced BMVs, as revealed by follow-up

angiography studies, and decreased the risk of hemorrhage.

The purpose of STA-MCA anastomosis differs according to the type of adult moyamoya disease. In patients with ischemic onset, the purpose of STA-MCA anastomosis is the suppression of ischemic attacks by improving the cortical hemodynamic impairment. Such improvement in the cortical hemodynamics then induces reduction of BMV. In patients with hemorrhagic onset, things are different with the purpose of the anastomosis being the prevention of rebleeding by reducing the hemodynamic stress on BMV. The anastomosis, instead of BMV, supplies blood to the cortex to reduce BMV. As there is no evidence about the effect of STA-MCA anastomosis on the risk of rebleeding, the Japanese adult moyamoya trial (JAM trial) is now ongoing in Japan.

Cerebral oxygen metabolism is significantly decreased in extensive BMV hemispheres. Kuwabara et al.[8] reported no significant reduction in $CMRO_2$ in pediatric moyamoya patients with BMV. We speculate that the reduction in oxygen metabolism in adult patients may be induced by persistent oligemia for several years. Such metabolic impairment may be improved by the development of transdural and leptomeningeal collateral channels, as found in our subgroup with diminished BMV hemispheres associated with well-developed transdural collaterals. This speculation is supported by some previous reports showing that in pediatric patients, ischemic symptoms diminished in parallel with the development of ethmoid and vault moyamoya vessels[2] and the intelligence of pediatric patients with moyamoya disease could be improved by revascularization surgery.[4] Even in adult moyamoya disease, the reduction in $CMRO_2$ can be improved by a successful STA-MCA bypass surgery.[10]

In conclusion, severe hemodynamic and metabolic impairments were found in adult patients with ischemic moyamoya disease when the extensive development of basal moyamoya vessels persists. The severity of these cerebral hemodynamic and metabolic impairments in adults with ischemic moyamoya disease highly depends on the type of remaining collateral circulation. Extensive development of basal moyamoya vessels is a sign of severe hemodynamic impairment in adults with ischemic moyamoya disease. The results of the present study may be limited to adult patients with ischemic onset, and may not apply to those with hemorrhagic onset.

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REFERENCES

1. Kudo T. Spontaneous occlusion of the circle of willis. *Neurology* 1968; 18: 485–496.
2. Suzuki J, Takaku A. Cerebrovascular 'moyamoya' disease: disease showing abnormal net-like vessels in base of brain. *Arch Neurol* 1969; 20: 288–299.
3. Nishimoto A, Takeuchi S. Abnormal cerebral vascular network related to the internal carotid arteries. *J Neurosurg* 1968; 29: 255–260.
4. Ishii R, Takeuchi S, Ibayashi K, Tanaka R. Intelligence in children with moyamoya disease: evaluation after surgical treatments with special reference to changes in cerebral blood flow. *Stroke* 1984; 15: 873–877.
5. Takeuchi S, Tanaka R, Ishii R, Tsuchida T, Kobayashi K, Arai H. Cerebral hemodynamics in patients with moyamoya disease. *Surg Neurol* 1985; 23: 468–474.
6. Ogawa A, Yoshimoto T, Suzuki J, Sakurai Y. Cerebral blood flow in moyamoya disease. Part 1: Correlation with age and regional distribution. *Acta Neurochir (Wien)* 1990; 105 (1–2): 30–34.
7. Kuwabara Y, Ichiya Y, Sasaki M, Yoshida T, Masuda K, Matsushima T, et al. Response to hypercapnia in moyamoya disease. Cerebrovascular response to hypercapnia in pediatric and adult patients with moyamoya disease. *Stroke* 1997; 28: 701–707.
8. Kuwabara Y, Ichiya Y, Otsuka M, Tahara T, Gunasekera R, Hasuo K, et al. Cerebral hemodynamic change in the child and the adult with moyamoya disease. *Stroke* 1990; 21: 272–277.
9. Taki W, Yonekawa Y, Kobayashi A, Ishikawa M, Kikuchi H, Nishizawa S, et al. Cerebral circulation and metabolism in adult's moyamoya disease: PET study. *Acta Neurochir (Wien)* 1989; 100: 150–154.
10. Morimoto M, Iwama T, Hashimoto N, Kojima A, Hayashida K. Efficacy of direct revascularization in adult Moyamoya disease: haemodynamic evaluation by positron emission tomography. *Acta Neurochir (Wien)* 1999; 141 (4): 377–384.
11. Ikezaki K, Han DH, Kawano T, Kinukawa N, Fukui M. A clinical comparison of definite moyamoya disease between South Korea and Japan. *Stroke* 1997; 28: 2513–2517.
12. Mugikura S, Takahashi S, Higano S, Shirane R, Kurihara N, Furuta S, et al. The relationship between cerebral infarction and angiographic characteristics in childhood moyamoya disease. *Am J Neuroradiol* 1999; 20: 336–343.
13. Hashikawa K, Matsumoto M, Moriwaki H, Oku N, Okazaki Y, Uehara T, et al. Split dose iodine-123-IMP SPECT: sequential quantitative regional cerebral blood flow change with pharmacological intervention. *J Nucl Med* 1994; 35: 1226–1233.
14. Imaizumi M, Kitagawa K, Hashikawa K, Oku N, Teratani T, Takasawa M, et al. Detection of misery perfusion with split-dose ^{123}I-iodoamphetamine single-photon emission computed tomography in patients with carotid occlusive diseases. *Stroke* 2002; 33: 2217–2223.
15. Yamada I, Himeno Y, Suzuki S, Matsushima Y. Posterior circulation in moyamoya disease: angiographic study. *Radiology* 1995; 197: 239–246.
16. Suzuki J, Kodama N. Moyamoya disease—a review. *Stroke* 1983; 14 (1): 104–109.
17. Okada Y, Shima T, Nishida M, Yamane K, Yamada T, Yamanaka C. Effectiveness of superficial temporal artery-middle cerebral artery anastomosis in adult moyamoya

disease: cerebral hemodynamics and clinical course in ischemic and hemorrhagic varieties. *Stroke* 1998; 29: 625–630.
18. Kawaguchi S, Okuno S, Sakaki T. Effect of direct arterial bypass on the prevention of future stroke in patients with the hemorrhagic variety of moyamoya disease. *J Neurosurg* 2000; 93: 397–401.
19. Shirane R, Mikawa S, Ebina T. A case of adult moyamoya disease showing progressive angiopathy on cerebral angiography. *Clin Neurol Neurosurg* 1999; 101: 210–214.