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Incidence and Clinical Features of Disease Progression in Adult Moyamoya Disease

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Background and Purpose—The progression of occlusive lesions in the major intracranial arteries was believed to be very rare in adult patients with moyamoya disease. The present study aims to clarify the incidence and clinical features of disease progression in adult moyamoya disease.

Methods—For the past 15 years, 120 adult Japanese patients were diagnosed with moyamoya disease. Of these, 63 patients were enrolled in this historical prospective cohort study on a total of 86 nonoperated hemispheres. All were followed up with a mean period of 73.6 months. MRI and magnetic resonance angiography were repeated every 6 to 12 months, and cerebral angiography was performed when disease progression was suspected on MRI and magnetic resonance angiography.

Results—Disease progression occurred in 15 of 86 nonoperated hemispheres (17.4% per hemisphere) or in 15 of 63 patients (23.8% per patient) during the follow-up period. Occlusive arterial lesions progressed in both anterior and posterior circulations, in both symptomatic and asymptomatic patients, and in both bilateral and unilateral types. Eight of 15 patients developed ischemic or hemorrhagic events in relation to disease progression. Multivariate analysis revealed that the odds ratio conferred by a male patient was 0.20 (95% CI, 0.04 to 0.97).

Conclusions—The incidence of disease progression in adult moyamoya disease is much higher than recognized before, and female patients may be at higher risk for it than male patients. Careful follow-up would be essential to prevent additional stroke occurrence in medically treated adult patients with moyamoya disease, even if they are asymptomatic or are diagnosed as having unilateral moyamoya disease. (***Stroke.*** **2005;36:2148-2153.**)

Key Words: adult ■ cerebral ischemia ■ disease progression ■ moyamoya disease

Moyamoya disease is characterized by progressive occlusion of the bilateral carotid forks associated with a fine vascular network at the base of brain, the "moyamoya" vessels.[1] The posterior cerebral artery is also involved in ≈30% of patients with moyamoya disease.[2] Both children and adults develop moyamoya disease, but their clinical features often differ. Thus, although most pediatric patients develop transient ischemic attack (TIA) or cerebral infarction, about half of adult patients experience intracranial bleeding. In addition, the occlusive lesions in the carotid forks frequently progress in pediatric patients, although it is believed quite rare in adult patients.[3,4] Only 8 cases have previously been reported to demonstrate the progression of occlusive lesions in adult patients with moyamoya disease.[3,5–11] However, there is no report that precisely denoted the incidence and features of stage progression in a large population of adult patients with moyamoya disease.

On the other hand, the recent development of a noninvasive diagnostic technique, magnetic resonance angiography (MRA), has clarified that the prevalence of asymptomatic adult patients with moyamoya disease is much higher than considered before.[12] However, the guideline for the management of asymptomatic adult moyamoya disease has not been established, even in Japan.[12–14] The natural course of adult moyamoya disease should also be elucidated in order to determine appropriate therapeutic strategies for asymptomatic patients. Therefore, in this study, we aimed to clarify the incidence and clinical features of disease progression in adult moyamoya disease.

Materials and Methods

Patients and Follow-Up

This study included 120 adult patients who were diagnosed with moyamoya disease at Hokkaido University Hospital and its affiliate hospitals in Sapporo between 1990 and 2004. All of them were >20 years of age at onset and were diagnosed with moyamoya disease based on the guidelines for the diagnosis of moyamoya disease set by the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of the Ministry of Health and Welfare of Japan. Of these 120 patients, 6 (5%) were deceased because of severe intracranial bleeding within 1 month after the onset. Using

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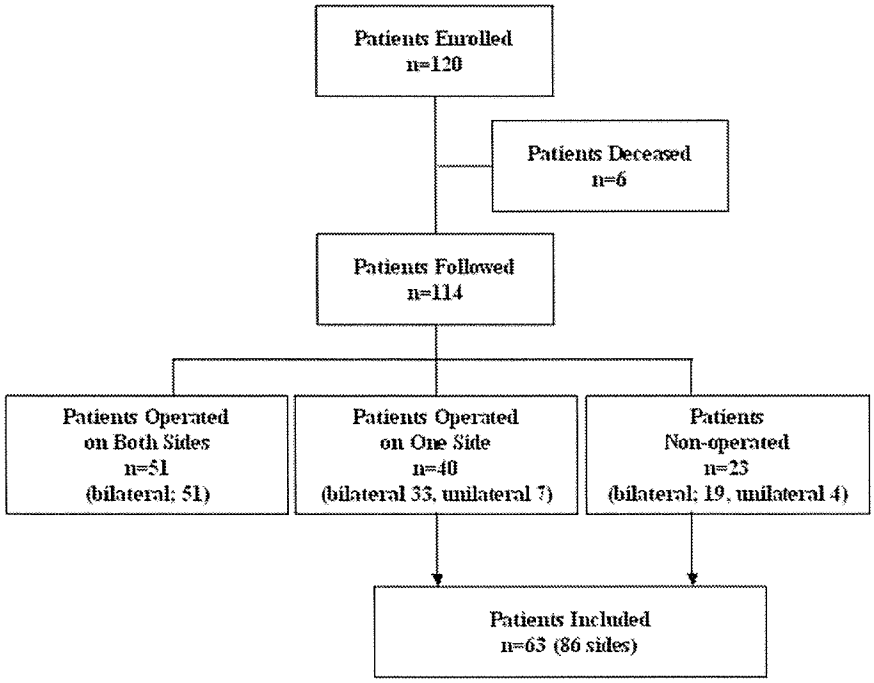

Figure 1. Diagram of adult patients with moyamoya disease included in this study.

^{133}xenon or ^{123}I-IMP single photon emission computed tomography, cerebral blood flow and its reactivity to acetazolamide were quantitatively measured in all of the patients at least 4 weeks after the onset.[15–18] The involved hemisphere was considered as the candidate for surgical revascularization when it had impaired reactivity to acetazolamide.[15–18] As a result, surgical revascularization was performed on 142 sides of 91 patients. Fifty-one patients underwent surgical revascularization on both sides. On the other hand, 40 patients underwent it on 1 side. Surgical procedures included superficial temporal artery to middle cerebral artery anastomosis combined with encephalo-myo-synangiosis or encephalo-duro-arterio-myo-synangiosis in all of these patients.[19] The other 23 patients were medically treated according to the above-mentioned criteria or patients' request. Therefore, we enrolled 63 patients in this study, for a total of 86 nonoperated sides, and evaluated their natural course (Figure 1). There were 23 male and 40 female patients. Of these, 52 patients were diagnosed with typical "bilateral" moyamoya disease (definite cases). The other 11 patients were diagnosed with "unilateral" moyamoya disease (probable cases). Their mean age at onset was 46.7±10.8 years. Their clinical type included ischemic type in 28 patients, bleeding type in 24, and asymptomatic in 11.

All 63 patients included in the present study were followed up in the outpatient clinic at Hokkaido University Hospital or its affiliate hospitals. The mean follow-up period was 73.6±49.0 months, ranging from 7 to 181 months. Both MRI and MRA were performed every 6 or 12 months, using a 1.5-T whole-body magnetic resonance imager. When the progression of the occlusive lesion in the major intracranial arteries was suspected, digital subtraction angiography was performed to verify it. Occlusive lesions in the carotid forks were graded according to Suzuki's angiographical staging.[1]

Statistical Analysis

To clarify the predictors of disease progression in adult moyamoya disease, primary comparisons were performed between the patients with and without disease progression. Categorical variables were compared by using a χ^2 test. Continuous variables were expressed as percentage or as mean±SD, and were compared by using the unpaired Student t test. Differences were considered to be statistically significant if the P value was <0.05. Subsequently, a multivariate logistic regression model was conducted to test the effect of gender, onset age, disease type, symptoms at onset, and previous surgery on disease progression. The statistical level of significance was also set at $P<0.05$. Statistical analysis was completed with StatView version 5.0 (SAS Institute Inc.).[20]

Results

Characteristics of Stage Progression

During follow-up periods, the occlusive lesions in the major intracranial arteries progressed in 15 of 86 sides (17.4% per hemisphere) or in 15 of 63 patients (23.8% per patient). Disease progression was verified in 2 men and 13 women, and their age at onset was 46.9±8.2 years (range, 32 to 60 years). Their symptoms at onset included TIA or cerebral infarction in 9 patients and intracranial bleeding in 4. The remaining 2 patients were asymptomatic when they were diagnosed with moyamoya disease.

