Results

Characteristics of Unstable Disease

Demographics of the 86 patients are summarized in Table 1. Among the 140 procedures performed in these patients, 6 procedures could not be assessed for disease progression for the following reasons: 2 MRI sessions were performed before surgery, but the interval was less than 2 weeks (3 procedures); only 1 MRI session was performed before surgery because the patient had suffered a minor stroke during admission to the neurological department at our hospital and was promptly referred to a neurosurgeon (1 procedure); and the surgeon did not require a second MRI before surgery because a baseline MRI had been performed shortly before referral (2 procedures). Postoperative DWI revealed neither silent nor symptomatic lesions in these 6 cases. Baseline characteristics of the 134 included and 6 excluded cases were compared, and no variable significantly differed between the 2 groups except for the prevalence of recent stroke (9% in the included group and 50% in the excluded group, $p = 0.017$).

Of the 134 procedures included in the primary analysis, 24 (17.9%) were classified as unstable disease (Table 2): 16 as rapid progression, 6 as repeat stroke, and 2 as both. Disease progression at an interval exceeding 6 months had occurred before 5 procedures, all of which were classified in the stable group.

Table 3 summarizes baseline characteristics of the stable and unstable groups. Compared with the stable group, the unstable group included more patients younger than 3 years ($p = 0.029$), more completed stroke as an initial manifestation ($p < 0.001$), more evidence of infarction ($p = 0.030$), and more underlying disease causing moyamoya syndrome ($p = 0.049$). The median interval between the 2 MRA sessions was 90.5 days (range 14–352 days) for the stable group and 81.5 days (range 27–175 days) for the unstable group.

TABLE 1. Demographic and clinical characteristics of 86 patients included in the study

Variable	Value*
Median age (yrs, IQR)	18.5 (7.75–39.25)
Female	56 (65.1)
Initial manifestation	
TIA	51 (59.3)
Completed stroke	18 (20.9)
Intracranial hemorrhage	11 (12.8)
Epilepsy	3 (3.5)
Asymptomatic	3 (3.5)
Underlying disease	7 (8.1)
No. of procedures	
1	37 (43.0)
2	44 (51.2)
3	5 (5.8)

IQR = interquartile range.
* Values are presented as the number of patients (%) unless noted otherwise.

TABLE 2. Details of classification of 134 procedures as stable or unstable disease

Variable	No. of Procedures
Stable disease (110 procedures)	
Neither progression nor repeated stroke	105
Progression over >6 mos	5
Unstable disease (24 procedures)	
Rapid progression w/in 6 mos	16
Repeated stroke w/in 6 mos	6
Both rapid progression & repeated stroke	2

Overall Outcome

Postoperative DWI-defined lesions were detected after 13 (9.3%) of 140 procedures (Fig. 3). Six lesions were clinically silent, while 7 caused transient or permanent symptoms. A permanent ischemic complication occurred in 4 procedures (2.9%). These symptomatic lesions, all of which occurred in the unstable disease group, represented a cortical infarction remotely located from the anastomosis site, while the remaining 9 lesions included cortical and subcortical infarctions (Fig. 3). Lesions on the side contralateral to the surgery were detected on DWI in 3 procedures. The patency of all bypasses was confirmed using MRA.

For patients who suffered a permanent ischemic complication, at the time of discharge 1 patient had an mRS score of 1, and 3 patients had an mRS score of 2. At the time of last follow-up, 2 of these patients had an mRS score of 1, and 2 patients had an mRS score of 2.

Association Between Unstable Disease and Postoperative DWI-Detected Lesions

The incidence of postoperative DWI-detected lesions in the unstable disease group was 33.3% (8 of 24 procedures), which was significantly higher than that in the stable disease group (5/110 procedures [4.5%], $p < 0.001$). Infarction causing permanent morbidity was seen after 4 procedures (16.7%) in the unstable disease group, while no permanent morbidity was observed in the stable disease group. No stroke occurred after the 14th postoperative day in either group.

For the univariate analysis, unstable disease ($p < 0.001$), underlying disease ($p = 0.028$), and recent stroke ($p = 0.012$) were identified as preoperative variables associated with postoperative DWI-detected lesions (Table 4). The primary analysis revealed that unstable disease was a statistically significant factor independently associated with DWI-detected lesions (OR 6.62 [95% CI 1.79–24.5]; Table 5). Unstable disease remains statistically significant in the sensitivity analysis (OR 5.36 [95% CI 1.47–19.6]).

Discussion

The results of the present study suggest that age younger than 3 years and underlying disease causing moyamoya syndrome are associated with unstable moyamoya disease. Our results indicate that, despite the relatively low overall ischemic complication rate (2.9%), unstable disease is an

TABLE 3. Demographic descriptions of stable and unstable moyamoya disease*

Variable	Stable (110 procedures)	Unstable (24 procedures)	p Value†
Age in yrs			
Mean ± SD	21.3 ± 15.1	18.0 ± 18.5	0.461
Median (range)	17.5 (0–52)	7.5 (1–51)	
Age <3 yrs	3 (2.7)	4 (16.7)	0.029
Female	77 (70.0)	13 (54.2)	0.184
Mean systolic BP in mm Hg	120.2 ± 15.2	120.7 ± 19.9	0.926
Mean diastolic BP in mm Hg	73.2 ± 15.6	75.4 ± 17.0	0.620
Initial manifestation			
Completed stroke	16 (14.5)	13 (54.2)	<0.001
TIA	74 (67.3)	4 (16.7)	<0.001
Intracranial hemorrhage	13 (11.8)	3 (12.5)	0.943
Other	7 (6.4)	4 (16.7)	
Underlying disease	7 (6.4)	5 (20.8)	0.049
Frequency of TIA >3 times/mo	8 (7.3)	3 (12.5)	0.339
Radiographic evidence of infarction	66 (60)	20 (83.3)	0.030
Recent stroke	5 (4.5)	7 (29.2)	<0.001
Unilateral disease	11 (10.0)	3 (12.5)	0.713
Suzuki stage			
I	5 (4.5)	1 (4.2)	
II	32 (29.1)	8 (33.3)	
III	59 (53.6)	14 (58.3)	
IV	14 (12.7)	1 (4.2)	
V	0	0	
Suzuki Stage ≥IV	14 (12.7)	1 (4.2)	0.270
PCA involvement	32 (29.1)	10 (41.7)	0.283
Severe hemodynamic compromise‡	72 (66.7)	18 (75.0)	0.412
Antiplatelet agent administration	92 (83.6)	21 (87.5)	0.709
Median MRI interval in days (range)	90.5 (14–352)	81.5 (27–175)	0.048

BP = blood pressure.

* Values are number of procedures (%) unless indicated otherwise. Mean values are presented as the mean ± SD.

† The p values were calculated with robust standard errors derived from the GEE approach with the independent working correlation structure.

‡ Data were unavailable for 2 procedures.

independent risk factor for perioperative DWI-detected lesions.

