Synergistic Interactions Between Direct and Indirect Bypasses in Combined Procedures: The Significance of Indirect Bypasses in Moyamoya Disease

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Received, July 22, 2015.
Accepted, November 28, 2015.

BACKGROUND: Whether additional indirect bypasses effectively contribute to revascularization in combined procedures remains unclear in patients with moyamoya disease.

OBJECTIVE: To evaluate the longitudinal changes associated with combined procedures while following up pediatric and adult patients long term and to assess whether any other clinical factors or hemodynamic parameters affected these changes to determine an optimal surgical strategy.

METHODS: We studied 58 hemispheres in 43 adults and 39 hemispheres in 26 children who underwent combined revascularization for moyamoya disease. To evaluate bypass development, we assessed the sizes of the superficial temporal artery and middle meningeal artery using magnetic resonance angiography. Multivariate analysis determined the effects of multiple variables on bypass development.

RESULTS: Indirect bypass (middle meningeal artery) development occurred in 95% and 78% of the pediatric and adult hemispheres, respectively. Of these, dual development of direct and indirect bypasses occurred in 54% of the pediatric hemispheres and in 47% of the adult hemispheres. Reciprocal superficial temporal artery regression occurred in 28% of the hemispheres during the transition from the postoperative acute phase to the chronic phase during indirect bypass development. Good indirect bypass development was associated with adult hemispheres at Suzuki stage 4 or greater (odds ratio, 7.4; 95% confidence interval, 1.4-39.4; $P = .02$). Disease onset type and preoperative hemodynamic parameters were not considered predictors for the development of surgical revascularization.

CONCLUSION: Simultaneous direct and indirect bypass development was most frequently observed, regardless of patient age and hemodynamic status. Applying indirect bypass as an adjunct to direct bypass could maximize revascularization in adults and children.

KEY WORDS: Adult, Cerebral blood flow, Combined bypass, Indirect bypass, Moyamoya disease, Pediatric

Neurosurgery 0:1–8, 2016 DOI: 10.1227/NEU.0000000000001201 www.neurosurgery-online.com

Moyamoya disease (MMD) is a steno-occlusive cerebrovascular disorder characterized by progressive occlusion of the supraclinoid internal carotid artery that results in the formation of an abnormal vascular network.[1-3] Medical therapy is not generally effective, and surgical revascularization is the only prophylactic therapy available to reduce the risk of subsequent stroke. Direct bypasses exert their effects immediately after surgery and improve cerebral hemodynamics.[4] Indirect bypasses can be performed regardless of the patient's age because of their technical simplicity and because the angiogenesis is induced several months after surgery.[5,6] Combining direct and indirect bypasses has the

ABBREVIATIONS: CBF, cerebral blood flow; **DTA,** deep temporal artery; **MCA,** middle cerebral artery; **MMA,** middle meningeal artery; **MMD,** moyamoya disease; **MRA,** magnetic resonance angiography; **SPECT,** single-photon emission computed tomography; **STA,** superficial temporal artery

advantages of both procedures, and this combined procedure can be performed with low complication rates and favorable clinical outcomes.[2,5,7-13] Furthermore, combined procedures may induce better revascularization than indirect bypasses alone.[14-17] Nevertheless, application of an indirect bypass as an adjunct to a direct bypass in adults remains controversial because it is believed that a particular subset of patients cannot attain good revascularization with indirect bypasses.[18] This is also associated with cosmetic issues if the temporal muscle is used as the donor tissue.

Recent studies that used conventional angiography have shown that both the middle meningeal artery (MMA) and deep temporal artery (DTA) function effectively as donor arteries and that the indirect bypasses that used the dura mater or temporal muscle were important for revascularization, even in adult patients.[19,20] However, few reports have described how direct and indirect bypasses interact with each other and their serial changes, as well as which clinical factors, for example, age or hemodynamic parameters, are associated with the degree of neovascularization.[21] Because the contribution from the indirect bypass will change over time in relation to the development of the collateral flow through the direct bypass, investigating the longitudinal changes associated with direct and indirect bypasses is necessary to assess the additional effects of indirect bypasses on combined revascularization procedures in MMD.

The main aims of this study were to evaluate how direct and indirect bypasses in combined procedures change during long-term follow-up and to analyze the clinical factors involved in these changes. We used magnetic resonance angiography (MRA) rather than conventional angiography to gather data from a large number of patients to serially evaluate bypass development.[5]

METHODS

This study was approved by the Research Ethics Committee of Hokkaido University Hospital.

Patients

This study included 97 hemispheres from 68 consecutive adult and pediatric patients who underwent combined surgical revascularization procedures for MMD at our hospital between 2003 and 2013. During this period, 1 patient who underwent only a direct bypass was excluded from this study, and this case was associated with a period of time when the operator changed and the surgical strategy was not cohesive. All patients fulfilled the guideline for the diagnosis of MMD set by the Research Committee on Moyamoya Disease established by the Ministry of Health, Labor and Welfare of Japan.

Surgical Procedures

The surgical procedures have been described previously in detail.[10,11] The procedure comprises a double superficial temporal artery (STA)–middle cerebral artery (MCA) anastomosis and indirect bypass. The frontal and parietal STA branches are dissected from the scalp. After a large frontotemporal craniotomy, the dura is opened while the MMA is preserved. Both STA branches are anastomosed to the cortical branches of the MCA as direct bypasses. A paramedian craniotomy is also performed in most patients to revascularize the area associated with the anterior cerebral artery using a periosteal flap. The dural flap is inverted and placed on the surface of the brain, and the temporal muscle is sutured to the edge of the dura to create the indirect bypass, which completes the encephalo-duro-myo-arterio-pericranial-synangiosis procedure.

Preoperative Radiological Examinations

All patients underwent preoperative magnetic resonance imaging, MRA, and conventional cerebral angiography. The disease was classified into 6 stages with the Suzuki staging system.[1] We used (^{123}I) N-isopropyl-p-iodoamphetamine single-photon emission computed tomography (SPECT) to assess the cerebral blood flow (CBF) and cerebrovascular reactivity to acetazolamide.[10,22] The CBF and cerebrovascular reactivity were considered reduced when they were <27 mL/min per 100 g and $<14\%$, respectively.[23] We performed ^{15}O-gas positron emission tomography (PET) on 49 adult hemispheres and 39 pediatric hemispheres to determine the CBF, cerebral blood volume, cerebral metabolic rate of oxygen, and oxygen extraction fraction.[24,25] Mean $\pm$ SD values were determined for 10 healthy subjects as follows: CBF, 44 $\pm$ 4 mL/min per 100 g; cerebral blood volume, 3.7 $\pm$ 0.7 mL/100 g; cerebral metabolic rate of oxygen, 3.3 $\pm$ 0.6 mL/min per 100 g; and oxygen extraction fraction, 0.43 $\pm$ 0.05. The values were considered reduced when any of them was less than the mean (-2 SD), and they were regarded as increased when any of them was more than the mean ($+2$ SD).

Evaluation of the Direct and Indirect Bypasses With MRA

We used MRA to evaluate bypass development because it is more practical for longitudinal assessments undertaken in outpatient clinics compared with conventional angiography, which is more invasive and requires longer examination times. MRA was performed preoperatively, immediately after the operation, and during follow-up. For the direct bypasses, we compared the preoperative and postoperative diameters of the STA on MRA (Figure 1A-1C). When the diameter increased postoperatively, the direct bypass development was considered good (Figure 1C). When the diameter did not change or was reduced postoperatively, the direct bypass development was considered moderate or poor, respectively (Figure 1B). Evaluations were conducted once immediately (within 1 day) after surgery and once at >3 months during follow-up when the latest images were evaluated. For the indirect bypasses, the MMA or DTA was assessed during follow-up (Figure 1D and 1E).[19] When these arteries were enlarged compared with the preoperative arteries, the indirect bypass development was considered good, and when the arteries had not changed or had become smaller, the indirect bypass development was considered poor. Thus, direct and indirect bypass development was categorized into 3 and 2 grades, respectively. Dynamic changes associated with the STA from the acute to the chronic phase and indirect bypass development were visualized with Circos.[26] In this study, 2 authors (H.U. and N.F.) independently evaluated bypass development using MRA. An excellent concordance between the observers was confirmed in advance by interobserver analyses ($\kappa = 0.92 \pm 0.04$; $P < .001$) before further analyses were undertaken.

The validity of the method (described above) for the evaluation of indirect bypass development was investigated with conventional angiography performed on 50 hemispheres within the present cases during the follow-up period. Changes in the MMA or DTA diameters observed on MRA were compared with the revascularization areas observed on

