MoyaMoya disease (MMD) is an idiopathic stenoocclusive disease of the bilateral internal carotid arteries, with characteristic abnormal vascular networks. Its presentation exhibits a bimodal distribution with age: children mostly exhibit an ischemic presentation, and adults usually present with hemorrhage or ischemia. Although the pathogenesis and natural course are not yet known, revascularization surgery has been satisfactory for patients with ischemic symptoms. For pediatric MMD, revascularization surgery is universally recommended, regardless of the severity of MMD, because most symptoms are ischemic, and children's brains are still developing. In adult-onset MMD, revascularization surgery is selectively recommended for patients with ischemic symptoms and hemodynamic compromise. However, the efficacy of surgery for the hemorrhagic subtype of MMD remains inconclusive, and the clinical course in asymptomatic patients who do not undergo surgery is not known.

The natural clinical course of hemodynamically stable adult moyamoya disease

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OBJECT Moyamoya disease (MMD) is a rare cerebrovascular disease and its natural history is still unclear. The authors aimed to investigate the natural course of hemodynamically stable cases of adult MMD, with the analysis of stroke risk factors.

METHODS Two hundred forty-one patients were included in this retrospective study. One hundred sixty-six (68.9%) were female, and mean age (± SD) at first visit was 41.3 ± 12.0 years (range 18–69 years). Unilateral involvement was identified in 33 patients, and 19 patients (7.9%) had a family history of MMD. According to the clinical presentations, patients were classified into hemorrhagic (n = 62, 25.7%), ischemic (n = 144, 59.8%), and asymptomatic (n = 35, 14.5%) groups. The mean duration of follow-up was 82.5 ± 62.9 months (range 7.3–347.0 months).

RESULTS The annual stroke risk was 4.5%, and the annual risks of rebleeding in the hemorrhagic group and recurrent ischemic events in the ischemic group were 4.3% and 3.0%, respectively. There was no significant difference in cumulative stroke risk between the 3 groups (p = 0.461). Risk factors included thyroid disease for overall strokes (HR 2.56, 95% CI 1.16–5.67), initial hemorrhagic presentation for hemorrhagic strokes (HR 2.53, 95% CI 1.24–5.17), and initial ischemic presentation for ischemic strokes (HR 2.69, 95% CI 1.15–6.27). Familiar MMD was a common risk factor for all types of stroke. Among the 3 clinical groups, the hemorrhagic group showed the worst clinical status at discharge and at most recent follow-up. Twenty-three patients (9.5%) eventually underwent revascularization surgery.

CONCLUSIONS There was no statistically significant difference in the incidence of stroke in the different clinical groups; clinical status, however, was most severe in patients with hemorrhagic presentation. In patients who experienced stroke during the follow-up period, the stroke type tended to correspond to their initial presentation. Close follow-up is needed in patients with thyroid disease and a family history of MMD.

http://thejns.org/doi/abs/10.3171/2014.9.JNS132281

KEY WORDS asymptomatic; hemorrhage; ischemia; moyamoya disease; clinical course; vascular disorders

ABBREVIATIONS KPS = Karnofsky Performance Scale; MMD = moyamoya disease; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage; SPECT = single photon emission computed tomography; TIA = transient ischemic attack.


INCLUDE WHEN CITING Published online October 31, 2014; DOI: 10.3171/2014.9.JNS132281.

DISCLOSURE This study was supported partly by Seoul National University Hospital Fund (0320120310, 2012-0581) and partly by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI10C2020).
Methods