The incidence of disease progression in moyamoya disease, which is receiving more attention especially regarding cases of unilateral disease, is not particularly rare. Disease progression occurs in 54% of pediatric patients over a mean period of 5.4 years and in 23.8% of adult patients over a mean period of 6.1 years.[19,21] A more recent study estimated the 3-year cumulative incidence of disease progression as 19% in children and adolescents with unilateral disease.[28] Younger age,[26,28] female sex,[19] contralateral angiographic abnormality,[20,26] and underlying cause of moyamoya syndrome[21] have been considered risk factors for contralateral progression of unilateral disease. The results of our study, which found younger age and underlying disease as risk factors for unstable disease, are in line with these reports. The mean time to progression estimated in the previous studies ranged from 14.3 to 34 months.[14,19,20] Our results may add important information to those of previous studies, because more rapid disease progression was observed in a substantial number of patients.

Several factors, such as age younger than 3 years,[16] female sex,[15] presence of underlying disease,[6,22] frequent TIAs,[16] radiographic evidence of preexisting infarction,[9,16,25] recent episode of stroke,[9,16] advanced angiographic stage,[11] and disease involvement in the PCA,[11] are believed to increase ischemic complications after bypass surgery for moyamoya disease. Although young age and preexisting infarction were generally considered major risk factors for surgical outcome in moyamoya disease, some controversy remains in the literature regarding what constitutes a risk factor. Our univariate result, indicating that underlying disease and recent stroke are significant, partly coincides with the literature. In addition, our multivariate results suggest that unstable disease is another independent risk factor for perioperative ischemic complications.

On the other hand, our results did not reveal a statistically significant impact of preexisting infarction on outcome,

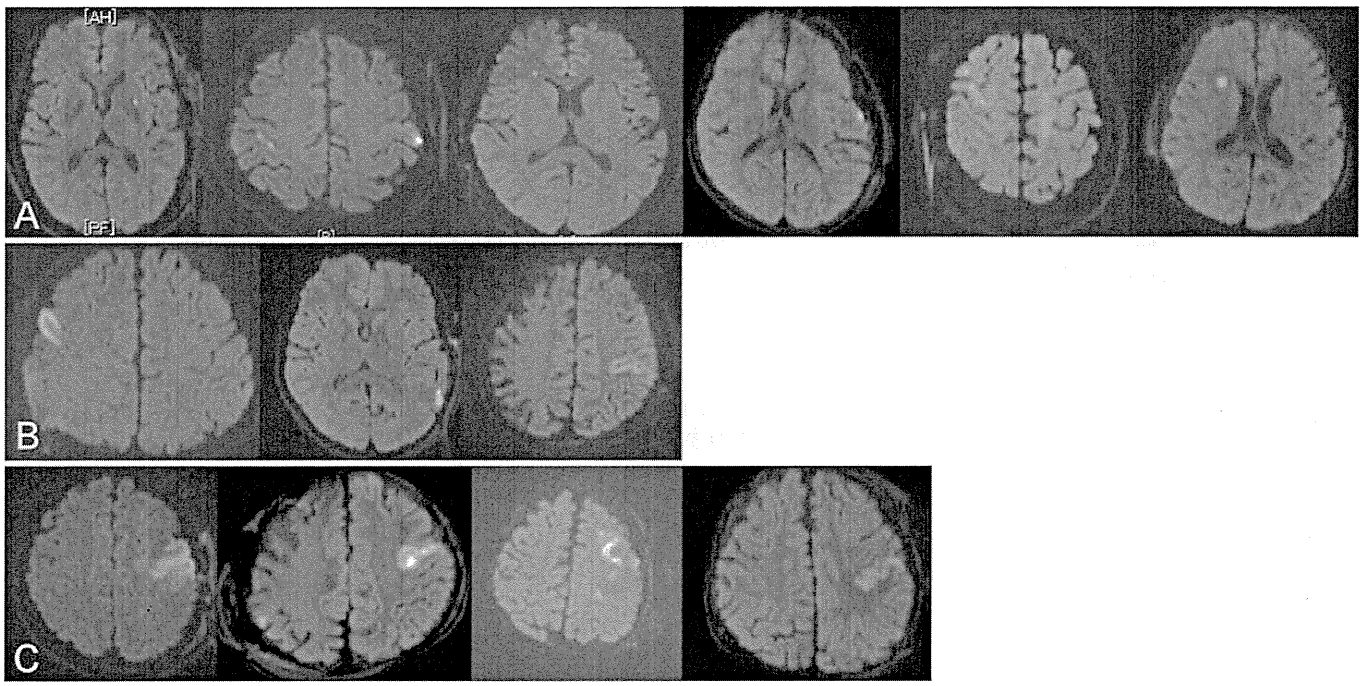

FIG. 3. Lesions detected on postoperative DWI. **A:** Silent lesions. **B:** Lesions causing transient symptoms. **C:** Lesions causing permanent symptoms.

which contradicts findings of some previous reports.[9,16,25] A possible explanation for this contradiction is that unstable disease, including infarct as defined, acted as an intervening variable in multivariate analysis, which might diminish the true effect of infarct on outcome. A relatively high odds ratio was observed for preexisting infarct, and a study with a larger sample size may have detected its statistically significant impact on perioperative ischemic complication. Another reason we did not find a significant effect from preexisting infarct might be a difference in surgical procedures. The prestigious study by Kim et al., concluding that age younger than 3 years and preexisting infarct were risk factors for surgical ischemic complication, addressed indirect bypass.[16] On the other hand, Guzman et al., analyzing the outcomes of 450 direct bypasses, found no association between age and perioperative ischemia.[6]

TABLE 4. Univariate analyses of putative factors and postoperative DWI-detected lesions

Variable	OR (95% CI)	p Value
Unstable moyamoya	10.5 (2.69–41.0)	<0.001
Preop factors		
Age (yrs)	0.99 (0.94–1.05)	0.792
Age <3 yrs	4.22 (0.39–46.1)	0.238
Female	0.53 (0.13–2.16)	0.379
Systolic BP	1.02 (0.97–1.07)	0.422
Diastolic BP	1.02 (0.97–1.08)	0.360
Underlying disease	6.28 (1.22–32.4)	0.028
Frequency of TIAs >3 times/mo	2.26 (0.43–12.0)	0.336
Radiographic evidence of infarction	7.62 (0.88–65.7)	0.065
Recent stroke	6.28 (1.51–26.1)	0.012
Unilateral disease	0.69 (0.08–6.11)	0.741
Suzuki Stage ≥IV	2.10 (0.29–7.89)	0.625
PCA involvement	0.97 (0.22–4.26)	0.969
Severe hemodynamic compromise*	6.31 (0.90–44.2)	0.064
Antiplatelet agent administration	2.38 (0.27–21.0)	0.436

* Data were unavailable for 2 procedures.

One possible mechanism of infarction developing after bypass surgery in the unstable disease group could be hemodynamic shift after direct bypass. Hayashi et al. discussed the mechanism of postoperative focal hypoperfusion detected by SPECT.[7] They speculated that the reversed MCA flow induced by the bypass graft could conflict with the original MCA flow, resulting in relative hypoperfusion in the remote territory of the MCA. Such a hemodynamic shift may be more prevalent in unstable disease. In unstable disease, leptomeningeal collateral flow may fail to develop sufficiently because of rapid disease progression. As a result, the bypass flow may conflict more strongly with the original antegrade flow supplying the MCA territory. Our finding that all symptomatic lesions occurring in unstable disease represent a cortical infarction remotely located from the anastomosis site may support this speculation.

