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.

References

1. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol 1969;20:288-299.
2. Hoshino H, Izawa Y, Suzuki N. Epidemiological features of moyamoya disease in Japan. Neurol Med Chir (Tokyo) 2012;52:295-298.
3. Pandey P, Steinberg GK. Neurosurgical advances in the treatment of moyamoya disease. Stroke 2011;42:3304-3310.
4. Liu W, Morito D, Takashima S, et al. Identification of RNF213 as a susceptibility gene for moyamoya disease and its possible role in vascular development. PLoS One 2011;6:e22542.
5. Kamada F, Aoki Y, Narisawa A, et al. A genome-wide association study identifies RNF213 as the first Moyamoya disease gene. J Hum Genet 2011;56:34-40.
6. Araki Y, Yoshikawa K, Okamoto S, et al. Identification of novel biomarker candidates by proteomic analysis of cerebrospinal fluid from patients with moyamoya disease using SELDI-TOF-MS. BMC neurol 2010;10:112.
7. Nakagawara J, Osato T, Kamiyama K, et al. Diagnostic imaging of higher brain dysfunction in patients with adult moyamoya disease using statistical imaging analysis for $^{[123I]}$iomazenil single photon emission computed tomography. Neurol Med Chir (Tokyo) 2012;52:318-326.
8. Sato H, Sato N, Tamaki N, et al. Chronic low-perfusion state in children with moyamoya disease following revascularization. Childs Nerv Syst 1990;6:166-171.
9. Matsushima Y, Aoyagi M, Masaoka H, et al. Mental outcome following encephaloduroarteriosynangiosis in children with moyamoya disease with the onset earlier than 5 years of age. Childs Nerv Syst 1990;6:440-443.
10. Karzmark P, Zeifert PD, Bell-Stephens TE, et al. Neurocognitive impairment in adults with moyamoya disease without stroke. Neurosurgery 2012;70:634-638.
11. Weinberg DG, Rahme RJ, Aoun SG, et al. Moyamoya disease: functional and neurocognitive outcomes in the pediatric and adult populations. Neurosurg Focus 2011; 30:E21.
12. Festa JR, Schwarz LR, Pliskin N, et al. Neurocognitive dysfunction in adult moyamoya disease. J Neurol 2010; 257:806-815.
13. Wechsler D. Wechsler Adult Intelligence Scale-Third Edition. San Antonio: The Psychological Corporation 1997.
14. Wechsler D. Wechsler Memory Scale-Revised. San Antonio: The Psychological Corporation 1987.
15. Dubois B, Slachevsky A, Litvan I, et al. The FAB: a Frontal Assessment Battery at bedside. Neurology 2000; 55:1621-1626.
16. Reitan RM. The Halstead-Reitan Neuropsychological Test Battery. Tucson: Neuropsychology Press 1985.
17. Heaton R, Chelune G, Talley J, et al. Wisconsin Card Sorting Test manual: revised and expanded. Odessa: Psychological Assessment Resources 1993.
18. Chikazoe J, Jimura K, Hirose S, et al. Preparation to inhibit a response complements response inhibition during performance of a stop-signal task. J Neuroscience 2009;29:15870-15877.
19. Baron-Cohen S, Wheelwright S, Hill J, et al. The "Reading the Mind in the Eyes" Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. J Child Psychol Psychiatry 2001;42:241-251.
20. Ohtaki M, Uede T, Morimoto S, et al. Intellectual functions and regional cerebral haemodynamics after extensive omental transplantation spread over both frontal lobes in childhood moyamoya disease. Acta Neurochir (Wien) 1998;140:1043-1053.
21. Mogensen MA, Karzmark P, Zeifert PD, et al. Neuroradiologic correlates of cognitive impairment in adult Moyamoya disease. AJNR Am J Neuroradiol 2012;33:721-725.
22. Karzmark P, Zeifert PD, Tan S, et al. Effect of moyamoya disease on neuropsychological functioning in adults. Neurosurgery 2008;62:1048-1051.
23. Ishii R, Takeuchi S, Ibayashi K, et al. Intelligence in children with moyamoya disease: evaluation after surgical treatments with special reference to changes in cerebral blood flow. Stroke 1984;15:873-877.
24. Imaizumi C, Imaizumi T, Osawa M, et al. Serial intelligence test scores in pediatric moyamoya disease. Neuropediatrics 1999;30:294-299.
25. Kaku Y, Iihara K, Nakajima N, et al. Cerebral blood flow and metabolism of hyperperfusion after cerebral revascularization in patients with moyamoya disease. J Cereb Blood Flow Metab 2012;32:2066-2075.
26. Zakzanis KK, Mraz R, Graham SJ. An fMRI study of the Trail Making Test. Neuropsychologia 2005;43:1878-1886.
27. Hirao K, Miyata J, Fujiwara H, et al. Theory of mind and frontal lobe pathology in schizophrenia: a voxel-based morphometry study. Schizophr Res 2008;105:165-174.
28. Brunet-Gouet E, Decety J. Social brain dysfunctions in schizophrenia: a review of neuroimaging studies. Psychiatry Res 2006;148:75-92.

J Neurosurg Pediatrics 12:626–632, 2013

Impact of posterior cerebral artery involvement on long-term clinical and social outcome of pediatric moyamoya disease

Clinical article

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Object. In the study of pediatric moyamoya disease, information on long-term social outcomes and risk factors for unfavorable social outcomes remains insufficient. The authors analyzed the long-term results of surgical revascularization for pediatric patients with moyamoya disease to determine whether the involvement of a stenoocclusive lesion in the posterior cerebral artery (PCA), relatively common in pediatric moyamoya disease, represents an underlying predictor for unfavorable social outcomes.

Methods. Prospectively collected data on 61 consecutive patients with moyamoya disease who had undergone combined bypass surgery were analyzed. Neuroradiological features and other baseline clinical factors were incorporated into univariate and multivariate analyses to determine any association with an unfavorable social outcome, defined as difficulty attending regular school or obtaining regular employment.

Results. Posterior cerebral artery involvement detected by angiography on admission was noted in 22 (36.1%) of the 61 patients. Follow-up data were acquired in 56 patients (91.8%), and the mean follow-up period was 15.8 years. While transient ischemic attacks were eliminated in 52 (92.9%) of these 56 patients after surgery, and late-onset ischemic stroke was observed in only 1 patient during the follow-up period, 10 (17.9%) experienced an unfavorable social outcome. Although younger age at onset, longer duration between onset and surgery, infarction present on preoperative neuroradiological images, and PCA involvement had been identified as risk factors for an unfavorable social outcome in univariate analysis, only infarction present on preoperative images and PCA involvement remained statistically significant after multivariate adjustment.

Conclusions. Posterior cerebral artery involvement can be considered one of the underlying risk factors for unfavorable social outcome and should be studied further to improve social outcome in pediatric moyamoya disease. *(http://thejns.org/doi/abs/10.3171/2013.9.PEDS13111)*

Key Words • **moyamoya disease** • **cerebral revascularization** • **social prognosis** • **posterior cerebral artery**

Moyamoya disease, characterized by progressive spontaneous occlusion of bilateral internal carotid arteries (ICAs) and development of abnormal collateral vessels, is one of the major causes of stroke in childhood. Surgical revascularization is believed to benefit pediatric patients with moyamoya disease. Such surgery is classified into 3 categories: direct, indirect, and combined bypass. While indirect bypass is more commonly applied to pediatric patients than direct or combined bypass, both types of surgery are equally effective for pediatric patients.[5] Recent studies have reported favorable long-term results for both direct and indirect bypasses in terms of preventing strokes or transient ischemic attacks.[3,6,13,16,18,25,31,32,36] However, social outcomes vary in terms of education and employment at adulthood, and a substantial portion of the patients suffer from social adaptation difficulties even after surgery.[27,29] Although reports associate several factors with unfavorable social or functional outcomes,[10,13,14,17,29] studies addressing this issue are lacking.

Involvement of a stenoocclusive lesion in the posterior circulation, especially in the posterior cerebral artery (PCA), is a relatively specific finding in juvenile-onset

Abbreviations used in this paper: ACA = anterior cerebral artery; EMS = encephalomyosynangiosis; ICA = internal carotid artery; MCA = middle cerebral artery; mRS = modified Rankin Scale; PCA = posterior cerebral artery; STA = superficial temporal artery.

moyamoya disease.[19] The PCA usually provides much collateral flow to the anterior circulation in moyamoya disease, and recent studies revealed a higher prevalence of ischemic and hemorrhagic stroke in patients with such PCA involvement.[7,22] However, any association between long-term outcomes and PCA involvement in moyamoya disease has not yet been closely examined.

We hypothesized that PCA involvement in pediatric moyamoya disease represents an underlying factor for poor social outcome. To test this hypothesis, we analyzed long-term follow-up data on consecutive patients who had survived at least 10 years after undergoing combined bypass surgery in childhood. Combined bypass surgery is superficial temporal artery (STA) to middle cerebral artery (MCA) anastomosis with encephalomyosynangiosis (EMS) Since the 1980s, our group has consistently adopted combined bypass as the first-choice treatment for pediatric patients with moyamoya disease.[12,13] This was, to the best of our knowledge, the longest follow-up study among the previous reports on direct or combined bypass for pediatric moyamoya disease.[3,6,11,13,16]

Methods

Patient Population

Between 1984 and 2003, the senior author (S.M.) performed combined bypass surgery on 61 pediatric patients with moyamoya disease at Kyoto University Hospital in Kyoto, Japan, and its satellite hospital. The senior author created a personal database by collecting data on these consecutive cases including patient identification number, age at admission, sex, age at symptom onset, primary clinical manifestations at onset, clinical condition at admission (translated later into the modified Rankin scale [mRS] score with age-specific modification[2,37]), date and procedure of surgery, and angiographic findings upon each patient's first or second admission. These patients were followed prospectively at our hospital. This study was approved by the ethics committee of the Kyoto University Graduate School of Medicine.