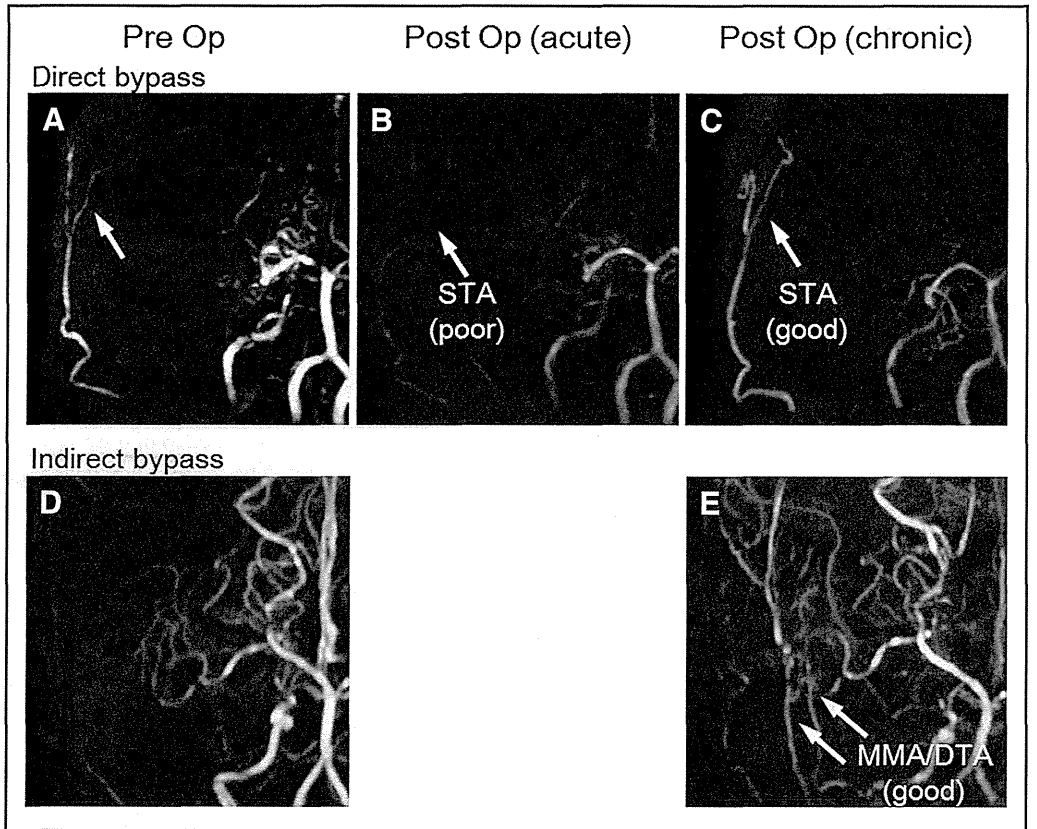

FIGURE 1. *Sequential follow-up using magnetic resonance angiography (MRA) showed longitudinal changes within direct (***A-C***) and indirect (***D** *and* **E***) bypasses.* **A,** *the signal associated with the left superficial temporal artery (STA) was evaluated for the direct bypasses.* **B,** *MRA on day 1 after surgery demonstrated a reduction in the diameter of the STA compared with the preoperative diameter, and the direct bypass was considered poor.* **C,** *MRA 7 years after surgery revealed an enlarged STA compared with the preoperative STA, and the direct bypass was considered good. The signals associated with the middle meningeal artery (MMA) and deep temporal artery (DTA) were evaluated for the indirect bypasses.* **E,** *MRA 8 years after surgery showed increases in the diameters of the DTA and MMA, and the indirect bypass development was considered good.*

conventional angiography with the grading system developed by Matsushima et al.[27] The revascularization was considered good when the revascularized area made up more than one-third of the MCA territory.

Data Analysis

The relationships between the development of surgical revascularization and several clinical factors, including the disease onset type, the angiographic stage, and the hemodynamic parameters determined by SPECT and PET, were evaluated. Continuous data are expressed as mean ± SD. We compared the data between groups using the χ^2 test or the unpaired t test, as appropriate. A multivariate logistic regression analysis was conducted to determine the effects of the clinical factors on bypass development. The multivariate analysis was performed with the use of the parameters that achieved significance levels of $P < .2$ in the univariate analysis. The level of significance was set at $P < .05$. The Cohen κ coefficients of concordance were calculated to determine intermodality agreements between MRA and conventional angiography evaluations. When $\kappa > 0.6$, the agreement was considered good.

RESULTS

Demographic Data

In the present study, 58 hemispheres in 43 adults and 39 hemispheres in 26 children (<18 years old) were revascularized. The mean ± SD ages of the adults and children were 43.2 ± 11.7 and 8.7 ± 4.5 years, respectively, and the patients' ages ranged from 1 to 71 years. The patients' clinical diagnoses were associated with ischemic symptoms, including transient ischemic attacks and infarctions in 78 hemispheres, intracranial bleeding in 10 hemispheres, and other symptoms in 9 hemispheres. A family history of MMD was documented in association with 33 hemispheres in 23 patients. The mean ± SD of the MRA follow-up duration was 47.0 ± 32.4 months (range, 3-150 months), and 89% of the patients were followed up for >12 months. The demographic data and changes in the patients' PET and SPECT parameters are summarized in Table 1.

TABLE 1. Summary of Clinical Data in Patients Included in This Study[a]

	Pediatric Patients	Adult Patients
Hemispheres, n	39	58
Age, y	8.6 ± 4.5 (1-16)	43.2 ± 11.7 (21-71)
Male/female	14/25	14/44
Clinical type, n		
Ischemia	35	43
Hemorrhage	1	9
Others	3	6
Suzuki stage, n		
1 and 2	6	2
3	19	28
4	14	17
5 and 6	0	8
PET/SPECT parameters, n/total		
CBF decrease	24/39	43/57
Cerebral blood volume increase	18/20	41/50
Oxygen extraction fraction increase	5/20	32/50
Cerebrovascular reactivity decrease	21/22	30/44
MRA follow-up, mo	37.4 ± 26.4 (3-94)	53.4 ± 34.6 (5-150)

[a]CBF, cerebral blood flow; MRA, magnetic resonance angiography; PET, positron emission tomography; SPECT, single photon emission tomography.

Validity of MRA for the Evaluation of Indirect Bypass Development

Fifty patients underwent conventional cerebral angiography during the postoperative follow-up period (Figure 2). Of 44 hemispheres that were considered to have good indirect bypass development on MRA, 43 hemispheres (97.7%) were considered to have good collateral vessel formations on conventional angiography. Of 6 hemispheres that were considered to have poor indirect bypass development on MRA, 4 hemispheres (66.7%) were considered to have poor collateral vessel formations on conventional angiography. Thus, when thresholds were set for the extent of revascularization as one-third of the MCA territory on conventional angiography, the sensitivity and specificity of the MRA evaluation were 95.5% and 80.0%, respectively. The agreements between MRA and conventional cerebral angiography were good for the evaluation of indirect bypass development ($\kappa = 0.69 \pm 0.16$; $P < .001$).

Longitudinal Changes in Direct and Indirect Bypasses

Table 2 summarizes the angiographic development of the direct and indirect bypasses during the chronic phase after the combined procedure. Good or moderate direct bypasses were observed in 87% and 92% of the pediatric and adult hemispheres, respectively. Good indirect bypasses were observed in 95% and 78% of the pediatric and adult hemispheres, respectively. Dual development of direct and indirect bypasses was most frequently observed (56% and 47% of the pediatric and adult hemispheres, respectively). None of the cases showed dual insufficiency of both the direct and indirect bypasses. In contrast to indirect bypass development, there were no significant differences between the adult and pediatric hemispheres with respect to direct bypass development during the chronic period.

Figure 3 illustrates the longitudinal changes and data relating to the STA from the acute to the chronic phases after surgery in the pediatric and adult hemispheres. When indirect bypasses developed in the adult hemispheres, 33% of the STAs (15 of 45) reduced in diameter reciprocally. When the indirect bypasses were insufficient, the diameter of the STA increased reciprocally in 92% of the hemispheres (12 of 13). When indirect bypasses developed in the pediatric hemispheres, 22% of the STAs (8 of 37) reduced in diameter reciprocally. The STAs were enlarged in 2 hemispheres that had insufficient development of the indirect bypasses. There was no significant difference between the pediatric and adult hemispheres with respect to the ratio of STA changes.

The long-term patency of the direct bypasses in the pediatric hemispheres was also assessed. The bypass development rates were classified by age for the pediatric cases; they are presented in Table 3. The direct bypasses were ultimately determined to be good or moderate in 87% of the pediatric cases. The direct bypasses were determined to be good, even in the 6 patients <3 years of age.

No changes in the bypass sizes were observed 12 months after surgery in 88% of the pediatric hemispheres and in 87% of the adult hemispheres. In most of these cases, the bypass sizes did not change at 3 to 6 months after surgery.

Factors That Affected the Development of the Direct and Indirect Bypasses

The disease onset type and the hemodynamic parameters (including CBF, cerebral blood volume, oxygen extraction fraction, and cerebrovascular reactivity) were not associated with the development of surgical revascularization in either the pediatric or adult patients (Table 4 and Figure 2). The MRA follow-up duration was not associated with bypass development in this study. Logistic regression analysis determined that the development of indirect bypasses was significantly better in the adult hemispheres that were at Suzuki stage 4 or greater than in those that were at Suzuki stage 3 or below (odds ratio, 7.4; 95% confidence interval, 1.4-39.4; $P = .02$). Thus, good indirect bypass development occurred in no less than 93% of the hemispheres at Suzuki stage 4 or greater. In contrast, good indirect bypass development occurred in 62% of the hemispheres at Suzuki stage 3 or below. Statistical analysis of indirect bypass development in the pediatric hemispheres was not performed because indirect bypasses developed in 95% of the cases.

DISCUSSION

In combined revascularization, the long-term patency of direct bypasses and the extent of neovascularization from

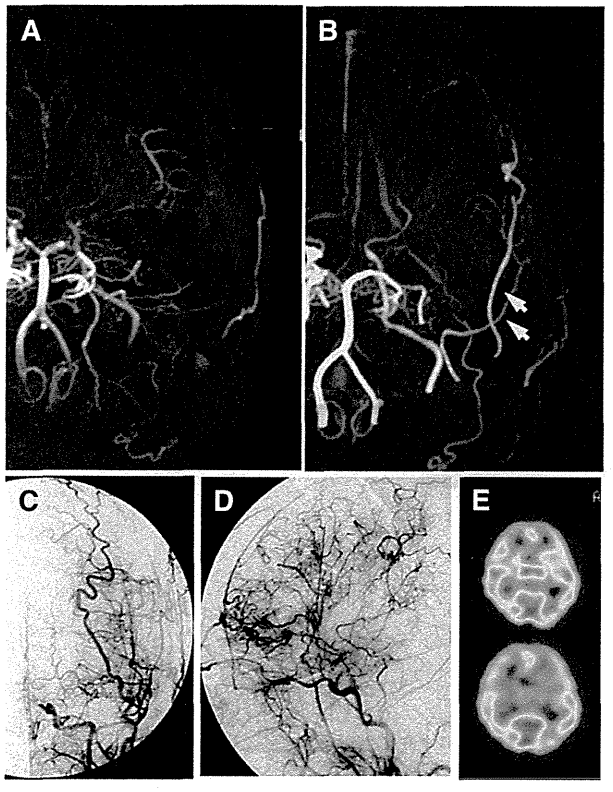

FIGURE 2. *Radiological findings from a 51-year-old woman who underwent left combined revascularization for moyamoya disease. Her preoperative Suzuki disease stage was 5.* **A,** *preoperative magnetic resonance angiography (MRA) depicted the left superficial temporal artery (STA), but the signals associated with the middle meningeal artery (MMA) and deep temporal artery (DTA) were weak.* **B,** *postoperative follow-up MRA demonstrated significant increases in the diameters of the MMA and DTA (arrow). In contrast, the signal associated with the STA declined compared with the preoperative signal.* **C** *and* **D,** *conventional cerebral angiography during the follow-up period confirmed that indirect surgical collateral vessels had developed and significantly and widely covered the hemisphere that underwent the operation.* **E,** *preoperative single photon emission tomography showed mild declines in the cerebral blood flow or cerebrovascular reactivity (not shown) in the left middle cerebral artery territory. The average values of these parameters in that region were 30 mL/min per 100 g and 21%, respectively.*

