Radiological Findings, Clinical Course, and Outcome in Asymptomatic Moyamoya Disease
Results of Multicenter Survey in Japan

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Background and Purpose—Although the development of a noninvasive MR examination has increased the opportunity to identify asymptomatic patients with moyamoya disease who have experienced no stroke episodes, their clinical features are still uncertain. This was the first multicenter, nation-wide survey focused on asymptomatic moyamoya disease in Japan and was designed to clarify their clinical features.

Methods—A clinical database of asymptomatic patients with moyamoya disease was collected from 12 participating hospitals in Japan between 2003 and 2006. In total, 40 patients were enrolled in this historical prospective cohort study. Of these, 6 underwent surgical revascularization, including superficial temporal artery to middle cerebral artery anastomosis and/or pial synangiosis. Their demographic and radiological findings as well as outcome were evaluated.

Results—On initial evaluation, cerebral infarction and disturbed cerebral hemodynamics were detected in 20% and 40% of the involved hemispheres, respectively. Angiographical stage was more advanced in more elderly patients. Of 34 nonsurgically treated patients, 7 experienced transient ischemic attack (n = 3), ischemic stroke (n = 1), or intracranial bleeding (n = 3) during follow-up periods (mean, 43.7 months). The annual risk for any stroke was 3.2%. Disease progression was associated with ischemic events or silent infarction in 4 of 5 patients. No cerebrovascular event occurred in the 6 patients who underwent surgical revascularization.

Conclusions—The findings revealed that asymptomatic moyamoya disease is not a silent disorder and may potentially cause ischemic or hemorrhagic stroke. Asymptomatic patients with moyamoya disease should be carefully followed-up to further clarify their outcome and to establish the management guideline for them. (Stroke. 2007;38:000-000.)

Key Words: cerebral infarction ■ disease progression ■ intracranial bleeding ■ moyamoya disease ■ ■ prognosis

Moyamoya disease is characterized by progressive stenosis of the terminal portion of the bilateral internal carotid arteries and is associated with an abnormal vascular network, called moyamoya vessels.1 The etiology of the disease is still unknown; however, several epidemiological studies have suggested the involvement of some genetic factors in its pathogenesis. The potential contribution of infections has also been pointed out, although specific pathogens have not been identified.2

It is well known that moyamoya disease causes transient ischemic attacks (TIAs), cerebral infarction, or intracranial bleeding in both children and adults. Intracranial bleeding, in particular, often results in a poor outcome.3,4 Cerebral revascularization surgery is believed to reduce the incidence and improve the long-term prognosis in patients with moyamoya disease.3,5,6 The recent development of noninvasive diagnostic modalities, including MRI and MRA, has led to the realization that the incidence of asymptomatic moyamoya disease may be higher than previously thought.7–9 “Asymptomatic” patients with moyamoya disease have previously been defined as those who have experienced neither ischemic nor hemorrhagic episode, although the definition is not determined.7–9 However, even in Japan, their epidemiology is still obscure, and guidelines for the management of asymptomatic moyamoya disease have not yet been established. Thus, it is essential to elucidate their clinical features and natural course so that guidelines for the management of asymptomatic patients can be established. As a preliminary study, we have previously analyzed the clinical data of 10 asymptomatic patients whose diagnoses were made at Hokkaido University Hospital as moyamoya disease. However, the results were limited in their usefulness because of small patient numbers and short follow-up periods.8

Based on these considerations, we conducted the first multicenter, nation-wide survey focused on asymptomatic patients.
with moyamoya disease to clarify clinical characteristics, radiological findings, and outcome. We believe that the accumulation of this clinical data will be valuable for the establishment of management guidelines for moyamoya disease.10

Materials and Methods

Participating Centers and Hospitals
In August 2003, we sent an invitation to participate to the members of the Research Committee on Moyamoya Disease of the Japan of Ministry of Health, Labor and Welfare of Japan, in 16 hospitals. Of these, 12 hospitals accepted our invitation, and a total of 40 asymptomatic patients were enrolled in this historical prospective cohort study (see Appendix). Follow-up data were collected from the 12 participating hospitals in March 2006.

Patients
All patients were Japanese and met the guidelines for the diagnosis of moyamoya disease set by the Research Committee on Moyamoya Disease of the Ministry of Health and Welfare of Japan. All of them previously had no ischemic or hemorrhagic episode and were neurologically free. Patients who experienced any episode suggestive of TIA, cerebral infarction, intracranial bleeding, seizure, or involuntary movement caused by moyamoya disease were excluded. MRI and MRA were performed in all patients, using a 1.5-T whole-body magnetic resonance imager. Cerebral angiography was performed in 37 of 40 patients. Using xenon CT, single photon emission tomography, or PET, cerebral blood flow and cerebrovascular reactivity to acetazolamide were determined in 35 of 40 patients.

