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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

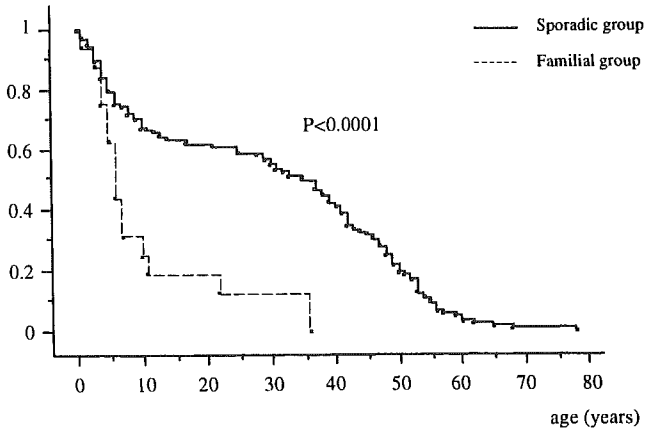


**Fig. 1** Graph showing the age at onset in familial and sporadic cases with moyamoya disease. Kaplan–Meier analysis reveals that the age at onset is significantly lower in familial than in sporadic group

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.

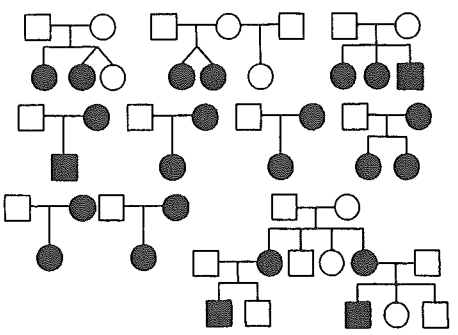

**Fig. 2** Ten pedigrees of familial moyamoya disease included in the present study

## 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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# 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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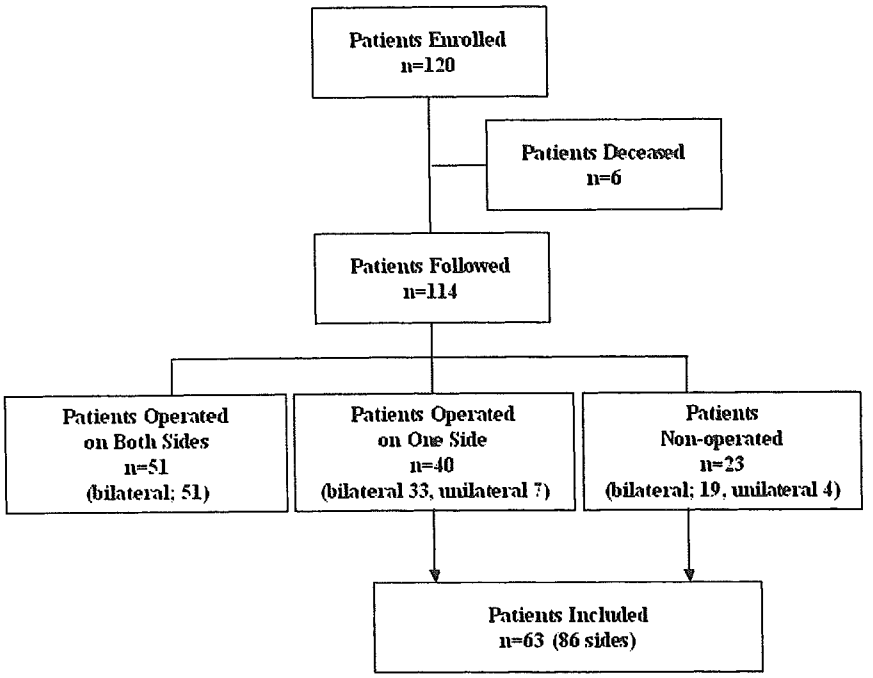


**Figure 1.** Diagram of adult patients with moyamoya disease included in this study.

$^{133}$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 $\chi^2$ 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 ($\chi^2$ 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,

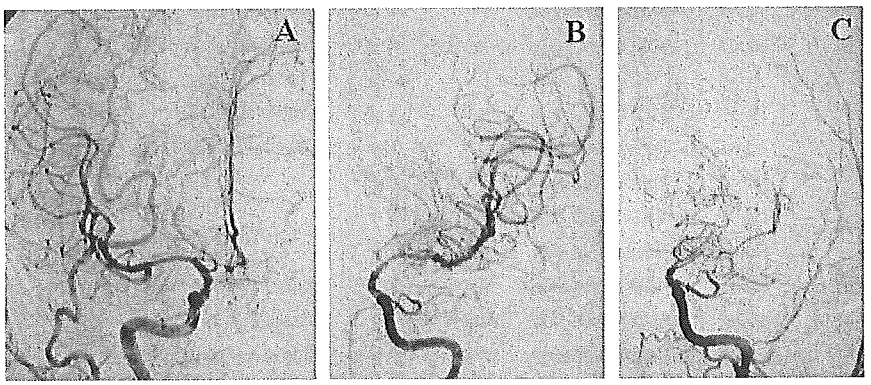


**Figure 2.** Right (a) and left internal carotid angiograms (b and c) of a 50-year-old woman (case 14), showing progression of an occlusive lesion in the left carotid fork during 3-year follow up (b and c).