Disease progression occurred in 4 of 11 patients (36.4%) with unilateral moyamoya disease and in 11 of 52 patients (21.2%) with bilateral moyamoya disease. Thus, the carotid fork of the contralateral side was involved in 4 patients with unilateral moyamoya disease, which meant progression from unilateral to bilateral type. The interval between their onset and disease progression varied from 1.5 to 8 years (60.0±36.3 months). All of the patients were women. In relation to the progression from unilateral to bilateral type, TIA or intracranial bleeding occurred in 3 patients, and a single photon emission tomography study revealed the deterioration of cerebral hemodynamics in another (case 3). All of them underwent additional bypass surgery (Table 1). On the other hands, 8 of 52 patients with bilateral moyamoya disease showed the progression of the occlusive lesion in the carotid fork. The other 3 patients with bilateral moyamoya disease developed an additional occlusive lesion in the posterior cerebral artery (PCA) during follow-up periods (Table 2). The interval between their onset and disease progression was 28.4±26.3 months, ranging from 1 month to 8 years, and was significantly shorter in patients with bilateral moyamoya

TABLE 1. Clinical Features of 4 Adult Patients Who Showed the Progression From Unilateral to Bilateral Moyamoya Disease

		Onset			Progression		
Case	Age/Gender	Symptom	Involved Side	Bypass Surgery	Symptom	Additional Side	Interval (yr)
1	52F	Bleeding	Rt	None	Bleeding	Lt	7
2	44F	Infarct	Lt	Lt	TIA	Rt	3.5
3	33F	Bleeding	Rt	Rt	None	Lt	8
4	45F	TIA	Lt	Lt	TIA	Rt	1.5

Rt indicates right; Lt, left.

disease than in those with unilateral moyamoya disease (P=0.0123). In relation to the disease progression, TIA or cerebral infarction occurred in 5 patients, and cerebral hemodynamics worsened in another 2 (cases 5 and 14). Subsequently, 8 patients underwent bypass surgery.

Independent Predictor of Disease Progression

The effects of various clinical factors on disease progression are shown in Table 3. The patients with and without disease progression were categorized into the progression group (n=15) and stable group (n=48), respectively. As the results of univariate analysis, there was no significant difference in onset age, disease type, symptoms at onset, and previous bypass surgery between the 2 groups. However, disease progression was noted in 13 of 40 female patients (32.5%), but in 2 of 23 male patients (8.7%), revealing that the incidence of disease progression was significantly higher in female patients than in male patients (χ^2 test, P=0.0327).

As the next step, multivariate logistic regression analysis showed that patients' gender was an independent predictor of disease progression during follow-up periods (P=0.0463). The odds ratio conferred by a male patient was 0.20 (95% CI, 0.04 to 0.97) for disease progression (Table 3).

Illustrative Cases

Case 14

A 50-year-old female experienced minor head injury because of a traffic accident in March 2001. Because brain MRI and MRA studies strongly suggested the presence of moyamoya disease, cerebral angiography was performed. Right carotid angiography showed the stenosis of the right anterior cerebral artery (Figure 2a). The left cerebral angiography revealed marked stenosis of the left internal carotid artery and middle cerebral artery associated with mild dilatation of the lenticulostriate arteries (Figure 2b). Although she was still asymptomatic, follow-up cerebral angiography in March 2004 showed progression of an occlusive lesion on the left side (Figure 2c). Single photon emission tomography studies also revealed the reduction of cerebral blood flow and its reactivity to acetazolamide. She underwent superficial temporal artery to middle cerebral artery anastomosis and encephalo-duro-arterio-myo-synangiosis. Postoperative course was uneventful.

Case 15

A 56-year-old female was admitted to our hospital because of a severe headache and consciousness disturbance in March 1996. Plain computed tomography scans revealed intracerebral hematoma in the right putamen (Figure 3a). Cerebral angiography on admission showed the marked stenosis of the bilateral carotid forks. The posterior cerebral arteries were intact. She was diagnosed with moyamoya disease. She completely recovered and was medically followed up because she and her family did not want surgical revascularization. The brain MRI and MRA were annually repeated at an outpatient clinic. Although the posterior cerebral arteries

TABLE 2. Clinical Features of 11 Adult Patients With Bilateral Moyamoya Disease Showing the Progression of Occlusive Lesion in the Major Intracranial Arteries

		Onset			Progression		
Case	Age/Gender	Symptom	Symptomatic Side	Bypass Surgery	Symptom	Progressed Lesion	Interval
5	53F	TIA	Rt	Rt	None	Lt PCA	2 y
6	37F	TIA	Lt	Lt	Infarct	Rt (2 → 4)	2 y
7	50F	TIA	Rt	Rt	None	Lt (2 → 4)	3 y
8	55M	None		None	Infarct	Lt (2 → 4)	3 y
9	48M	Bleeding	Lt	None	Infarct	Lt (3 → 4)	1 mo
10	32F	TIA	Lt	None	None	Lt (2 → 3)	3 mo
11	50F	Infarct	Lt	None	None	Lt (2 → 3)	9 mo
12	60F	TIA	Rt	Rt	Infarct	Lt PCA	11 mo
13	41F	TIA	Lt	None	TIA	Rt (3 → 4)	3 y
14	50F	None		None	None	Lt (3 → 4)	3 y
15	54F	Bleeding	Rt	None	None	Rt PCA	8 y

Occlusive lesions in the carotid forks were graded according to Suzuki's angiographical staging; Rt indicates right; Lt, left.

TABLE 3. Clinical Features of the Patients With Stage Progression of Adult Moyamoya Disease (Progression Group) and Without (Stable Group)

Variables	Progression Group	Stable Group	Univariate Analysis	Multivariate Analysis	Odds Ratio (95% CI)
No. of patients	15	48			
Gender					
Male	2	21	P=0.0327	P=0.0463	0.20 (0.04–0.97)
Female	13	27			
Age at onset (y)	46.9±8.2	47.0±9.9	P=0.9754		
Disease type					
Bilateral	11	41	P=0.2819		
Unilateral	4	7			
Symptoms at onset					
Ischemia	9	19	P=0.3793		
Bleeding	4	20			
Asymptomatic	2	9			
Bypass surgery					
Yes	7	33	P=0.1210		
No	8	15			

Continuous data are expressed as mean±SD.

were intact in March 2004 (Figure 3b), a marked stenosis developed in the right posterior cerebral artery in March 2005 (Figure 3c).

Discussion

This study is the first to focus on clinical manifestations of the progression in the major intracranial arteries in a large population of patients with adult moyamoya disease. The results clearly showed that the incidence of disease progression was ≈20% in adult patients with moyamoya disease, which is higher than what was considered before. Disease progression occurred in both unilateral and bilateral moyamoya disease, in both anterior and posterior circulation, and in both symptomatic and asymptomatic patients. An ischemic or hemorrhagic episode was noted in more than half of patients when the occlusive lesions progressed. Multivariate analysis revealed that female patients had a higher risk of disease progression than male patients.

As described above, the disease progression in adult moyamoya disease has previously been recognized as very rare, and 8 patients have been reported to exhibit it as case reports.[3,5–11] In addition, Kawano et al[21] reported 4 adult patients who showed progression from unilateral to bilateral type in their series of 64 cases with unilateral moyamoya disease, although their clinical data were limited. Clinical information of these 12 patients is summarized in Table 4. Thus, the occlusive lesions in the carotid fork advanced in both sides or in the nonoperated side in 4 adult patients with bilateral moyamoya disease.[3,6–8] In addition, unilateral moyamoya disease has been reported to progress to bilateral type in 8 adult patients.[5, 9–11, 21] As shown in this study, disease progression occurred within 1 year after the onset in 2 of 4 patients with bilateral moyamoya disease, whereas it occurred 1 to 6 years after the onset in patients with unilateral moyamoya disease. When analyzing 8 patients with sufficient clinical information (case 1 to 5 and 10 to 12), 3 developed ischemic or hemorrhagic episode because of disease progression. Gender difference was not observed in these 8 cases, which is different from the present result. It may result from the difference of patients' background among the studies. However, Kawano et al[21] reported female predominance in patients with unilateral moyamoya disease showing progression to a bilateral type, correlating well with the present result.

Unilateral moyamoya disease accounts for ≈20% of all of the moyamoya disease in Japan.[22] According to previous surveys,

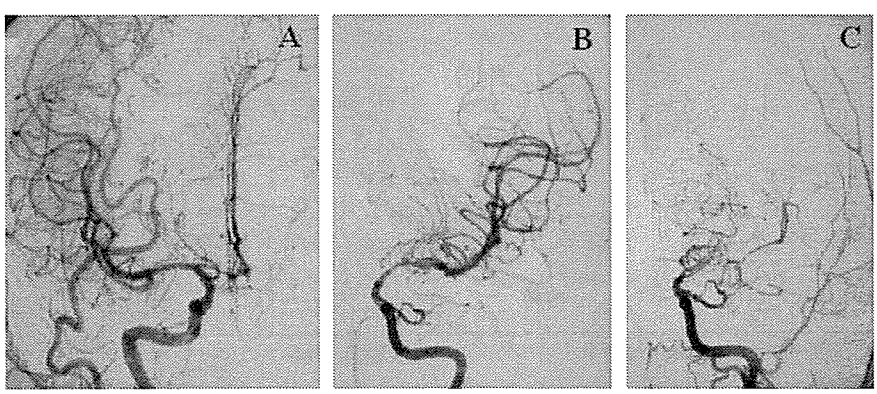

Figure 2. Right (a) and left internal carotid angiograms (b and c) of a 50-year-old woman (case 14), showing progression of an occlusive lesion in the left carotid fork during 3-year follow up (b and c).