Diagnosis and Radiological Assessment

Moyamoya disease was diagnosed in the patients according to criteria proposed by the Research Committee on Moyamoya Disease in Japan.[4,28,34] The diagnoses were confirmed by cerebral angiography in all cases. Children with a typical occlusive finding in the unilateral ICA alone were also considered to have moyamoya disease.[30] Children with autoimmune disease, meningitis, brain tumor, Down syndrome, neurofibromatosis Type 1, or a history of head irradiation were excluded from the present study.

For all patients, we recorded the presence and distribution of infarction before surgery as revealed through CT in early cases or MRI. The hemisphere in which infarctions was dominantly distributed and the presence of bilateral infarctions were also recorded. In cases in which either the original CT scans or MR images were preserved, one of the authors (T.F.) quantitatively assessed the size of infarction on preoperative images in which the patient name was hidden. The area of infarction was measured with Adobe Photoshop software through manual tracing of the lesion on the image slice with the maximum lesion size. If the targeted slice contained more than 2 lesions, the total area of all visible lesions was calculated.

Findings of all angiograms, which had first been reviewed by the senior author on patient admission, were checked again by a coauthor (K.Y.) who was blinded to all clinical information. Unilateral lesion of the ICA was defined as unilateral stenosis or occlusion of the terminal portion of the ICA with the formation of moyamoya vessels accompanied by no or a subtle lesion around the contralateral terminal portion of the ICA. The severity of disease progression in the ICA was evaluated with a 4-stage system,[24] with a higher ICA stage representing more advanced stenoocclusive lesions in the anterior circulation. If the two hemispheres were classified as different ICA stages, the higher stage was recorded. Involvement of the PCA was defined as the presence of occlusion or stenosis greater than 50% in the P_1 to P_3 segment of either PCA (Fig. 1).

Treatment Protocol

Surgical revascularization was indicated for patients with cerebral ischemic manifestations. Single photon emission computed tomography (SPECT) was performed in all but the first few cases to detect hemodynamic impairment, which was considered an indicator suggesting surgical revascularization. All patients underwent direct or combined bypass consisting of STA-MCA anastomosis with or without EMS in each MCA territory as a first-line treatment. Encephalomyosynangiosis, an indirect bypass procedure using the pedicle flap of the temporalis muscle, was usually combined with STA-MCA anastomosis for patients under 10 years of age. All surgeries were performed by the senior author (S.M.). Previously published studies detail the surgical procedure.[13] Briefly, a horseshoe-shaped scalp incision is made surrounding the parietal branch of the STA, and the temporalis muscle is dissected along the horseshoe incision to make the pedicle flap. The dura is widely opened, preserving the main branch of the meningeal arteries. After a conventional

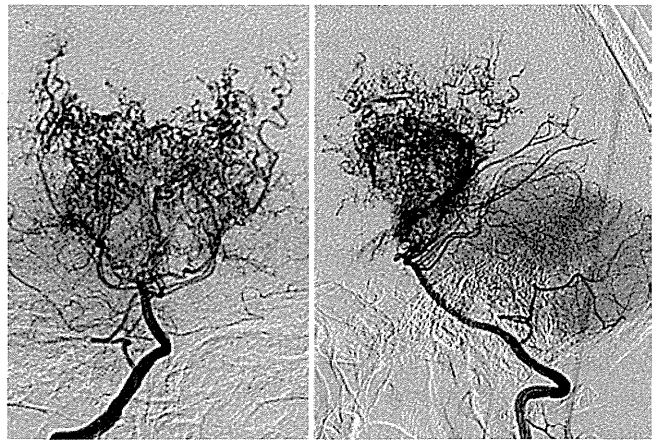

Fig. 1. Anteroposterior **(left)** and lateral **(right)** views of a vertebral artery angiogram revealing heavy involvement of bilateral PCAs characterized by occlusion at the P_3 segment and extensive development of collateral moyamoya vessels.

procedure of STA-MCA single anastomosis, the pedicle flap of the temporalis muscle is placed over the brain surface and sutured to the edge of the remaining dura.

For patients with bilateral ICA involvement, the more symptomatic or hemodynamically impaired side is revascularized first. The second revascularization for the contralateral MCA territory is performed at least 1 month after the first revascularization. To assess bypass patency and improvement of cerebral blood flow, angiography and SPECT were performed 3 months after the second revascularization. In most cases these bypasses widely covered the brain surface beyond the MCA territory.[21] If SPECT reveals insufficient hemodynamic improvement in the anterior or posterior cerebral artery territories, additional direct revascularizations are considered to the territories of the anterior cerebral artery (ACA) or PCA using the frontal branch of the STA or occipital artery.

Follow-Up Data Collection

All follow-up data were acquired through a medical interview and neurological examination at the outpatient neurosurgical clinic. The data obtained at the last visit were used for analysis. Transient ischemic attacks were classified into 4 categories by frequency: eliminated, rare (several times per year), frequent (several times per month or per week), or exacerbated after surgery. The mRS score for each patient was recorded. Late-onset stroke was defined as ischemic stroke or intracranial hemorrhage occurring more than 30 days after surgery, causing certain neurological symptoms, and identified by neuroradiological modalities.

The patients were interviewed about educational background, employment history, and current occupation. Educational background was assessed in all patients and classified by type of school: regular class at ordinary school, special class, or school for the disabled. Employment was assessed in all patients except homemakers and those currently enrolled as students. An unfavorable social outcome was defined as patient difficulty in either attending regular classes or obtaining regular employment.

Statistical Analysis

To compare baseline characteristics, a t-test, the Wilcoxon rank-sum test, or the Fisher exact test was used as appropriate. The mRS scores at the last follow-up evaluation and those at first admission were compared by means of the Wilcoxon signed-rank test. Variables including sex, age of onset, time interval between onset and first bypass surgery, presence of infarction in the preoperative image, infarction area, side of infarction, bilateral infarction, unilateral ICA lesion, ICA stage, involvement of the PCA, and late-onset stroke were incorporated into univariate analysis to identify factors associated with an unfavorable social outcome. The Fisher exact test and logistic regression analysis were used for univariate analysis. Variables with a p value < 0.1 on univariate analyses were selected for further multivariate analysis. The ICA stage was incorporated into multivariate analysis regardless of its p value in univariate analysis in light of the likelihood of correlation between ICA stage and PCA involvement.[24] Variables including missing data were not incorporated into multivariate analysis. Multiple logistic regression analysis was used for multivariate analysis. Two-sided p values < 0.05 were considered statistically significant. All statistical analyses were performed with JMP software (version 9, SAS Institute Inc.).

Results

Patient Background

Table 1 summarizes patient backgrounds before surgery. The female-to-male ratio was 1.3 to 1, and the median age at onset was 6 years (mean 6.5 years, range 0–15 years). No patient experienced intracranial hemorrhage at disease onset. At the time of first admission, 47 patients (77.0%) had an mRS score of 0, 6 (9.8%) a score of 1, 6 (9.8%) a score of 2, and 2 (3.3%) a score of 3. Involvement of the PCA was detected in 22 patients (36.1%).

Infarction, assessed preoperatively with CT in 25 patients (41.0%) and with MRI in 36 patients (59.0%), was detected in 34 patients (55.7%). At the time of retrospective assessment of the infarction area, the original image was not available in 8 of the 61 patients because of the expiration of the film storage period. The median and mean areas of preoperative infarction measured in the remaining cases were 6.4 mm^2 and 206.1 mm^2, respectively (range 0–1652.9 mm^2).

Surgery

A total of 119 surgeries were performed for 61 patients. Table 2 summarizes the number of revascularization surgeries. All patients underwent at least 1 STA-MCA anastomosis. Forty-three patients (76.8%) underwent bypass surgeries twice, while 5 (8.2%) underwent additional revascularization to the ACA or PCA territory. One patient experienced a small infarction in the temporooccipital region immediately after STA-MCA anastomosis, resulting in transient disorientation but no permanent deficit. The patency of the bypasses was confirmed in all cases by means of postoperative angiography.

Follow-Up

The mean follow-up period (± SD) was 15.8 ± 7.0 years, and the mean age at last follow-up was 24.0 ± 6.8 years. Follow-up information was not available in 5 patients (8.2%): 2 were followed up by institutes outside Japan, and 3 were lost to follow-up when their attendant doctors in the outpatient clinic were transferred after surgery. The remaining 56 patients for whom follow-up data were acquired were assessed for further analysis. Baseline characteristics were not statistically different between patients with and without follow-up data (Table 1).