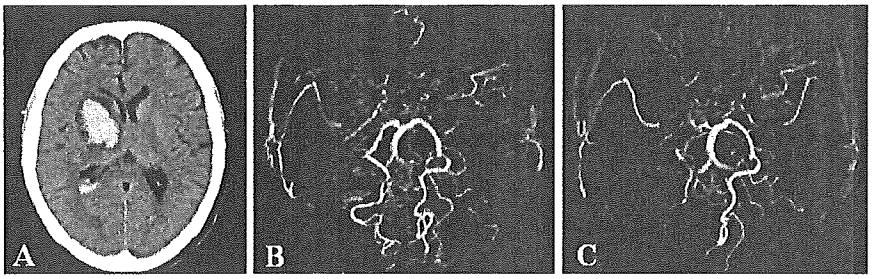


**Figure 3.** Plain computed tomography (a) and MRA (b and c) of a 56-year-old woman (case 15), showing the development of an occlusive lesion in the right posterior cerebral artery between March 2004 (b) and March 2005 (c).

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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CASE REPORT

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# A case of moyamoya disease presenting with chorea

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**Abstract** *Case report:* We describe a 15-year-old girl with moyamoya disease whose initial manifestation was chorea-like involuntary movements. T2-weighted magnetic resonance imaging showed high signal intensity lesions in the left frontal lobe, right parieto-occipital lobes, and frontal subcortical white matter. Single-photon emission computed tomography (SPECT) showed diffuse hypoperfusion of the whole brain. Bilateral direct and indirect cerebrovascular bypass surgeries were performed. Chorea disappeared 2 days after the surgery. Follow-up SPECT demonstrated increased cerebral perfusion in the bilateral frontal, temporal, and parietal regions. *Conclusions:* Chorea accompanied with moyamoya disease can be properly managed by revascularization surgery. Moyamoya disease should be remembered as being one of the differential diagnoses of chorea, which is treatable by surgery.

**Keywords** Moyamoya disease · Involuntary movements · Subcortical white matter · Surgical treatment · Chorea · Ischemia · Cerebral perfusion

## Introduction

Moyamoya disease is known to produce variable neurological symptoms. It tends to manifest as a transient ischemic attack or seizure in children, whereas the hemorrhagic stroke is more common in adult patients. Among other miscellaneous symptoms, the involuntary movements of chorea have been known to occur in 3–6% of patients with moyamoya disease [1]. However, this combination has rarely been reported and the mechanism of these involuntary movements accompanied by moyamoya disease and the effect of revascularization surgery have been investigated very little.

In this case report, we describe a 15-year-old girl with moyamoya disease whose initial manifestation was chorea-like involuntary movements and in whom revascularization surgery was quite effective. The mechanism of chorea due to moyamoya disease and the effect of the revascularization surgery on chorea are discussed.

## Case report

A 15-year-old right-handed girl was observed throwing pens or chopsticks unwarily without any inducement. Several days later, she noticed the involuntary movements of her right arm extending and bending back and forth occasionally. Ten days later, the same symptoms had extended to all four limbs.

Physical examination on admission revealed occasional involuntary movements in all four limbs. Neurological examination was unremarkable except for left inferior homonymous quadrantanopia. The high mental function examination WISC-R ranked 58, which was lower than the normal level. Her father had onset of transient ischemic attacks (TIA) that was attributed to moyamoya disease when he was 35 years old. Her elder sister had undergone an operation for a scalp arteriovenous malformation (AVM).

Magnetic resonance imaging (MRI) of the brain showed high intensity lesions on a T2-weighted image in the left

frontal lobe, right parieto-occipital lobes, and frontal subcortical white matter. No significant intensity change was observed on the T1-weighted images, the T2-weighted images, and on the water suppressed proton weighted images of the bilateral basal ganglia and thalamus (Fig. 1). Diffusion-weighted imaging was not performed. These MR images suggested that the lesion was mainly the cerebral infarction of the cortex and white matter, but not the basal ganglia. The possibility of some degenerative disease could not be fully ignored, but the following angiographical findings supported the suggestion that the ischemic lesion was due to moyamoya disease.

On the digital subtraction angiography (DSA) of the bilateral carotid and vertebral arteries, the bilateral anterior cerebral artery (ACA), and the middle cerebral artery (MCA) could not be identified. Numerous small collater-