TABLE 2. Angiographic Development of Direct and Indirect Bypass in the Context of Combined Procedures[a]

	Pediatric Patients, n (%)	Adult Patients, n (%)	*P*
Good (D)/good (I)	22 (56)	27 (47)	.34
Moderate (D)/good (I)	10 (26)	10 (17)	.31
Poor (D)/good (I)	5 (13)	8 (14)	.93
Good (D)/poor (I)	2 (5)	13 (22)	.02
Poor (D)/poor (I)	0 (0)	0 (0)	
Total	39	58	

[a](D), direct bypass; (I), indirect bypass.

indirect bypasses are believed to have a complementary or inverse relationship.[5] However, contrary to expectations, dual development of direct and indirect bypasses within the same hemispheres occurred most frequently in both pediatric and adult patients. Multivariate analysis showed that indirect bypass development in adult patients was significantly associated with advanced stages of the disease but not with the hemodynamic parameters. In contrast to our prior speculation, advanced angiographic changes with compensated hemodynamics, which are frequently observed in middle-aged adults, were no exception to the favorable growth of indirect bypasses.

Using the bulk of the temporal muscle certainly causes cosmetic concerns, particularly among female patients. Given that direct STA-MCA bypasses can be undertaken more readily in adults than in children, one could ask why the additional use of the temporal muscle is necessary. We have applied encephalo-duro-myo-arterio-synangiosis as an adjunct to direct bypasses because sometimes the direct anastomosis can become obliterated or regress after the surgery, and the additional indirect bypass can provide surety in such scenarios. The development of neovascularization from the indirect bypass may reduce the flow through the direct bypass. However, the longitudinal image analyses revealed that the dual growth of the direct and indirect bypasses was the most frequent in the later period, which supports the rationale for our surgical strategy.

The universal application of the direct and indirect procedures allowed us to determine the factors that are associated with better development of indirect bypasses. The findings showed that none of the parameters measured with SPECT and PET predicted the degree of bypass development. This suggests that the severity of the hemodynamic compromise does not contribute to the degree of bypass development, even though a more severe hemodynamic compromise had been believed to induce more collateral vessels.[28] Instead, we found that favorable indirect bypass development occurred in hemispheres at advanced disease stages that had pre-existing transdural anastomoses (ethmoidal or vault moyamoya vessels). Recently reported findings have shown that the degree of neovascularization is more extensive when combined procedures are undertaken as opposed to indirect bypasses undertaken alone.[14-17] Hence, we can hypothesize that direct bypasses may enhance and promote neovascularization through the indirect bypasses in particular populations.

Few publications have described the long-term patency of direct bypasses in MMD, and, in particular, the outcomes from direct bypasses performed in small children have rarely been reported. Nevertheless, the direct bypasses were rated as patent in >90% of the patients who were <10 years old. It was also evident from this study that pediatric patients demonstrated favorable growth of

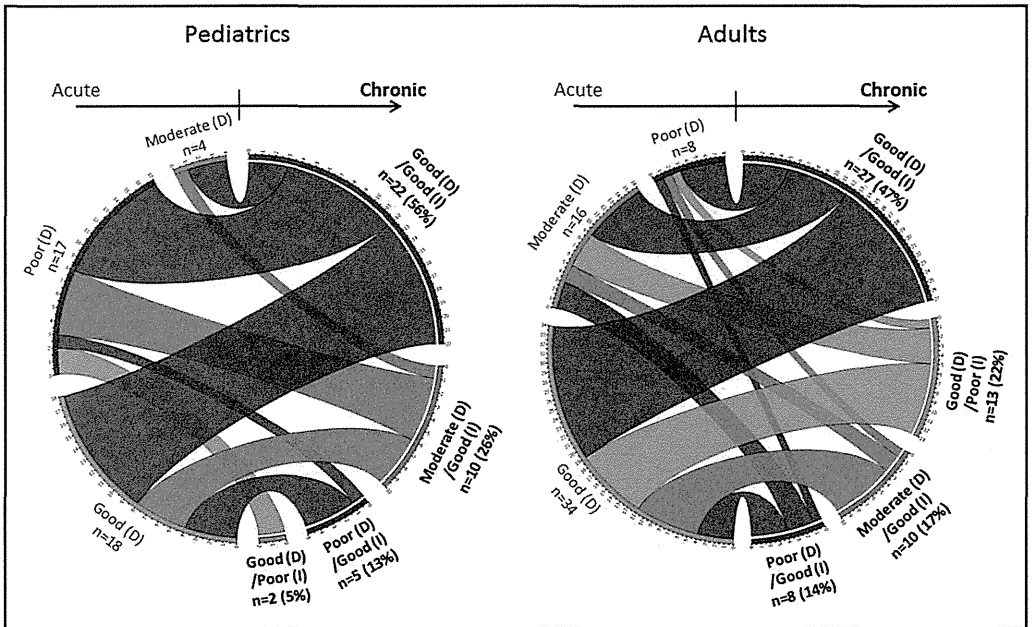

FIGURE 3. *Schema showing the longitudinal changes in the superficial temporal arteries (STAs) of the pediatric hemisphere (***left***) and adult hemisphere (***right***) from the acute to the chronic phase. The widths of the lines are proportional to the numbers of cases. (D) and (I) indicate direct and indirect bypasses, respectively. For example, good (D)/poor (I) represents good direct bypass development with poor indirect bypass development. In the pediatric hemispheres, 18, 4, and 17 STAs during the acute phase were judged as having good, moderate, and poor bypass development, respectively (depicted in the left half of the circle). Similarly, in the adult hemispheres, 34, 16, and 8 STAs during the acute phase were judged as having good, moderate, and poor bypass development, respectively. The direct and indirect bypass development ratios in the pediatric and adult hemispheres are the same as those shown in Table 2 (depicted in the right halves of the circles).*

their indirect bypasses in the long term. The authors of previous articles have suggested that direct bypasses in pediatric patients may minimize the risk of immediate postoperative ischemic complications.[7] Therefore, although revascularization may be achieved after both direct and indirect procedures, we performed direct bypasses because the final outcomes can be critically influenced by immediate complications postoperatively.[29,30]

The different follow-up durations in this study should be considered. The findings from this study showed that approximately 90% of the pediatric and adult cases did not show changes in their bypass sizes at 12 months after surgery. In most of the cases, the bypass size did not change 3 to 6 months after surgery. Because 89% of the cases were followed up for >12 months, the variations in follow-up durations would not have affected the final results from this study. Indeed, the MRA follow-up durations were not associated with direct and indirect bypass development in the present analysis. However, changes in the sizes of the bypasses were observed 2 to 3 years after surgery in a few pediatric and adult patients. In some cases, the direct and indirect bypass developments were pronounced, whereas in other cases, the direct bypasses had regressed at a later stage of follow-up. Therefore, long-term follow-up is essential in MMD.

TABLE 3. Long-Term Patency of Direct and Indirect Bypass in Pediatric Patients

Age, y	Hemisphere, n	Direct Bypass, n (%)			Good Indirect Bypass, n (%)
		Good	Moderate	Poor	
<3	6	6 (100)	0 (0)	0 (0)	6 (100)
4-10	20	10 (50)	9 (45)	1 (5)	19 (95)
11-16	13	7 (54)	2 (15)	4 (31)	12 (92)
Total	39	23 (59)	11 (28)	5 (13)	37 (95)

Limitations

The present study has several limitations. MRA may not precisely assess the caliber changes in the donor arteries. Furthermore, the integrity of the collateral flow through an indirect bypass may not be sufficiently represented by MMA or DTA visualization. Nevertheless, we consider that MRA could be feasible for longitudinal qualitative evaluations of bypass development because a good correlation between the extent of the revascularized area and the donor artery enlargement was confirmed in a subgroup of the present cases. A quantitative analysis of the blood flows and perfusion areas of donor arteries would provide further insight.[21] The present study did not reveal whether the extent of surgical

TABLE 4. Correlation Between Clinical Factors and Development of Direct and Indirect Bypass[a]

	Children					Adults							
	Direct			Indirect		Direct			Indirect				
	Good (n = 22)	Poor (n = 5)	Univariate Analysis, *P*	Good (n = 37)	Poor (n = 2)	Good (n = 38)	Poor (n = 10)	Univariate Analysis, *P*	Good (n = 45)	Poor (n = 13)	Univariate Analysis, *P*	Multivariate Analysis, *P*	Odds Ratio (95% Confidence Interval)
Male sex	8	2	.72	14	0	8	3	.86	10	4	.79		
Clinical type													
Ischemia	18	5	.59	34	1	29	12	.37	32	11	.60		
Hemorrhage	1	0		1	0	4	4		8	1			
Others	3	0		2	1	5	1		5	1			
Suzuki stage (≥4)	10	2	.78	14	0	16	6	.37	27	2	.010	.02	7.4 (1.4-39.4)
Ivy sign	19	5	.93	31	0	15	1	.17	15	3	.66		
PET/SPECT parameters, n/total													
CBF decrease	14/21	1/5	.16	23/37	1/2	28/37	8/10	.89	34/45	9/12	.74		
Cerebral blood volume increase	10/10	4/5	.71	17/19	1/1	25/32	9/9	.30	33/40	8/10	.78		
Oxygen extraction fraction increase	3/10	1/5	.84	5/19	0/1	18/32	6/9	.86	26/40	6/10	.94		
Cerebrovascular reactivity decrease	11/11	4/4		19/20	2/2	23/31	5/8	.83	23/34	7/10	.81		
Good indirect bypass	21	5	.41			27	10	.12					
Good direct bypass				21	1				27	11	.13	.23	
MRA follow-up, mo	36.5 ± 27.7	48.8 ± 25.3	.37	37.5 ± 26.5	51.5 ± 19.1	46.4 ± 29.4	37.5 ± 26.5	.34	54.2 ± 35.8	61.2 ± 39.7	.36		

[a]CBF, cerebral blood flow; MRA, magnetic resonance angiography; PET, positron emission tomography; SPECT, single photon emission tomography.

revascularization correlated with the clinical outcomes. It was difficult to evaluate this in the present study because the clinical outcome criteria were not defined and the postoperative complication rate was relatively low, which precluded systematic analyses.[10,12] Finally, we did not determine the correlations between the hemodynamic parameters and indirect bypass development, which could relate to the inconsistent use of the modalities for preoperative hemodynamic evaluations among the present cases. Optimal preoperative neuroimaging studies may enable the development of tailored surgical procedures in the future.