Outcome

Transient ischemic attacks were eliminated in 52 cases (92.9%) and rare in 4 (7.1%) during the follow-up period. Late-onset ischemic or hemorrhagic stroke occurred in 4 patients (7.1%). One patient suffered from acute subdural hematoma due to a traffic accident 33 months af-

TABLE 1: Comparison of baseline characteristics of groups with and without follow-up data

Variable	Total	Followed Up	Lost to Follow-Up	p Value
no. of patients	61	56	5	NA
females (%)	35 (57.4)	33 (58.9)	2 (40.0)	0.642
mean age of admission in yrs ± SD	8.6 ± 3.7	8.7 ± 3.7	7.8 ± 3.1	0.596
mean age of onset in yrs ± SD	6.5 ± 3.5	6.6 ± 0.5	5.8 ± 1.5	0.629
median delay in yrs until surgery (IQR)	1 (0–3)	1 (0–3)	1 (0.5–4)	0.756
infarction on preop image (%)	34 (55.7)	32 (57.1)	2 (40.0)	0.647
median area in mm^2 (IQR)*	6.4 (0–156.0)	7.6 (0–167.9)	0 (0–128.5)	0.351
lt hemisphere infarction (%)	29 (47.5)	26 (46.4)	3 (60.0)	0.662
bilat infarction (%)	6 (9.8)	5 (8.9)	1 (20.0)	0.415
unilat ICA lesion (%)	6 (9.8)	6 (10.7)	0	1.000
ICA stage (%)				
I	7 (11.5)	6 (10.7)	1 (20.0)	
II	29 (47.5)	27 (48.2)	2 (40.0)	
III	23 (37.7)	21 (37.5)	2 (40.0)	
IV	2 (3.3)	2 (3.6)	0	
≥III	25 (41.0)	23 (41.1)	2 (40.0)	1.000
PCA involvement	22 (36.1)	21 (37.5)	1 (20.0)	0.645

* Data on the infarction area were not available in 8 of the 61 patients. IQR = interquartile range; NA = not applicable.

ter STA-MCA anastomosis, which resulted in ischemic stroke in the affected hemisphere. Three patients suffered from intracranial hemorrhage at the mean age of 26 years (range 24–29 years). One patient experienced a second hemorrhage, which resulted in a fatal outcome. The overall incidence of late-onset stroke was not significantly associated with an unfavorable social outcome (Table 3). At the time of the last follow-up, 40 patients (71.4%) had an mRS score of 0, 5 (8.9%) a score of 1, 8 (14.3%) a score of 2, 2 (3.6%) a score of 3, and 1 (1.8%) a score of 6. Among the patients with follow-up, no significant difference in mRS scores was evident between first admission and last follow-up ($p = 0.182$).

Seven (18.9%) of 37 patients who were not currently students or homemakers encountered difficulty in obtaining regular employment. Six patients (10.7%) currently or previously attended special classes or a school for the disabled. In summary, 10 (17.9%) of 56 patients had an unfavorable social outcome: 4 had difficulty obtaining regular employment, 3 had difficulty attending regular classes, and 3 had both difficulties. Univariate analysis revealed that younger age at onset, longer delay between onset and surgery, infarction present on the preoperative image, and PCA involvement were significantly associated with an unfavorable outcome (Table 3). The area of infarction was also significantly larger in patients with an unfavorable outcome than in those with a favorable outcome, although the infarction area could not be measured in 7 of the patients with follow-up because original images were no longer available. Advanced ICA lesion (Stage III or IV), unilateral ICA lesion, left hemisphere infarction, and bilateral distribution of infarction were not significantly associated with outcome.

Variables including the age of onset, delay between onset and surgery, infarction present in the preoperative image, ICA stage, and PCA involvement were incorporated into a further multivariate analysis (Table 4). In this analysis, only infarction present on the preoperative image (OR 9.96, 95% CI 1.08–355.82) and PCA involvement (OR 7.44, 95% CI 1.22–67.79) were identified as significant factors associated with an unfavorable social outcome. The frequency of an unfavorable social outcome was stratified by PCA involvement and delay between onset and surgery to estimate the impact of the combination of these factors on social outcome. The frequency of an unfavorable social outcome reached 50% when PCA involvement and a surgical delay exceeding 3 years were combined, while that in patients with neither risk factor was 0% (Table 5).

TABLE 2: Number of revascularization surgeries by type*

Mode of Revascularization Surgery	No. of Surgeries
STA-MCA anastomosis w/ EMS	97
STA-MCA anastomosis w/o EMS	13
STA-ACA bypass	2
OA-PCA bypass	1
other	6

* OA = occipital artery.

Discussion

Despite the favorable long-term outcomes overall, our results reveal that 17.9% of pediatric patients with moyamoya disease continued to suffer from social adaptation difficulties as they matured, even after bypass surgery. The results also suggest that PCA involvement and presence of infarction on preoperative images are independently associated with an unfavorable social outcome.

TABLE 3: Univariate analyses for factors associated with long-term social outcome in all patients with follow-up*

Variable	Favorable Outcome (n = 46)	Unfavorable Outcome (n = 10)	p Value
female	26 (56.5)	7 (70.0)	0.500
mean age of onset in yrs ± SD	7.1 ± 3.6	4.1 ± 1.8	0.021
median delay until surgery in yrs (IQR)	1 (0–2)	3 (1.5–9.25)	0.015
infarction on preop image	23 (50.0)	9 (90.0)	0.021
median area in mm^2 (IQR)†	0 (0–67.9)	370.1 (58.8–1220.5)	0.028
lt hemisphere infarction	20 (43.5)	6 (60.0)	0.487
bilat infarction	3 (6.5)	2 (20.0)	0.214
unilat ICA lesion	6 (13.0)	0 (0)	0.578
ICA stage ≥3	17 (37.0)	6 (60.0)	0.288
PCA involvement	13 (28.3)	8 (80.0)	0.004
overall late-onset stroke	2 (4.4)	2 (20.0)	0.142

* All data given as number of patients (%) unless otherwise indicated.
† Data regarding the infarction area were not available in 7 of the 56 patients with follow-up.

Our results indicating that more than 80% of patients had a favorable social outcome appear comparable to those of past studies, in which the frequency of patients with a normal intelligence quotient or capable of independent daily activities remained 63.5%–87%.[13,17,25,31] Nevertheless, our results, along with those of several pioneering studies, shed light on the salient issue of social adaptation in pediatric moyamoya disease. Nakashima et al. reported that approximately 10% of patients had severe difficulty in social or school life because of intellectual impairment.[27] While Phi et al. reported good long-term social outcomes in terms of education and employment, their results also revealed that a certain proportion of patients had difficulty planning their marriages and acquiring driver's licenses, and that approximately 20% of the respondents were dissatisfied with their treatment outcomes.[29]

Several factors, including preoperative neurological impairment,[10,17,29] infarction,[13,14] age of symptom onset,[10,13] and duration after onset,[9] have been reported as affecting social or functional outcomes. Our result in univariate analysis is consistent with these reports. In addition, our result in multivariate analysis suggests that PCA involvement, which has so far received less attention in long-term follow-up studies, is also an independent risk factor for unfavorable social outcomes. Involvement of the PCA is more likely to occur in younger children[19,22] and thus may act as a potential confounder affecting social outcome in the previous studies. Although several studies reported that PCA involvement is associated with a high prevalence of preexisting infarction at diagnosis,[22,23] our results from the multivariate analysis suggest that both the preexisting infarction and PCA involvement are independently associated with an unfavorable social outcome.

We speculate on several possible reasons why PCA involvement is associated with unfavorable social outcomes. Involvement of the PCA may more accurately represent the overall progression of a stenoocclusive lesion in pediatric moyamoya disease.[20,23] The other possible explanation is that PCA involvement may cause further reduction in cerebral blood flow because the PCA usually provides important collateral flow to the affected anterior circulation via leptomeningeal anastomosis in patients with moyamoya disease. In particular, a pair of posterior pericallosal arteries, branches of the PCA, is well developed in moyamoya disease as a collateral pathway to the medial frontal cortex. The medial frontal cortex involves various executive, emotional, and behavioral functions,[33] and decreased cerebral blood flow in this area may impede social adaptation abilities even with minimal infarct. Interestingly, Nakagawara et al. speculated that long-standing mild hemodynamic ischemia in the medial frontal lobe could lead to selective neuron loss detected by SPECT imaging with benzodiazepine receptor radioligand, and cognitive dysfunction in patients with moyamoya disease.[26]

Our study has some limitations. First, the result of our multivariate analysis has a relatively large confidence interval, which can be attributed to the limited number of cases. However, the baseline characteristics of this study,

TABLE 4: Multivariate analyses for factors associated with unfavorable long-term social outcome in all patients with follow-up

Variable	p Value	Adjusted OR (95% CI) for Unfavorable Social Outcome
mean age of onset	0.122	0.80 (0.58–1.06) for every yr
median delay until surgery	0.118	1.32 (0.94–2.03) for every yr
infarction on preop image	0.042	9.96 (1.08–355.82)
ICA stage ≥3	0.704	0.67 (0.07–5.11)
PCA involvement	0.029	7.44 (1.22–67.79)

TABLE 5: Frequency of unfavorable social outcomes stratified by PCA involvement and delay until bypass surgery

Length of Delay (yrs)	Without PCA Involvement	With PCA Involvement
<3	0	30.8%
≥3	28.5%	50.0%

such as peak age of onset and female-to-male ratio, were similar to those in previous large epidemiology studies.[1,15,38] Our sample thus can be considered reflective of the general population of pediatric patients with moyamoya disease. Second, our analysis did not include 8.2% of patients because of loss of follow-up, which could cause a certain bias if the trends of these patients differed significantly from those of the analyzed patients. Given that the baseline characteristics did not differ statistically between patients with and without follow-up data, however, such bias is likely minimal. Third, whether our results can be generalized to patients treated with an indirect bypass, such as encephaloduroarteriosynangiosis, is debatable. Generalization of our results may be partially allowed because recent reviews show that direct and indirect bypasses are equally effective over the long term.[5,30,35]

Viewed from a practical perspective, early revascularization may be required for patients with PCA involvement because the risk of an unfavorable social outcome markedly increases with the combination of PCA involvement and a delay in surgical treatment (Table 5). An aggressive revascularization strategy to the PCA or even ACA territory can also be proposed for patients with PCA involvement. A more recent study revealed that a stenoocclusive lesion of the PCA could progress even after surgery and reduce cerebral blood flow.[8] Careful follow-up is needed to minimize an unfavorable social outcome after bypass surgery of pediatric moyamoya disease.