Patient Selection

Under the approval of the Seoul National University Hospital Institutional Review Board, we retrospectively reviewed the medical records of 241 patients who had been diagnosed with adult MMD from July 1983 to April 2011 and who had not undergone revascularization surgery at the time of diagnosis. Inclusion criteria were as follows: 1) adult patients (age ≥ 18 years); 2) initial symptoms related to hemorrhage or ischemia or asymptomatic presentation; 3) compatibility with the diagnostic guidelines; 4) hemodynamically stable status on single photon emission computed tomography (SPECT); 5) medical records pertaining to evaluation of certain concomitant medical conditions at the first visit and during the follow-up period, such as hypertension, smoking, diabetes mellitus, hyperlipidemia, or cardiovascular or peripheral vascular, endocrinological, or immunological diseases; and 6) follow-up duration of 6 months or more. All patients were initially evaluated with cerebral angiography, CT, and MRI, and SPECT. Patients were considered to demonstrate hemodynamically stable status on SPECT if their basal perfusion status was normal or mildly decreased and their vascular reserve capacity after acetazolamide challenge did not decrease by more than 50% of the basal perfusion. Patients with rare symptoms such as involuntary movement and seizure that were not secondary to ischemia or bleeding were excluded.

The patients’ demographic and clinical characteristics are summarized in Table 1. The male to female ratio was 1:2.2, and the mean age (± SD) at the first visit was 41.3 ± 12.0 years (range 18–69 years). Of the 33 patients with unilateral involvement, 20 had left-side involvement and 13 right-side involvement. Of the patients with familial MMD, 17 (89.5%) were symptomatic and 2 were asymptomatic, with all 19 being from different families. The mean Suzuki grades for the right and left hemispheres were 3.9 ± 0.5 (n = 221, range 2–5) and 3.9 ± 0.6 (n = 228, range 2–5), respectively. Hypertension was a dominant medical problem (30.3%), and thyroid diseases were present in 1 patient with hypothyroidism from Hashimoto disease and in 11 with hyperthyroidism from Graves’ disease.

Evaluation of Clinical Course

Initial clinical manifestations were divided into 3 groups as follows: hemorrhagic group (intracranial hemorrhage—intracerebral, intraventricular, or subarachnoid), ischemic group (ischemic symptoms of transient ischemic attack [TIA] and cerebral infarction), and asymptomatic group (asymptomatic presentation, including true asymptomatic as well as nonspecific symptoms such as headache and dizziness). There were 62 patients in the hemorrhagic group (25.7%), 144 in the ischemic group (59.8%), and 35 in the asymptomatic group (14.5%). Of the 62 patients in the hemorrhagic group, 9 (14.5%) had subarachnoid hemorrhage (SAH) with or without intracerebral or intraventricular hemorrhage, and 53 (85.5%) had intracerebral and/or intraventricular hemorrhage without SAH. Of the 144 patients in the ischemic group, 70 had TIAs (48.6%) and 74 had infarctions (51.4%).

We analyzed the natural clinical course of MMD with respect to 3 different aspects during the follow-up: 1) annual risk of stroke, 2) risk factors for stroke event, and 3) clinical outcome. Clinical outcomes were evaluated with the modified Rankin Scale (mRS) and Karnofsky Performance Scale (KPS) at the initial visit (status at discharge) and last follow-up evaluation. The overall mean duration of follow-up was 82.5 ± 62.9 months (range 7.3–347.0 months). Stratified by clinical group, the mean values for duration of follow-up were 95.4 ± 90.3 months (range 7.3–347.0 months) in the hemorrhagic group, 77.3 ± 65.1 months (range 7.3–331.9 months) in the ischemic group, and 81.5 ± 50.6 months (range 18.4–188.4 months) in the asymptomatic group.

Statistical Analysis

Continuous variables were expressed as mean ± SD. Categorical variables were compared by using Pearson’s chi-square test. The annual risk of stroke was calculated with a person-year method, and the cumulative stroke risk was evaluated using the Kaplan-Meier method. Comparisons of risks in the different groups were performed using log-rank tests. A stroke event was defined as a symptomatic hemorrhage or ischemia that occurred in the pathological hemisphere, regardless of laterality, during the follow-up period. The timing of the stroke event was determined from the initial presentation to the first symptomatic stroke. The endpoints were the occurrence of stroke (uncensored), the last follow-up evaluation (censored), and surgical intervention (censored). Cox proportional hazard analysis was performed to evaluate risk factors for stroke during