Our study has several limitations. First, the study excluded from the primary analysis 6 procedures before which only 1 session of MRA had been performed. The impact of possible bias caused by this exclusion may be minimal, however, because the sensitivity analysis also revealed statistical significance of unstable disease. Second, the retrospective study design meant that the interval between the 2 MRA sessions and the modality of MRA varied among patients. This might have caused a selection bias regarding the classification of unstable disease. Third, the result of

TABLE 5. Estimated ORs and 95% CIs for primary and sensitivity multivariate analyses

Variable	Primary Analysis		Sensitivity Analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Unstable moyamoya	6.62 (1.79–24.5)	0.005	5.36 (1.47–19.6)	0.011
Underlying disease	2.98 (0.56–15.8)	0.200	3.68 (0.72–18.8)	0.117
Radiographic evidence of infarction	3.75 (0.39–36.3)	0.254	4.07 (0.42–39.9)	0.228
Recent stroke	1.88 (0.58–6.09)	0.295	1.36 (0.44–4.21)	0.593

the multivariate analysis has a relatively large confidence interval, which is attributable to the small number of cases. Larger prospective studies are therefore necessary to confirm the significant impact of unstable moyamoya disease on perioperative ischemic complications. These studies might also reveal the statistical significance of other variables such as preexisting infarct.

Considering the devastating nature of unstable moyamoya disease reported to date,[4,17,18] early surgical revascularization might be recommended. Kim et al. similarly stressed the importance of early surgical intervention for aggressive moyamoya disease observed in children.[17] On the other hand, our finding, which detected the unstable state as an independent surgical risk factor, shed light on the need for preoperative diagnosis and specific perioperative management of unstable moyamoya disease. In terms of the diagnosis, performing MRA immediately before surgery might be useful, as the disease progression could be detected through a comparison with previous findings. In terms of treatment, perioperative management should be focused more on preventing ischemic complications. Although intentional lowering of blood pressure is considered for patients with hyperperfusion complications,[3] those with unstable disease should instead be maintained in a normotensive or slightly hypertensive state. Strict control of blood CO_2 level during surgery, in which $PaCO_2$ is maintained between 37 and 40 mm Hg at our institution, should also be undertaken. More aggressive use of antiplatelet agents could be adopted as a possible option for unstable disease. Although we adopted direct bypass as the first choice for treating moyamoya disease, tentative indirect bypass followed by elective direct bypass may be considered for unstable disease. This strategy can be indicated especially when acute hemorrhagic infarction after direct bypass as well as hemodynamic shift is concerned. The efficacy of these possible methods of management of unstable disease should be tested in future studies.

Conclusions

Unstable moyamoya disease, reasonably defined as cases of rapid progression or repeated stroke, represents a clinically challenging condition. It is more prevalent in patients younger than 3 years and those with underlying disease causing moyamoya syndrome. Unstable moyamoya disease is a possible risk factor associated with perioperative ischemic complication. The concept of unstable moyamoya disease may contribute to further improvement in the surgical results of moyamoya disease as a result of focused perioperative management arising from appropriate surgical risk stratification.

Acknowledgments

We are grateful to Dr. Tosiya Sato, Professor of the Department of Biostatics, Kyoto University School of Public Health, for providing advice on statistics and performing the GEE analyses. We also appreciate the efforts of Dr. Noritaka Sano, Ms. Yuko Tanaka, and Ms. Yuka Aramaki in collecting patient records.

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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

Table 4. *Discriminate analysis for prediction model*

Neuropsychologic test	*F* value	*P* value (Prob > F)
Intelligence (WAIS-III)		
Verbal IQ	.807	.404
Performance IQ	.282	.614
Full Scale IQ	.69	.438
Verbal comprehension	.087	.778
Perceptual organization	.118	.743
Working memory	16.75	.005**
Processing speed	.033	.861
Memory (WMS-R)		
Verbal Index	.014	.911
Visual Index	.017	.901
General Index	.002	.964
Attn/Conc Index	.139	.723
Delayed Index	.143	.719
Frontal lobe function		
Frontal Assessment Battery	.063	.811
Trail Making Test A	.792	.408
Trail Making Test B	1.662	.245
Wisconsin Card Sorting Test	.19	.678
Go/No-GO task	.059	.817
No-Go/Go task	.231	.648
Apathy Scale	1.073	.340
Theory of Mind (Eyes)	8.636	.022*

Abbreviations: Attn, Attention; Conc, Concentration; Eyes, Reading the Mind in the Eyes; IQ, intelligence quotient; Prob, Probability; WAIS-III, Wechsler Adult Intelligence Scale-Third Edition; WMS-R, Wechsler Memory Scale-Revised.
*$P < .05$, **$P < .01$.

standard deviations below the mean of healthy individuals, other reports have shown memory to be unaffected in adult moyamoya subjects.[11,22] Usually, a lack of memory impairment associated with spared hypoperfusion in the medial temporal lobe is characteristic of moyamoya disease. However, our results showing impairment within group 2 on 3 subtests of the WMS-R could not be explained from the SPECT data, indicating specific hypoperfusion in the rest state and impaired cerebrovascular reserve in the medial temporal lobe. This point remains unresolved, whereas memory function maybe associated not only with the medial temporal lobe but also with widespread subcortical neuronal connections.

Frontal Lobe Functions

An extensive focus on frontal lobe function has not yet been taken by previous research regarding moyamoya disease. CBF and IMZ studies have shown that anteromedial frontal cortices fed by anterior circulation develop blood insufficiencies.[7,25] For this reason, several neuropsychologic test batteries to evaluate frontal lobe functioning in relation to hemodynamic compromise were used for this preliminary study. Among these batteries, only scores from the TMT-B and Eyes tasks were shown to be statistically lower in group 1 compared with group 2. The TMT-B can estimate frontal lobe function in terms of problem solving and motor planning.[26] Performance on this test is known to be poor in adult patients with moyamoya disease,[12,22] and results from group 2, required time to complete the task was longer than group 1, were compatible with these other studies. Theory-of-mind tasks examine one's ability to infer the mental status of others. Here we used the revised version of the Eyes test.[19,27] This test had been given to patients with other kinds of psychiatric disorders, and recent neuroimaging studies of normal subjects indicate that performing the Eyes task activates linked brain regions including the medial prefrontal cortex, orbitofrontal cortex, amygdala, temporal poles, and superior temporal sulcus.[28] Hirao et al[27] has demonstrated that the mean accuracy in the Eyes task generated by schizophrenic patients was significantly lower than that of normal subjects. Furthermore, they provided a correlation analysis between Eyes task impairment and structural alterations using Voxel-based morphometry, which indicated specific regional abnormalities in the left ventrolateral prefrontal cortex of schizophrenic patients. To our knowledge, this is the first report to show deficiency in theory-of-mind ability in patients with moyamoya disease. Although we did not include a structural study, long-term chronic hypoperfusion in the anterior circulation could produce a dysfunction in medial and lateral regions of the anterior frontal lobe, which might induce the theory-of-mind impairment observed in group 2.