Conclusions

The results of the present study support the hypothesis that the involvement of a stenoocclusive lesion in the PCA is one of the possible risk factors for an unfavorable social outcome from pediatric moyamoya disease. The finding of PCA involvement in pediatric moyamoya disease should receive more attention to ensure further improvement in social outcomes at adulthood.

Acknowledgment

We appreciate the efforts of Yuko Tanaka in collecting patient records.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Funaki. Acquisition of data: Funaki. Analysis and interpretation of data: Funaki. Drafting the article: Funaki. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Funaki. Statistical analysis: Funaki.

References

1. Baba T, Houkin K, Kuroda S: Novel epidemiological features of moyamoya disease. **J Neurol Neurosurg Psychiatry 79:** 900–904, 2008
2. Bigi S, Fischer U, Wehrli E, Mattle HP, Boltshauser E, Bürki S, et al: Acute ischemic stroke in children versus young adults. **Ann Neurol 70:**245–254, 2011
3. Czabanka M, Peña-Tapia P, Scharf J, Schubert GA, Münch E, Horn P, et al: Characterization of direct and indirect cerebral revascularization for the treatment of European patients with moyamoya disease. **Cerebrovasc Dis 32:**361–369, 2011
4. Fukui M: Guidelines for the diagnosis and treatment of spontaneous occlusion of the circle of Willis ('moyamoya' disease). Research Committee on Spontaneous Occlusion of the Circle of Willis (Moyamoya Disease) of the Ministry of Health and Welfare, Japan. **Clin Neurol Neurosurg 99 (2 Suppl 2):**S238–S240, 1997
5. Fung LW, Thompson D, Ganesan V: Revascularisation surgery for paediatric moyamoya: a review of the literature. **Childs Nerv Syst 21:**358–364, 2005
6. Guzman R, Lee M, Achrol A, Bell-Stephens T, Kelly M, Do HM, et al: Clinical outcome after 450 revascularization procedures for moyamoya disease. Clinical article. **J Neurosurg 111:**927–935, 2009
7. Hishikawa T, Tokunaga K, Sugiu K, Date I: Clinical and radiographic features of moyamoya disease in patients with both cerebral ischaemia and haemorrhage. **Br J Neurosurg 27:** 198–201, 2012
8. Huang AP, Liu HM, Lai DM, Yang CC, Tsai YH, Wang KC, et al: Clinical significance of posterior circulation changes after revascularization in patients with moyamoya disease. **Cerebrovasc Dis 28:**247–257, 2009
9. Imaizumi C, Imaizumi T, Osawa M, Fukuyama Y, Takeshita M: Serial intelligence test scores in pediatric moyamoya disease. **Neuropediatrics 30:**294–299, 1999
10. Imaizumi T, Hayashi K, Saito K, Osawa M, Fukuyama Y: Long-term outcomes of pediatric moyamoya disease monitored to adulthood. **Pediatr Neurol 18:**321–325, 1998
11. Ishikawa T, Houkin K, Kamiyama H, Abe H: Effects of surgical revascularization on outcome of patients with pediatric moyamoya disease. **Stroke 28:**1170–1173, 1997
12. Karasawa J, Kikuchi H, Furuse S, Kawamura J, Sakaki T: Treatment of moyamoya disease with STA-MCA anastomosis. **J Neurosurg 49:**679–688, 1978
13. Karasawa J, Touho H, Ohnishi H, Miyamoto S, Kikuchi H: Long-term follow-up study after extracranial-intracranial bypass surgery for anterior circulation ischemia in childhood moyamoya disease. **J Neurosurg 77:**84–89, 1992
14. Kim SK, Seol HJ, Cho BK, Hwang YS, Lee DS, Wang KC: Moyamoya disease among young patients: its aggressive clinical course and the role of active surgical treatment. **Neurosurgery 54:**840–846, 2004
15. Kuriyama S, Kusaka Y, Fujimura M, Wakai K, Tamakoshi A, Hashimoto S, et al: Prevalence and clinicoepidemiological features of moyamoya disease in Japan: findings from a nationwide epidemiological survey. **Stroke 39:**42–47, 2008
16. Kuroda S, Houkin K, Ishikawa T, Nakayama N, Iwasaki Y: Novel bypass surgery for moyamoya disease using pericranial flap: its impacts on cerebral hemodynamics and long-term outcome. **Neurosurgery 66:**1093–1101, 2010
17. Matsushima Y, Aoyagi M, Nariai T, Takada Y, Hirakawa K: Long-term intelligence outcome of post-encephalo-duro-arterio-synangiosis childhood moyamoya patients. **Clin Neurol Neurosurg 99 (2 Suppl 2):**S147–S150, 1997
18. Miyamoto S, Akiyama Y, Nagata I, Karasawa J, Nozaki K, Hashimoto N, et al: Long-term outcome after STA-MCA anastomosis for moyamoya disease. **Neurosurg Focus 5(5):**E7, 1998
19. Miyamoto S, Kikuchi H, Karasawa J, Nagata I, Ihara I, Yamagata S: Study of the posterior circulation in moyamoya disease. Part 2: Visual disturbances and surgical treatment. **J Neurosurg 65:**454–460, 1986
20. Miyamoto S, Kikuchi H, Karasawa J, Nagata I, Ikota T, Takeuchi S: Study of the posterior circulation in moyamoya disease. Clinical and neuroradiological evaluation. **J Neurosurg 61:**1032–1037, 1984

21. Miyamoto S, Nagata I, Hashimoto N, Kikuchi H: Direct anastomotic bypass for cerebrovascular moyamoya disease. **Neurol Med Chir (Tokyo) 38 Suppl:**294–296, 1998
22. Mugikura S, Higano S, Shirane R, Fujimura M, Shimanuki Y, Takahashi S: Posterior circulation and high prevalence of ischemic stroke among young pediatric patients with Moyamoya disease: evidence of angiography-based differences by age at diagnosis. **AJNR Am J Neuroradiol 32:**192–198, 2011
23. Mugikura S, Takahashi S, Higano S, Shirane R, Kurihara N, Furuta S, et al: The relationship between cerebral infarction and angiographic characteristics in childhood moyamoya disease. **AJNR Am J Neuroradiol 20:**336–343, 1999
24. Mugikura S, Takahashi S, Higano S, Shirane R, Sakurai Y, Yamada S: Predominant involvement of ipsilateral anterior and posterior circulations in moyamoya disease. **Stroke 33:** 1497–1500, 2002
25. Mukawa M, Nariai T, Matsushima Y, Tanaka Y, Inaji M, Maehara T, et al: Long-term follow-up of surgically treated juvenile patients with Moyamoya disease. Clinical article. **J Neurosurg Pediatr 10:**451–456, 2012
26. Nakagawara J, Osato T, Kamiyama K, Honjo K, Sugio H, Fumoto K, et al: Diagnostic imaging of higher brain dysfunction in patients with adult moyamoya disease using statistical imaging analysis for [123I]iomazenil single photon emission computed tomography. **Neurol Med Chir (Tokyo) 52:**318–326, 2012
27. Nakashima H, Meguro T, Kawada S, Hirotsune N, Ohmoto T: Long-term results of surgically treated moyamoya disease. **Clin Neurol Neurosurg 99 (2 Suppl 2):**S156–S161, 1997
28. Nishimoto A, Takeuchi S: Abnormal cerebrovascular network related to the internal cartoid arteries. **J Neurosurg 29:**255–260, 1968
29. Phi JH, Wang KC, Cho BK, Lee MS, Lee JH, Yu KS, et al: Long-term social outcome in children with moyamoya disease who have reached adulthood. Clinical article. **J Neurosurg Pediatr 8:**303–309, 2011
30. Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis, Health Labour Sciences Research Grant for Research on Measures for Infractable Diseases: Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). **Neurol Med Chir (Tokyo) 52:**245–266, 2012
31. Scott RM, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA: Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. **J Neurosurg 100 (2 Suppl Pediatrics):**142–149, 2004
32. Starke RM, Komotar RJ, Hickman ZL, Paz YE, Pugliese AG, Otten ML, et al: Clinical features, surgical treatment, and long-term outcome in adult patients with moyamoya disease. Clinical article. **J Neurosurg 111:**936–942, 2009
33. Stuss DT: Functions of the frontal lobes: relation to executive functions. **J Int Neuropsychol Soc 17:**759–765, 2011
34. Suzuki J, Takaku A: Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. **Arch Neurol 20:**288–299, 1969
35. Takahashi JC, Miyamoto S: Moyamoya disease: recent progress and outlook. **Neurol Med Chir (Tokyo) 50:**824–832, 2010
36. Ulrich PT, Januschek E: Revascularisation surgery and long-term follow-up in juvenile Moyamoya syndrome: a retrospective analysis. **Acta Neurochir Suppl 112:**39–43, 2011
37. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J: Interobserver agreement for the assessment of handicap in stroke patients. **Stroke 19:**604–607, 1988
38. Wakai K, Tamakoshi A, Ikezaki K, Fukui M, Kawamura T, Aoki R, et al: Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. **Clin Neurol Neurosurg 99 (2 Suppl 2):**S1–S5, 1997

Manuscript submitted March 7, 2013.
Accepted September 10, 2013.
Please include this information when citing this paper: published online October 18, 2013; DOI: 10.3171/2013.9.PEDS13111.

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JNS

CLINICAL ARTICLE

J Neurosurg 122:400–407, 2015

Unstable moyamoya disease: clinical features and impact on perioperative ischemic complications

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OBJECT Unstable moyamoya disease, reasonably defined as cases exhibiting either rapid disease progression or repeated ischemic stroke, represents a challenge in the treatment of moyamoya disease. Despite its overall efficacy, direct bypass for such unstable disease remains controversial in terms of safety. This study aims to reveal factors associated with unstable disease and to assess its impact on postoperative silent or symptomatic ischemic lesions.