| TABLE 1. Clinical features of 241 patients with adult MMD* |
|----------------|----------------|
| Characteristic | Value |
| Sex            |       |
| Male           | 75    |
| Female         | 166   |
| Age (yrs)      |       |
| Mean           | 41.3 ± 12.0 |
| Range          | 18–69 |
| Laterality     |       |
| Bilateral involvement | 208     |
| Unilateral involvement | 33     |
| Familial type (%) | 19 (7.9) |
| Initial clinical manifestations (%) | |
| Hemorrhagic group | 62 (25.7) |
| Ischemic group   | 144 (59.8) |
| Asymptomatic group | 35 (14.5) |
| Concomitant medical diseases (%) | |
| Hypertension    | 73 (30.3) |
| Hyperlipidemia  | 30 (12.4) |
| Thyroid disease | 12 (5.0) |
| Follow-up duration (mos) | |
| Mean           | 82.5 ± 62.9 |
| Range          | 7.3–347.0 |

* Unless specified otherwise, values indicate the number of patients.
follow-up, and variables with significance values of \( p < 0.2 \) were selected for multivariate analysis. Included risk factors were sex, age, initial clinical manifestations (hemorrhagic, ischemic, and asymptomatic, including nonspecific symptoms), bilaterality (bilateral or unilateral involvement of distal internal carotid arteries), familiality (more than 1 first-degree relative with MMD), and concomitant medical diseases such as hypertension, hyperlipidemia, and thyroid disease that were already known or newly detected at the first visit or during the follow-up period, all of which were medically managed after identification. A \( p \) value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 19.0 software (IBM SPSS Inc.).

Results

Incidence of Stroke

The annual risk of stroke is presented for patients in all 3 groups in Table 2. During the entire follow-up period, the rate of any stroke in all patients was 4.5%/person-year. Stroke events occurred more frequently in the hemorrhagic group than in either the ischemic or the asymptomatic group (5.7% vs 4.2% and 3.4%, respectively). Hemorrhagic events tended to occur at a higher rate in the hemorrhagic group than in the ischemic group (4.3% vs 1.2%), and ischemic events occurred at a higher rate in the ischemic group than in the hemorrhagic group (3.0% vs 1.4%). In the asymptomatic group, the risk of hemorrhagic stroke was higher than the risk of ischemic stroke (2.5% vs 0.8%).

Overall, the 5- and 10-year cumulative risks of any stroke were 17% and 31%, respectively. The 5- and 10-year risks of hemorrhagic stroke were 10% and 19%, respectively, and risks of ischemic stroke were 9% and 20%, respectively, with no significant difference (\( p = 0.857 \) Fig. 1 left). By group, the 5- and 10-year risks of any stroke were 15% and 40% in the hemorrhagic group, 17% and 33% in the ischemic group, and 15% and 25% in the asymptomatic group, respectively (Fig. 1 right). There were no significant between-group differences in stroke risk (\( p = 0.461 \) in total, \( p = 0.288 \) between the hemorrhagic and ischemic groups, \( p = 0.697 \) between the ischemic and asymptomatic groups, \( p = 0.265 \) between the hemorrhagic and asymptomatic groups).

The 5- and 10-year cumulative risks of recurrent hemorrhagic and ischemic events are demonstrated in Fig. 2. In a comparison of recurrent ischemic risk between patients with infarction and those with TIA alone within the ischemic group, there was no significant difference (\( p = 0.290 \)). In addition, the numbers of infarction or TIA events were similar in patients with infarction and those with TIA alone within the ischemic group (infarction, \( p = 0.618 \); TIA, \( p = 0.631 \)).

Risk Factors for Stroke

Univariate analyses for risk factors identified 2 significant factors for any stroke (familial MMD and thyroid disease), 4 risk factors for hemorrhagic stroke (male sex, hemorrhagic presentation, hyperlipidemia, and familial MMD), and 4 risk factors for ischemic stroke (ischemic presentation, hypertension, familial MMD, and thyroid disease). In multivariate analyses (Table 3), familial MMD was a common significant factor in any, hemorrhagic, and ischemic strokes. Thyroid disease was a risk factor for any stroke, and initial symptoms of either hemorrhage or ischemia were risk factors for the same types of stroke during follow-up.