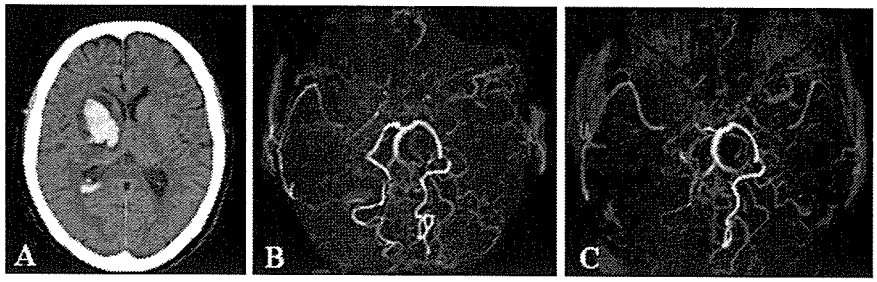

Figure 3. Plain computed tomography (a) and MRA (b and c) of a 56-year-old woman (case 15), showing the development of an occlusive lesion in the right posterior cerebral artery between March 2004 (b) and March 2005 (c).

unilateral moyamoya disease has been recognized as stable in adults.[21,23,24] However, this study revealed that about one-third of patients progressed to the typical bilateral type. The discrepancy may result from the difference in follow-up periods. Thus, mean follow-up periods were within 3 years in previous studies.[21,23,24] On the other hand, the patients included in this study were followed up for a mean period of ≈6 years. Because the interval between initial diagnosis and disease progression is significantly longer in unilateral moyamoya disease than in the bilateral type, long-term follow-up would be essential to discuss the prognosis of unilateral moyamoya disease. Indeed, disease progression was confirmed 7 to 8 years after the initial diagnosis in 2 patients (cases 1 and 3, Table 1).

In this study, 3 patients developed additional occlusive lesions in the PCA during follow-up periods. To our best knowledge, there is no report describing the phenomenon in adult moyamoya disease. The development of additional PCA lesions implies the increased risk for recurrent ischemic stroke, because the PCA is playing an important role as a major collateral circulation in moyamoya disease as pointed out before.[2,25,26] In this study, cerebral infarction occurred in 1 patient, and cerebral hemodynamics deteriorated in another 2. Therefore, the importance of carefully observing the whole intracranial arteries should be remembered during follow-up.

Noninvasive examinations using MRI and MRA have revealed that the incidence of asymptomatic moyamoya disease is much higher than believed before.[12] However, the prognosis of asymptomatic patients is still unclear, and the standardized strategy for them has not been established.[12–14] This study revealed that the occlusive arterial lesions advanced in 2 of 11 asymptomatic patients (18.2%) during 3 years, leading to cerebral infarction (case 8) or disturbed cerebral hemodynamics (case 14). The findings should be taken into consideration when establishing the management guideline for asymptomatic patients with moyamoya disease, although additional survey would be necessary on the basis of a larger population of asymptomatic patients. Furthermore, MRI and MRA studies at outpatient clinics could accurately detect disease progression before recurrent onsets including TIA, cerebral infarction, and intracranial bleeding in 7 of 15 patients, suggesting the importance of continuous imaging studies.

Based on multivariate analysis in this study, female gender may be a significant predictor of disease progression in adult moyamoya disease. None of the other factors were related to disease progression. Previous epidemiological surveys have shown that a male-to-female ratio of moyamoya disease is ≈1:1.8,[27] suggesting the female predominance in moyamoya disease. Furthermore, female predominance is more pronounced in familial moyamoya disease. Thus, Kanai et al[28] reported that a male-to-female ratio in familial moyamoya disease was 1:3.3. A recent study[29] also showed that male-to-female ratios were 1:5 and 1:1.6 in familial and sporadic cases, respectively, indicating

TABLE 4. Summary of Clinical Features in 12 Reported Case With Moyamoya Disease Showing Progression of Occlusive Arterial Lesions

			Onset	Progression			
Initial Diagnosis	Age	Gender	Symptom	Side	Symptom	Interval	Authors (Year)
Bilateral moyamoya disease							
1	25	M	Infarct	Both sides	None	17 y	Takeshita et al (1995)[6]
2	56	F	Infarct	Nonoperated side	None	5 mo	Shirane et al (1999)[3]
3	47	F	Infarct	Nonoperated side	TIA	1 mo	Oka et al (2000)[8]
4	37	M	Infarct	Both sides	Bleeding	4 y	Tomida et al (2000)[7]
Unilateral moyamoya disease							
5	30	F	TIA	Both sides	None	4 y	Aoki et al (1989)[11]
6	27		TIA	Noninvolved side		1 y	Kawano et al (1994)[21]
7	30		TIA	Noninvolved side		6 y	
8	41		TIA	Noninvolved side		5 y	
9	63		Bleeding	Noninvolved side		1 y	
10	38	M	Infarct	Noninvolved side	Bleeding	2.5 y	Wanifuchi et al (1996)[10]
11	54	M	Infarct	Noninvolved side	None	4 y	Fujiwara et al (1997)[5]
12	21	F	Infarct	Noninvolved side	None	2.5 y	Kagawa et al (2004)[9]

enhanced female predominance in familial moyamoya disease. The results strongly suggest that female gender may be highly susceptible to the unknown factors causing moyamoya disease and may promote disease progression more easily.

Recently, the prospective, randomized clinical trial has been accepted to provide the highest level of evidence. The present study has some problems for evidence-based medicine. Thus, this study has bias in the patient selection. The patients who underwent bypass surgery on both sides were excluded, because it is well known that occlusive lesions in the carotid fork rapidly progress and often result in complete occlusion when surgical collaterals start to supply enough blood flow after surgery.[30–32] As a result, this study included the patients who underwent bypass surgery on one side and those who were medically treated and observed their natural course. Therefore, we cannot exclude the possibility that the present results are diluted because less severe patients were included in this study.

In conclusion, the process of occlusive arterial change in adult moyamoya disease is still active. Disease progression can occur in both anterior and posterior circulations, in both symptomatic and asymptomatic patients, and in both unilateral and bilateral types. Careful and long-term neurological and radiological follow-up would be essential in adult patients with moyamoya disease to prevent additional stroke events and to improve their outcome.

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ORIGINAL PAPER

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Clinical features of familial moyamoya disease

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Abstract *Objects:* This study aims to clarify the genetic background of moyamoya disease by comparing clinical features between familial and sporadic cases to reveal the responsible genes for familial moyamoya disease. *Methods:* This study included 155 Japanese patients with moyamoya disease, which included 24 familial cases (10 family pedigrees) and 131 sporadic cases. Clinical features were compared between the familial and sporadic cases. *Results and conclusion:* A female preponderance was significantly more prominent in the familial than in the sporadic group (P=0.0421). Mean age at onset was significantly lower in familial than in sporadic cases (P=0.004). In eight parent–offspring pairs, mean age at onset was significantly lower in the second than in the first generation (P<0.0001). These results suggest that familial moyamoya disease is associated with genetic anticipation and female predominance and that a genetic analysis study focused on expanded triplet repeats may clarify the pathogenesis of the disease.

Keywords Moyamoya disease · Genetics · Anticipation · Familial case · Age at onset · Female predominance · Triplet repeat

Introduction

Moyamoya disease (spontaneous occlusion of the circle of Willis) is characterized by a progressive stenosis or occlusion of the terminal portions of the bilateral internal carotid arteries associated with abnormal vascular network at the base of the brain ("moyamoya" vessels; [19]). Clinically, of special interest is that moyamoya disease occurs in both children and adults. Most pediatric patients develop transient ischemic attack (TIA) or cerebral infarction, whereas adult patients more frequently suffer intracranial hemorrhage. The man-to-woman ratio is 1:1.8 [22].

The pathogenesis of moyamoya disease is still unknown. Several epidemiological studies suggest that infection in the head and neck regions may be related to moyamoya disease, although a certain infectious pathogen has not been determined [23]. Alternatively, specific cytokines such as basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factors have been proposed as pathogenetic factors for moyamoya disease because these substances are detected at high levels in the cerebrospinal fluid and the involved arteries of patients with moyamoya disease [20, 26]. Furthermore, it has been widely accepted that some genetic factors may play an important role in the pathogenesis of moyamoya disease. The hypothesis is based on the facts that familial occurrence has been recognized in approximately 10–15% of patients and that the incidence of moyamoya disease is much higher in Far Eastern than in western countries [24]. Thus, according to recent literature review, 172 familial cases of 76 pedigrees have been reported. Of these, 38 parent–offspring pairs of 16 pedigrees and 128 sibling pairs of 51 pedigrees have been described [15]. Compared with the general population, first- or second-degree relatives are known to have a 30- to 40-fold significantly increased risk of moyamoya disease [10]. Identical twins associated with

moyamoya disease have also been reported [11]. The incidence is 0.35 per 100,000 in Japan, but only 201 and 105 patients have been reported from Europe and USA, respectively, between 1972 and 1989 [4]. The incidence is higher in Japanese population than in the Hawaiian population [5].