Discriminate Analysis

To determine which neuropsychologic tasks can best detect neurocognitive dysfunction in adult patients with moyamoya disease in a clinical setting, we conducted a discriminate analysis using crude data from all neuropsychologic tasks. Results showed that the Working Memory and Eyes tasks were the best predictors, and a model limited to those tasks successfully classified the patients into 2 groups. This indicates that these 2 tasks have the statistical power to diagnose neurocognitive dysfunction in adult patients with moyamoya disease. Impairment of these tasks could be the specific neurocognitive deficits that inflict adult moyamoya patients.

Limitations

There are several limitations to this preliminary study. First, the definition of "difficulty with social independence" is still unclear, and selecting these patients was not objective, so it maybe biased. A structured evaluation system determined through a multicenter study is required. Second, in considering the effect of CBF on neurocognitive function, a history of revascularization surgery should be matched. However, the aim of this study is not to

compare neurocognitive function before and after the revascularization surgery, but to collect long-term consequence of neurocognitive function in adult patients with moyamoya disease. Third, the number of patients enrolled in this study was too small. Characteristics such as age, type of onset, and radiological abnormality were not matched between groups. However, it is particularly worth nothing that the several group differences were revealed even in small set of patients and detailed neuropsychologic tasks. This preliminary study would be fundamental data for a large-scale research and contributes to understand the characteristics of cognitive dysfunction in adult patients with moyamoya disease.

Conclusions

This study profiled neurocognitive function in adult patients with moyamoya disease using structured neuropsychologic tasks. We showed that a broad range of cognitive functions is disrupted particularly in the patients with difficulty in social independence. We found that scores from the Working Memory (WAIS-III) and Eyes tasks are a novel clinical approach to detect such disadvantaged subjects even if they lack obvious abnormalities in brain images. Our findings also reveal subtle impairments in intelligence function (Working Memory, WAIS-III) in the socially independent patient population. To obtain sufficiently powered evidence regarding the cognitive deficits reported here, a multicenter prospective study is needed in patients with moyamoya disease.

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Acta Neurochir (2014) 156:551–559
DOI 10.1007/s00701-013-1975-7

CLINICAL ARTICLE - VASCULAR

Incidence of late cerebrovascular events after direct bypass among children with moyamoya disease: a descriptive longitudinal study at a single center

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Received: 27 June 2013 / Accepted: 4 December 2013 / Published online: 22 December 2013

Abstract
Background The potential for late cerebrovascular events following surgical revascularization presents a challenge in the treatment of pediatric moyamoya disease. Limited information is available on the incidence of such events after direct bypass. The objective of this descriptive study was to examine the incidence of late cerebrovascular events after direct bypass for pediatric moyamoya disease.
Methods The study cohort comprised consecutive patients with moyamoya disease who had undergone direct bypass at less than 18 years of age in the authors' institute between 1978 and 2003. They were prospectively followed until the end of the study period or, if applicable, the time of death.
Results Fifty-six of 58 enrolled patients (96.6 %) were followed for a mean period of 18.1 years. Four patients experienced late cerebrovascular events, comprising one stroke and three hemorrhages, an average of 13 years after surgery, one of whom experienced a fatal second hemorrhage. The only late ischemic stroke in the cohort occurred after a severe head injury and emergent craniotomy. The incidence of late cerebrovascular events was 0.41 % per year (95 % confidence interval, 0.15–1.08); 10-year, 20-year, and 30-year cumulative incidences were 1.8 %, 7.3 %, and 13.1 %, respectively.
Conclusions Despite the efficacy of surgical revascularization, pediatric patients remain at risk of future cerebrovascular events, especially hemorrhage, after reaching adulthood and thus require careful long-term follow-up.

Keywords Moyamoya disease · Pediatrics · Cerebral revascularization · Cohort study · Stroke · Hemorrhage

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Introduction

Moyamoya disease is characterized by progressive spontaneous stenosis or occlusion of the terminal portion of the bilateral internal carotid arteries and development of abnormal collateral vessels at the base of the brain. Epidemiological studies have shown that the age distribution of disease onset has two peaks: childhood and the 40s [1, 20, 37]. In childhood, ischemic symptoms such as transient ischemic attack and stroke are the main initial manifestations. In adult patients, intracranial hemorrhage is as common as ischemic symptoms and often results in serious sequelae [1, 38]. Although numerous follow-up studies have supported the evidence that revascularization surgery is effective at preventing ischemic symptoms in pediatric patients with moyamoya disease [3, 8, 16, 21, 24, 27, 29, 31, 32, 36], more recent studies have reported that the slight risk of late cerebrovascular events, including both ischemic stroke and hemorrhage, remains even after revascularization surgery [8, 12, 27, 31]. Considering the bimodal age distribution of disease onset, a late cerebrovascular event is likely to occur after pediatric patients reach

adulthood and thus is a future potential problem for them. Estimation of the incidence of a late cerebrovascular event is essential for planning the follow-up of pediatric patients. However, only a few studies have focused on this issue, and long-term prospective studies are rare. Furthermore, in those studies addressing the issue of a late cerebrovascular event, surgical revascularization generally takes the form of indirect bypass such as encephalo-duro-arterio-synangiosis; consequently, there is a lack of information on late cerebrovascular events following direct bypass surgery, such as superficial temporal artery (STA) to middle cerebral artery (MCA) bypass.

In this study, we prospectively followed a cohort comprising consecutive patients with moyamoya disease, all of whom had undergone direct bypass in childhood. The objective of the study was to examine the incidence and features of late cerebrovascular events after direct bypass for pediatric moyamoya disease.

Methods

The study protocols for the present study were reviewed and approved by the ethics committee of the Kyoto University Graduate School of Medicine.

Inclusion criteria

This study includes consecutive pediatric patients surgically treated mainly by the senior author at Kyoto University Hospital and its satellite hospital between April 1978 and March 2003. The inclusion criteria were as follows:

1. Japanese patients under 18 years of age at first admission for moyamoya disease
2. Diagnosed with moyamoya disease following angiography according to the criteria proposed by the Research Committee on Moyamoya Disease in Japan [5, 30]
3. Had undergone direct bypass in this institute
4. Children with a typical occlusive finding at the terminal portion of the unilateral internal carotid artery alone were also included [30]

Patients from outside Japan were excluded from the present study because of racial differences and difficulties with follow-up. Also excluded were children with autoimmune disease, meningitis, brain tumor, Down syndrome, neurofibromatosis type 1, or a history of head irradiation. Since 1978, we have been employing a direct bypass method comprising STA-MCA bypass as a first-line treatment for pediatric moyamoya disease [16]. For patients under 10 years of age, encephalo-myo-synangiosis (EMS) [14], an additional indirect bypass procedure using the pedicle flap of the temporalis muscle was combined with STA-MCA bypass. All but two surgeries were performed by the senior author: in the earliest case, the first two surgeries were performed by another surgeon and the subsequent ones by the senior author. Patients with involvement of the bilateral internal carotid artery underwent STA-MCA bypass first on the more symptomatic or hemodynamically impaired hemisphere and then on the contralateral hemisphere. The second revascularization was performed no earlier than 4 weeks after the first revascularization because patients require the time for recovery from unstable cerebral hemodynamics including hyperperfusion, which can occur shortly after direct bypass [15, 35]. Angiography was performed 3 months after the second revascularization to assess bypass patency. If examinations 3 months after the second revascularization suggested insufficient hemodynamic improvement in the anterior or posterior cerebral artery territories, additional direct revascularizations to these areas were considered.