Clinical Outcomes

Clinical states at the initial and final periods are presented in Fig. 3. The initial clinical scores for all patients were 79.8 ± 14.1 (range 30–100) on KPS and 1.9 ± 1.2 (range 0–5) on mRS. The final clinical scores were 85.8 ± 17.7 (range 0–100) and 1.3 ± 1.4 (range 0–6), respectively, on the same measures. At each period, the hemorrhagic group showed the worst clinical status in terms of both KPS and mRS scores.

A total of 23 patients (9.5%) underwent revascularization surgery because of the aggravation or occurrence of ischemic symptoms and hemodynamic instability. Among them, 17 (73.9%) were in the ischemic group and 4 (17.4%) were in the hemorrhagic group. The mean duration of follow-up duration for these patients was 48.8 ± 32.6 months (range 10.9–157.2 months).

Four patients died in the hemorrhagic group (6.5%); in all 4 cases, the cause of death was recurrent hemorrhage.

Discussion

From this retrospective cohort study with a relatively large number of patients, we obtained valuable information about the natural course of adult MMD. The annual risk of stroke was 4.5%/person-year, and the 5- and 10-year cumulative risks of any stroke were 17% and 31%, respectively. The cumulative risks of hemorrhage and ischemia were similar during the mean follow-up period of 82.5 months. Regardless of the initial clinical presentation (hemorrhagic, ischemic, or asymptomatic), there was no significant difference in the cumulative risk for any stroke. However, the clinical status at any period in the study was worst in patients with hemorrhagic presentation. Patients with hemorrhagic presentation tended to show a higher incidence of recurrent hemorrhage, although patients with ischemic symptoms demonstrated a higher rate of recurrent ischemia than the other groups. In our multivariate analyses, familial MMD and thyroid disease were risk factors for any stroke event during follow-up, and familial MMD and hemorrhagic presentation were identified as risk factors for a hemorrhagic stroke. Familial MMD and ischemic presentation were significant risk factors for ischemic events.

<table>
<thead>
<tr>
<th>TABLE 2. Annual risk of stroke*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>Hemorrhagic group</td>
</tr>
<tr>
<td>Ischemic group</td>
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<tr>
<td>Asymptomatic group</td>
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</table>

* Values indicate %/person-year.
Fig. 1. Kaplan-Meier curves for stroke events during follow-up. **Left:** There was no significant difference between hemorrhagic and ischemic strokes in all patients (p = 0.857). **Right:** There was no significant difference in overall stroke events among the groups with different clinical presentations (p = 0.461). Figure is available in color online only.

**Fig. 2.** Kaplan-Meier curves for stroke event in each group. **Left:** The 5- and 10-year cumulative risks of rebleeding in the hemorrhagic group were 23% and 34%, respectively. **Right:** The 5- and 10-year risks of recurrent ischemia in ischemic group were 13% and 28%, respectively. Figure is available in color online only.
Ischemia, including TIA and infarction, is the most frequent symptom in both pediatric and adult MMD. Nonetheless, there have been few studies on the natural course of ischemia in MMD. Hallemeier et al. reported a cumulative 5-year risk of stroke of 82% in adult patients with ischemic presentation who were conservatively managed. In an earlier study of pediatric MMD, 50%–90% of patients were found to experience neurological deficits due to recurrent ischemia. In another study of pediatric MMD, 79% of the patients suffered from recurrent ischemia with intellectual impairment, and the mortality rate was 3.7% (1 of 27 patients died). In the present study of adult MMD, the annual risk of ischemia was 2.2% in all patients and 3.0% in patients with ischemic presentation. In addition, the 5- and 10-year cumulative risks of ischemic events were 9% and 20%, respectively, in all patients, and 13% and 28% in patients with ischemic presentation.