METHODS This retrospective cohort study included both pediatric and adult patients with moyamoya disease who had undergone 140 consecutive direct bypass procedures at Kyoto University Hospital. "Unstable moyamoya disease" was defined as either the rapid progression of a steno-occlusive lesion or repeat ischemic stroke, either occurring within 6 months of surgery. The extent of progression was determined through a comparison of the findings between 2 different MR angiography sessions performed before surgery. The clinical variables of the stable and unstable disease groups were compared, and the association between unstable disease and postoperative diffusion-weighted imaging (DWI)–detected lesion was assessed through univariate and multivariate analyses with generalized estimating equations.

RESULTS Of 134 direct bypass procedures performed after patients had undergone at least 2 sessions of MR angiography, 24 (17.9%) were classified as cases of unstable disease. Age younger than 3 years ($p = 0.029$), underlying disease causing moyamoya syndrome ($p = 0.049$), and radiographic evidence of infarction ($p = 0.030$) were identified as factors associated with unstable disease. Postoperative DWI-defined lesions were detected after 13 of 140 procedures (9.3%), although only 4 lesions (2.9%) could be classified as a permanent complication. The incidence of postoperative DWI-detected lesions in the unstable group was notable at 33.3% (8 of 24). Univariate analysis revealed that unstable disease ($p < 0.001$), underlying disease ($p = 0.028$), and recent stroke ($p = 0.012$) were factors associated with DWI-detected lesions. Unstable disease remained statistically significant after adjustment for covariates in both the primary and sensitivity analyses (primary analysis: OR 6.62 [95% CI 1.79–24.5]; sensitivity analysis: OR 5.36 [95% CI 1.47–19.6]).

CONCLUSIONS Unstable moyamoya disease, more prevalent in younger patients and those with underlying disease, is a possible risk factor for perioperative ischemic complications. Recognition of unstable moyamoya disease may contribute to an improved surgical result through focused perioperative management based on appropriate surgical risk stratification.

http://thejns.org/doi/abs/10.3171/2014.10.JNS14231

KEY WORDS moyamoya disease; rapid progression; cerebral revascularization; intraoperative complication; vascular disorders

A major characteristic of moyamoya disease is the chronic progression of stenosis in the terminal portion of the internal carotid artery (ICA).[24] The rate of this progression varies by patient. Angiographic progression can occur in one-half of pediatric patients and one-quarter of adult patients,[19,21] while angiographic findings in the remaining patients are stable for years. Some patients demonstrate extremely rapid progression from disease onset, resulting in poor outcome.[4,17,18] Fujiwara et al. and Kim et al. reported similar cases in which rapid an-

ABBREVIATIONS ACA = anterior cerebral artery; DWI = diffusion-weighted imaging; GEE = generalized estimating equation; ICA = internal carotid artery; MCA = middle cerebral artery; MRA = MR angiography; mRS = modified Rankin Scale; PCA = posterior cerebral artery; STA = superficial temporal artery; TIA = transient ischemic attack.

SUBMITTED January 31, 2014. **ACCEPTED** October 21, 2014.

INCLUDE WHEN CITING Published online November 28, 2014; DOI: 10.3171/2014.10.JNS14231.

DISCLOSURE The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

giographic progression resulted in fatal outcome.[4,18] Kim et al. reported that younger patients were more likely to suffer from an aggressive clinical course, of whom a substantial number experienced repeat stroke.[17]

While the impact of such unstable disease on clinical outcome is receiving more focused attention, few studies have attempted to clearly define this condition. Accurate risk stratification in moyamoya disease requires objective definition of disease instability. According to the articles mentioned above,[4,17,18] disease progression and repeat stroke are considered essential factors reflecting instability of moyamoya disease. The concept of unstable moyamoya disease defined as either rapid disease progression or repeat stroke seems reasonable, considering that unstable angina pectoris, the concept representing instability of angina pectoris, is also characterized as an exacerbating or recurrent symptom with rapid progression of stenosis in the coronary artery.[1,23,27]

Treatment of unstable moyamoya disease is challenging because patients with the disease commonly develop stroke during the perioperative period or even while awaiting surgery.[7,17] Direct bypass, such as superficial temporal artery–to–middle cerebral artery (STA-MCA) bypass, has the advantage of contributing to increased cerebral blood flow soon after surgery.[10] The safety and efficacy of direct bypass for unstable disease are, however, controversial.[7,17]

This retrospective cohort study had 2 objectives: to detect clinical factors associated with unstable moyamoya disease and to determine whether the presence of such instability is associated with postoperative silent or symptomatic ischemic lesions detected on diffusion-weighted imaging (DWI).

Methods

This study was approved by the ethics committee of the Kyoto University Graduate School of Medicine.

Selection Criteria

A total of 88 pediatric and adult patients with moyamoya disease underwent 148 revascularization surgeries at Kyoto University Hospital between 2009 and 2013. The inclusion criteria for the present study were as follows: diagnosis of moyamoya disease or moyamoya syndrome; patients who underwent direct revascularization at Kyoto University Hospital in 2009 or thereafter; and patients who underwent routine postoperative DWI no longer than 14 days after surgery.

Diagnoses were made according to the criteria proposed by the Research Committee on Moyamoya Disease in Japan.[24] "Moyamoya syndrome" is defined as a secondary moyamoya phenomenon caused by an underlying disease such as an autoimmune disease, meningitis, brain tumor, hyperthyroidism, Down syndrome, neurofibromatosis Type 1, or a history of head irradiation.[24] The present study also included unilateral disease in which only 1 side of the ICA was involved. "Direct bypass" was defined as a direct anastomotic procedure including STA-MCA, STA–anterior cerebral artery (ACA), and occipital artery–posterior cerebral artery (PCA) bypasses.

Of the 148 consecutive revascularization procedures, 3 were excluded because they involved only indirect bypass in the ACA territory. Although postoperative MRI with DWI was mandatory in our treatment protocol, postoperative DWI was not performed after 5 procedures (these cases were excluded from the study) because a postoperative MRI scan was performed but no DWI was acquired (4 procedures), and because no MRI was performed since the patient sought early discharge (1 procedure). None of these 5 patients presented with a new neurological deficit after surgery. Consequently, 140 procedures conducted in 86 patients were included in the present study (Fig. 1).

Variables

Unstable moyamoya disease, a primary variable of interest, was defined as a condition with evidence of either rapid stenosis progression or repeated stroke. "Rapid stenosis progression" was defined as progression of a steno-occlusive lesion in an ICA, ACA, MCA, or PCA that had occurred within 6 months (Fig. 2). Whether the progression had occurred was determined using an MR angiography (MRA) scoring system,[8] and the scores were compared between 2 different sessions performed before surgery. Almost all patients referred to our institution had already undergone MRA, the results of which could be used as control imaging. If only 1 imaging session had been performed before surgery, or if the interval between the 2 sessions was less than 2 weeks, the data were eliminated from further analysis. Decreased antegrade flow due to bypass in the ipsilateral MCA territory was not regarded as stenosis progression. "Repeat stroke" was defined as newly developed symptomatic infarctions confirmed on DWI and occurring at least twice during an interval not exceeding 6 months.

The other variables possibly affecting surgical outcome were identified from previous literature: age younger than 3 years,[16] female sex,[15] presence of underlying disease causing moyamoya syndrome,[6,22] transient ischemic attacks (TIAs) occurring at a frequency exceeding 3 times per month,[16] radiographic evidence of preexisting infarc-

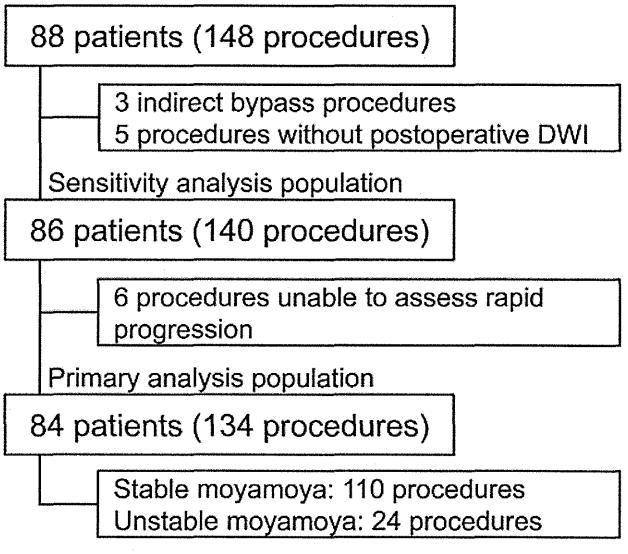

FIG. 1. Flowchart for patient inclusion.