Clinical studies of familial cases have suggested that moyamoya disease is most likely inherited in a polygenic mode or in an autosomal-dominant fashion with a low penetrance. Microsatellite linkage analysis has recently identified the genetic loci on chromosomes 3, 6, and 17 [8, 9, 25]. However, the responsible genes have not been identified yet [15].

Based on these considerations, the present study aims to facilitate the transition from linkage analyses to the identification of responsible genes by analyzing clinical manifestations among familial and sporadic cases of moyamoya disease.

Materials and methods

Patients

The current study included 155 patients with moyamoya disease. Of these, 141 were admitted to our hospital between 1969 and 2002 and were diagnosed as having moyamoya disease on cerebral angiography based on the guidelines for the diagnosis of moyamoya disease set by the Research Committee on Moyamoya Disease (Spontaneous Occlusion of the Circle of Willis) of the Ministry of Health and Welfare of Japan. All patients were Japanese and were residents of Hokkaido Island, a northern part of Japan. All of them presented with TIA, cerebral infarction, or intracranial hemorrhage. When they were diagnosed as having moyamoya disease, their family history was precisely evaluated, and the members of their family underwent cerebral angiography or magnetic resonance angiography (MRA) when they had at least one episode suggesting the symptoms of moyamoya disease or when they strongly desired MRI/MRA examination as a screening tool. As a result, an additional 14 patients were diagnosed as having moyamoya disease, bringing the total number of patients included in this study to 155. Of these, 110 patients were categorized as definite cases and the other 45 as probable cases. This study did not include quasi-moyamoya cases.

To characterize the clinical features in familial moyamoya disease, the authors compared the gender, age at onset, and symptoms at onset of the patients between the familial and sporadic cases.

Statistical analysis

All data were expressed as mean±SD. Categorical variables were compared using the chi-square test. Continuous variables were compared using a two-tailed unpaired Student's t test. The cumulative onset free-survival rate was compared between the studied groups using the Kaplan–Meier method and Mantel–Cox log-rank statistics. Differences were considered to be statistically significant if the P value was <0.05. All statistical analyses were performed using StatView ver 5.0 (SAS Institute Inc., USA).

Results

Familial and sporadic moyamoya disease

Of the 155 patients included in this study, familial occurrence was observed in 24 patients of 10 pedigrees (familial group). The other 131 patients were sporadic cases (sporadic group). The clinical features of both groups are summarized in Table 1.

There were 4 men and 20 women in the familial group, while there were 50 men and 81 women in the sporadic group. Therefore, a female preponderance was significantly more prominent in the familial than in the sporadic group (chi-square test, $P=0.0421$). Age at onset ranged from 1 to 36 years (11.8±11.7 years) in the familial group and from 1 to 78 years (30.0±20.9 years) in the sporadic group. As a result, mean age at onset was significantly lower in the familial than in the sporadic group (unpaired t test, $P=0.0043$). Kaplan–Meier analysis and Mantel–Cox log-rank statistics also showed that age at onset was significantly lower in the familial than in the sporadic group (Fig. 1; $P<0.0001$).

Table 1 Summary of clinical characteristics in familial and sporadic group of moyamoya disease

	Familial group	Sporadic group	Significance
n	24	131	
Gender (male/female)	4:20	50:81	$P=0.0421$
Age at onset (years)	11.8±11.7	30.0±20.9	$P=0.0043$
Clinical diagnosis at onset	TIA: 19	TIA: 43	$P<0.0001$
	Cerebral infarct: 0	Cerebral infarct: 48	
	Intracranial bleeding: 3	Intracranial bleeding: 37	
	None: 2	None: 3	

TIA Transient ischemic attack

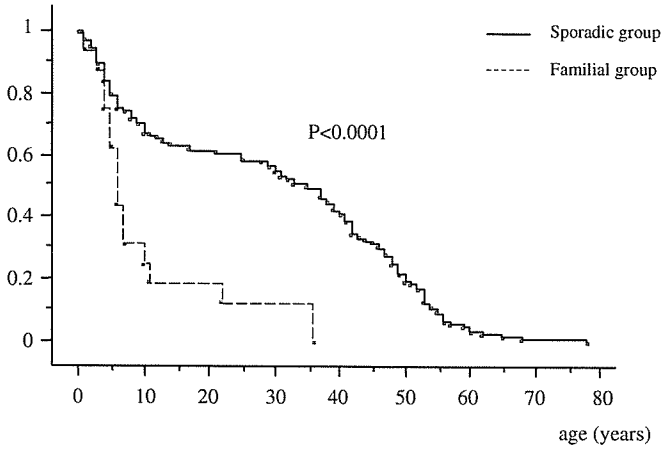

Fig. 1 Graph showing the age at onset in familial and sporadic cases with moyamoya disease. Kaplan–Meier analysis reveals that the age at onset is significantly lower in familial than in sporadic group

In the familial group (n=24), clinical symptoms at onset included TIA in 19 patients (79.2%), intracranial hemorrhage in 3 (12.5%), and none in 2 (8.3%). On the other hand, in the sporadic group (n=131), clinical symptoms at onset included TIA in 43 patients (32.8%), completed ischemic stroke in 48 (36.6%), intracranial hemorrhage in 37 (28.2%), and none in 3 (2.3%). Thus, the symptoms at onset were significantly different between the two groups (chi-square test, P<0.0001), and completed ischemic stroke developed more often in the sporadic than in the familial group.

Clinical features of familial moyamoya disease

As a next step, the authors analyzed the clinical features of familial moyamoya disease to characterize their genetic properties. Of 10 pedigrees, there were eight parent–offspring pairs, all of which were mother–offspring pairs. There were four sibling pairs, one of which was twins (Fig. 2). Of the eight parent–offspring pairs, seven parents were symptomatic and one was asymptomatic. The seven symptomatic parents presented with the symptoms related to moyamoya disease when they were 22 to 36 years old (30.7±7.5 years). On the other hand, their children presented with the symptom when they were 5 to 11 years old (7.2±2.7 years). Thus, mean age at onset was significantly lower in the second than in the first generation (unpaired t test, P<0.0001). Of the eight parents, symptoms at onset included TIA in five and intracranial hemorrhage in three, whereas all of their children experienced TIA at onset.

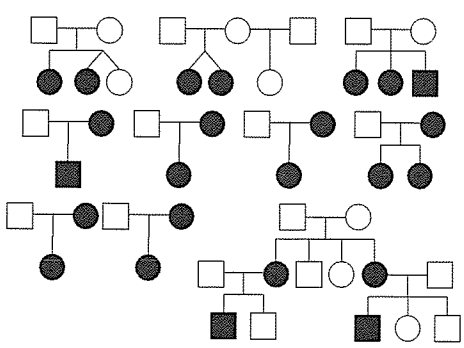

Fig. 2 Ten pedigrees of familial moyamoya disease included in the present study

Discussion

Epidemiological features of familial moyamoya disease

The current study demonstrates several clinical features of familial moyamoya disease. First, the female preponderance in sporadic moyamoya disease is overrepresented in familial moyamoya disease, although the bias in the data sample cannot be excluded. Furthermore, a significant mother–offspring transmission is observed in the present study. The man-to-woman ratio of moyamoya disease is generally known as 1:1.8 [22]. However, a previous survey of familial moyamoya disease has also shown more pronounced female predominance, that is, 1:3.3 [10], consistent with the present result. The authors have recently reviewed previous literature on familial moyamoya disease and found 16 parent–offspring pairs of moyamoya disease [14]. There are 5 men and 11 women in the first generation, whereas there are 8 boys and 12 girls in the second generation. These clinical findings strongly suggest that women are highly susceptible to some genetic factors of familial moyamoya disease. Otherwise, the unknown genetic factors responsible for familial moyamoya disease might have some different effects on the gender. No reports have revealed that familial moyamoya disease is related with the X or Y chromosome. The responsible gene of the disease may exhibit a different pattern of expression according to gender. Recent studies have revealed that the methylation pattern of CpG island differs between genders and that the malfunction of methylation reflects the pathogenesis of certain genetic diseases such as Prader–Willi syndrome and Angelman syndrome [13].

Second, by the use of unpaired Student's t test and Kaplan–Meier analysis, this study indicates that mean age at onset is significantly lower in familial than in sporadic moyamoya disease. Previous clinical studies have revealed a similar result in some inheritable cerebrovascular or neurological disorders. Familial subarachnoid hemorrhage (SAH) is characterized, in comparison with SAH from sporadic aneurysms, by an earlier age at the time of SAH

[2, 12, 16]. A similar phenomenon has been observed in familial migraine and cluster headache [17, 21]. These findings seem to suggest that genetic factors affect age at onset of familial moyamoya disease. The patients in the sporadic group more often present with cerebral infarct and intracranial hemorrhage than do those in the familial group (Table 1). The difference most likely results from the finding that mean age at onset is significantly higher in the sporadic than in the familial group.