Protocol

Data including age at symptom onset, primary clinical manifestations (categorized as completed ischemic stroke, transient ischemic attack, intracranial hemorrhage, or epilepsy), and angiographical findings, translated later into a four-stage system [26], were collected upon first admission. A completed ischemic stroke was defined as a neurological symptom exceeding 24 h in duration and the presence of a corresponding ischemic lesion revealed through neuroradiological modalities. Patients were followed by the outpatient neurosurgical clinic until the end of the study period or until the time of death, if applicable. The final status of each patient was determined between January 2011 and April 2013 through regular follow-up at the outpatient clinic or through a telephone interview and mailed questionnaire if the patient did not visit the hospital during that period.

A late cerebrovascular event, an outcome of the present study, was defined as all ischemic and hemorrhagic strokes with neurological symptoms occurring more than 30 days after surgery and confirmed thorough neuroradiological modalities. Hemorrhages included intraventricular, parenchymal, and subarachnoid types. All patients had been encouraged to visit our hospital promptly if experiencing weakness in an extremity, sensation abnormality, speech disturbance, hemianopsia, or severe headache with vomiting. In such cases, an emergent radiological assessment including computed tomography and magnetic resonance imaging was performed to determine whether the patient was experiencing a cerebrovascular event.

Single photon emission tomography (SPECT) was performed between 2011 and 2013 in some patients who had provided their informed consent. Regional cerebral blood flow (rCBF) was quantitatively measured with iodine-123-

labelled N-isopropyl-p-iodoamphetamine (IMP) [10]. A region of interest was automatically set in each vascular territory.

Statistical analysis

The person-years method was used to calculate the incidence of late cerebrovascular event. The incidence was calculated by dividing the number of patients experiencing the outcome by person-years counted until the end of the study period or occurrence of the outcome. The Poisson distribution was used to calculate 95 % confidence intervals (95 % CIs) of the incidence. The Kaplan-Meier method was used to estimate the cumulative incidence. The rCBF values among three vascular territories were compared with the Kruskal–Wallis test [19]. Statistical analyses were performed with JMP 9 software (SAS Institute, Cary, NC, USA).

Results

A total of 58 patients met the criteria, all of whom gave informed consent and were enrolled in this study. The sex and age distributions at disease onset are summarized in Table 1. The overall female-to-male ratio was 1.4, and the peak age at onset was 6 years (mean, 6.4; range, 0–15; 95% CI, 5.5–7.3). Transient ischemic attack was the most common primary manifestation (75.9 %), followed by completed stroke (17.2 %) and epilepsy (5.2 %). No patients presented with intracranial hemorrhage at disease onset. Angiographical stages in anterior circulation assessed on admission were 1 in 7 (12.1 %) cases, 2 in 27 (46.6 %) cases, 3 in 22 (37.9 %) cases, and 4 in 2 (3.4 %) cases; those in posterior circulation were 1 in 36 (65.5 %) cases, 2 in 6 (10.9 %), and 3 in 13 (23.6 %) cases. A total of 114 bypass surgeries were performed. Additional revascularization to the anterior or posterior cerebral artery territories was performed in five (8.6 %) patients, of which three underwent direct bypass using another branch of the STA or the occipital artery and two underwent omental transplantation [17]. The patency of all bypasses was confirmed by postoperative angiography.

Table 1 Age distribution at disease onset and at end of follow-up

Age in years	At disease onset		At end of follow-up	
	Female	Male	Female	Male
0–4	13	6	0	0
5–9	15	13	0	0
10–14	5	5	1	0
15–19	1	0	6	2
20–24	0	0	6	8
25–29	0	0	9	6
30–34	0	0	7	5
35–39	0	0	2	0
40–44	0	0	0	1
45–50	0	0	2	0
Deceased	–	–	0	1
Lost to follow-up	–	–	1	1

The mean follow-up period was 18.1 years (range, 9–33.7; 95 % CI, 16.5–19.7). Age distribution at the end of the study is shown in Table 1; mean age at the end of the study was 26.5 years (range, 13–45; 95 % CI, 24.6–28.4). The outcome at the end of the study was not available in two patients, for a follow-up rate of 96.6 % (56/58). These two patients had been followed for 21 and 23 months after surgery, respectively, before they stopped visiting our hospital. Their postoperative courses were uneventful and had experienced no new neurological symptoms as of the last day of follow-up. We were unable to contact them at the end of the study because they had relocated.

Four of the 56 followed patients (7.1 %) experienced at least one late cerebrovascular event during observation period (Table 2). The mean interval between the initial surgery and the late cerebrovascular event was 13.0 years. One experienced an ischemic stroke after a head injury at 8 years of age. Three experienced an intracranial hemorrhage at a mean age of 26 years (range, 24–29), an average of 16.8 years (range, 13.9–20.9) after surgery. One of the patients experienced a second hemorrhage, which resulted in a fatal outcome. In all patients with late-onset hemorrhage, the bypasses were still patent at the time of the hemorrhagic event.

Until the end of the study, 986.6 person-years of follow-up (577.8 person-years for females and 408.8 person-years for males) were counted. The incidence of overall late cerebrovascular events calculated by the person-years method was 4/986.6 or 0.41 % per year (95 % CI, 0.15–1.08). The incidences of late ischemic and hemorrhagic events were 1/1004.7 or 0.10 % per year (95 % CI, 0.01–0.71) and 3/995.4 or 0.30 % per year (95 % CI, 0.10–0.93), respectively. According to the Kaplan-Meier method, the 10-year, 20-year, and 30-year cumulative incidences of late cerebrovascular events were 1.8 %, 7.3 %, and 13.1 %, respectively (Fig. 1).

The follow-up SPECT was obtained in 11 patients, and rCBF was measured in 22 hemispheres. The median rCBF (interquartile range) in the anterior, middle, and posterior cerebral artery territories were 40.5 (37.3–47.7), 38.9 (34.3–47.9), and 38.6 (34.5–47.6) ml/100 g/min, respectively. No statistically significant differences in rCBF were found among vascular territories (p=0.580).

Illustrative cases

Case 1 (late ischemic stroke) This patient had been experiencing transient motor weakness in the extremities triggered by hyperventilation since he was 3 years of age and was admitted

Table 2 Summary of patients experiencing late cerebrovascular events

Case	Age at onset in years, Sex	Primary manifestation	Age at OP in years	Type of late cerebrovascular event	Age at late cerebrovascular events in years	Time elapsed between OP and first late cerebrovascular event in years	mRS at end of follow-up
1	3 M	TIA	6	Ischemic stroke[a]	8	2.75	2
2	6 F	TIA	10	Thalamic hemorrhage	25	13.9	2
3	7 F	TIA	9	Intraventricular hemorrhage	24	15.5	0
4	4 M	TIA	8	Intraventricular hemorrhage	29 and 33	19.9	6

TIA transient ischemic attack, *OP* operation, *mRS* modified Rankin Scale

[a] The stroke occurred after a severe head injury and emergent craniotomy

to our hospital. At 6 years of age he was diagnosed with moyamoya disease (Fig. 2a–c) and underwent STA-MCA bypasses with EMS in both hemispheres. Postoperative angiography revealed good patency of bypasses (Fig. 2d). Although his symptoms disappeared after surgery, he experienced an acute subdural hematoma due to a traffic accident at 8 years of age (Fig. 2e) and underwent an emergent craniotomy at another hospital. Four days after surgery an infarction developed in the affected side of the frontal cortex (Fig. 2f), although the bypasses appeared to have remained patent in magnetic resonance angiography after surgery. He was discharged to home with a mild cognitive disturbance.