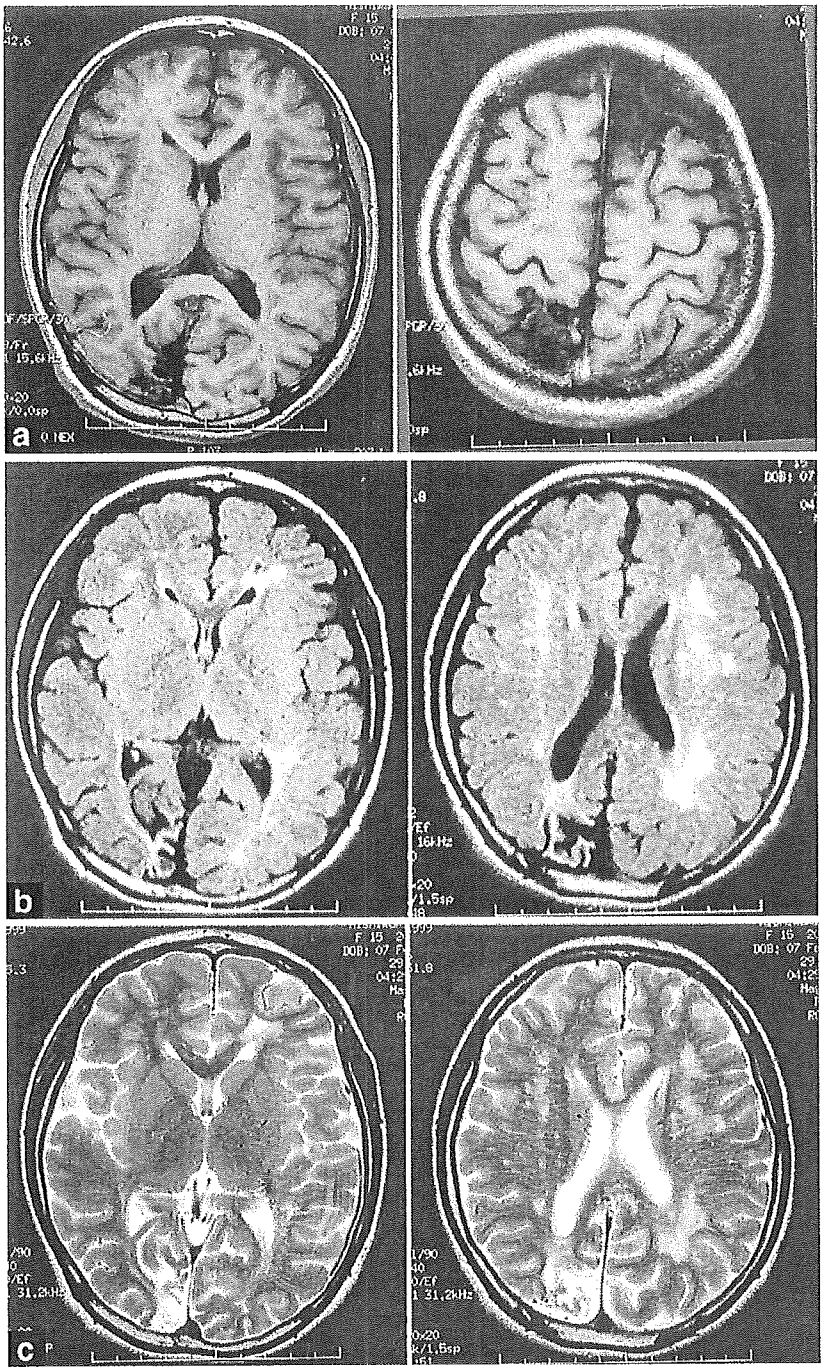


**Fig. 1** **a** T1-weighted magnetic resonance images reveal cortical infarction. **b** Water suppressed proton images (FLAIR) reveal no abnormal intensity in the basal ganglia and an abnormally high signal lesion in the subcortical white matter. **c** T2-weighted magnetic resonance images reveal similar findings to those seen on the FLAIR images

al vessel networks were found at the base of the brain (Fig. 2a, b), collateral flow from the occipital artery and the internal maxillary artery to the internal carotid regions (Fig. 2c, d). *N*-Isopropyl-*p*-(I-123) iodoamphetamine ($^{123}$I-IMP) single-photon emission computed tomography (SPECT) showed a focal perfusion defect in the left frontal and right occipital regions. The quantitative study showed diffuse hypoperfusion within the whole brain (Fig. 3a). The mean cerebral blood flow at the level of the body of the ventricle was 33.2 ml/100 g/min on the right side and 32.2 ml/100 g/min on the left side.

Two weeks after admission, a right superficial temporal artery–middle cerebral artery (STA–MCA) bypass and encephalo-duro-arterio-myo-synangiosis (EDAMS) were performed. The same surgery was performed on the other side 3 weeks later. The chorea disappeared 2 days after the first operation. One week after the second operation, 100 mg aspirin was taken per day as medical therapy.

The follow-up DSA 6 months after the operation revealed MCA and anterior cerebral artery regions were filled via the STA and the deep temporal artery (Fig. 2e, f). The SPECT demonstrated that cerebral perfusion had