CONCLUSION

Indirect bypasses developed effectively in both pediatric and adult patients, even in the presence of direct bypasses. The only preoperative factor that predicted indirect bypass development was advanced disease stages in adult patients. The severity of the hemodynamic compromise did not affect the neovascularization that occurred through the indirect bypasses. Currently, the universal application of indirect bypasses is considered an optimal surgical strategy to maximize revascularization in MMD.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Published March 24, 2016 as 10.3174/ajnr.A4728

Characteristics of Diffusional Kurtosis in Chronic Ischemia of Adult Moyamoya Disease: Comparing Diffusional Kurtosis and Diffusion Tensor Imaging

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ABSTRACT

BACKGROUND AND PURPOSE: Detecting microstructural changes due to chronic ischemia potentially enables early identification of patients at risk of cognitive impairment. In this study, diffusional kurtosis imaging and diffusion tensor imaging were used to investigate whether the former provides additional information regarding microstructural changes in the gray and white matter of adult patients with Moyamoya disease.

MATERIALS AND METHODS: MR imaging (diffusional kurtosis imaging and DTI) was performed in 23 adult patients with Moyamoya disease and 23 age-matched controls. Three parameters were extracted from diffusional kurtosis imaging (mean kurtosis, axial kurtosis, and radial kurtosis), and 4, from DTI (fractional anisotropy, radial diffusivity, mean diffusivity, and axial diffusivity). Voxelwise analysis for these parameters was performed in the normal-appearing brain parenchyma. The association of these parameters with neuropsychological performance was also evaluated.

RESULTS: Voxelwise analysis revealed the greatest differences in fractional anisotropy, followed, in order, by radial diffusivity, mean diffusivity, and mean kurtosis. In patients, diffusional kurtosis imaging parameters were decreased in the dorsal deep white matter such as the corona radiata and superior longitudinal fasciculus ($P < .01$), including areas without DTI abnormality. Superior longitudinal fasciculus fiber-crossing areas showed weak correlations between diffusional kurtosis imaging and DTI parameters compared with tissues with a single-fiber direction (eg, the corpus callosum). Diffusional kurtosis imaging parameters were associated with general intelligence and frontal lobe performance.

CONCLUSIONS: Although DTI revealed extensive white matter changes, diffusional kurtosis imaging additionally demonstrated microstructural changes in ischemia-prone deep white matter with abundant fiber crossings. Thus, diffusional kurtosis imaging may be a useful adjunct for detecting subtle chronic ischemic injuries.

ABBREVIATIONS: AD = axial diffusivity; AK = axial kurtosis; CPT = continuous performance task; DKI = diffusional kurtosis imaging; FA = fractional anisotropy; IQ = intelligence quotient; MK = mean kurtosis; MD = mean diffusivity; MMD = Moyamoya disease; RD = radial diffusivity; RK = radial kurtosis; RST = Reading Span Test; SLF = superior longitudinal fasciculus; TMT = Trail-Making Test

Moyamoya disease (MMD) is characterized by compensatory development of enlarged and weak basal perforating arteries (Moyamoya vessels) due to bilateral occlusive changes in the internal carotid system.[1] In addition to cerebral ischemia and intracranial hemorrhage, patients with MMD demonstrate neurocognitive issues, such as executive dysfunction, attention deficits, and working-memory disturbances.[2,3] Brain atrophy may explain cognitive impairment in the absence of infarction, but detection of these changes has been hampered by the limited sensitivity of conventional neuroimaging methods. Diffusion tensor imaging is useful for determining white matter integrity and providing parameters sensitive to changes in axons, myelin, and organelle structures.[4,5] Indeed, DTI analysis has revealed a widespread decline in white matter integrity in the normal-appearing brain with MMD.[3] Thus, DTI can detect

Received August 26, 2015; accepted after revision January 7, 2016.

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The authors have no personal or institutional financial interest in the drugs and imaging modalities described herein.

This study was supported by a grant from the Research Committee on Moyamoya Disease, sponsored by the Ministry of Health, Labor, and Welfare of Japan and the Creation of Innovation Centers for Advanced Interdisciplinary Research Areas Programs, Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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http://dx.doi.org/10.3174/ajnr.A4728

Table 1: Characteristics of the study participants

	Control	Moyamoya Disease	*P* Value
No. of subjects	23	23	–
Age (mean) (range) (yr)	39.0 + 8.1 (25–56)	40.9 + 9.5 (21–58)	.48
Sex (F/M) (No. of subjects)	13:10	17:6	.35
Risk factor (DM, HT, HL) (No. of subjects)	0	5	.049
Symptoms (No. of subjects)			
Asymptomatic	–	13	
TIA	–	10	

Note:—DM indicates diabetes mellitus; HT, hypertension; HL, hyperlipidemia.

early-stage ischemic injury, which potentially predicts future cognitive outcomes. However, DTI is constrained by technical insufficiencies: It is based on the assumption that water molecules diffuse freely and that diffusion can be characterized by a Gaussian distribution.[5]

In addition, the tensor model is based on the observation that in many tissues, water diffusion is anisotropic (ie, the diffusion is more liberal in some directions and more restricted in others). This anisotropic diffusion can be geometrically depicted as an ellipsoid, described by eigenvectors and eigenvalues. This model performs well in regions where fibers are aligned along a single axis. However, it fails in regions with several fiber populations aligned along intersecting axes because it cannot simultaneously map several diffusion maxima.[6] Furthermore, because hypoxic-ischemic injury induces neurodegeneration and regression of dendrite arborization in gray matter, the diffusion properties of gray matter may also reveal the early stages of ischemic injury.[7,8] Nevertheless, analyzing isotropic or near-isotropic tissue such as gray matter by DTI may not be valid because its major parameter, fractional anisotropy (FA), reflects structure only if it is spatially oriented.[6] A more recent method called diffusional kurtosis imaging (DKI) quantifies the deviation of water molecule diffusion from the Gaussian distribution without assuming any specific diffusion model.[6,9] Its parameters are thought to represent the complexity of tissue microstructure.[6] Previous studies have suggested that DKI is sufficiently sensitive to detect age-related alterations in white matter microstructure.[10,11] Furthermore, measurements of diffusion anisotropy by DKI can reveal sex-related and pathologic changes in gray matter.[12,13] Thus, using DKI to evaluate the diffusion properties of gray matter and white matter in patients with MMD may be useful for detecting subtle microstructural changes due to ischemia.

Diffusional kurtosis has been investigated to explore tissue reversibility in acute cerebral infarction.[14-16] However, there is a paucity of information regarding the microstructural properties measured by DKI in chronic ischemia in living humans. To expand on our prior DTI study, we investigated whether adults with MMD and no overt cerebral infarctions have altered diffusional kurtosis in the entire cerebrum. An exploratory voxel-based whole-brain analysis was performed to map regional DKI parameters and to compare DKI and DTI parameters. We also explored correlations of diffusion parameters with measures of neurocognitive impairment in an ROI analysis.

MATERIALS AND METHODS

Participants

This prospective study was approved by the Research Ethics Committee of Hokkaido University Hospital, and written informed consent was obtained from all participants. Participants in the present study are the same as those of our previous study analyzing the relationship between DTI parameters and neuropsychological test scores.[3] The selection period was 25 months (April 2012 through April 2014). Twenty-three patients (6 men and 17 women; 21–58 years of age; mean age, 40.9 ± 9.5 years) were enrolled. The control group also consisted of 23 subjects (10 men and 13 women; 25–56 years of age; mean age, 39.0 ± 8.1 years). A brief summary of patient characteristics is provided in Table 1.

Neuropsychological Assessment

Neuropsychological examinations consisted of the Wechsler Adult Intelligent Scale-III, Wisconsin Card Sorting Test, Trail-Making Test (TMT; parts A and B), continuous performance task (CPT), Stroop test, and Reading Span Test (RST). The details of neuropsychological examinations and the results are provided in the On-line Appendix.[3]

MR Image Acquisition

MR imaging was performed with a 3T scanner (Achieva TX; Philips Healthcare, Best, the Netherlands). 3D magnetization-prepared rapid acquistion of gradient echo T1-weighted imaging and axial single-shot spin-echo echo-planar DKI were acquired to evaluate subtle gray and white matter alterations, respectively. The scan parameters for DKI were as follows: TR = 5051 ms, TE = 85 ms, flip angle = 90°, FOV = 224 × 224 mm^2, matrix size = 128 × 128, b-values = 0, 1000, and 2000 s/mm^2, number of diffusion gradient directions = 32, section thickness = 3 mm, intersection gap = 0 mm, number of sections = 43, and NEX = 1. The 3D-MPRAGE imaging was performed with TR = 6.8 ms, TE = 3.1 ms, flip angle = 8 °, and TI = 1100 ms.