Case 2 (late hemorrhage) This patient had presented with transient right-side motor weakness experienced frequently since 6 years of age and was admitted to our hospital at 10 years of age. She was diagnosed with moyamoya disease. Angiography on admission revealed occlusion of the bilateral internal carotid arteries and posterior cerebral arteries with extensive development of abnormal collateral vessels known as moyamoya vessels (Fig. 3a, b). She underwent STA-MCA bypasses with EMS in both hemispheres. The transient ischemic attacks disappeared after surgery and administration of aspirin was ceased. Fourteen years after surgery, she was admitted to our hospital with left thalamic hemorrhage at 24 years of age (Fig. 3c). Angiography revealed that moyamoya vessels in the anterior circulation had decreased with good patency of the bypasses, while those in the posterior circulation had remained (Fig. 3d–f). No apparent decrease in CBF was detected in the posterior cerebral artery territory. She was discharged and is working as a homemaker with dysesthesia of the left side and mild memory disturbance.

Case 4 (late hemorrhage) This patient had presented with transient right side motor weakness when crying since 4 years of age and admitted to our hospital at 8 years of age. He was diagnosed with moyamoya disease and underwent STA-MCA bypasses with EMS in both hemispheres. Although he remained symptom-free for more than 10 years, he was admitted to our hospital with an intraventricular hemorrhage at 29 years of age (Fig. 4a). Angiography confirmed good patency of the bypasses but revealed abnormal dilated collaterals and peripheral microaneurysms in the posterior choroidal artery (Fig. 4b–d). He was treated conservatively and had recovered well without any neurological deficit. Additional revascularization was not indicated because the bypasses had broadly spanned the hemispheres. Direct treatment of the peripheral microaneurysms, such as endovascular embolization, was abandoned because of technical difficulty and the patient's objection. He was closely followed at our clinic; however, he experienced a second intraventricular hemorrhage at 33 years of age (Fig. 4e), which resulted in a fatal outcome.

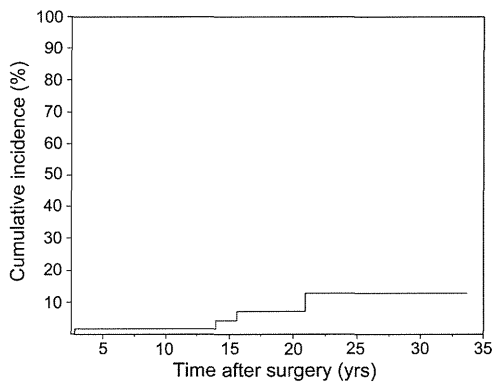

Fig. 1 Cumulative incidence of late cerebrovascular events

Discussion

Our results estimated the incidence of late cerebrovascular events as 0.41 % per year, which is far higher than the overall incidence of stroke in the general population in Japan [33]. This result coincides with those of recent long-term follow-up studies. We found two articles on pediatric moyamoya disease meeting the criteria of a mean follow-up period exceeding 10 years, a cohort of at least ten patients, and a follow-up rate exceeding 80 % [12, 27]. One addressed long-term follow-up after indirect bypass [27], while the other addressed patients

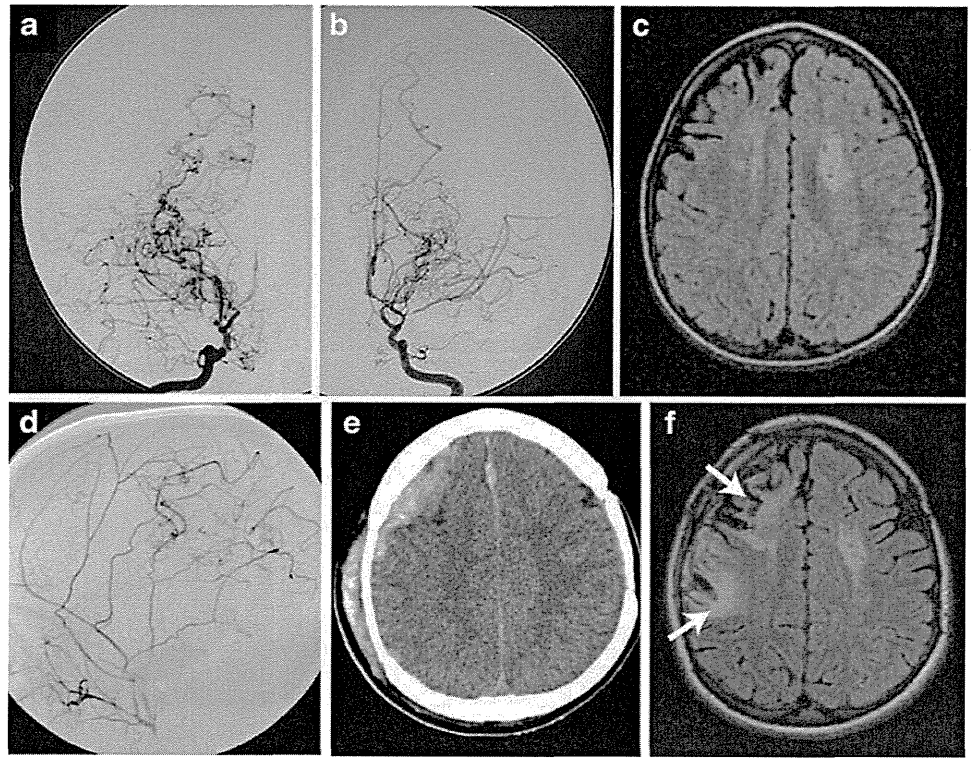

Fig. 2 Case 1. **a**, **b** Angiography before bypass surgery; right (**a**) and left (**b**) internal carotid angiography demonstrating occlusion at the terminal portion of the internal carotid artery with development of moyamoya vessels; **c** magnetic resonance imaging (MRI) before bypass surgery demonstrating subcortical infarction in the bilateral frontal lobe; **d** right external carotid angiography after bypass surgery revealing good patency of the bypass; **e** computed tomography performed at another hospital immediately after a head injury from a traffic accident, demonstrating acute subdural hematoma; **f** MRI after emergent craniotomy demonstrating newly-developed infarction in the frontal cortex (*arrows*)

treated either conservatively or with mainly indirect bypass [12]. The calculated incidences of late cerebrovascular events in these reports ranged between 0.24 and 0.85 % per year (Table 3).