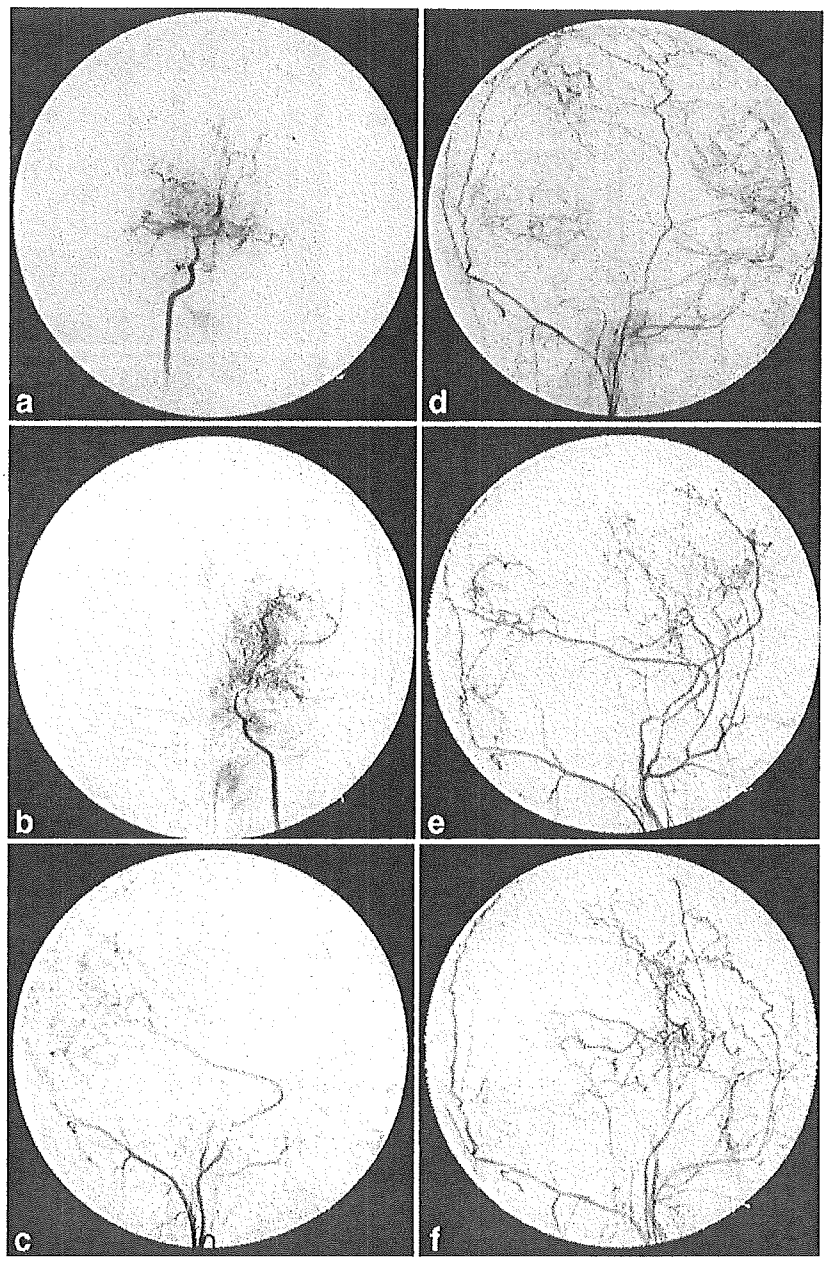


**Fig. 2** **a, b** Preoperative angiography of the internal carotid arteries showed stenosis of both internal carotid arteries at the supraclinoid portion and numerous collateral vessel networks at the base of the brain. **c, d** Preoperative angiography of the bilateral external carotid arteries showed collateral flow from the occipital artery and internal maxillary artery to the internal carotid regions. **e, f** Postoperative angiography of the bilateral external carotid arteries showed that collateral flow increased markedly

