Incidence and Clinical Features of Disease Progression in Adult Moyamoya Disease

Satoshi Kuroda, MD, PhD, Tatsuya Ishikawa, MD, PhD, Kiyohiro Houkin, MD, PhD, Rina Nanba, MD, PhD, Masaaki Hokari, MD, PhD, Yoshinobu Iwasaki, MD, PhD

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 approximately 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
133xenon or 123I-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 χ² 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.).

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...
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...
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 \( \approx 20\% \) 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 \( \approx 20\% \) of all of the moyamoya disease in Japan.\(^22\) According to previous surveys.

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

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

Continuous data are expressed as mean±SD.
unilateral moyamoya disease has been recognized as stable in adults. 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. 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. 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. However, the prognosis of asymptomatic patients is still unclear, and the standardized strategy for them has not been established. 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, suggesting the female predominance in moyamoya disease. Furthermore, female predominance is more pronounced in familial moyamoya disease. Thus, Kanai et al reported that a male-to-female ratio in familial moyamoya disease was 1:3.3. A recent study also showed that male-to-female ratios were 1:5 and 1:1.6 in familial and sporadic cases, respectively, indicating

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