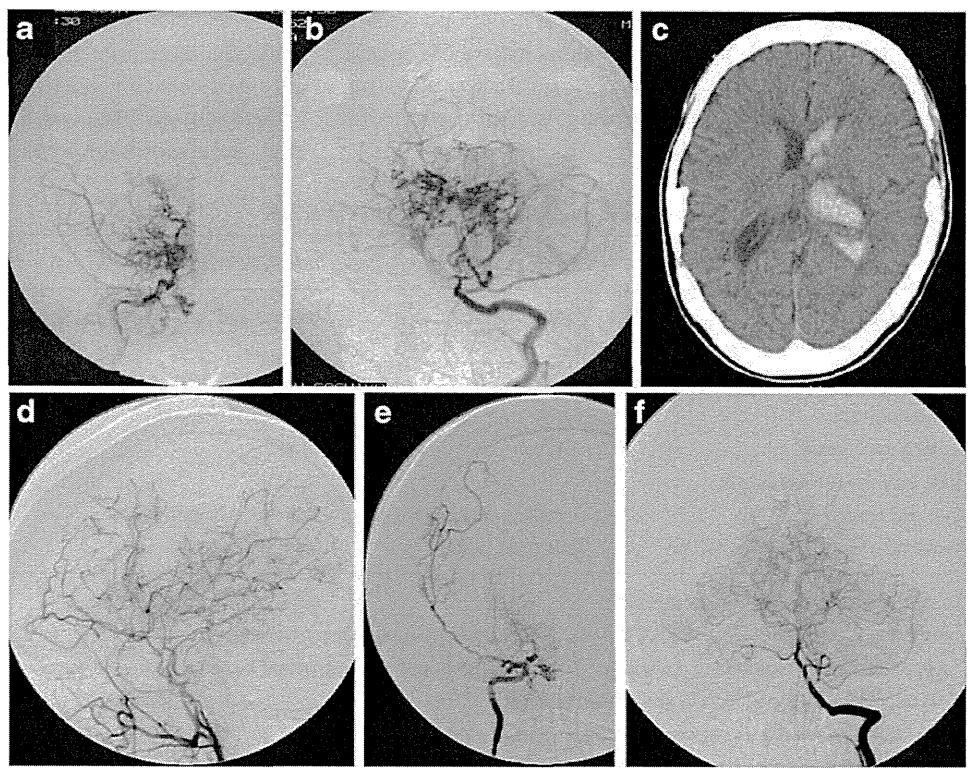

Fig. 3 Case 2. **a**, **b** Angiography before bypass surgery; **a** right internal carotid angiography demonstrating occlusion at the terminal portion of the internal carotid artery with development of moyamoya vessels; **b** left vertebral angiography demonstrating occlusion of the bilateral posterior cerebral artery with development of moyamoya vessels; **c** computed tomography showing left thalamic hemorrhage occurring 14 years after surgery; **d**–**f** angiography after thalamic hemorrhage; **d** right external carotid angiography revealing good patency of the bypass; **e** right internal carotid angiography revealing a marked decrease in moyamoya vessels in the anterior circulation; **f** left vertebral angiography revealing remaining moyamoya vessels in the posterior circulation

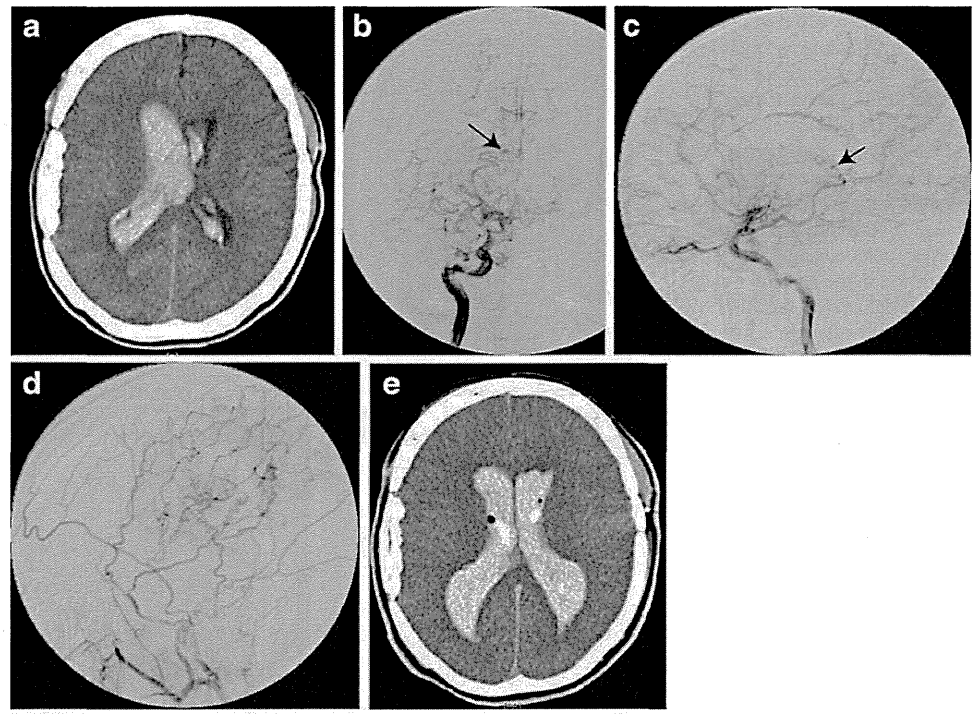

Fig. 4 Case 4. **a** Computed tomography at first hemorrhage; **b–d** angiography after the first hemorrhage; anteroposterior (**b**) and lateral (**c**) views of the internal carotid angiography after first hemorrhage revealing occlusion of the internal carotid artery and dilated posterior choroidal artery accompanied with microaneurysms (*arrows*); **d** external carotid angiography showing good patency of the bypass; **e** computed tomography at second hemorrhage demonstrating massive intraventricular hemorrhage, resulting in fatal outcome

Considering that most children had experienced an ischemic symptom at disease onset, the incidence of ischemic stroke revealed in our study (0.1 % per year) seems quite low. In our series, only one case experienced an ischemic stroke, an event that might not have occurred had he not experienced a severe head injury. Bypass surgery for moyamoya disease is usually successful at improving cerebral blood flow [13, 28, 34]. While the natural history of pediatric moyamoya disease is devastating [2], revascularization surgery can be effective at preventing ischemic stroke for decades.

In the present study, hemorrhage occurred more frequently than ischemic stroke during the follow-up period. This finding is coincident with the previous studies (Table 3) [12, 27]. Interestingly, all late hemorrhages in our study occurred in those patients who had first experienced ischemic symptoms. From a long-term perspective, hemorrhages should receive more attention than strokes do because hemorrhage affects outcome more severely [18, 25, 38]. On the other hand, our results do not coincide with those reported by Scott et al. [31], which showed 4 late-onset ischemic strokes in their 126 cases but no hemorrhage after pial synangiosis without direct

Table 3 Incidence of late cerebrovascular events in previous and present studies

	Mukawa et al.	Imaizumi et al.	Present study
Treatment	Indirect bypass	Indirect and direct bypasses, or conservative[a]	Direct bypass
No. of patients	172	25	58
Mean follow-up period in years (range)	14.3 (3–32)	18.8 (NA)	18.1 (9–33.7)
Follow-up rate	83 %	80.6 %	96.6 %
Total person-years	2,459.6[b]	470.0[b]	986.6
Late cerebrovascular events			
No. and mode	3 strokes, 3 hemorrhages[c]	1 stroke, 3 hemorrhages	1 stroke[d], 3 hemorrhages[e]
Incidence, % per year (95 % CI)	0.24 (0.11–0.54)	0.85 (0.32–2.27)	0.41 (0.15–1.08)

CI confidence interval, *NA* not available

[a] Including 9 cases treated by indirect bypass, 1 by direct bypass, and 15 conservatively

[b] Approximated by multiplying the number of samples by mean follow-up period because the person-years were not readily available

[c] All three patients experienced a second hemorrhage

[d] The stroke occurred after a severe head injury and emergent craniotomy

[e] One of the three patients experienced second hemorrhage

bypasses. The controversy might be attributable to a difference in race, surgical procedure, or target disease; their study was conducted in North America and included moyamoya syndrome comprising autoimmune disease, meningitis, brain tumor, Down syndrome, neurofibromatosis type 1, and so on.