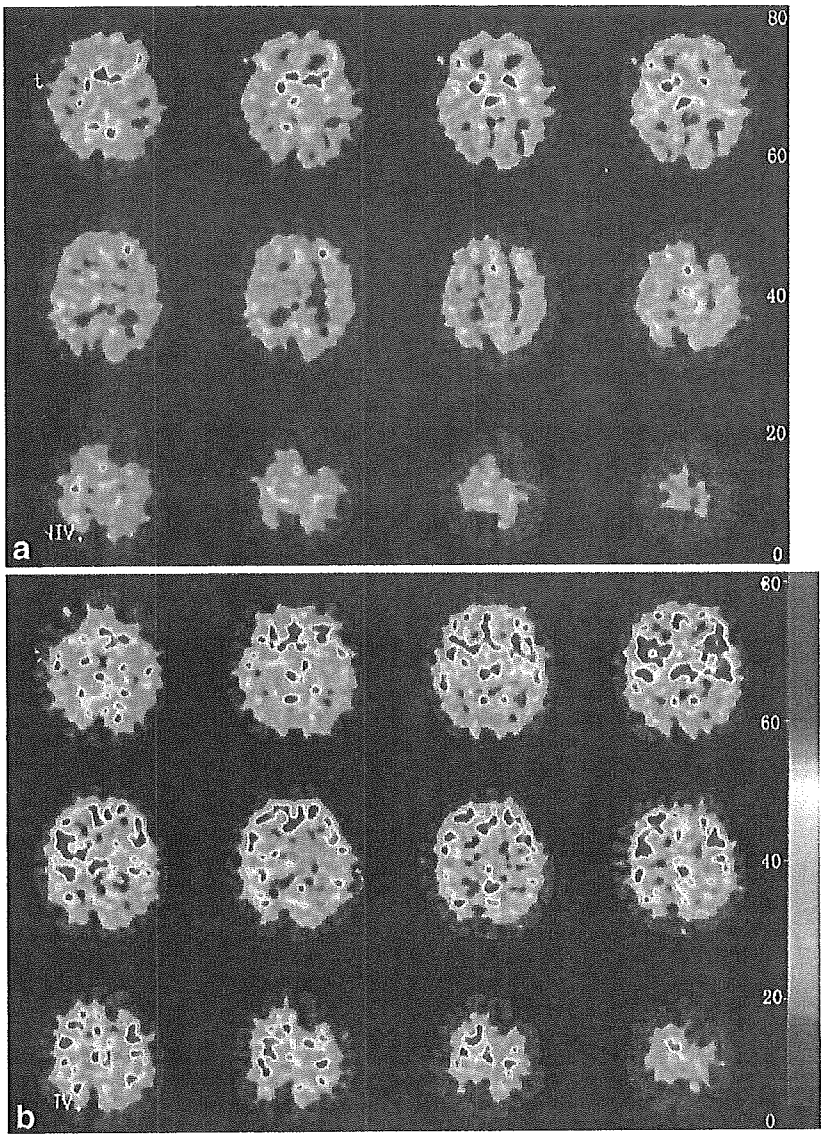


**Fig. 3** Quantitative cerebral blood flow images (SPECT). **a** Diffuse cerebral hypoperfusion in the whole brain before surgery. **b** Cerebral perfusion increased markedly within the whole brain after surgery

increased in the bilateral frontal, temporal and parietal regions (Fig. 3b). The mean cerebral blood flow increased to 43.5 ml/100 g/min on right side and 43.2 ml/100 g/min on left side, which were significant increases compared with the preoperative values. The high WISC-R score measuring mental function improved from 58 to 65. The involuntary movements have not recurred for 2 years although MRI revealed no significant change.

## Discussion

Chorea is an uncommon abnormal movement that can be seen in a wide range of disorders. These diseases are classified as follows: inherited disorders, drug-induced diseases, systemic diseases, rheumatic diseases, vascular-related diseases, tumor-related diseases, and other rare causes [2]. The probable pathophysiologic mechanism of chorea seems to result from under-activity in the indirect pathway from the basal ganglia-thalamocortical motor circuits [3]. Although there are obvious degenerative lesions in the caudate and putamen in Huntington's disease, the inherited disorders that are characterized by chorea, ischemic dysfunctions of the basal ganglia, cortex, subcortical white matter, thalamus, and subthalamic nucleus, have been suggested as causes of many subtypes of involuntary movements [4, 5].

The common clinical presentations of pediatric moyamoya disease are transient ischemic attacks that are typically induced by hyperventilation, epileptic seizures, and migraine-like headaches. Involuntary movement disorder including chorea is not always a common clinical presentation in moyamoya disease. However, recently, there

have been several reports describing cases of moyamoya disease presenting with movement disorder [6–13] and it has been known to occur in 3–6% of patients. In most reported cases of chorea with moyamoya disease, the ischemic changes in the basal ganglia-thalamocortical circuits are considered to be responsible for involuntary movements including chorea, although some papers revealed that cortical ischemic lesions are responsible for chorea [14–19]. It is well known that cerebral ischemia is generally an important cause of some movement disorders. In our case, the MRI of the brain showed high signal intensity lesions on T2-weighted images in the left frontal lobe, right parieto-occipital lobes, and frontal subcortical white matter, but showed no significant ischemic change in the bilateral basal ganglia. This suggests that any interruption of the basal ganglia-thalamocortical circuits might cause the involuntary movements.

The surgical therapy for moyamoya disease can be categorized as direct revascularization, indirect revascularization, or a combination of both. It is reported that combined surgery (STA–MCA bypass with EDAMS) for pediatric moyamoya disease was effective in reducing the risk of postoperative ischemic attacks compared with indirect surgery [20]. In the present case, we performed an STA–MCA bypass combined with EDAMS bilaterally. The involuntary movements disappeared 2 days after the first operation. The follow-up DSA showed that MCA and ACA regions were filled through the external carotid system. The SPECT revealed remarkable perfusion improvement in the subcortical white matter. These results suggest that proper surgical treatment can increase cerebral perfusion, improve clinical symptoms, and prevent the development of the disease.

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# 小児脳卒中の治療

## ——もやもや病に対する外科的治療を中心に——

*Treatment for cerebrovascular disease in children : Surgical management to moyamoya disease in children*

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◆key words：Willis 動脈輪閉塞症，MR，血行再建術，脳卒中，もやもや病

## はじめに

小児期の脳卒中は近年3.3人/10万人との報告がみられるが[1]，これは最近の診断治療技術の発展により増加傾向にあると考えられ，本邦における正確な発生頻度については今なお不明である。

成人の脳卒中と異なる特徴としては多彩な小児科領域の疾患群の合併症として発症することが多いということ，出産時外傷を代表とした外傷機転が関与することが少なくないことなどがあげられるが，いわゆる acute infantaile hemiplegia として，原因不明のものも多い。高血圧，糖尿病などの動脈硬化が原因となることはまれで，凝固異常，血液疾患，心奇形，血管奇形，結合織病，代謝異常，悪性腫瘍などさまざまな原因があり，これらの疾患を検索する必要がある。

そのなかでも，もやもや病（特発性 Willis 動脈輪閉塞症）は小児の脳虚血の原因疾患の第一の原因であろうと考えられている。もやもや病の基本的病態は Willis 動脈輪前半部を中心とした動脈の狭窄性病変の進行であり，それに伴い多くの側副路が発達する。「もやもや」という言葉はその側副路が脳血管撮影上にて映し出される状態を表す言葉で，しかも経時的に閉塞病変や側副路の発達の程度が変化する。この代償的な側副血行路が主幹動脈の閉塞の進行に追いつかず，過不足ない血流の供給が困難な状態に陥った際に症状が発現すると考えられる。本稿ではその代表的なもやもや病の診断，そして外科的治療を中心に解説する。