Image Processing

Registration between the echo-planar images with no diffusion weighting (b=0 s/mm^2) and the corresponding DKI data and correction for eddy current distortion were performed at the MR imaging operator console. The DKI data were processed by using Matlab R2012b (MathWorks, Natick, Massachusetts) and Diffusional Kurtosis Estimator (Version 2.5.1; http://nitrc.org/projects/dke).[17] Seven DKI and DTI parameters were extracted from the Diffusional Kurtosis Estimator: mean kurtosis (MK), radial kurtosis (RK), axial kurtosis (AK), FA, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). The DTI parameters (FA, MD, RD, and AD) were calculated from a portion of the DKI data by using a monoexponential model that assumes a Gaussian probability diffusion function by using data from b-values of 0 and 1000 s/mm^2.[17]

Following calculation of DKI and DTI parameters, the b=0 echo-planar images were warped to the standardized T2 template

of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12). This transformation matrix was applied to the DKI/DTI parameter map of each patient. The warped DKI/DTI maps were averaged and smoothed with a 6-mm full width at half maximum Gaussian kernel to form customized DKI/DTI templates. Native DKI/DTI maps of all patients and control subjects were then warped to the customized, respective DKI/DTI templates. Individual maps were then smoothed with a 6-mm full width at half-maximum Gaussian kernel. The warped and smoothed DKI/DTI maps were used for group comparisons between the controls and patients with MMD. To investigate the pathology underlying DKI parameters and the influence of fiber crossings on DTI parameters, we investigated the correlations of DKI and DTI parameters in white matter tracts consisting of either a single fiber direction or crossing fibers (ie, multiple directions).[18] The ROIs were placed on the genu of the corpus callosum (ie, a structure with a single fiber direction) and deep white matter tracts corresponding to the bilateral superior longitudinal fasciculus (SLF) (multiple fiber directions) by using the JHU white matter atlas available in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/).[19]

Data Analysis

Whole-brain diffusion parameters were compared voxel by voxel between the controls and patients with MMD by using SPM8, which implemented the general linear model. We used the 2-sample *t* test model, and age was considered a covariate. An explicit mask generated by averaging the normalized CSF space of all participants was applied. To explore group differences across both gray matter and white matter, we set statistical significance at $P < .01$ without correction for family-wise error and clusters of 50 voxels or more. The number of voxels demonstrating a significant difference between the controls and patients with MMD was extracted. The Pearson product-moment correlation coefficient was calculated to investigate the correlation between the DKI and DTI parameters by using DKI/DTI values extracted from the ROI analysis.

We also investigated whether the significant changes in DKI/DTI parameters were associated with neuropsychological examination scores. A threshold T value of 2.42, corresponding to $P < .01$ without correction for family-wise error, was applied to the T contrast map of DKI/DTI parameters obtained by comparing controls and patients, and binary mask images containing voxels above the threshold value were generated. The DKI/DTI parameter values included in the masks were extracted from DKI/DTI of the patients with MMD. The Pearson product-moment correlation coefficients were used for analyses involving the Wechsler Adult Intelligent Scale-III, TMT (parts A and B and the difference in score between TMT-A and TMT-B [B–A]). Patients were further subgrouped into 2, according to their performance scores, error numbers, and reaction time on the Wisconsin Card Sorting Test, Stroop test, CPT, and RST; and the DKI/DTI parameters were compared between these 2 subgroups by using *t* tests (Online Appendix). For all correlations and comparisons, a P value $< .05$ was considered statistically significant to explore the possible relationship between neuropsychological scores and diffusion parameters.

RESULTS

Spatial Distribution of DTI/DKI Differences on Voxel-Based Analysis

Areas with decreased MK included the right frontal white matter, bilateral thalami, portions of the occipital white matter, corona radiata, corpus callosum, and portions of frontal and parietal white matter corresponding to the posterior segment of the superior longitudinal fasciculus (Fig 1). The decrease in FA was most extensive within the white matter (161,625 voxels), with its decrease amounting to 12,833 voxels (7.9%) (Fig 2). Significant MK, RK, and AK decreases were observed in 6180 voxels (3.8%), 3828 voxels (2.4%), and 3043 voxels (1.9%), respectively. In contrast, 9028 voxels (5.6%) showed a significant increase in MD; 10,062 (6.2%), in RD; and 548 (0.3%), in AD compared with controls. Figure 1 shows DKI/DTI overlap maps, with MK/RK/AK/FA decreases and MD/RD increases. Areas with FA decrease were more extensive than those with MK decrease; however, the posterior segment of the SLF showed a decrease in only MK/RK. The increase in MD/RD was remarkable in the corona radiata; however, the posterior segment of the SLF showed a decrease in MK/RK without an increase in MD/RD. Decreased AK was observed without changes in AD for the bilateral thalami, corona radiata, and portions of the temporo-occipital white matter. There was no cortical gray matter with altered DKI/DTI parameters in patients.

Correlation of DTI and DKI Parameters

Correlations between DKI and DTI parameters were examined in both the genu of the corpus callosum and the bilateral SLF (Table 2). In the corpus callosum of both controls and patients with MMD, MK correlated positively with FA ($r > 0.78$, $P < .01$), while inverse correlations with MK were found for MD/RD/AD ($r < -0.82$, $P < .001$). In the corpus callosum, RK correlated inversely with RD ($r < -0.84$, $P < .001$), and AK inversely correlated with AD of the corpus callosum ($r < -0.64$, $P < .001$). A significant correlation between MK and FA was observed in the left SLF of controls, but this was to a lesser degree compared with that in the corpus callosum. No correlation was found between MK and FA in the right SLF of controls. In both controls and patients, correlations between MK and MD/RD/AD were found in the right and left SLFs, albeit to a lesser degree than corpus callosum correlations. The results of correlation between DKI and DTI parameter values are summarized in Table 2.

Association of DKI/DTI Parameters with Neuropsychological Performance Tests

The DKI parameter (AK) showed significant correlations with motor intelligence quotient (IQ), full-scale IQ, perceptual organization, and processing speed evaluated on the Wechsler Adult Intelligent Scale-III (Fig 3*A*, $r > 0.42$, $P < .05$). Both DKI (MK) and DTI (FA, MD, and RD) parameters showed significant correlations with the TMT part B (Fig 3*B*, $r > 0.44$, $P < .05$). The Stroop test performance showed moderate positive correlations with MK, RK, and FA and negative correlations with MD, RD, and AD ($P < .05$). RST was associated with MK and AK ($P < .05$). The correlations between diffusion parameters and neuropsychological scores (Wisconsin Card Sorting Test, Stroop Test, CPT, and RST) are shown in Table 3.

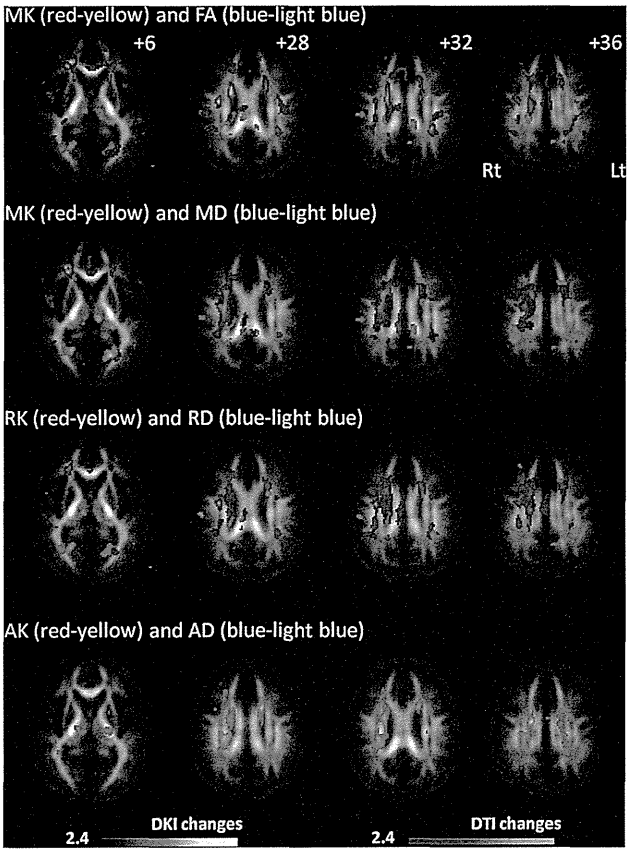

FIG 1. Changes in diffusional kurtosis imaging and diffusion tensor imaging parameters in Moyamoya disease shown in maps of 3 diffusional kurtosis parameters (mean kurtosis, radial kurtosis, and axial kurtosis) and 4 diffusion tensor parameters (fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity). Areas with significant changes in a combination of DKI/DTI parameters are as follows: decreased MK (red-yellow)/decreased FA (blue-light blue), decreased MK (red-yellow)/increased MD (blue-light blue), decreased RK (red-yellow)/increased RD (blue-light blue), and decreased AK (red-yellow)/increased and decreased AD (blue-light blue). Values from statistical parametric mapping analysis are projected onto axial sections of the average brain space of FA (z = 12, 28, 32, 36 mm). MK decrease is observed in the thalamus, a portion of the genu and body of the corpus callosum, corona radiata, frontoparietal subcortical white matter, and superior longitudinal fasciculus. RK decrease is observed in part of the frontoparietal subcortical white matter, thalamus, corona radiata, and occipital white matter. AK decrease is observed in the thalamus, temporo-occipital white matter, part of the SLF, and corona radiata. The radiologic convention is adopted, with the left side of the brain on the right side of axial panels. The color scale represents T values, with colored regions exceeding the significance threshold of $P < .01$ ($T = 2.42$) with a minimum cluster size of 50 voxels. Rt indicates right; Lt, left.

DISCUSSION

We explored the added benefit of diffusional kurtosis measurements in the assessment of ischemic burden due to chronic ischemia in adult MMD. This study confirmed our prior finding that chronic ischemia in MMD preferentially affects the microstructure of normal-appearing white matter.[3] Detecting microstructural changes due to chronic ischemia potentially enables early identification of patients at risk of cognitive impairment.[3,20] However, detecting microstructural changes has been hampered by the limited sensitivity of DTI in fiber-crossing areas.[7] In this study, DKI demonstrated microstructural changes, predominantly in the dorsal part of the deep white matter, where conventional MR imaging frequently demonstrates ischemic lesions.[21] The significant changes in DKI parameters were associated with neuropsychological scores reflecting general intelligence, executive function, attention, and working memory. Thus, DKI is considered a useful adjunct to conventional DTI, particularly for its ability to detect nascent microstructural changes in areas with abundant fiber crossings.