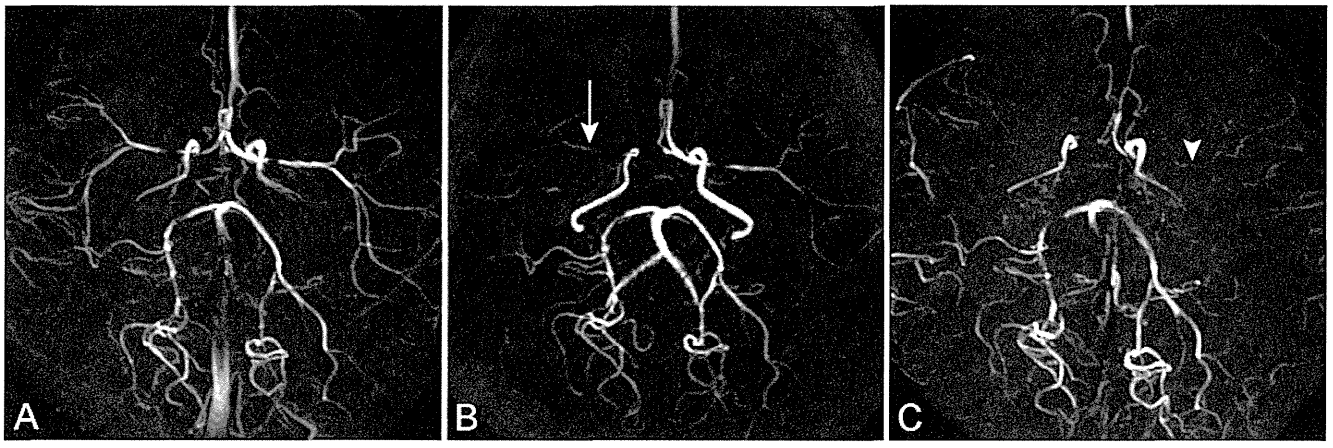

FIG. 2. Serial MRA images obtained in a 1-year-old boy representing rapid disease progression. **A:** Image obtained 2 months before referral to our hospital, revealing moderate stenosis in the terminal portion of the ICA and M_1 segment of the MCA bilaterally. **B:** Image obtained at admission to our hospital, revealing signal decrease in the right MCA compared with that obtained 2 months previously, suggesting rapid disease progression in the right MCA. The patient subsequently underwent direct bypass for the right MCA territory. **C:** Image obtained 2 months after surgery, revealing an invisible signal in the left MCA, suggesting rapid disease progression in the left MCA.

tion,[9,16,25] recent stroke occurring no more than 6 weeks before surgery or evidence of recent stroke on preoperative DWI,[9,16] advanced stage moyamoya (Suzuki Stages IV, V, and VI) in the ICA,[11] and disease involvement in the PCA.[11] "Unilateral disease" was defined as unilateral stenosis or occlusion of the terminal portion of the ICA with the formation of moyamoya vessels accompanied by no lesion or a subtle lesion around the contralateral terminal portion of the ICA. "Severe hemodynamic compromise" was defined as a defect in the cerebral blood flow both at rest and after acetazolamide challenge revealed on SPECT. Administration of antiplatelet agents was also recorded.

Surgery

All patients underwent MRI, SPECT, and angiography before surgery. Surgical revascularization was indicated for patients with cerebral ischemic manifestation. Patients presenting with other symptoms, such as epilepsy and intracranial hemorrhage, were also considered candidates for surgical revascularization as long as hemodynamic compromise existed. All patients underwent direct bypass, STA-MCA anastomosis, or combined bypass comprising STA-MCA anastomosis and encephalo-myo-synangiosis as a first-line treatment.[13] After completing 2 sessions of revascularization for the MCA territories, some patients required additional revascularization surgeries for the ACA and PCA territories. Our surgical procedures and treatment protocol are described in previous literature.[5,12,13] Antiplatelet agents, if administered, were discontinued for 3 days before surgery and 2 days after surgery.

During general anesthesia, $PaCO_2$ and end-tidal CO_2 were closely monitored, and the level of $PaCO_2$ was strictly maintained between 37 and 40 mm Hg.

Outcome

All silent and symptomatic ischemic lesions, a primary outcome in this study, were diagnosed by neuroradiologists based on the results of DWI performed no longer than 14 days after surgery. A symptomatic lesion was defined as one causing a decline in the modified Rankin Scale (mRS) score. Such lesions were classified into either of 2 categories: cortical infarction or subcortical infarction. The patency of the bypass was also assessed using MRA performed in the same imaging session.

Statistical Analysis

Since more than half of the patients underwent multiple procedures, postoperative outcomes for such patients might not be statistically independent. In consideration of these dependencies, we used the generalized estimating equation (GEE) approach for the demographic descriptions of stable and unstable moyamoya disease as well as univariate and multivariate logistic regression analyses.[2] All p values and confidence intervals were calculated with robust standard error estimates from the GEE approach with the independent working correlation structure.

Because of rare outcome events, we selected preoperative variables only with p values < 0.05 as covariates adjusted for the multivariate GEE logistic analysis. In light of its clinical importance, radiographic evidence of infarction was incorporated into the multivariate analysis regardless of its p value. As mentioned in *Results*, assessment of disease progression was not possible for 6 procedures; hence, these procedures were excluded from the primary analysis. We also conducted a sensitivity analysis that included the 6 procedures, all of which were assumed to be those of unstable disease (Fig. 1), considering the possibility that such patients might undergo only 1 MRA session because of rapid progression. We fit the same GEE logistic regression for both the primary and sensitivity analyses. Two-sided values of $p < 0.05$ and 95% confidence intervals of odds ratios that do not include 1 were considered significant. All analyses were performed using JMP (version 9) software and Windows SAS (version 9.3, SAS Institute Inc.).

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,

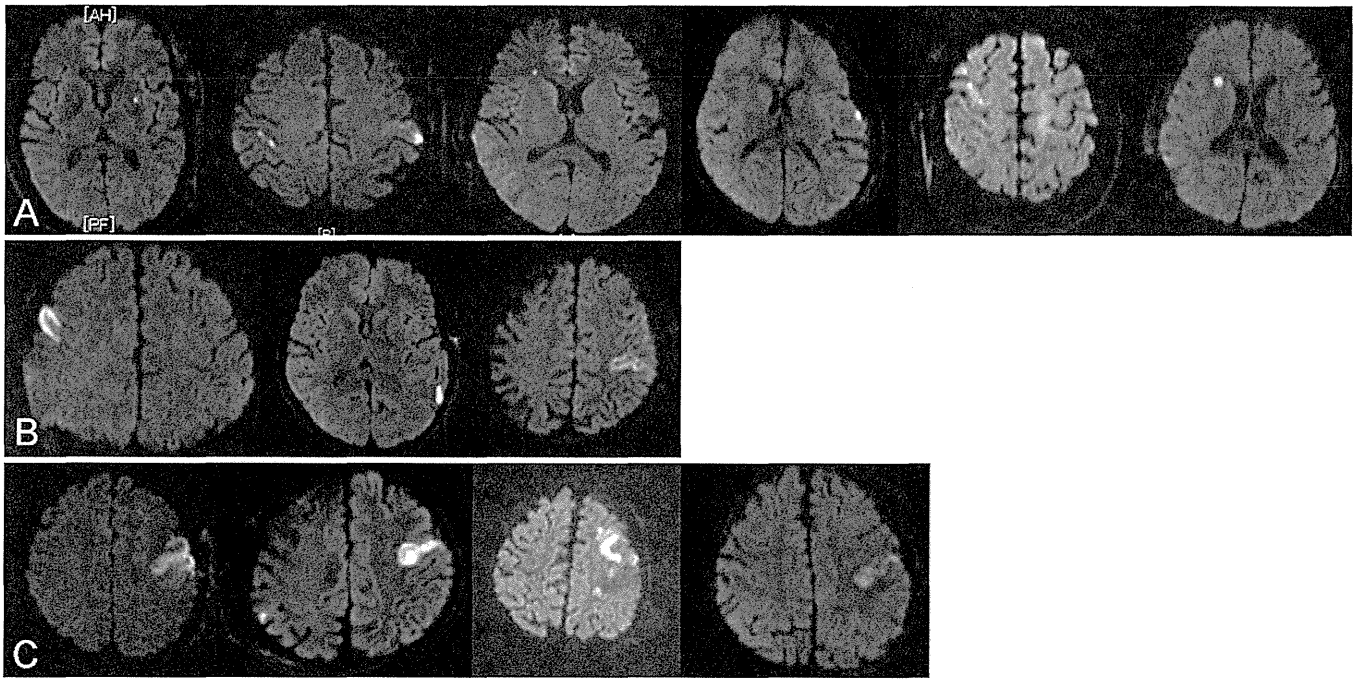

FIG. 3. Lesions detected on postoperative DWI. **A:** Silent lesions. **B:** Lesions causing transient symptoms. **C:** Lesions causing permanent symptoms.

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.

References

1. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al: A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. **Circulation 51 (4 Suppl):**5–40, 1975
2. Diggle P, Heagerty PJ, Liang KY, Zeger SL: **Analysis of Longitudinal Data, ed 2.** Oxford, UK: Oxford University Press, 2002
3. Fujimura M, Inoue T, Shimizu H, Saito A, Mugikura S, Tominaga T: Efficacy of prophylactic blood pressure lowering according to a standardized postoperative management protocol to prevent symptomatic cerebral hyperperfusion after direct revascularization surgery for moyamoya disease. **Cerebrovasc Dis 33:**436–445, 2012
4. Fujiwara F, Yamada H, Hayashi S, Tamaki N: [A case of adult moyamoya disease showing fulminant clinical course associated with progression from unilateral to bilateral involvement.] **No Shinkei Geka 25:**79–84, 1997 (Jpn)
5. Funaki T, Takahashi JC, Takagi Y, Yoshida K, Araki Y, Kikuchi T, et al: Impact of posterior cerebral artery involvement on long-term clinical and social outcome of pediatric moyamoya disease. **J Neurosurg Pediatr 12:**626–632, 2013
6. Guzman R, Lee M, Achrol A, Bell-Stephens T, Kelly M, Do HM, et al: Clinical outcome after 450 revascularization procedures for moyamoya disease. Clinical article. **J Neurosurg 111:**927–935, 2009
7. Hayashi T, Shirane R, Fujimura M, Tominaga T: Postoperative neurological deterioration in pediatric moyamoya disease: watershed shift and hyperperfusion. **J Neurosurg Pediatr 6:**73–81, 2010
8. Houkin K, Nakayama N, Kuroda S, Nonaka T, Shonai T, Yoshimoto T: Novel magnetic resonance angiography stage grading for moyamoya disease. **Cerebrovasc Dis 20:**347–354, 2005
9. Hyun SJ, Kim JS, Hong SC: Prognostic factors associated with perioperative ischemic complications in adult-onset moyamoya disease. **Acta Neurochir (Wien) 152:**1181–1188, 2010
10. Ishikawa T, Houkin K, Kamiyama H, Abe H: Effects of surgical revascularization on outcome of patients with pediatric moyamoya disease. **Stroke 28:**1170–1173, 1997
11. Jung YJ, Ahn JS, Kwon H, Kwun BD: Ischemic complications occurring in the contralateral hemisphere after surgical treatment of adults with moyamoya disease. **J Korean Neurosurg Soc 50:**492–496, 2011
12. Karasawa J, Kikuchi H, Furuse S, Kawamura J, Sakaki T: Treatment of moyamoya disease with STA-MCA anastomosis. **J Neurosurg 49:**679–688, 1978