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## 診　断

### 1. 症　状

もやもや病の脳虚血症状は過呼吸時に生じる脱力発作が有名であるが，その他にも不随意運動，精神発達遅延，片頭痛様の頭痛，発熱などを契機として起こる脳梗塞など，非常に多彩な臨床病型を呈することを知っておく必要がある[2]。基本的に頭痛症状のみの場合以外に対しては後述の外科的治療を考慮する必要があり，患児の ADL や全身状態，症状の程度を総合的に検討し手術適応を決定することになる。

### 2. 画像診断（診断基準）

もやもや病の診断基準を表1にあげる[3]。診断には脳血管撮影もしくは MRA による脳血管の画像診断が必須であるが，小児の場合は脳血管撮影よりも侵襲の少ない MR 検査にて診断をつけるべきと考える[4]。

その要点は，

(1) 頭蓋内内頸動脈終末部，前および中大脳動脈近位部に狭窄または閉塞がみられる。

(2) その付近に異常血管網が動脈相においてみられる。

(3) これらの所見が両側性にある。

現在，両側性に病変が認められる症例は確実例。一側例は疑い例として定義されている。また他の基礎疾患に伴う類似の血管病変は「類もやもや病（quasi-moyamoya disease）」と称し，もやもや病とは区別する。これらの所見を基本として病期分類を表2に示すが[5]，これは必ずしも臨床的な重症度とは相関しない。

MR 検査で注意する点としては，大脳基底核部の

表1　Willis 動脈輪閉塞症の診断基準

(1) 診断上，脳血管撮影は必須であり，少なくとも次の所見がある
①頭蓋内内頸動脈終末部，前および中大脳動脈近位部に狭窄または閉塞がみられる
②その付近に異常血管網が動脈相においてみられる
③これらの所見が両側性にある

(2) ただし，磁気共鳴画像（MRI）と磁気共鳴血管撮影（MRA）により脳血管撮影における診断基準に照らして，下記のすべての項目を満たし得る場合は通常の脳血管撮影は省いてもよい（「MRI・MRA による画像診断のための指針」を参照のこと）
① MRA で頭蓋内内頸動脈終末部，前および中大脳動脈近位部に狭窄または閉塞がみられる
② MRA で大脳基底核部に異常血管網がみられる
（注） MRI 上，大脳基底核部に少なくとも一側で 2 つ以上の明らかな flow void を認める場合，異常血管網と判定してよい
③①と②これらの所見が両側性にある

(3) 特発性 Willis 動脈輪閉塞症は原因不明の疾患であり，下記の特別な基礎疾患に伴う類似の脳血管病変は除外する

| | | |
|---|---|---|
| ①動脈硬化 | ②自己免疫疾患 | ③髄膜炎 |
| ④脳腫瘍 | ⑤ Down 症候群 | ⑥ von Recklinghausen 病 |
| ⑦頭部外傷 | ⑧頭部放射線照射 | ⑨その他 |

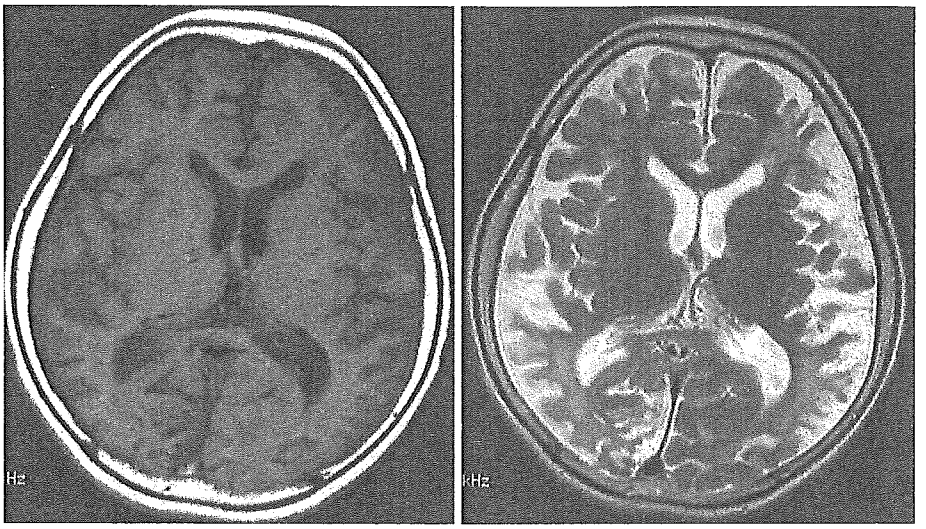
(4) 診断の参考となる病理学的所見
①内頸動脈終末部を中心とする動脈内膜肥厚と，それによる内腔狭窄ないし閉塞が通常両側性に認められる。とくに肥厚内膜内に脂質沈着を伴うこともある
②前・中大脳動脈，後大脳動脈など Willis 動脈輪を構成する諸動脈に，しばしば内膜の線維性肥厚，内弾性板の屈曲，中膜の菲薄化を伴う種々の程度の狭窄ないし閉塞が認められる
③ Willis 動脈輪を中心として多数の小血管（穿通枝および吻合枝）がみられる
④しばしば軟膜内に小血管の網状集合がみられる