In this study, we demonstrated that DTI showed widespread regions with alterations in FA, MD, and RD. The finding is consistent with previous studies, in which DTI showed more extensive white matter changes compared with DKI parameters. Other studies have demonstrated superior sensitivity of DKI to detect white matter changes compared with DTI.[11,22,23] DKI showed significant decreases in frontoparietal subcortical structures and deep white matter. A decrease in DKI parameters, a shift of diffusional kurtosis toward free water diffusion, has commonly been interpreted as a reduction in tissue complexity.[24] Considering the location of the DKI alterations, a reduction in complexity is thought to reflect microstructural changes in myelin and/or axonal attenuation. In the corona radiata, DTI (MD/RD) demonstrated more significant changes compared with DKI (MK/RK). Deep white matter tracts are vulnerable to chronic ischemia because they are located in the terminal field of the blood supply. Myelin degeneration or increased periventricular extracellular fluid may increase RD, while tissue complexity in a radial direction may be maintained, in some part, by glial proliferation.[25] In a previous study, a trend toward decreased AD was found via analysis of tract-specific spatial statistics,[3] whereas the voxel-based analysis of the present study did not show definitive AD changes in white matter. AD decreases in axonal fragmentation; however, axonal degeneration or reduced axonal attenuation can increase AD. In contrast with AD, AK showed significant changes in the

Table 2: Correlation between DKI and DTI parameters[a]

	Corpus Callosum				Rt. SLF				Lt. SLF			
	CNT		MMD		CNT		MMD		CNT		MMD	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
MK vs FA	0.78	.000	0.80	.000	0.08	.715	0.60	.002	0.42	.047	0.47	.022
MK vs MD	−0.90	.000	−0.86	.000	−0.60	.002	−0.68	.000	−0.41	.049	−0.49	.017
MK vs RD	−0.90	.000	−0.87	.000	−0.54	.008	−0.73	.000	−0.49	.018	−0.55	.006
MK vs AD	−0.87	.000	−0.82	.000	−0.50	.014	−0.46	.028	−0.19	.386	−0.35	.101
RK and RD	−0.88	.000	−0.84	.000	−0.72	.000	−0.56	.005	−0.47	.025	−0.38	.072
AK and AD	−0.75	.000	−0.64	.000	−0.44	.036	−0.61	.001	−0.47	.025	−0.68	.000

Note:—Rt. indicates right; Lt., left; CNT, controls; *r*, Pearson product-moment correlation coefficient.

[a] All *P* values, except .715, .386, 101, and ,072, indicate significant correlation between DKI and DTI parameters.

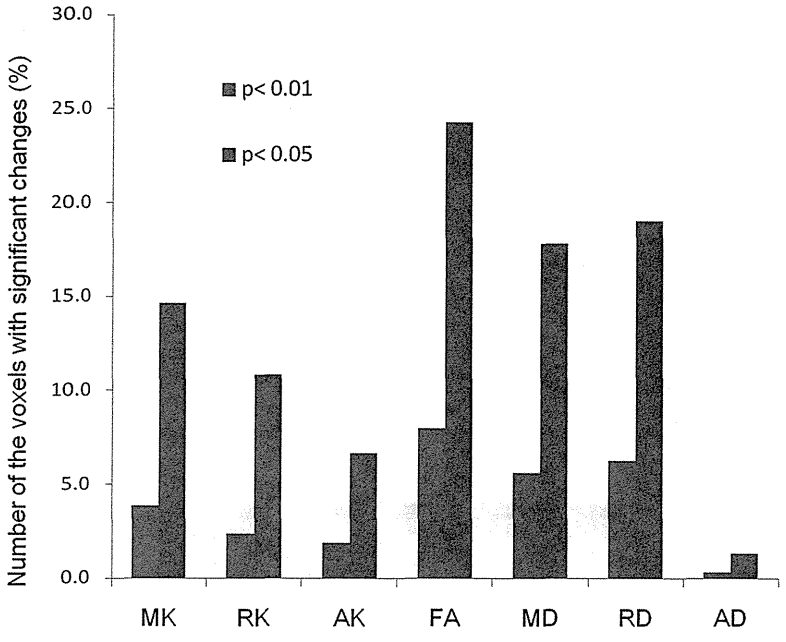

FIG 2. The bar graph indicates the number of the voxels with significant changes relative to the total number of white matter voxels in statistical parametric mapping comparing controls and patients with Moyamoya disease. Bar heights indicate decreases in MK/RK/AK/FA and increases in MD/RD/AD for 2 levels of threshold applied in group comparisons (blue, $P < .01$; red, $P < .05$, respectively).

corona radiata in the voxel-based analysis. Thus, alterations in AD would be marginal at best in patients, while tissue complexity parallel to the principal diffusion direction could be decreased in the corona radiata of patients. Weak correlations between FA and MK in the SLF of controls could be attributed to the crossing/kissing of white matter fibers. The SLF contains abundant crossing fibers projecting from the corona radiata and corpus callosum.[18] Several fiber populations aligned along intersecting axes in 1 voxel would diminish anisotropy.[26]

The DKI parameters in patients showed moderate positive correlations with impaired general intelligence and frontal lobe dysfunction. These results are consistent with previous reports showing a relationship between cognitive performance and white matter fiber tracts integrating parietofrontal cortical areas.[27-29] In MMD, performance IQ is preferentially affected compared with verbal IQ.[1] In the present study, AK was significantly correlated with neuropsychological performance on tests evaluating executive function and working memory (motor IQ, perceptual organization, and processing speed), while no correlation was found with verbal IQ. In an experimental animal model of chronic white matter ischemia, damage to myelin preceded axonal damage, suggesting that the change in myelin is the primary pathologic event.[30] Our observation of a stronger correlation between AK, rather than AD, and general intellectual ability measured by the Wechsler Adult Intelligent Scale-III may imply that a reduction in axonal density and/or axonal degeneration, a more advanced stage of chronic ischemic injury, is better described by AK than AD. Previous investigations by using DTI and probabilistic tractography have shown correlations between neuropsychological examinations and the FA of subcortical white matter. Consistent with previous studies, we observed correlations between DTI parameters and the scores of neuropsychological tests evaluating frontal lobe function in the present study. A significant correlation of FA/MD/RD with scores on the Trail-Making Test suggests that demyelination alone could affect part of the frontal lobe functions.

Transient ischemic attack followed by hyperventilation is a characteristic symptom of childhood MMD, and syncope attacks are occasionally observed in both children and adults with MMD.[1] The spatial characteristics of nascent brain injury are important for understanding frontal-dominant neurocognitive dysfunction in adult MMD. Pyramidal neocortical neurons (layers 3, 5, and 6) in the prefrontal cortex are known to be highly vulnerable to hypoxic-ischemic insults.[31,32] These hypoxic-ischemic insults can damage the brain and potentially induce neuronal death or regression of dendritic structure.[8] We speculate that microstructural alteration precedes gross volumetric reductions in gray matter. Previous study has revealed gray matter atrophy in the posterior cingulate cortex, suggesting that more widespread gray matter changes might be observed in diffusion parameters, particularly in the frontal lobe.[3] DKI could reveal early microstructural changes less constrained by partial volume effects.[33] Nevertheless, despite discrete white matter damage, no substantial changes in diffusion parameters were found in the cortical gray matter in MMD. Pathologic tissue changes such as glial proliferation may underlie the lack of significant changes in the diffusion parameters of the cortices. A new diffusion MR imaging technique, including neurite orientation dispersion and density imaging, may detect subtle microstructural changes in the cortex and is potentially sensitive to initial ischemic changes before the overt volumetric reductions.[34,35]

The present study revealed microstructural change in the thalamus, a finding that has never been emphasized with regard to cognitive function in MMD. The mediodorsal thalamus connects to the prefrontal cortex. This is potentially important because innervation of the thalamoprefrontal circuit could modulate prefrontal neural circuits, which are associated with cognitive as well as affective performance.[36]

There are several limitations to this study. The statistical power to detect group differences in DKI parameters is significantly influenced by the number of subjects in a study.[37] Therefore, the spatial characteristics of the DKI/DTI alterations found in this study may not represent the topography of ischemic burden in adult MMD.[37] We extracted DKI/DTI values from the contrast T maps generated from group comparisons between controls and patients to explore the relationship between abnormal diffusion parameters in patients and neuropsychological test performance. Although we found an association with neuropsychological test scores, voxel-based correlation analysis would per-