Hemorrhage is the major cause of poor clinical outcome and death in patients with MMD. According to one report, mortality rates were 7% after initial bleeding and 29% after rebleeding. In this study, the incidences of stroke during follow-up were similar among the clinical groups of hemorrhagic, ischemic, and asymptomatic patients. However, the initial and final clinical outcomes were worst in patients with a hemorrhagic presentation, and all of the deaths resulted from a recurrent hemorrhage. The incidence of hemorrhagic presentation is known to be higher in adult MMD than in pediatric MMD, and higher in Asian patients than in Western ones. As reported, the incidence rates are 46%–62.4% in Korea, 52%–56% in China and Taiwan, 21% in Japan, and 13%–29% in United States, and the rate in our study was 25.7%. In our institute, surgically treated patients have been more numerous than conservatively treated patients (by a factor of approximately 2–3, unpublished data), and many of these patients have ultimately undergone surgery because of their ischemic symptoms. Thus, the actual incidence of hemorrhagic presentation seems to be less than 25.7%.

Rebleeding has been reported with an incidence ranging from 17% to 61% in patients with initial bleeding and an annual rebleeding rate ranging from 1.7% to 7.1% in adult MMD patients (Table 4). In this study, the annual bleeding rate was 2.3% in all patients and 4.3% in those with hemorrhagic presentation. In addition, 14.1% of all patients and 30.6% of patients with hemorrhagic presentation experienced one or more hemorrhagic events during follow-up. Because hemorrhage is not an indication for revascularization surgery in our institute, most patients with hemorrhagic presentation were included in this study; consequently, the results pertaining to the natural course of hemorrhagic MMD are thought to be valid as presented.

There are few studies reporting on risk factors for recurrent ischemia and hemorrhage and their clinical outcomes. Hypertension and young age at onset are significant fac-
tors affecting prognosis in untreated MMD, and age > 36 years at onset and microbleeds on MRI are significant risk factors for hemorrhage. Female sex and stroke presentation within 3 years are significant risk factors for stroke or hemorrhage. This study showed that familial MMD was a common risk factor for stroke, thyroid disease was a risk factor for any stroke, ischemic presentation was a significant factor for recurrent ischemia, and hemorrhagic presentation was a risk factor for rebleeding. Interestingly, familial MMD was a common risk factor for all types of stroke event during follow-up, which has not been reported previously. Genetic studies are actively underway, and a recent study showed that patients with a specific variant of RNF213 presented with an early onset and severe form of MMD. However, it is possible to miss some familial MMD patients because not all the relatives of patients in this study were screened. Further study is needed to find out whether familial MMD really exhibits an aggressive clinical course. Thyroid disease was found to be another risk factor for stroke. Although observational studies of the relationship between hyperthyroidism and MMD have been reported, the clinical impact of hyperthyroidism on MMD has never been evaluated. Further studies are expected to elucidate the relationship between thyroid disease and MMD in terms of clinical prognosis.

Subsequent episodes of bleeding occurred at a higher rate in patients with a hemorrhagic presentation, and subsequent ischemic events occurred at a higher rate in patients with an ischemic presentation; these correlations were also found in the analysis of risk factors. Previous reports have supported these relationships. The recurrence of ischemia can be reduced by revascularization surgery; however, recurrence of bleeding cannot. The value of revascularization surgery for the prevention of recurrent bleeding remains controversial. Effective treatment modalities should be devised, especially in patients with hemorrhagic presentation, because hemorrhage itself is the most influential cause of morbidity and mortality.

It is important to know the natural history of asymptomatic patients because the disease itself progresses even if its symptoms do not. Unfortunately, there is little information about asymptomatic patients. According to Kurada et al., the annual risk of stroke was 3.2%, and clinical outcomes were satisfactory (mRS score ≤ 2) in 97.5% of patients. In this study, the annual risk of stroke in asymptomatic patients was 3.4%, with no statistical difference between groups. The stroke incidence rate was somewhat higher in asymptomatic patients than was expected, and the annual risk of hemorrhage was 2.5%. One report suggested a 6% mortality rate from bleeding in asymptomatic patients. Although clinical status was better in asymptomatic patients than in the other groups, close follow-up should be considered even in asymptomatic patients.