Third, the current study reveals that mean age at onset is significantly lower in the second than in the first generation among the eight parent–offspring pairs. These results are the same with that of a recent literature review on familial moyamoya disease. Thus, the parent–offspring pairs of 16 pedigrees have previously been reported. Mean age at onset of the 16 parents is significantly higher than that of their 20 children, 39.5±12.8 and 12.7±8.0 years, respectively ($P<0.0001$; [15]). These results strongly suggest that anticipation may be closely associated with familial moyamoya disease.

Anticipation and expansion of repeat sequence

The clinical phenomenon of decreasing age at onset and/or increasing severity of symptoms of a disease in successive generations within a pedigree has been termed anticipation [1]. In total, 73 familial disorders have been reported to be linked to anticipation. Of these, responsible genes have previously been clarified in 20 familial disorders, most of which are neurological or neuropsychiatric disorders, such as myotonic dystrophy and Huntington's disease. Recent studies have strongly suggested that anticipation is caused by pathogenic unstable triplet repeat. In many of these disorders, repeat size correlates with severity and inversely with age at onset rather than penetrance. As the repeats tend to expand during transmission between generations, the age at onset tends to decrease and the severity tends to increase. This instability has led to the description of pathogenic repeat sequences as dynamic mutations [7, 18].

Of the eight parent–offspring pairs in the present study, all were maternal inheritance. There is increasing evidence that imprinting phenomenon may be associated with anticipation in some familial neurological disorders, including Huntington's disease. Genomic imprinting has been defined as "the differential expression of genetic material, at either a chromosome or allelic level, depending on whether the genetic material has come from the male or female parent" [6]. Previous studies have suggested that the methylation of CpG island that often functions as a strong promoter plays a central role in genomic imprinting [6]. Therefore, genomic imprinting may also affect the predominance of maternal inheritance in familial moyamoya disease.

Limitation of the current study

As described above, the responsible genes for familial moyamoya disease have not been determined, although microsatellite linkage analyses have shown the genetic loci on chromosomes 3, 6, and 17 [8, 9, 25]. Indeed, positional cloning analysis has failed to identify the possible genes [15]. Therefore, the present results can be a guiding principle in research efforts for elucidating the genes.

The present study is the first attempt to statistically analyze the clinical features of familial moyamoya disease and strongly suggests the association of anticipation. Of course, however, it should be reminded that the signs of anticipation may be attributed to several sampling and observation biases, including the tendency to select the parents with late onset and the offspring with early onset [3]. Another possible bias that may mimic anticipation can result from shared environmental factors because the affected individuals within families are not widely distributed geographically and across time. Therefore, a larger sample size of familial moyamoya disease would be necessary to minimize all possible biases, verifying the present results.

Another difficulty should also be taken into consideration in analyzing the clinical manifestations of familial moyamoya disease. Thus, only 40 years has passed since moyamoya disease was identified as a clinical entity [19], and it is very difficult to obtain accurate medical records of three- or four-generation families with moyamoya disease. A prospective follow-up study over several generations within families may clarify the clinical feature of familial moyamoya disease.

Conclusion

In this study, the authors statistically analyzed the clinical features of familial and sporadic cases of moyamoya disease. The results strongly suggest that anticipation may be closely related to familial moyamoya disease, although further studies are necessary. The present results may shed light on future research for identifying the genes responsible for familial moyamoya disease.

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Cerebral Oxygen Metabolism and Neuronal Integrity in Patients With Impaired Vasoreactivity Attributable to Occlusive Carotid Artery Disease

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Background and Purpose—It is still unclear that impaired cerebrovascular reactivity (CVR) to acetazolamide is comparable to elevated oxygen extraction fraction (OEF) on positron emission tomography (PET) in patients with occlusive carotid diseases. Therefore, in this study, the authors aimed to clarify whether OEF is elevated in all patients with reduced cerebral blood flow (CBF) and CVR (type 3) on single photon emission computed tomography (SPECT), and, if not, to specify the underlying pathophysiology of type 3 but normal OEF.

Methods—This study included 46 patients who had decreased CBF and CVR on *N*-isopropyl-*p*-^{123}I-iodoamphetamine SPECT in the ipsilateral middle cerebral artery area attributable to occlusive carotid diseases. Hemodynamic and metabolism parameters were determined in all patients by ^{15}O-gas PET, and neuronal integrity was evaluated in 19 patients using ^{11}C-flumazenil (FMZ) PET.

Results—OEF was significantly elevated in 20 (43.5%) of 46 type 3 patients. Another 26 type 3 patients had normal OEF. Regression analysis showed that OEF significantly correlated with cerebral metabolic rate for oxygen and ^{11}C-FMZ binding potential but not with other parameters. Subcortical infarction had no significant effect on OEF values.

Conclusions—The results strongly suggest that type 3 patients with reduced CBF and CVR may be divided into 2 pathophysiologically different subgroups: misery perfusion attributable to hemodynamic compromise and matched hypometabolism attributable to incomplete infarction. Type 3 but normal OEF may represent a transition stage from misery perfusion to matched hypometabolism. (***Stroke.* 2006;37:393-398.**)

Key Words: acetazolamide ■ cerebral ischemia ■ flumazenil ■ metabolism ■ oxygen

There is increasing evidence that hemodynamically compromised patients with internal carotid artery (ICA) occlusion are at higher risk for subsequent ischemic stroke. Over these 20 years, an elevated oxygen extraction fraction (OEF) determined by positron emission tomography (PET) has been believed to represent critical reduction of cerebral perfusion pressure, named as "misery perfusion" or "stage II."[1,2] Recent statistical analyses have proven that an elevated OEF can be an independent risk factor for subsequent ischemic stroke in patients with occlusive carotid artery disease.[3–5]

Alternatively, cerebrovascular reactivity (CVR) to CO_2 or acetazolamide has also been used to assess cerebral perfusion reserve in patients with occlusive carotid diseases because single photon emission computed tomography (SPECT) or cold xenon computed tomography (CT) is more widely available and can be done at lower costs than PET. Recent studies have proven that quantitative measurements of cerebral blood flow (CBF) and CVR can also be a predictor for subsequent ischemic stroke in patients with ICA or middle cerebral artery (MCA) occlusion. Thus, Kuroda et al (2001) reported that relative risk conferred by reduced CBF and CVR (type 3) was 8.0 (95% CI, 1.9 to 34.4) for ipsilateral stroke.[6] Subsequently, Ogasawara et al also reported similar results.[7] Based on these observations, SPECT has been expected to identify misery perfusion or stage II more easily than PET if CVR is comparable to OEF.[8]

However, it is still controversial whether impaired CVR is directly linked to OEF elevation in patients with occlusive carotid artery diseases or not. Thus, previous studies have reported a significant correlation between OEF and CVR to acetazolamide or CO_2.[9–14] However, the number of patients included in these studies was not so large, and their hemodynamic and metabolic parameters varied widely among the subjects. On the other hand, recent study has shown that ≈40% of patients with reduced CVR have normal OEF when both parameters are evaluated in each patient.[15] The issue is

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quite important because there may be a significant difference in sensitivity for detecting the patients at higher risk for subsequent stroke between CVR and OEF.

On the other hand, ^{11}C-flumazenil (FMZ) PET has been accepted as a noninvasive, variable tool to investigate neuronal integrity because FMZ is a specific ligand to the central type of benzodiazepine receptors that are exclusively localized in the neurons. Recent studies have shown that ^{11}C-FMZ PET can detect ischemia-induced selective neuronal necrosis that is not visible on either CT or MRI.[16,17]

Therefore, in this study, the authors aimed to clarify whether OEF is elevated in all patients who are diagnosed as type 3 on SPECT, and, if not, to specify the underlying pathophysiology of normal OEF in spite of type 3. For this purpose, the authors measured the parameters for oxygen metabolism and for neuronal integrity in type 3 patients with occlusive, using ^{15}O-gas and ^{11}C-FMZ PET, respectively.