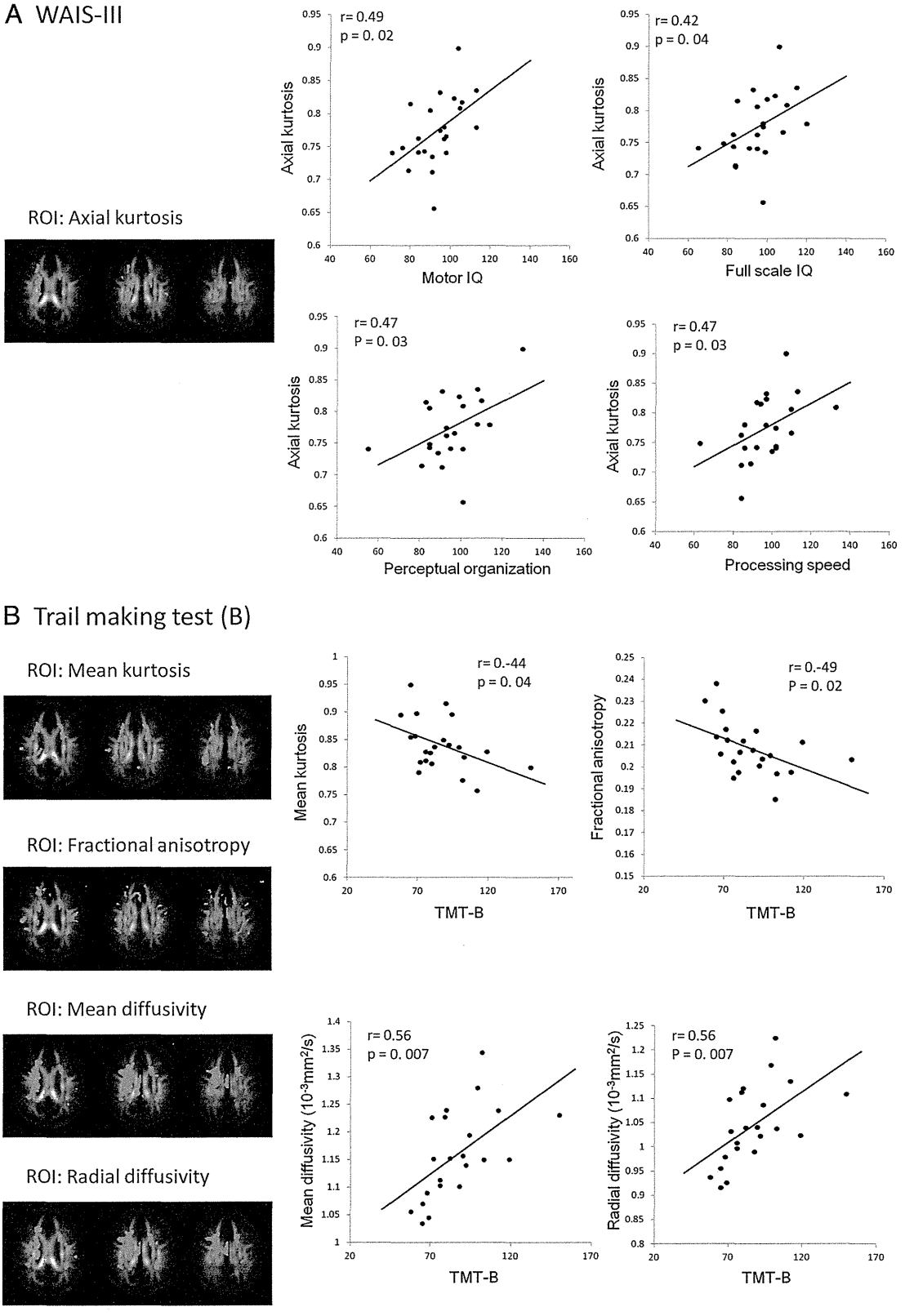

FIG 3. Scatterplots indicating a significant correlation between neuropsychological test performance and diffusion parameters. Pearson moment-production correlation coefficient *r* and *P* values are demonstrated in each scatterplot. ROIs (green) for each parameter (AK, MK, FA, MD, and RD) are demonstrated with FA template images generated from 23 controls and 23 patients. *A*, Performance scores evaluated on the Wechsler Adult Intelligent Scale-III are significantly associated with axial kurtosis. Axial kurtosis is positively correlated with full-scale IQ ($r = 0.42$, $P = .04$) and subscores such as motor IQ ($r = 0.49$, $P = .02$), perceptual organization ($r = 0.47$, $P = .03$), and processing speed ($r = 0.47$, $P = .03$). *B*, Trail-Making Test, part B is inversely correlated with DKI/DTI parameters (MK; $r = -0.44$, $P = .04$; and FA; $r = -0.49$, $P = .02$) and positively correlated with DTI parameters (MD; $r = 0.56$, $P = .007$; and RD; $r = 0.56$, $P = .007$).

Table 3: Correlations of diffusion parameters with neuropsychological examinations[a]

	WCST	Stroop	CPT	RST
MK	–	.004[b]	–	.048[b]
RK	–	.007[b]	–	–
AK	–	.045[c]	–	.036[c]
FA	–	.024[b]	–	–
MD	–	.012[b]	–	–
RD	–	.014[b]	–	–
AD	–	.031[c]	–	–

Note:—WCST indicates Wisconsin Card Sorting Test, Stroop; Stroop test.

[a] Data are *P* values. Correlations of diffusional kurtosis imaging and diffusion tensor imaging parameters with neuropsychological examinations were evaluated in patients with MMD. Three diffusional kurtosis parameters (MK, RK, and AK) and 4 diffusion tensor parameters (FA, MD, RD, and AD) were analyzed. Diffusion parameters and locations that demonstrated significant relationships with clinical variables follow.

[b] Two-tailed *t* test.

[c] One-tailed *t* test.

mit an objective evaluation of the neural substrates associated with cognitive impairment. Finally, we used a combination of b-values of 0 and 1000 s/mm^2 for DTI. DTI parameters are reported as dependent on b-values. For DKI, the b-values of 0, 1000, and 2000 s/mm^2 used in the present study would be feasible for practical clinical applications. Nevertheless, a different combination of b-values and methods for parameter estimation could alter the relationship between DKI and DTI with regard to sensitivity and specificity, which requires further investigation.[21]

CONCLUSIONS

The results of the present study suggest an additional value of DKI as an adjunct to DTI. DKI parameters can become useful neuroimaging markers to track ischemic burden in adult MMD.

Disclosures: Ken Kazumata—*RELATED: Grant*: This study was supported by a grant from the Research Committee on Moyamoya Disease, sponsored by the Ministry of Health, Labor, and Welfare of Japan.* Khin K. Tha—*RELATED: Grant*: This work was supported (in part) by the Creation of Innovation Centers for Advanced Interdisciplinary Research Areas Program, Ministry of Education, Culture, Sports, Science, and Technology, Japan.* Masaki Ito—*RELATED: Grant*: Research Committee on Moyamoya Disease, sponsored by the Ministry of Health, Labor, and Welfare of Japan*; *UNRELATED: Grants/Grants Pending*: Masaki Ito was funded by a fellowship (grant) ¥2,000,000 J (approximately US $18,000) for 1 year from SENSHIN Medical Research Foundation donated by the Mitsubishi Corporation, Japan. Funding began April 1, 2015. Takeo Abumiya—*RELATED: Grant*: grant from the Research Committee on Moyamoya Disease, sponsored by the Ministry of Health, Labor, and Welfare of Japan.* *Money paid to the institution.

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Cognitive Function of Patients with Adult Moyamoya Disease

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Background: Neurocognitive impairment is one of several unsolved social issues faced by patients with moyamoya disease. Although efforts have been made to investigate cognitive function using neuropsychologic tasks, generalizability has been limited. Here, in a preliminary study, we used structured neuropsychologic tasks to establish a standardized neuropsychologic assessment for adult moyamoya patients with and without difficulty in social independence. *Methods:* Ten patients with neuroradiologically confirmed adult moyamoya disease (3 male, 7 female) participated. Half of all subjects did not have difficulty with social independence (group 1) and the others had (group 2). Group differences were evaluated after basic cognitive abilities and frontal lobe function were tested. *Results:* Although the mean age of group 1 was substantially higher than that of group 2, disease duration did not differ significantly between groups. Means scores for intelligence functions including all subtests for basic cognitive abilities were higher in group 1 compared with group 2. Scores from only 2 frontal lobe evaluation tasks (Trail Making Test B and Theory of Mind) were significantly different between groups. *Conclusions:* This preliminary study provides a profile of neurocognitive dysfunction in adult patients with moyamoya disease using structured neuropsychologic tasks. A broad range of cognitive functions was disrupted particularly in the patients who had difficulty with social independence. To obtain stronger evidence regarding neurocognitive dysfunction in patients with moyamoya disease, a multicenter prospective study is essential. **Key Words:** Moyamoya disease—cognitive impairment—neuropsychologic tests—adult.

Moyamoya disease is an uncommon cerebrovascular condition characterized by progressive occlusion of bilateral internal carotid arteries and is known to cause strokes in relatively younger people.[1,2] Several efforts to identify its pathogenesis have recently detected gene mutations and deletions that make people susceptible to the familial form of the disease, and further investigation might clarify the direct mechanisms underlying the disease.[3-6] Extracranial–intracranial bypass surgery has been established as an effective neurosurgical intervention that increases cerebral blood flow (CBF) and guards against ischemic attacks. However, difficulty with social independence accompanied by cognitive impairment has recently been recognized as an important unsolved social issue faced by patients with adult moyamoya disease.[7] These patients are physically independent in daily life, but economically dependent because cognitive impairment leads to difficulty obtaining vocational skills. Here, we define the status of

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Received February 19, 2014; revision received April 17, 2014; accepted April 23, 2014.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.04.032

these patients as "difficulty with social independence." Generally, cognitive impairment has been described as a neuropsychologic sequela occurring after strokes that manifest as disturbances in memory, attention, performance, and social behavior in pediatric cases.[8,9] However, recent reports have focused on adult cases with neurocognitive impairment even without radiological evidence of major stroke.[7,10] Nakagawara et al[7] indicated that even if infarction has not yet occurred, brain dysfunction was associated with persistent hemodynamic compromise in the medial frontal lobes that can be visualized using [^{123}I]iomazenil (IMZ)-single photon emission computed tomography (SPECT). This technique has the potential to become a tool for diagnosing cognitive impairment in adult moyamoya patients who do not show major abnormalities on computed tomography scans or magnetic resonance imaging. In contrast, a common methodology for neuropsychologic evaluation of these patients is yet to be determined, even to the extent that which questions to include remains undecided. Because previous studies have selected considerably different tasks for this evaluation, results have been unsurprisingly inconsistent.[10-12] Therefore, we address this concern by administering structured tests to 2 groups of adult moyamoya patients, 1 with difficulty in social independence and the other without.