In this study, patient demographical data, radiological findings, medical and surgical treatment, and outcome were precisely analyzed.

Statistical Analysis
Continuous variables were expressed as percentage or as mean±SD. Statistical analysis was performed using χ2 test and Kruskal-Wallis test as appropriate. The statistical level of significance was set at P<0.05. Statistical analysis was completed with StatView version 5.0 (SAS Institute, Inc).

Results

Demographic Features
Of 40 asymptomatic patients with moyamoya disease, there were 13 males and 27 females. Thus, the female-to-male ratio was 2.1. Their mean age at diagnosis was 41.4±12.6 years, ranging from 13 to 67 years (Figure 1). Thirty-seven patients had typical “bilateral” moyamoya disease (definite cases) diagnosed, and the remaining 3 had “unilateral” moyamoya disease diagnosed (probable cases). Therefore, the total number of involved hemispheres was 77.

Figure 1. Distribution of age and gender in 40 patients enrolled in this study because of asymptomatic moyamoya disease.

Figure 2. Radiological findings of a 65-year-old woman with asymptomatic moyamoya disease. Note multiple cerebral infarctions in both hemispheres on MRI (A) and reduction of cerebral blood flow and its reactivity to acetazolamide on single photon emission tomography before (B) and after intravenous injection of acetazolamide (C).
Clues to the diagnosis were tension-type headache in 14 patients, dizziness in 5, and head trauma in 4. Five patients were incidentally diagnosed on MRI and MRA performed for a brain health check-up. Five diagnoses were made on MRI and MRA performed for screening, because a member of their family had moyamoya disease diagnosed. They were siblings in 2 and offspring in 3. The remaining 7 cases were diagnosed on MRI and MRA performed because of an unrelated disease in other organs.

Radiological Findings
MRI detected cerebral infarction in 16 (20.8%) of 77 involved hemispheres, or in 12 (30%) of 40 patients (Figure 2). However, there was no cerebral infarction in the uninvolved hemispheres or in the vertebrobasilar territories. No intracranial bleeding was noted. Disease stage, as determined by cerebral angiography, varied widely. Of 72 examined hemispheres, four (5.6%) were graded as stage 1, 10 (13.9%) as stage 2, 33 (45.8%) as stage 3, 21 (29.2%) as stage 4, 2 (2.8%) as stage 5, and 2 (2.8%) as stage 6. Thus ~75% of the hemispheres were graded as stage 3 or stage 4. Correlation analysis revealed that older patients had significantly more advanced disease stage (\(P=0.0134\); Figure 3).

Cerebral blood flow studies showed that 39 (55.7%) of 70 examined hemispheres had normal cerebral blood flow and cerebrovascular reactivity to acetazolamide. However, 24 hemispheres (34.3%) had moderate impairment of cerebral hemodynamics, ie, normal cerebral blood flow but reduced cerebrovascular reactivity to acetazolamide. Seven (10%) had reduced cerebral blood flow and cerebrovascular reactivity, suggesting a marked reduction of cerebral perfusion pressure (Figure 2).11

Treatments and Outcome
Of 40 subjects, 6 underwent bypass surgery, including superficial temporal artery to middle cerebral artery anastomosis, on one or both hemispheres. Eleven patients were medically treated with anticonvulsants, antiplatelet agent, or other pharmacological agents. The remaining 24 patients were conservatively followed-up as outpatients. All patients were followed-up for a mean period of 43.7 months, with a range of 1 to 150 months.

Of 6 patients who underwent bypass surgery, none experienced any ischemic or hemorrhagic episodes during follow-up periods.

<table>
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<tr>
<th>Case</th>
<th>Age</th>
<th>Gender</th>
<th>Cerebral Infarction</th>
<th>CBF/CVR Study</th>
<th>Angiographical Stage</th>
<th>Bypass Surgery</th>
<th>Cerebrovascular Event</th>
<th>Radiological Change</th>
<th>Follow-Up Period (months)</th>
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CBF, cerebral blood flow; CVR, cerebrovascular reactivity; ICH, intracerebral hemorrhage.
Of other 34 nonsurgically treated patients, 7 experienced cerebrovascular events. Of these, 3 patients had TIA, 1 had ischemic stroke, and 3 had intracranial bleeding. Thus, 4 patients had ischemic or hemorrhagic stroke during follow-up periods (Table 1). The annual risk for any stroke was 3.2%. Figure 4 shows a Kaplan-Meier curve to demonstrate the time to cerebrovascular event.

Table 2 shows the relationship between cerebral hemodynamics at initial diagnosis and cerebrovascular events in nonsurgically treated patients. Disturbed hemodynamics was significantly linked to ischemic episodes \( (P<0.05) \). Disease progression caused TIA and ischemic stroke in both patients who showed normal hemodynamics on initial evaluation.