In our study, a total of 23 patients (9.5%) underwent revascularization surgery. Eighteen of these patients initially presented with ischemic symptoms, representing 11.4% of patients with ischemic presentation. The rate of delayed operation during follow-up has been reported to range from 15% to 42%. Direct comparison is not thought to be reasonable because there are some differences among studies in terms of age, clinical status, ethnicity, and indications for revascularization surgery. However, these data can be useful for counseling patients.

This study has some limitations. First, it is retrospective, so selection bias may exist. Second, it is not a truly thorough natural history of MMD because patients were followed up not from the beginning of disease but rather from the initial visit to our institute. However, this situation may be more natural in the clinical setting because of the rarity of the disease and the difficulty of early diagnosis. Third, patients with ischemic presentation who were included in this study had more benign disease than those who underwent revascularization surgery for ischemia at initial presentation and were not included. Thus, our reported incidence of recurrent ischemic events during the follow-up might be lower than the real incidence. Fourth, the mean follow-up durations may not be long enough to evaluate the full natural history of the disease, even though the mean duration of follow-up in this study was the longest to date among published reports. Fifth, only 3 concomitant medical diseases were included in the evaluation of risk factors. Although we tried to include other factors that have been shown to be related to MMD in the previous studies, the incidence of such factors was too low to analyze (< 5 cases per factor).

Conclusions

In conclusion, there were no differences in the incidence of stroke among clinical groups of hemorrhagic, ischemic, and asymptomatic patients. However, clinical status was the worst in patients with hemorrhagic presentation. During the follow-up period, patients tended to more fre-

**TABLE 4. Literature review about stroke recurrence in adult MMD under conservative management**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>No. of Pediatric Patients</th>
<th>Follow-Up Duration</th>
<th>Stroke Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu et al., 1998</td>
<td>35</td>
<td>7</td>
<td>40 ± 31 mos</td>
<td>Stroke: 10.3%/person-yr (hemorrhage, 1.7%; ischemia, 8.6%)</td>
</tr>
<tr>
<td>Gross &amp; Du, 2013</td>
<td>42</td>
<td>0</td>
<td>Mean 2.9 yrs</td>
<td>Stroke: 13.3%/person-yr; hemorrhage: 1.7%/person-yr</td>
</tr>
<tr>
<td>Hallermeier et al., 2006</td>
<td>34</td>
<td>0</td>
<td>Median 5.1 yrs</td>
<td>5-yr stroke: 65% after initial symptoms</td>
</tr>
<tr>
<td>Kobayashi et al., 2000</td>
<td>42</td>
<td>1</td>
<td>Mean 80.6 mos</td>
<td>Hemorrhage: 7.1%/person-yr</td>
</tr>
<tr>
<td>Kuroda et al., 2007</td>
<td>40</td>
<td>1</td>
<td>Mean 43.7 mos</td>
<td>Stroke: 3.2%/person-yr (hemorrhage, 2.4%; infarction, 0.8%)</td>
</tr>
<tr>
<td>Morioka et al., 2003</td>
<td>36</td>
<td>2 or 3</td>
<td>12.7 ± 7.1 yrs</td>
<td>Hemorrhage: 29 incidents of rebleeding in 21 patients (61.1%)</td>
</tr>
<tr>
<td>Present study</td>
<td>241</td>
<td>0</td>
<td>82.5 ± 62.9 mos</td>
<td>Stroke: 4.5%/person-yr (hemorrhage, 2.3%; ischemia, 2.2%)</td>
</tr>
</tbody>
</table>

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quenty experience the same type of stroke as their initial presentation. Further study is needed to reduce rebleeding rates in patients with the hemorrhagic type of MMD and to elucidate the clinical relationship between thyroid disease and MMD and the clinical course of familial type of MMD. Close follow-up should be performed in patients with ischemic and asymptomatic presentations.

References


**Author Contributions**

Conception and design: Kim, Cho, Chung, Oh. Acquisition of data: Kim, Cho, Jeon, Kang, Sohn. Analysis and interpretation of data: Kim, Cho, Chung. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kim. Statistical analysis: Cho, Chung. Study supervision: Kim, Oh.

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