Materials and Methods

Participants

Ten patients with neuroradiologically confirmed adult moyamoya disease (3 men and 7 women; mean age, 34.2 years; range, 19-51 years) participated in this study. Because this survey was formed by completely anonymous retrospective information, this study did not have the ethics committee approval. All subjects were proficient in Japanese. To identify specifics regarding neuropsychologic assessment in moyamoya patients who have difficulty with social independence, the 10 patients were divided into 2 groups. Group 1 comprised 5 patients without difficulty in social independence. The subjects in this group had a higher educational background without need for special education programs, better socioeconomic status, and did not need public support. Group 2 comprised 5 patients who had difficulty with social independence. Two of the 5 patients required a special education program, and all were socioeconomically disadvantaged and needed public support. The mean duration of the disease was 9.1 years. Only 1 patient had a history of small intracerebral hemorrhage (periventricular region) at onset. Other patients had histories of transient ischemic attacks or minor ischemic strokes. Magnetic resonance imaging revealed these minor strokes in 4 patients, whereas the remaining subjects showed no abnormalities in the radiological assessment. No subjects showed radiological abnormality evidenced by an ischemic lesion affected by more than 2 cortical arteries. [^{123}I]iodoamphetamine-SPECT showed 1 case of resting-state CBF impairment in group 1 and 3 cases in group 2. Cerebrovascular reserve impairment was found in 9 of the 10 cases. Revascularization surgery comprising superficial temporal artery–middle cerebral artery bypass was performed in 9 of the 10 patients and their preoperative symptoms were relieved. All patients were physically independent, with modified Rankin Scale scores no greater than 2 at the time of study inclusion. Table 1 and Table 2 summarize the clinical characteristics and radiological features of each patient group.

Neuropsychologic Assessment

Basic cognitive ability was evaluated using the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) to assess intelligence, the Wechsler Memory Scale-Revised (WMS-R) to assess memory,[13,14] and supplemental subtests for each task. Several frontal functioning tests were also administered to detect specific neuropsychologic deficits associated with adult moyamoya disease that co-occurs with difficulty in social independence. The Frontal Assessment Battery tested general frontal cognitive ability. The Trail Making Test Part A assessed speed of information processing,[15,16] and the Trail Making Test Part B (TMT-B) and the Wisconsin Card Sorting Test assessed executive ability.[16,17] The Go/No-Go and No-Go/Go tasks were used to measure response inhibition,[18] and the Apathy Scale measured the extent of apathy. The Reading the Mind in the Eyes (Eyes) task is a theory-of-mind task that was given to examine the ability to infer the mental status of others.[19]

Data Analysis

To identify group differences regarding clinical profiles and neuropsychologic tasks, a univariate analysis was performed. *P* values were calculated based on the 2-tailed *t* test for parametric data and the Mann–Whitney *U* test for nonparametric data. Next, to determine which factors contributed to the differentiation between groups, a discriminate analysis was applied to the data set. A predictive model was then constructed after a stepwise variable selection procedure. Finally, the contribution rate that discriminated between the groups and the expected classification rate were calculated along with their *F* and *P* values. These statistical data were generated using JMP software, Version 10.0.2 (SAS Institute Inc, Cary, NC). A *P* value less than .05 was considered statistically significant.

Results

The mean scores for clinical variables and neuropsychologic assessments of each patient group are given in

Table 1. *Summary of clinical characteristics of each patient group*

Case no	Group	Age, y	Sex	Disease duration, y	Revascularization surgery	Special education	Employment and economic independence
1	1	51	F	1	bil STA-MCA + EMS	No	Yes
2	1	42	F	1	lt STA-MCA + EMS	No	Yes
3	1	51	M	0	lt STA-MCA + EMS	No	Yes
4	1	44	F	9	bil STA-MCA + EMS	No	No
5	1	28	F	3	lt STA-MCA + EMS	No	Yes
6	2	20	F	19	bil STA-MCA + EMS	Yes	No
7	2	19	M	12	bil STA-MCA + EMS	Yes	No
8	2	19	F	11	bil STA-MCA + EMS	Yes	No
9	2	25	M	0	no	No	No
10	2	43	F	35	bil STA-MCA + EMS	No	No

Abbreviations: bil, bilateral; EMS, encephalomyosynangiosis; lt, left; M, male; F, female; STA-MCA, superficial temporal artery–middle cerebral artery bypass.

Group 1 indicates patients without difficulty in social independence. Group 2 indicates patients with difficulty in social independence.

Table 3. The mean age of group 1 was substantially higher than that of group 2, but the disease duration for each group was not significantly different. Group 1 also had significantly higher mean scores than group 2 for intelligence functions including subtests for basic cognitive abilities. In contrast, scores for memory functions showed significant differences in 3 subtests (General Index, Attention/Concentration Index, and Delayed Index) between groups. Although scores were equivalent between groups on a number of tasks that assessed frontal lobe functions, those obtained from the TMT-B test were significantly higher in group 2, whereas those from the Eyes test were significantly higher in group 1. After loading all data from neuropsychologic tasks into statistical software, a discriminate analysis was performed. The result indicated that the Working Memory (a WAIS-III subtest) and Eyes tasks contributed significantly to the discrimination of the groups (Table 4).

Discussion

The present study demonstrated that impairments were mainly in intelligence and memory function. In addition, some frontal lobe function was particularly affected in adult moyamoya patients with difficulty in social independence.

Table 2. *Summary of radiological features of each patient group*

		Lesions on MR imaging		SPECT findings	
Case no.	Group	Minor stroke	Bleeding	Rest	CVR
1	1	-	-	Preserved	Impaired in bil ACA and MCA territory
2	1	-	lt. paraventricular region	Preserved	Preserved
3	1	lt basal ganglia	-	Impaired in lt MCA territory	Impaired in lt MCA territory
4	1	-	-	Preserved	Impaired in bil ACA and MCA territory
5	1	-	-	Preserved	Impaired in bil ACA territory
6	2	rt frontal lobe CoI.	-	Impaired in rt ACA territory	Impaired in rt ACA territory
7	2	-	-	Preserved	Impaired in bil ACA and MCA territory
8	2	bil occipital and temporal lobe CoI.	-	Impaired in bil PCA territory	Impaired in bil ACA, MCA and PCA territory
9	2	-	-	Impaired in rt ACA and MCA territory	Impaired in rt ACA and MCA territory
10	2	-	-	Preserved	Impaired in bil ACA and MCA territory

Abbreviations: ACA, anterior cerebral artery; bil, bilateral; CoI, cortical infarction; CVR, cerebrovascular reserve; lt, left; MCA, middle cerebral artery; MR, magnetic resonance; PCA, posterior cerebral artery; rt, right; SPECT, single photon emission computed tomography.

Group 1 indicates patients without difficulty in social independence. Group 2 indicates patients with difficulty in social independence.

Table 3. *Summary of clinical variables and neuropsychologic assessments in each group*

Variables	Group 1, N = 5 Mean (SD)	Group 2, N = 5 Mean (SD)	Statistics *P* value
Clinical variables			
Age, y	43.2 (9.4)	25.2 (10.3)	.0273*
Disease duration, y	2.8 (3.6)	15.4 (12.9)	.09
Intelligence (WAIS-III)			
Verbal IQ	103.6 (17.5)	67.2 (6)	.009**
Performance IQ	95.6 (10.7)	60.6 (10.5)	.0086**
Full scale IQ	100 (15.2)	61.4 (6.9)	.009**
Verbal comprehension	108.2 (19)	72.4 (15.4)	.0088**
Perceptual organization	98.6 (12.5)	63.6 (7.6)	.009**
Working memory	91.8 (11.2)	61.4 (3.3)	.008**
Processing speed	98 (8.6)	62.4 (12.8)	.009**
Memory (WMS-R)			
Verbal Index	99.2 (26.9)	69.6 (7.2)	.1161
Visual Index	111.6 (12)	76.8 (28.9)	.0749
General Index	103.2 (25.4)	65 (14.3)	.0283*
Attn/Conc Index	100.6 (8.9)	68.4 (14)	.009**
Delayed Index	106 (24.3)	64.4 (16)	.0283*
Frontal lobe functions			
Frontal Assessment Battery	16.8 (.8)	16.6 (1.1)	.8266
Trail Making Test A	35 (17.4)	72.8 (30.4)	.0593
Trail Making Test B	71.8 (24.4)	120.4 (37.4)	.0465*
Wisconsin Card Sorting Test	3.8 (2.3)	3 (2)	.5232
Go/No-Go task	276.2 (39)	330.8 (122.5)	.6015
No-Go/Go task	99.2 (9.2)	105.2 (27)	.754
Apathy Scale	13.8 (2.5)	16.6 (3.6)	.2418
Theory of Mind (Eyes)	24 (3.2)	16.8 (1.6)	.0086**

Abbreviations: Attn, Attention; Conc, Concentration; Eyes, Reading the Mind in the Eyes; IQ, intelligence quotient; SD, standard deviation; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition; WMS-R, Wechsler Memory Scale-Revised.

Group 1 indicates patients without difficulty in social independence. Group 2 indicates patients with difficulty with difficulty in social independence.

*$P < .05$, **$P < .01$.

Evaluation of the Results in This Study

Neuropsychologic Examination

Recent work using IMZ-SPECT has demonstrated the association between cortical neuron loss in bilateral frontal medial cortices and cognitive dysfunction. Considering that evidence, we have adopted several tasks to examine frontal lobe functions. To date, this is the first adoption of this comparative method regarding cognitive function of moyamoya disease.[7,9-12,20-22] Therefore, the data presented here are novel and not comparable with prior studies. A definition of "neurocognitive dysfunction" using the evaluations from all the proposed tasks was not presumed in considering the objective of this study.

Intelligence and Memory Function

On measures of intelligence abilities using WAIS-III and its subtests, mean scores from all patients in group 2 were found to be lower than that of group 1. Previous research has demonstrated loss of intellectual functions in pediatric-onset cases.[8,9,20,23,24] Our results from group 2 were consistent with those based on the age of onset. In contrast, the mean level of intelligence ability in group 1 was preserved. These data are consistent with a report suggesting cognition in adult moyamoya cases is relatively spared.[22] The proportion of gainfully used subjects in that report (84%) is comparable with that in this one (80%). Interestingly, within group 1, Working Memory scores were lower compared with scores from other WAIS-III subtests. This maybe specifically related to adult moyamoya cases that do not include difficulty with social independence. The underlying CBF impairment or neuronal loss induced by prolonged hemodynamic compromise could lead to a mild disorder in intellectual functioning that manifests in working memory deficits. However, memory ability assessed by the WMS-R was not different from other abilities, including those assessed by all WMS-R subtests. This highlights the difficulty assessing memory status in the adult moyamoya population, which is still controversial. Although Festa et al[12] have reported an overall memory score 1.1