No death was observed during the patient follow-up periods. The outcome in March 2006 was categorized based on a modified Rankin scale score of \( 0 \) (n=38), 1 (n=1, ischemic stroke) and 4 (n=1, intracranial bleeding). Thus, favorable outcome (defined as modified Rankin scale \( \leq 2 \)) was observed in 39 (97.5%) of the 40 patients.

Follow-Up MRI and MRA
None of 6 surgically treated patients had any new cerebral infarction and intracranial bleeding on follow-up MRI.

Of other 34 nonsurgically treated patients, 7 had new lesions on follow-up MRI (Table 1). Of these, 3 had new cerebral infarction, asymptomatic in 1 patient and asymptomatic in 2. Other 4 patients had new intracerebral hemorrhage, asymptomatic in 1 patient and symptomatic in 3. Of 34 nonsurgically treated patients, 5 showed progression of disease stage on follow-up MRA or cerebral angiography (Figure 5). Disease progression was asymptomatic in 1 patient, but caused silent cerebral infarction in 1, TIA in 2, and ischemic stroke in another (Table 1).

Discussion
This study is the first multicenter, nation-wide survey focused on asymptomatic patients with moyamoya disease and has important implications for defining its clinical features, radiological findings, and prognosis. Our findings are summarized as follows. Cerebral infarction and disturbed cerebral hemodynamics were detected in \( \approx 20\% \) and \( 40\% \) of the involved hemispheres, respectively. Angiographical stage was more advanced in more elderly patients. Of 34 nonsurgically treated patients, 7 experienced TIA, ischemic stroke or intracranial bleeding during a mean follow-up period of 43.7 months. Cerebral infarction or intracerebral hemorrhage did not occur in 6 patients who underwent surgical revascularization.

Epidemiology of Asymptomatic Moyamoya Disease
Previously, asymptomatic cases of moyamoya disease have only been sporadically reported.\(^7,9\) Screening of family members with moyamoya disease has also identified small numbers of asymptomatic patients.\(^12,13\) Therefore, the incidence of asymptomatic moyamoya disease had been considered to be very low. However, Yamada et al\(^14\) reported the results of a nation-wide questionnaire conducted in 1994 and identified 33 asymptomatic patients (1.5%) out of a total of 2193 patients. Recently, Nanba et al\(^8\) (2003) reviewed their single-center experiences and precisely reported the clinical features of 10 asymptomatic patients with moyamoya disease. Therefore, although an accurate prevalence of asymptomatic moyamoya disease is still unknown, it may be much higher than considered before. The female-to-male ratio and mean age of the patients in these studies were similar to those of moyamoya disease as a whole.\(^15\)

Of the 40 patients, 23 had moyamoya disease diagnosed when they visited hospitals for treatment of complaints unrelated to moyamoya disease. Although it is known that moyamoya disease is sometimes associated with migraine,\(^16\) the headaches of these patients were considered to be tension-type. The remaining 17 patients had no symptoms and had moyamoya disease diagnosed incidentally during screening examinations using MRI and MRA. Thus, noninvasive MR examination would increase the opportunity to detect asymptomatic moyamoya disease in future.\(^17\)
Silent Radiological Findings
Silent cerebral infarction was noted in \( \approx 20\% \) of the involved hemispheres but was not detected in other territories. The incidence was almost same as that of silent cerebral infarction (21%) in 1015 elderly patients aged 60 to 90 years (mean, 72 years).\(^{18}\) According to a population-based consecutive autopsy study in Japan, the incidence of silent cerebral infarction was 4.4% in 40- to 59-year-old population.\(^{19}\) Therefore, moyamoya disease may be related to the development of silent cerebral infarction even in asymptomatic patients. Although adults with moyamoya disease have also been known to have intracranial bleeding, no intracranial bleeding was observed in this study. However, very recent studies have shown that T2*-weighted MRI can detect microbleeds in a certain subgroup of patients with moyamoya disease.\(^{20,21}\) With this technique, however, further study would be necessary to predict their risk for intracranial bleeding by assessing the presence of microbleeds.

In this study, cerebral blood flow measurements demonstrated that \( \approx 40\% \) of the involved hemispheres had a moderate or severe reduction of cerebral perfusion reserve, despite the fact that patients remained asymptomatic. Recent studies have proven that both increased oxygen extraction fraction and impaired reactivity to acetazolamide can be independent predictors for subsequent ischemic stroke in patients with occlusive carotid artery diseases.\(^{11,22-24}\) Therefore, critical follow-up would be essential for patients found to have increased oxygen extraction fraction or impaired cerebrovascular reactivity.