Subjects and Methods

Patients

The present study included a total of 46 patients who were admitted to our hospital between January 1999 and December 2004. All of them met the following criteria: (1) severe stenosis (>90%) or occlusion of the ipsilateral ICA or MCA; (2) no or, if any, small infarction on MRI; and (3) reduced CBF and CVR to acetazolamide in the ipsilateral MCA territory on [^{123}I]*N*-isopropyl-*p*-iodoamphetamine (^{123}I-IMP) SPECT (see below). There were 36 men and 10 women with a mean age of 68.2 years (range 48 to 79 years). Their clinical symptoms included transient ischemic attack or amaurosis fugax in 18 patients and minor completed stroke (Rankin score 1 or 2) in 25. The other 3 patients were asymptomatic. Digital subtraction angiography showed ICA occlusion in 27 patients, ICA severe stenosis in 8, MCA occlusion in 5, and MCA severe stenosis in 6. All studies were performed ≥4 weeks after the last ischemic episode because the studies in an earlier period might affect the correct interpretation of the data.[18]

SPECT Measurements

All patients were scanned with a triple-head γ camera (GCA-9300/DI; Toshiba) to determine CBF and CVR to acetazolamide, as described previously.[16] Briefly, quantitative blood flow was determined by using the ^{123}I-IMP injection and single-scan autoradiographic technique. CBF was quantitatively measured before and 15 minutes after intravenous injection of 10 mg/kg acetazolamide on the separate days with an interval of 2 to 3 days. To evaluate cerebral hemodynamics, 10-mm diameter circular regions of interest (ROIs) were symmetrically placed in the ipsilateral and contralateral MCA territories. As described previously,[6,18,19] CVR to acetazolamide was quantitatively calculated as: CVR (%)=$100\times(CBF_{ACZ}-CBF_{rest})/CBF_{rest}$, where CBF_{rest} and CBF_{ACZ} represent CBF before and after intravenous injection of acetazolamide, respectively. Normal control values of CBF (mean±SD=38.1±5.4 mL/min per 100 g) and CVR (30.0±8.0%) in the MCA territory were obtained from 10 normal volunteers free of cerebrovascular disease. The values were rated as reduced when any of them were less than mean−2 SD. Thus, in the current study, patients were judged as type 3 when CBF was <27 mL/min per 100 g and CVR was <14%.[16]

PET Measurements

All patients were scanned with ECAT EXACT HR+ (Siemens) as described previously.[16] The intervals between SPECT and PET measurements were within 2 weeks. One-minute inhalation of ^{15}O-CO (2 GBq/min) followed by 3-minute static scanning and 3-time arterial blood sampling were performed to measure cerebral blood volume (CBV). After 15-minute inhalation of ^{15}O-O_2 (0.5 GBq/min), a steady-state O_2 image was scanned and 3-time arterial blood sampling was performed for 5 minutes to measure OEF and cerebral metabolic rate for oxygen ($CMRO_2$). Finally, to determine CBF, steady-state CO_2 image was scanned and 3-time arterial blood sampling was performed for 5 minutes after 15-minute inhalation of ^{15}O-CO_2 (0.5 GBq/min). Normal PET values were obtained from 10 volunteers: CBF, 44±4 mL/min per 100 g; $CMRO_2$, 3.3±0.6 mL/min per 100 g; CBV, 3.7±0.7 mL/min, and OEF, 0.43±0.05 (mean±SD). Each PET parameter was obtained using 10-mm diameter circular ROIs. The values were rated as decreased when any of them were less than mean−2 SD and rated as increased when any of them were more than mean+2 SD.

The dynamic FMZ PET was studied in 19 of 46 patients at the same time that ^{15}O-gas PET was performed, as reported previously.[16] Briefly, the injected dose of ^{11}C-FMZ was 370 MBq for each patient. The binding potential (BP) images were calculated pixel by pixel using the reference tissue model.[20]

Data Analysis

To evaluate various parameters obtained from ^{123}I-IMP SPECT, ^{15}O-gas PET, and ^{11}C-FMZ PET, the SPECT and PET images were automatically coregistered to axial T1-weighted MRI images. The SPECT, PET, and MRI images were registered using fully automatic multimodality image registration algorithm on Unix-based workstation (Indigo 2; SGI Inc.).[21]

All data were expressed as mean±SD. The data between 2 groups were compared by use of χ^2 test or paired *t* test as appropriate. Differences with a *P* value of <0.05 were considered statistically significant.

Results

^{15}O PET Parameters

CBF, CBV, $CMRO_2$, and OEF in type 3 patients are shown in the Table. There were significant differences in CBF, $CMRO_2$, and OEF between the ipsilateral and contralateral MCA areas. However, there was no significant difference in CBV between them.

Relationships between OEF and other PET parameters were analyzed in the ipsilateral hemispheres (Figure 1). There was no significant correlation between OEF and CBF (R^2=0.001;

Quantitative Data of Hemodynamic and Metabolic Parameters in the Ipsilateral and Contralateral MCA Areas in Type 3 Patients

	Type 3 Patients			
	Ipsilateral MCA Area	Contralateral MCA Area	Significance	Control Value
n	46	46		10
CBF, mL/100 g/min	24.8±4.5	31.9±6.3	*P*<0.0001	44.0±4.0
CBV, mL/100 g	4.2±1.1	3.8±1.1	NS	3.70±0.70
$CMRO_2$, mL/100 g/min	1.98±0.48	2.27±0.48	*P*=0.0045	3.30±0.60
OEF	0.46±0.09	0.40±0.05	*P*<0.0001	0.43±0.05

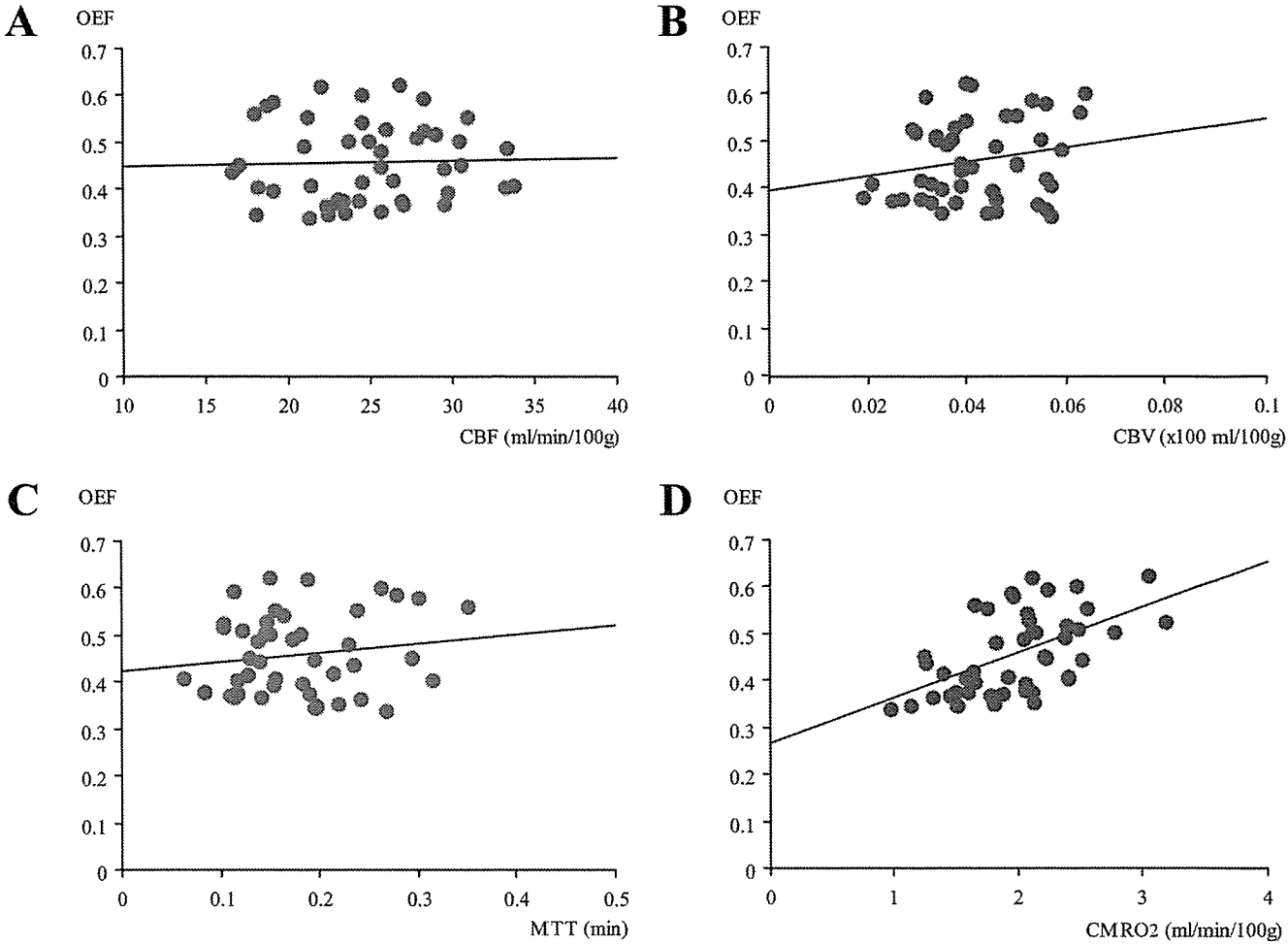

Figure 1. Regression analysis of the relationships between OEF and CBF (A), CBV (B), MTT (C), or $CMRO_2$ (D) in 46 type 3 patients.

P=0.841), between OEF and CBV (R^2=0.041; P=0.1794), or between OEF and mean transit time (MTT; R^2=0.023; P=0.3169). On the other hand, there was significant, positive correlation between OEF and $CMRO_2$ (R^2=0.081; P=0.006).