13. Karasawa J, Kikuchi H, Furuse S, Sakaki T, Yoshida Y: A surgical treatment of "moyamoya" disease "encephalo-myo synangiosis." **Neurol Med Chir (Tokyo) 17:**29–37, 1977
14. Kelly ME, Bell-Stephens TE, Marks MP, Do HM, Steinberg GK: Progression of unilateral moyamoya disease: a clinical series. **Cerebrovasc Dis 22:**109–115, 2006
15. Khan N, Achrol AS, Guzman R, Burns TC, Dodd R, Bell-Stephens T, et al: Sex differences in clinical presentation and treatment outcomes in Moyamoya disease. **Neurosurgery 71:**587–593, 2012
16. Kim SH, Choi JU, Yang KH, Kim TG, Kim DS: Risk factors for postoperative ischemic complications in patients with moyamoya disease. **J Neurosurg 103 (5 Suppl):**433–438, 2005
17. Kim SK, Seol HJ, Cho BK, Hwang YS, Lee DS, Wang KC: Moyamoya disease among young patients: its aggressive clinical course and the role of active surgical treatment. **Neurosurgery 54:**840–846, 2004
18. Kim TW, Seo BR, Kim JH, Kim YO: Rapid progression of unilateral moyamoya disease. **J Korean Neurosurg Soc 49:**65–67, 2011
19. Kuroda S, Ishikawa T, Houkin K, Nanba R, Hokari M, Iwasaki Y: Incidence and clinical features of disease progression in adult moyamoya disease. **Stroke 36:**2148–2153, 2005
20. Lee SC, Jeon JS, Kim JE, Chung YS, Ahn JH, Cho WS, et al: Contralateral progression and its risk factor in surgically treated unilateral adult moyamoya disease with a review of pertinent literature. **Acta Neurochir (Wien) 156:**103–111, 2014
21. Lin N, Baird L, Koss M, Kopecky KE, Gone E, Ullrich NJ, et al: Discovery of asymptomatic moyamoya arteriopathy in pediatric syndromic populations: radiographic and clinical progression. **Neurosurg Focus 31(6):**E6, 2011
22. Mallory GW, Bower RS, Nwojo ME, Taussky P, Wetjen NM, Varzoni TC, et al: Surgical outcomes and predictors of stroke in a North American white and African American moyamoya population. **Neurosurgery 73:**984–992, 2013
23. Moise A, Théroux P, Taeymans Y, Descoings B, Lespérance J, Waters DD, et al: Unstable angina and progression of coronary atherosclerosis. **N Engl J Med 309:**685–689, 1983
24. Research Committee on the Pathology and Treatment of Spontaneous Occlusion of the Circle of Willis: Guidelines for diagnosis and treatment of moyamoya disease (spontaneous occlusion of the circle of Willis). **Neurol Med Chir (Tokyo) 52:**245–266, 2012
25. Sato K, Shirane R, Yoshimoto T: Perioperative factors related to the development of ischemic complications in patients with moyamoya disease. **Childs Nerv Syst 13:**68–72, 1997
26. Smith ER, Scott RM: Progression of disease in unilateral moyamoya syndrome. **Neurosurg Focus 24(2):**E17, 2008
27. Yeghiazarians Y, Braunstein JB, Askari A, Stone PH: Unstable angina pectoris. **N Engl J Med 342:**101–114, 2000
28. Yeon JY, Shin HJ, Kong DS, Seol HJ, Kim JS, Hong SC, et al: The prediction of contralateral progression in children and adolescents with unilateral moyamoya disease. **Stroke 42:**2973–2976, 2011

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JNS

CLINICAL ARTICLE

Periventricular anastomosis in moyamoya disease: detecting fragile collateral vessels with MR angiography

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OBJECT The authors' aim in this paper was to determine whether periventricular anastomosis, a novel term for the abnormal collateral vessels typical of moyamoya disease, is reliably measured with MR angiography and is associated with intracranial hemorrhage.

METHODS This cross-sectional study sampled consecutive patients with moyamoya disease or moyamoya syndrome at a single institution. Periventricular anastomoses were detected using MR angiography images reformatted as sliding-thin-slab maximum-intensity-projection coronal images and were scored according to 3 subtypes: lenticulostriate, thalamic, and choroidal types. The association between periventricular anastomosis and hemorrhagic presentation at onset was evaluated using multivariate analyses.

RESULTS Of 136 eligible patients, 122 were analyzed. Eighteen (14.8%) patients presented with intracranial hemorrhage with neurological symptoms at onset. Intra- and interrater agreement for rating of the periventricular anastomosis score was good (κ_w = 0.65 and 0.70, respectively). The prevalence of hemorrhagic presentation increased with the periventricular anastomosis score: 2.8% for Score 0, 8.8% for Score 1, 18.9% for Score 2, and 46.7% for Score 3 ($p < 0.01$ for trend). Univariate analysis revealed that age ($p = 0.02$) and periventricular anastomosis score ($p < 0.01$) were factors tentatively associated with hemorrhagic presentation. The score remained statistically significant after adjustment for age (OR 3.38 [95% CI 1.84–7.00]).

CONCLUSIONS The results suggest that periventricular anastomosis detected with MR angiography can be scored with good intra- and interrater reliability and is associated with hemorrhagic presentation at onset in moyamoya disease. The clinical utility of periventricular anastomosis as a predictor for hemorrhage should be validated in further prospective studies.

http://thejns.org/doi/abs/10.3171/2015.6.JNS15845

KEY WORDS moyamoya disease; cerebral hemorrhage; magnetic resonance angiography; periventricular anastomosis; sensitivity and specificity; reproducibility; vascular disorders

Moyamoya disease is characterized by chronic progressive stenosis of the terminal portion of the bilateral internal carotid artery. Development of numerous abnormal collateral vessels at the base of the brain, another characteristic of moyamoya disease, might be of clinical importance in relation to hemorrhage.[15] Periventricular anastomosis is a novel term for such collaterals according to vascular morphology[5] and is defined as anastomosis between the perforating or choroidal artery and medullary artery in the periventricular area. Although several researchers have documented some characteristics of such anastomoses,[2,11,14,22] we are among the first to have taken a systemic approach to the task. In moyamoya disease, cerebral microbleeds are most commonly observed in the periventricular area.[11,18,20] It thus seems reasonable to hypothesize that periventricular anastomosis is related to hemorrhage. This hypothesis has, however, remained unproven.

ABBREVIATIONS MRA = MR angiography; STS-MIP = sliding-thin-slab maximum-intensity projection.

SUBMITTED April 13, 2015. **ACCEPTED** June 18, 2015.
INCLUDE WHEN CITING Published online November 27, 2015; DOI: 10.3171/2015.6.JNS15845.

Sliding-thin-slab maximum-intensity projection (STS-MIP) is a common imaging reformation for CT or MR angiography (MRA) that facilitates visualization of target vessels by eliminating the effect of other vessels overlapping and obscuring the view.[4,12] Time-of-flight MRA reformatted using STS-MIP might be useful in assessing periventricular anastomosis. No previous study, however, has documented such usefulness, and information on the reliability of the imaging modality in terms of detecting anastomosis is lacking.

This cross-sectional study had 2 objectives: to estimate the reliability of the detection and scoring of periventricular anastomosis with MRA and to determine whether periventricular anastomosis detected with MRA is associated with hemorrhage in moyamoya disease.

Methods

This study was approved by the ethics committee of the Kyoto University Graduate School of Medicine.

Participants and Setting

All patients with moyamoya disease or moyamoya syndrome who first visited Kyoto University Hospital after 2009 were eligible for the study. Diagnosis of moyamoya disease was determined according to the proposed criteria.[19] "Moyamoya syndrome" is defined as a secondary moyamoya phenomenon caused by accompanying disorders such as autoimmune disease, meningitis, brain tumor, hyperthyroidism, Down syndrome, neurofibromatosis Type 1, or a history of head irradiation. Patients who had undergone MRI and did not meet the imaging requirements indicated below and who had already undergone bypass surgery or another specific treatment elsewhere were excluded from the study. The study population was consecutively sampled. All data for the study were collected during the first visit or upon admission.

Imaging Acquisition and Processing

A 3-T MR scanner (Magnetom Trio, Siemens), which successfully reveals abnormal collateral vessels in moyamoya disease,[6] was introduced in 2009 for image acquisition in patients with moyamoya disease. The time-of-flight MRA source images were scanned as usual axial sections with a 32-channel head coil under the following parameters: 20-msec repetition time, 3.7-msec echo time, 20° flip angle, 0.7-mm slice thickness, 220 × 172–mm field of view with a 384 × 300 matrix, and 0.57 × 0.57–mm pixel size. The imaging field extended from the level of the foramen magnum to beyond the upper margin of the body of the lateral ventricle. The generalized autocalibrating partially parallel acquisition (GRAPPA) technique[7] was used to acquire a relatively wide scan field in less scan time (5 minutes and 34 seconds).