Clinical and Radiological Course
This study clearly demonstrates that disease stage is more advanced in older patients. Although disease progression in adult moyamoya disease was believed to be very rare before, a recent study has shown that disease progression occurs in \( \approx 20\% \) of patients during a mean follow-up period of 6 years.\(^{25}\) Occlusive arterial lesions progress in both anterior and posterior circulation, in both bilateral and unilateral types, and in both symptomatic and asymptomatic patients. Multivariate analysis has revealed that female gender is an independent risk factor for disease progression.\(^{25}\) Therefore, it should be emphasized that disease progression may occur silently and cause ischemic or hemorrhagic stroke even in asymptomatic patients. Aging-related atherosclerosis may also be involved in disease progression in elderly patients. Indeed, this study demonstrates that disease progression occurred in 5 asymptomatic patients, caused TIA or ischemic stroke in 3 patients, and resulted in silent cerebral infarction in one. The findings strongly suggest that it is quite important to repeat MRI and MRA at regular intervals when asymptomatic patients are conservatively followed-up to detect disease progression before ischemic stroke occurs.

There is no guideline to direct how asymptomatic patients with moyamoya disease should be managed.\(^{8}\) In this study, of the 34 nonsurgically treated patients, 7 patients experienced cerebrovascular episodes, including TIA. The annual risk for ischemic or hemorrhagic stroke was 3.2%. Disease progression was closely related to the onset of ischemic episodes. Nanba et al\(^{8}\) reported that 1 of 10 asymptomatic patients experienced ischemic stroke during follow-up periods. Yamada et al\(^{14}\) also evaluated the natural course of 33 asymptomatic patients with moyamoya disease; they reported that 2 patients died from intracranial bleeding, and 4 patients experienced TIA during a mean follow-up period of 44 months.

Of note, there is a peculiarity common to the present study and the report by Yamada et al.\(^{14}\) None of patients who underwent surgical revascularization had any cerebrovascular event during follow-up periods, except for surgical morbidity.\(^{14}\) These findings may suggest that asymptomatic moyamoya disease is not a silent disorder and readily progresses to cause ischemic or hemorrhagic stroke. Surgical revascularization may be indicated, at least, in patients who have disturbed cerebral hemodynamics if surgical morbidity is low enough, because the procedure is considered effective for improving cerebral blood flow and metabolism and preventing ischemic stroke.\(^{26,27}\) It is still unclear whether surgical revascularization could reduce the incidence of intracranial bleeding caused by moyamoya disease, although a randomized clinical trial in Japan is ongoing.\(^{28}\) Even if patients are conservatively followed-up, precise and regular MRI/MRA examinations could be essential for improving long-term outcome by predicting subsequent ischemic and hemorrhagic stroke, because repeated MRI/MRA have the ability to detect disease progression and silent microbleeds before the onset of ischemic or hemorrhagic stroke.\(^{20,21,25}\)

Limitation of This Study
There are certain limitations to this study that should be noted. This study is a historical prospective cohort study and not a prospective cohort study. The subjects included in this study were collected from 12 hospitals. These hospitals are considered representative of the major institutions in Japan responsible for the management of moyamoya disease. Ide-
ally, however, a prospective cohort or randomized study should be performed on the basis of a larger population of asymptomatic patients to build the accurate evidence on the clinical features and outcome of this disease.

Conclusions
This multicenter, nation-wide survey reveals that the prevalence of asymptomatic patients with moyamoya disease may be higher than previously thought. Although these patients are still “asymptomatic,” their radiological findings are not always normal. A certain subgroup has silent cerebral infarction, advanced arterial lesions, and impaired cerebral hemodynamics. Of 34 nonsurgically treated patients, 7 transitioned to become “symptomatic” patients during follow-up periods. Silent radiological findings were added in 3 other patients. None of patients who underwent surgical revascularization experienced any cerebrovascular event during follow-up periods. Careful and long-term neurological and radiological follow-up would be essential to improve the outcome of these patients by preventing ischemic and hemorrhagic stroke. Further prospective studies may be necessary to finalize the management guideline for asymptomatic patients with moyamoya disease.

Appendix
All of clinical data in this study were collected from Department of Neurosurgery, Iwate Medical University; Department of Neurology, Keio University; Department of Neurosurgery, Chugoku Rosai Hospital; Department of Neurosurgery, Nara Medical University; Department of Neurosurgery, Nagasaki University; Departments of Neurology and Neurosurgery, Kyushu Medical Center; Department of Neurosurgery, Nagasaki University; Nagoya City University; Departments of Neurology and Neurosurgery, Kitasato University; Department of Neurosurgery, Gifu University; Department of Neurosurgery, Sapporo Medical University; and Department of Neurosurgery, Hokkaido University.

Sources of Funding
This study was supported by a grant from the Research Committee on Moyamoya Disease sponsored by the Ministry of Health, Labor, and Welfare of Japan.

Disclosures
None.

References
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for the Research Committee on Moyamoya Disease in Japan

Stroke. published online March 29, 2007;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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