[診断の判定]
(1)〜(4)に述べられている事項を参考として，下記のごとく分類する。なお脳血管撮影を行わず剖検を行ったものについては，(4)を参考として別途に検討する
確実例：
(1)あるいは(2)のすべての条件および(3)を満たすもの。ただし，小児では一側に(1)あるいは(2)の①，②を満たし，他側の内頸動脈終末部付近にも狭窄の所見が明らかにあるものを含む
疑い例：
(1)あるいは(2)および(3)のうち，(1)あるいは(2)の③の条件のみを満たさないもの

（吉本高志，他：最新の診断，手引（2001 年）．厚生省特定疾患ウィリス動脈輪閉塞症調査研究班　平成 12 年度総合研究報告書，2001，pp 73 〜 95）

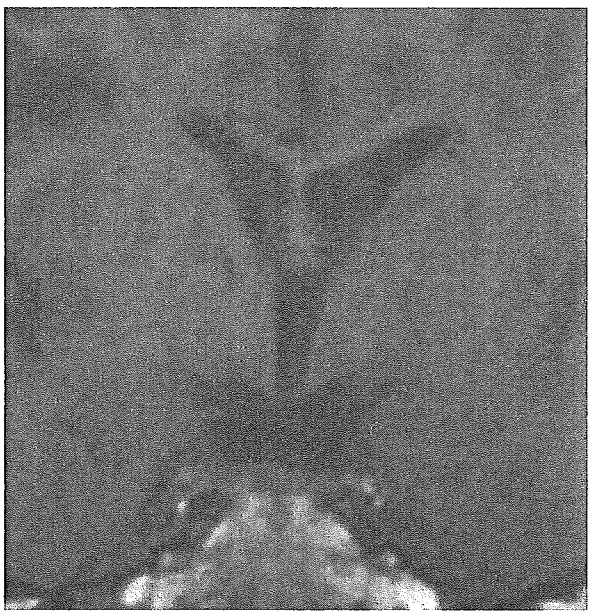
表2　もやもや病の血管撮影上の病期分類[9]

| | |
|---|---|
| 第 1 期： | carotid fork 狭小期。carotid fork 部の狭窄が認められる以外，まったく異常が認められない |
| 第 2 期： | moyamoya 初発期。caritid fork 部の狭窄およびわずかな basal moyamoya がみられ，脳主幹動脈は拡張像を呈する |
| 第 3 期： | moyamoya 増勢期。basal moyamoya が発達し，その構成血管は太く粗である。前および中大脳動脈は脱落し始める |
| 第 4 期： | moyamoya 細微期。もやもや血管の 1 本 1 本が細小化し，貧弱で網状となる。前および中大脳動脈は造影されなくなるが，篩骨部にもやもや血管（ethmoidal moyamoya）が発達してくる |
| 第 5 期： | moyamoya 縮小期。もやもや血管の縮小化がさらに進み，その範囲も carotid fork 部直上に限局する。外頸動脈系を介する側副路が増加してくる |
| 第 6 期： | moyamoya 消失期。頭蓋内内頸動脈系はまったく造影されず，もやもや血管も完全に消失し，脳内血管は外頸動脈系もしくは椎骨動脈系からだけ灌流される |



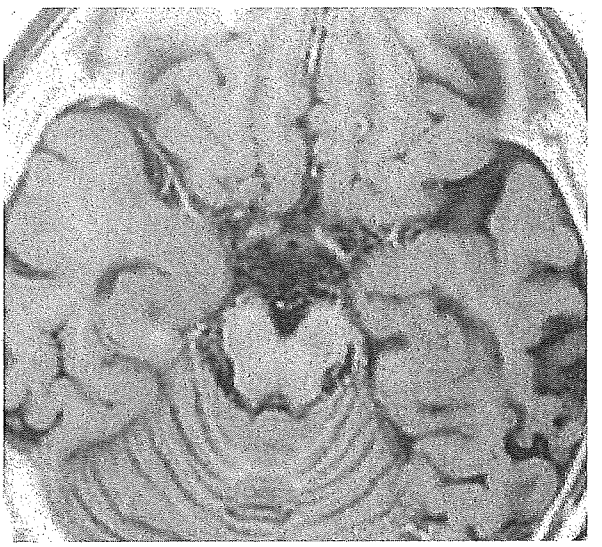
T1 強調画像では基底核部の signal void 所見を認めるが，T2 強調画像では不明瞭である