Then the values of OEF, $CMRO_2$, and CBV were evaluated in each patient. Although OEF was significantly higher in the ipsilateral MCA area than in the contralateral side, OEF was significantly elevated in only 20 (43.5%) of 46 patients. OEF was kept within normal limits in the other 26 patients (Figure 2).

$CMRO_2$ was significantly higher in patients with elevated OEF than in those with normal OEF: 2.26±0.41 and 1.78±0.42 mL/100 g per minute, respectively (P=0.0002; Figure 3). Of 20 patients with elevated OEF, 14 (70%) had normal $CMRO_2$ and the other 6 (30%) had decreased $CMRO_2$ (<2.1 mL/100 g per minute). On the other hand, of 26 patients with normal OEF, 7 (26.9%) had normal $CMRO_2$ and the other 19 (73.1%) had decreased $CMRO_2$. Thus, normal $CMRO_2$ was more frequently observed in patients with elevated OEF than in those with normal OEF (P=0.0032; Figure 3).

There was no significant difference in CBV between patients with elevated OEF and with normal OEF: 4.4±1.1 and 4.0±1.1 mL/100 g, respectively (P=0.2357; Figure 3). However, of 20 patients with elevated OEF, 9 (45%) had increased CBV. Of 26 patients with normal OEF, only 4 (15.4%) had increased CBV. As the result, increased CBV was more frequently denoted in patients with elevated OEF than in those with normal OEF (P=0.0264; Figure 3).

^{11}C-FMZ Binding Potential

To evaluate the neuronal integrity in patients with type 3 ischemia, ^{11}C-FMZ PET was performed in 19 (41.3%) of 46 patients. The relationships between the ratio of the ipsilateral to contralateral ^{11}C-FMZ BP and metabolic parameters were analyzed. There was a significant, positive correlation between the ratio and OEF (R^2=0.507; P=0.0006; Figure 4). The ratio also significantly correlated with $CMRO_2$ (R^2= 0.324; P=0.011).

MRI

Using T2-weighted MRI, the localization of cerebral infarction was evaluated to clarify its effects on cerebral oxygen metabolism and neuronal integrity. Subcortical infarction in the ipsilateral hemisphere was found in 7 of 20 patients with elevated OEF and in 16 of 26 patients with normal OEF. There was no significant effect of subcortical infarction on OEF value in type 3 patients (χ^2 test P=0.0743).

Discussion

The present results revealed that hemodynamic and metabolic parameters in type 3 patients are not uniform, and that they

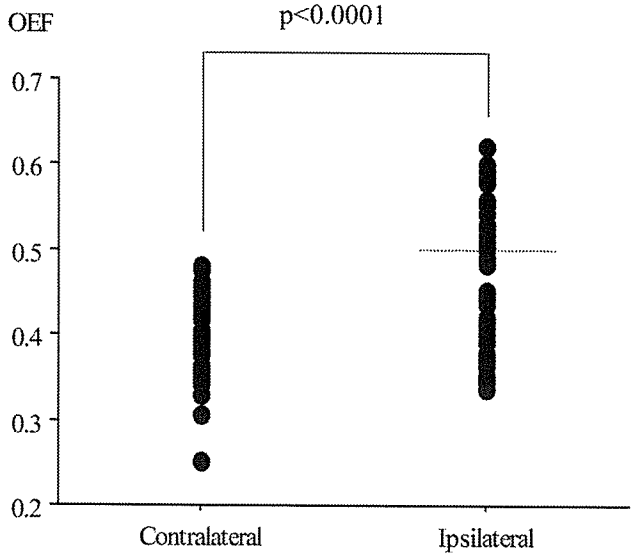

Figure 2. Plot of OEF values in the ipsilateral and contralateral hemisphere of type 3 patients. Dotted line indicates the upper limit of normal OEF value.

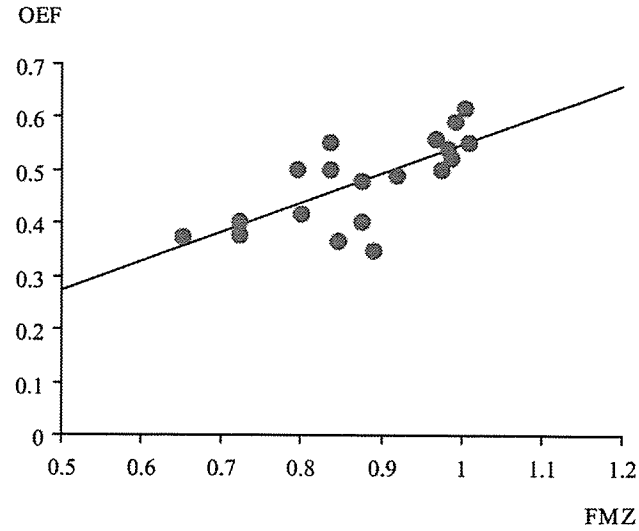

Figure 4. Regression analysis of the relationship between OEF and the BP for ^{11}C-FMZ in 19 type 3 patients.

can be largely classified into 2 subgroups according to OEF value. OEF was significantly elevated in ≈40% of type 3 patients and was within normal limits in the others, indicating that type 3 is not always identical to misery perfusion or stage II. $CMRO_2$ was significantly higher in patients with elevated OEF than in those with normal OEF (Figure 3A) and significantly correlated with OEF (Figure 1D). Therefore, OEF may depend on the metabolic demand in the ischemic tissue.

As the next step, ^{11}C-FMZ BP and the localization of cerebral infarction were evaluated to specify the underlying pathophysiology of $CMRO_2$ reduction in the area with type 3 but normal OEF. Subcortical infarction in the ipsilateral hemisphere was not directly related to type 3 but normal OEF, although previous reports suggested its involvement.[15] However, there was a significant correlation between OEF and the ^{11}C-FMZ BP in type 3 patients. Because γ-aminobutyric acid receptors are abundant in the cortex and sensitive to ischemic damage, the specific ligand to their subunits, the central type of benzodiazepine receptors, has been used as a marker of preserved morphological integrity. Garcia et al emphasized the importance of selective neuronal necrosis (incomplete infarction) in human stroke as a pathologic entity.[17] Recently, the authors demonstrated that $CMRO_2$ and ^{11}C-FMZ BP were reduced to ≈80% of the contralateral side, but there was no significant side-to-side difference in CBV and OEF in patients with reduced CBF and normal CVR (type 4) and concluded that type 4 represents oxygen hypometabolism attributable to ischemia-related selective neuronal damage.[16] Previous studies have shown that the patients with type 4 may not be at high risk for subsequent stroke when medically treated.[6,18] The PET parameters in patients with type 3 ischemia but normal OEF are quite similar to those in the patients with type 4.

Based on these observations, type 3 may include 2 pathophysiologically different conditions: misery perfusion (or stage II ischemia) attributable to hemodynamic compromise, and matched hypometabolism attributable to incomplete infarction. Although the authors have simply graded cerebral hemodynamics of the patients with occlusive carotid artery diseases into 4 types, type 3 should be subdivided into "true type 3," with elevated OEF, and "type 3.5," with normal OEF, in discussing their pathophysiology and long-term prognosis. It is obscure why CVR is impaired in patients with type 3 but normal OEF. As Yamauchi et al pointed out, such

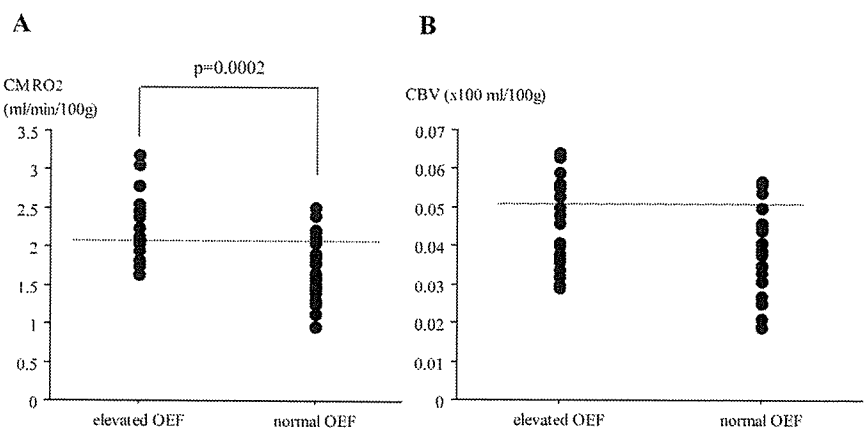

Figure 3. Plots of ipsilateral values of $CMRO_2$ (A) and CBV (B) in patients with elevated and normal OEF. Dotted lines indicate the lower limit of normal $CMRO_2$ value (A) and the upper limit of normal CBV value (B).

patients may have complex hemodynamic and metabolic changes in response to both reduced perfusion pressure and ischemic tissue damage.[14]

Present results mirror previous descriptions, that is, using ^{133}xenon inhalation method and SPECT, the authors divided 32 patients with ICA occlusion into 4 types and serially measured CBF and CVR after superficial temporal artery to MCA anastomosis. Seven patients were diagnosed as having type 3 before surgery. The CVR normalized in all type 3 patients, suggesting postoperative improvement of cerebral perfusion reserve. But CBF returned to normal range in 3 (42.8%) of 7 type 3 patients. As the result, SPECT parameters altered from type 3 to type 4 in other 4 patients.[18] Furthermore, they recently assessed long-term prognosis of 77 patients who were medically treated because of ICA or MCA occlusion. Of 11 type 3 patients, 4 (36.4%) developed ipsilateral ischemic stroke during follow-up periods.[6] The present results may explain these varieties in type 3 patients.