Revascularization surgeries are assumed to reduce the hemodynamic burden on moyamoya vessels and thus to prevent hemorrhage in moyamoya disease [23]. Moyamoya vessels and peripheral artery aneurysms can decrease if bypasses are successfully patent [7, 22]. In some cases in our study, however, the moyamoya vessels or microaneurysms in the posterior circulation remained despite the good patency of bypasses, resulting in late hemorrhage (Cases 2 and 4). One possible explanation for this condition is that the bypass flow might be insufficient to reduce the hemodynamic burden to moyamoya vessels, as the bypass flow might depend more on the severity of preoperative ischemia (indicating greater demand for blood flow) than on the development of moyamoya vessels. Another possible reason is, as Goda et al. [7] reported, that the fragile collateral formation from posterior circulation might not fully decrease after revascularization surgery for anterior circulation. The involvement of a steno-occlusive lesion in posterior circulation thus might be a risk factor for late-onset intracranial hemorrhage. Although additional direct or indirect revascularization to posterior cerebral artery might be effective at improving remaining ischemia [9, 11, 17], whether this treatment option can also reduce the risk of future hemorrhage remains unproved. Determining underlying risk factor and treatment for late hemorrhage are an important issue to be addressed.

In the present study, all late hemorrhages occurred in patients aged in their mid- or late-20s after more than 13 years had passed since bypass surgery. This result is coincident with that reported by Mukawa et al. [27], in which late hemorrhage occurred between 8 and 21 years after revascularization surgery. According to the theory that bleeding in adult patients results from long collateral vessel exposure to hemodynamic burden from a young age, the incidence of hemorrhage may be increasing with the duration of the disease. A follow-up period of less than 10 years might result in underestimation of the incidence of late-onset hemorrhage. This might partially explain the fact that some long-term follow-up studies after surgical revascularization detected no late-onset hemorrhage [4, 7, 21]. In cross-sectional studies, the onset age of hemorrhagic-type moyamoya disease is distributed mainly throughout the 30s and 40s [18, 25, 38]. The mean age of hemorrhage onset in our study seemed younger than that revealed in the cross-sectional studies. This might be attributed to longer disease duration in our study population, which includes only patients with juvenile-onset moyamoya disease. Further follow-up might be important because many patients in our study had not yet reached their 30s or 40s (Table 1).

Because the incidence of initial hemorrhage in the natural course of moyamoya disease remains unclear, our study did not strictly answer the question of whether bypass surgery in childhood is effective at preventing future hemorrhage. However, the incidence of hemorrhage revealed in the present study (0.3 % per year) is far lower than that of recurrent hemorrhage in moyamoya disease (7.09 % per year) [18]. Further investigations might be needed to elucidate whether bypass surgery is effective at primary prevention of hemorrhage in moyamoya disease.

Several reports on indirect bypass have illustrated late cerebrovascular events in pediatric patients with moyamoya disease [12, 27]. To our knowledge, however, no previous study of direct bypass has focused on the incidence of late cerebrovascular events except for a very large study including both pediatric and adult patients [8]. Our result suggests that the incidence of such events after direct bypass is comparable to that after indirect bypass because of the overlap of 95 % CIs (Table 3). This speculation is consistent with a recent review showing that direct and indirect bypasses have equivalent long-term effectiveness [6]. Recent studies have reported excellent results of direct bypass for moyamoya disease [8, 21]. Direct comparisons between direct and indirect bypasses may be needed in future studies to determine whether both surgical options exhibit an equivalent incidence of late onset stroke.

Limitations

Our study included two (3.4 %) patients lost to follow-up. Despite the high follow-up rate compared with previous studies, this loss might induce selection bias if it involves serious outcomes.

Although age and sex distributions in the present study were similar to those in large epidemiological studies of moyamoya disease [1, 20, 37], our use of hospital-based sampling might not accurately reflect the population of pediatric patients with moyamoya disease.

Our results revealed normalized rCBF long after bypass surgery, but the number of patients undergoing SPECT is limited. Further investigation of long-term changes in rCBF and angiographical stages is required to determine whether these factors affect late hemorrhage.

Conclusions

The objective of the present study was to estimate the incidence of late cerebrovascular events after direct bypass surgery in pediatric patients with moyamoya disease. The results suggest that such patients remain at risk of a late cerebrovascular event (0.41 % per year) even after revascularization surgery, although the incidence seems quite low compared with the natural history of moyamoya disease. Among late

cerebrovascular events, hemorrhage might be more common than ischemic stroke and should receive more attention. Late hemorrhage might be more likely to occur in patients in their late 20s who had undergone surgery more than 10 years previously, suggesting the importance of careful long-term follow-up.

Acknowledgments We are grateful to Dr. Takeo Nakayama, Professor at the Department of Health Informatics, Kyoto University School of Public Health, for providing statistical advice. We also thank Yuko Tanaka for her efforts at collecting patient records.

Conflicts of interest None.

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Comment

The natural history of patients with moyamoya disease after revascularisation is still not well known. This manuscript deals with 56 children with a mean follow-up interval of 18.1 years; one ischemic stroke and three hemorrhages were observed. One of three hemorrhages was due to rupture of a small aneurysm at the posterior choroidal artery. These four events occurred after 13 years on average after revascuralisation surgery. The reviewer read this report with great interest as he had experience recently of an adult female patient (50 years old) who had suffered a huge hemorrhage in the right temporal lobe and right ventricle around 24 months after revascularisation surgery (bilateral STA-MCA bypass plus one STA-ACA bypass in one stage and patency of all the bypasses were confirmed with DSA). Whether revascularisation surgery prevents future hemorrhagic event or not—and, if yes, to what extent—has to be resolved. Interestingly, the hemorrhages reported in this paper and also in our patient were only in adults, occurring 18 years later and 1 year later respectively.

The mechanism of failure of prevention of hemorrhage that occurred so long after revascularisation surgery in the former case and so shortly after in the latter has also to be solved. Anyway, occurrence of hemorrhage seems to be associated with adulthood irrespective of revascularisation surgery.

By the way, fatal rerupture of the small intraventricular aneurysm of the posterior choroidal artery could have been prevented by its surgical removal, although some papers propose its shrinkage or disappearance by revascularisation.

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