図 1　MRI 画像



T1 強調画像冠状断は基底核部の拡張血管の走行を理解しやすい

図 2　MRI 画像



T2 強調画像を白黒反転すると basal moyamoya の発達を理解しやすい

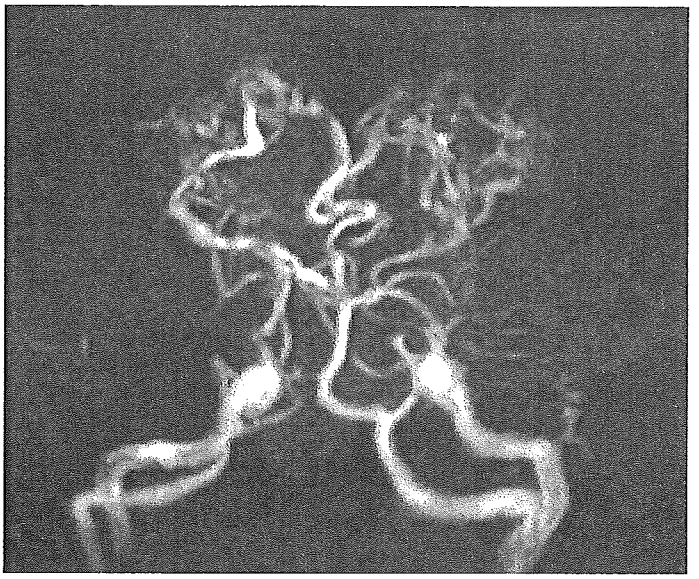
図 3

flow void は T2強調画像では観察しづらく，撮像の際には原則として T1強調画像，T2強調画像を必要とする。急性期の場合はさらに FLAIR 画像や拡散強調画像が有用なのは通常の虚血症例の場合と変わらない（図 1 ～4 ）。

脳血流検査（SPECT，PET）は，本来通常の脳虚血症例と同様に有用な情報を得られる検査であるが，成人の血流検査とは異なり小児の場合，定量的な検査を完全に行うことは必ずしも容易ではなく，また好発年齢の乳幼児から学童期は血流が大きく変化する時期でもあり正常値の判定も困難である。成人の場合は脳血流検査が手術適応の重要な判断材料になるが，これはそのまま小児に適応することは，逆に手術時機を逸する危険性が否定できないので注意が必要である。

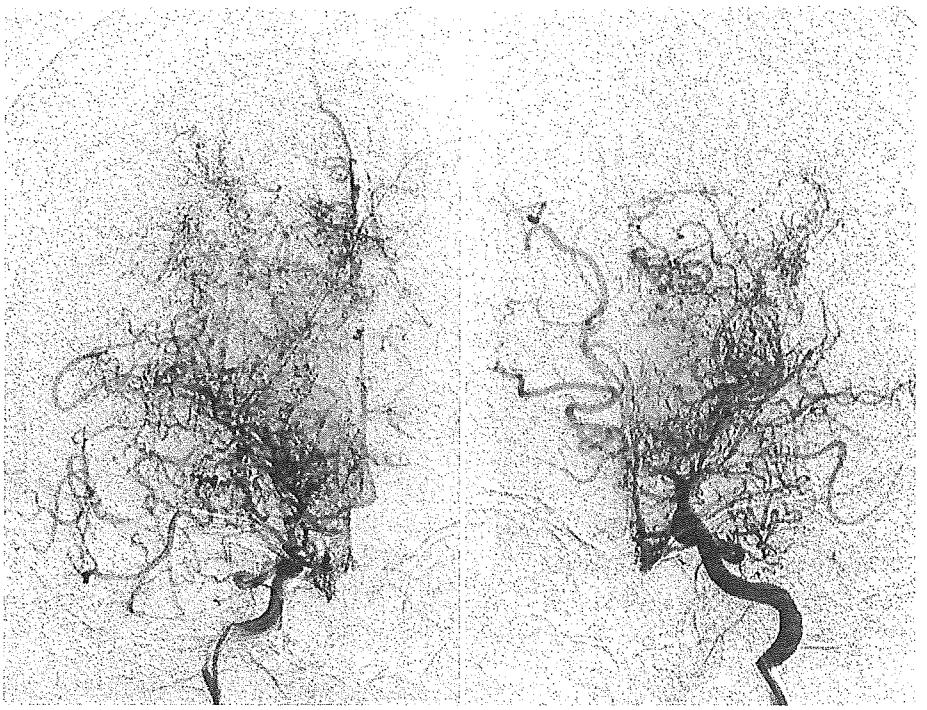
## 治療方針

先に述べたように頭痛以外の虚血症状が出現している場合，治療を考慮することになるが，現在もやもや病に対する薬物治療は痙攣，不随意運動に対する対症療法以外になく，狭窄病変の進行に対する根



両側内頸動脈末梢部から前大脳動脈，中大脳動脈の閉塞を認める

図4　MRA



MRA では判断困難なもやもや血管の発達が著明である

図5　図4と同一症例の脳血管撮影

本的な治療法はない。外科的治療には直接的血行再建術と間接的血行再建術があり，外科的治療の目標は側副血行路を新生し血行動態を安定させることにある[6)~8)]。

直接的血行再建術は頭蓋外の動脈を直接頭蓋内動脈に吻合することにより血流を確保することを目的とし，代表的なものに浅側頭動脈-中大脳動脈吻合術があるが，術後早期から脳循環を改善することが可能になる反面，改善できる範囲は局所にかぎられる。それに対し間接的血行再建術とは脳と血行豊富な組織を接着することによりその組織と脳の間に新生血管が発生する現象を利用した手術であり，広汎な領域の虚血を補い得るが血管新生には少なからず時間を必要とする。したがって，それぞれを独立した手術として施行するのではなく双方の利点を生かし，また患者の血行動態によりさまざまな方法で組