The MRA data thus acquired were reformatted as STS-MIP images in a coronal plane perpendicular to the lateral ventricle and represented as 5- to 15-mm-thick slabs of overlapping volumes (Fig. 1). A window width of 250 and a window level of 120 arbitrary units were used to differentiate the vessels, ventricle, and parenchyma. STS-MIP images were generated on a workstation integrated into the picture-archiving and communication system (Aquarius iNtuition Viewer version 4.4.7, TeraRecon, Inc.).

Measurement of Periventricular Anastomosis

Periventricular anastomosis, a primary factor of interest, was measured using STS-MIP MRA. Presence of anastomosis was determined by a rater (T.F.) who was blinded to other clinical information. To estimate intrarater reliability, the rater rated the images twice at a 1-month interval on a subsample of the last 34 consecutive patients. Another rater (T.M.) independently rated images from the same subsample to determine interrater reliability. Raters had participated in an advance self-training session on 10 representative cases in which periventricular anastomosis had been confirmed.

The classification and definition of periventricular anastomosis followed that of our previous study.[5] In brief, anastomosis was defined as a connection beginning at the perforating or choroidal arteries and ending at the medial end of the medullary or insular arteries in the periventricular area. Anastomoses were classified into 3 subtypes (Fig. 1): 1) lenticulostriate, beginning at the lenticulostriate artery and connecting to the medullary artery at the lateral corner of the frontal horn or body of the lateral ventricle; 2) thalamic, beginning at the thalamotuberal or thalamoperforating arteries and connecting to the medullary or insular arteries beneath the ependyma of the lateral or third ventricle (medial type), or beginning at the thalamogeniculate (or rarely, choroidal) artery and connecting to the insular artery superior to the inferior horn or at the lateral corner of the body of the lateral ventricle (lateral type); and 3) choroidal, beginning at the plexal segment of the anterior or posterior choroidal arteries and connecting to the medullary artery beneath the lateral wall of the trigon of the lateral ventricle. Detection of at least the proximal part of the medullary artery was considered a positive indicator for the presence of periventricular anastomosis. For the thalamic type, a vessel signal extending outside the thalamus or inside the third ventricle was judged as a positive indicator. Each subtype of anastomosis was determined as "present" with a positive finding in at least one hemisphere, and determined as "absent" with a negative finding in both hemispheres. Each subtype was scored 1 for "present" and 0 for "absent," and the sum of these subscale scores for each patient represented the periventricular anastomosis score; the scores thus ranged from 0 to 3.

To avoid information bias from detection of hemorrhage, MRA images from the chronic phase were used for the assessment of patients who had experienced hemorrhagic stroke.

Other Variables

The outcome variable was hemorrhage as a mode of presentation (hemorrhagic presentation), defined as intracranial hemorrhage at onset causing any neurological symptom and detected with CT.

Possible confounders affecting results, including age, sex, concurrence of disorders causing moyamoya syndrome, history of hypertension and diabetes, unilateral

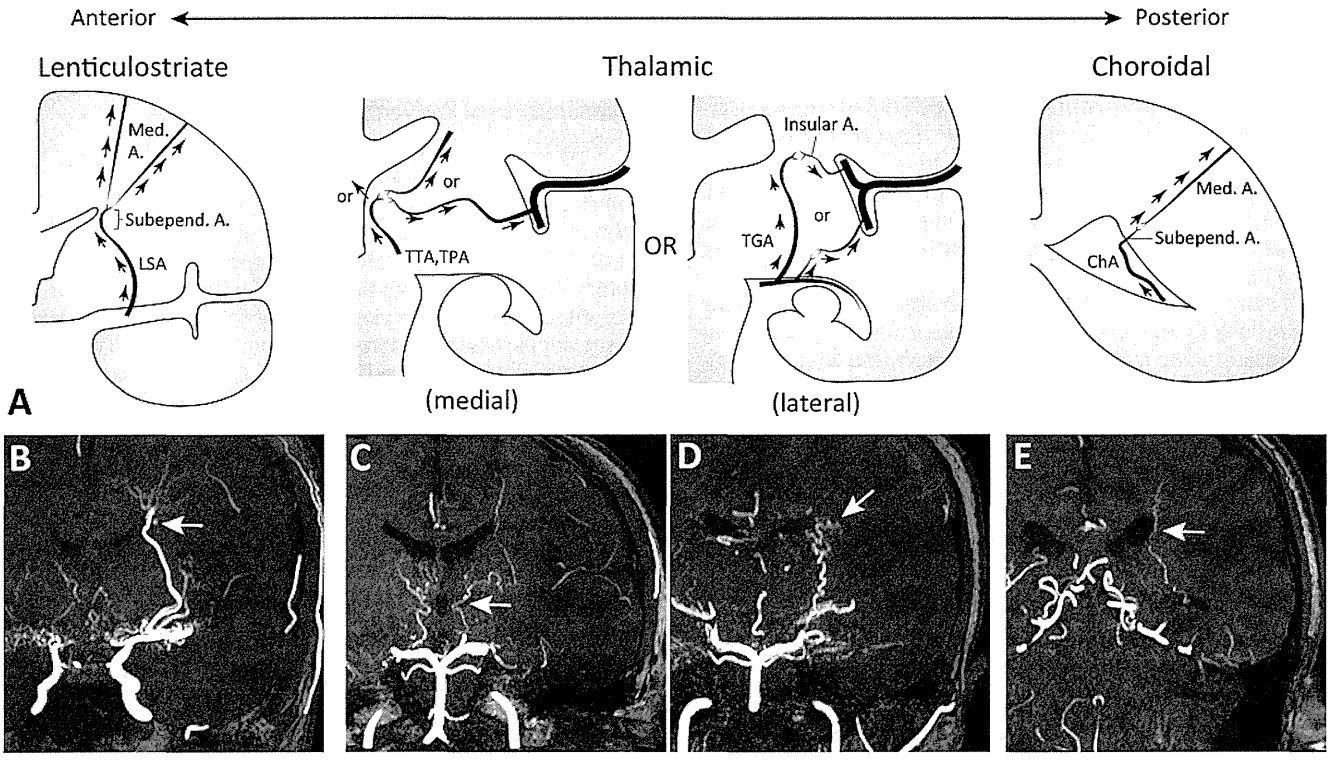

FIG. 1. Schematic illustration **(A)** and STS-MIP MR angiograms **(B–E)** showing periventricular anastomosis. B: Lenticulostriate type. C and D: Thalamic type. E: Choroidal type. The periventricular anastomosis score is 3 (lenticulostriate, 1; thalamic, 1; and choroidal, 1) given all images are from the same patient. A = artery; ChA = choroidal artery; LSA = lenticulostriate artery; Med = medullary; subepend = subependymal; TGA = thalamogeniculate artery; TPA = thalamoperforating artery; TTA = thalamotuberal artery. Panel A: Modified with permission from Funaki et al: *Neurol Med Chir (Tokyo) 55:*204–209, 2015.

disease, and evidence of severe hemodynamic compromise, were also measured. Hypertension is diagnosed if systolic and diastolic blood pressure at first visit or on admission exceeded 140 mm Hg and 90 mm Hg, respectively, or if the patient was receiving antihypertensive agents. Diabetes mellitus was defined as use of insulin or oral glucose inhibitors. Severe hemodynamic compromise was defined as a defect in the cerebral blood flow both at rest and after acetazolamide challenge revealed in single photon emission computed tomography.

Statistical Analysis

Intra- and interrater agreement on the presence of each periventricular anastomosis was assessed using the kappa statistic (κ), and agreement on rating the periventricular anastomosis score was assessed using weighted kappa (κ_w). The Wilcoxon rank-sum test and Fisher's exact test were used as appropriate for the comparison of baseline characteristics. The Cochrane and Armitage test for trend[1] was used to assess the trend in an ordinal variable. Significant factors in the univariate baseline comparison were incorporated into multiple logistic regression models. The periventricular anastomosis score was analyzed not only as an ordinal variable but also as an interval variable and was incorporated into models. We considered p values of < 0.05 and 95% CI of OR not including 1 significant. All analyses were performed using JMP software (version 11, SAS Institute Inc.).

Results

A total of 136 patients were diagnosed with moyamoya disease or moyamoya syndrome at our hospital between January 2009 and August 2014. Fourteen patients were excluded from the study for the following reasons: the MRA scan field was not sufficiently wide (6 patients); the assessment of MRI was difficult because of metallic artifact (1 patient); the patient had already undergone bypass surgery at another hospital (6 patients); and the patient had undergone coil embolization due to a peripheral aneurysm in the anterior choroidal artery (1 patient).

Of the remaining 122 patients included in the analysis, 18 (14.8%) had presented with hemorrhage at onset, 66 (54.1%) with ischemic attack, 19 (15.6%) with cerebral infarction, and 3 (2.5%) with seizure. Sixteen patients (13.1%) were asymptomatic or had subtle symptoms such as headache.

Reliability

Intrarater and interrater reliability for the presence of each subtype of periventricular anastomosis are summarized in Table 1. Very good agreement was observed for the lenticulostriate type ($\kappa = 0.85$ for intrarater agreement and 0.93 for interrater agreement). Agreement for the choroidal type ranged from moderate to good ($\kappa = 0.70$ for intrarater agreement and 0.54 for interrater agreement). Agreement for the thalamic types was moderate ($\kappa =$