However, as recent studies have clarified, hemodynamic and metabolic responses to reduced perfusion pressure are not so simple. Patients with "classic" misery perfusion (elevated OEF and CBV) are at highest risk for subsequent stroke.[22] However, CBV changes widely vary in patients with occlusive carotid artery disease. This study also showed that CBV widely varied in spite of OEF values. Further studies would clarify the CBV responses to chronic cerebral ischemia more precisely.

This study showed that type 3 is not equal to misery perfusion. However, SPECT and acetazolamide test are still useful modalities because they can simply select the patients at higher risk for subsequent ischemic stroke at lower costs than PET, as described previously.[6,7] Thus, it is very valuable to establish the methodology to detect misery perfusion more efficiently with the use of SPECT because PET is not widely available. Based on a significant linear correlation between OEF and ^{11}C-FMZ BP in this study, the authors propose to evaluate whether ^{123}I-iomazenil (IMZ) SPECT can detect misery perfusion or stage II ischemia in type 3 patients more efficiently. ^{123}I-IMZ is an alternative benzodiazepine receptor ligand for SPECT and has been reported that a reduction of its binding reflects oxidative hypometabolism caused by neuronal damage in hemodynamically impaired areas in patients with cerebrovascular disease.[23–25] Therefore, SPECT may be able to identify the patients with misery perfusion by measuring CVR and ^{123}I-IMZ binding, if the results on ^{123}I-IMZ SPECT are comparable to those on ^{11}C-FMZ PET in patients with occlusive carotid artery diseases.

Conclusion

Previous studies have shown that type 3 (reduced CBF and CVR) as well as elevated OEF is statistically independent predictors for subsequent stroke in patients with occlusive carotid artery diseases.[3,4,6,26] However, this study clearly showed that OEF was elevated in ≈40% of patients with reduced CBF and CVR (type 3). Significant, positive linear relationships were observed between OEF and $CMRO_2$ and between OEF and ^{11}C-FMZ BP. Type 3 may include 2 pathophysiologically different conditions: misery perfusion (or stage II) attributable to hemodynamic compromise and matched hypometabolism attributable to incomplete infarction. Further studies would be necessary to define the SPECT parameter to select the patients at higher risk for subsequent stroke more specifically.

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Simultaneous Superficial Temporal Artery to Middle Cerebral or Anterior Cerebral Artery Bypass With Pan-synangiosis for Moyamoya Disease Covering Both Anterior and Middle Cerebral Artery Territories

—Technical Note—

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Abstract

Some patients with moyamoya disease treated by conventional surgical procedures may develop postoperative refractory ischemia and perioperative cerebral infarction in the anterior cerebral artery (ACA) territory. We present a novel operative procedure for moyamoya disease to avoid the risk of ischemia in the ACA territory, which consists of simultaneous superficial temporal artery (STA) to middle cerebral artery (MCA) or ACA bypass with pan-synangiosis, encephalo-duro-arterio-myo-synangiosis for the lateral frontal and temporal areas, and encephalo-galeo-arterio-synangiosis for the medial frontal area. This procedure can establish direct bypass to the ACA territory at the first intervention. Simultaneous STA-MCA and STA-ACA bypasses with pan-synangiosis is suitable for patients with moyamoya disease associated with severely impaired perfusion of the ACA territory requiring direct bypass surgery.

Key words: moyamoya disease, superficial temporal artery-anterior cerebral artery bypass, encephalo-galeo-arterio-synangiosis, anterior cerebral artery, intellectual outcome

Introduction

Moyamoya disease, an occlusive disease of the circle of Willis, is characterized by the progressive stenosis of the bilateral internal carotid arteries at the terminal portion and the appearance of network-like moyamoya vessels at the base of the brain. Various methods of vasoreconstructive surgery are accepted as treatment for moyamoya disease, including direct bypass such as superficial temporal artery (STA) to middle cerebral artery (MCA) bypass[8]; indirect bypass such as encephalo-duro-arterio-synangiosis,[20] encephalo-duro-arterio-myo-synangiosis (EDAMS),[12] and omentum transplantation[9]; multiple burr holes[1,11]; and a combination of direct and indirect bypasses.[4,10,12] Such methods provide good neovascularization through the extracranial arteries and reduced risk of cerebral ischemia after the surgery. Revascularization surgery for pediatric moyamoya disease has been consistently effective in eliminating ischemic neurological symptoms irrespective of the use of direct or indirect bypass surgery.[6,8,12,19]

Vasoreconstructive surgery is usually performed to cover the lateral frontal, temporal, and parietal lobes, which are territories of the MCA, with satisfactory results in most patients. However, patients have suffered refractory ischemic episodes due to insufficient flow to the anterior cerebral artery (ACA) territory.[5,7,17] Vascular reconstruction targeted to the territory of the ACA is important, because insufficient blood flow in the ACA territory

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Table 1 Profiles of the patients undergoing simultaneous superficial temporal artery to middle cerebral or anterior cerebral artery bypass with pan-synangiosis

Case No.	Preoperative symptoms	Age at onset (yrs)	Age at surgery (yrs)	Sex	First surgery side	Second surgery side	Perioperative complications	Postoperative symptoms
1	TIA	7	9	F	rt	lt	none	TIA disappeared
2	TIA	10	12	F	lt	rt	none	TIA disappeared
3	TIA	3	5	F	lt	rt	none	TIA disappeared
4	TIA	5	6	F	rt	lt	none	TIA disappeared
5	headache	6	8	M	lt	rt	none	headache attenuated
6	TIA	7	10	M	lt	rt	tiny cerebral infarct	TIA frequency reduced
7	infarct	3	6	F	rt		none	no more ischemic episodes, improved intellectual ability (Tanaka-Binet Intelligence Scale: 56→76)
8	TIA, headache	5	14	F	lt	rt	none	TIA disappeared
9	infarct, seizure	25	25	F	lt	rt	none	no more ischemic episodes, improved intellectual ability (WAIS-R: 66→81)
10	infarct	30	31	F	lt		none	no more ischemic episodes, improved intellectual ability (WAIS-R: 72→89)
11	infarct	23	23	M	lt		none	no more ischemic episodes
12	TIA	25	25	F	rt	lt	none	TIA disappeared
13	TIA	32	32	F	lt		none	TIA frequency reduced
14	TIA	59	59	M	lt		none	TIA disappeared
15	TIA	38	38	F	rt	lt	none	TIA disappeared
16	TIA	47	47	F	rt		none	TIA disappeared

TIA: transient ischemic attack, WAIS-R: Wechsler Adult Intelligence Scale-Revised.

would result in cerebral infarction before reoperative surgery.[15] However, such reconstruction is based on indirect bypass, which has no immediate effect to improve cerebral perfusion, and is sometimes unsuccessful especially in adult patients with moyamoya disease. Revascularization from indirect bypass by encephalo-myo-synangiosis[8] or EDAMS[12] begins to develop 2 weeks after surgery and becomes well developed at 3 months postoperatively.

Here we describe a method of simultaneous STA-MCA and STA-ACA bypass with pan-synangiosis to establish both direct and indirect bypasses to both ACA and MCA territories, thus providing an effective vasoreconstructive procedure for moyamoya disease associated with impaired blood flow in the ACA territory.

Materials and Methods

We have performed vasoreconstructive surgery in 35 hemispheres of 22 patients with moyamoya disease since 1996. During this period, 26 hemispheres of 16 patients, four males and 12 females aged 5 to 59 years, were treated with simultaneous STA-MCA and STA-ACA bypass with pan-synangiosis (EDAMS for the lateral frontal and temporal areas and encephalo-galeo-arterio-synangiosis [EGAS] for the medial frontal area). Selection criteria for STA-ACA and STA-MCA bypasses were based on cerebral blood flow (CBF) study and angiographical findings; i.e. impaired blood flow in the ACA territory, and occlusion of the proximal portion of the ACA. STA-ACA bypass was not performed if no branches of the ACA were suitable for anastomosis. Clinical profiles of the patients who underwent the complete procedure including STA-ACA bypass are shown in Table 1. Moyamoya disease manifested as transient ischemic attacks (TIAs) in 11 patients, cerebral infarction in four, and only headache in one.

Surgical Procedures

The surgical technique for the lateral area of the brain was previously reported.[4] This technique can establish both direct and indirect bypasses even in