Clinical Course, Surgical Management, and Long-Term Outcome of Moyamoya Patients With Rebleeding After an Episode of Intracerebral Hemorrhage
An Extensive Follow-Up Study

Yasuko Yoshida, MD, PhD; Takashi Yoshimoto, MD, PhD; Reizo Shirane, MD, PhD; Yoshiharu Sakurai, MD, PhD

Background and Purpose—Revascularization surgery for moyamoya patients is believed to prevent cerebral ischemic attacks by improving cerebral blood flow. However, measures preventing the occurrence of hemorrhagic moyamoya in patients have not yet been established in the literature due to the low rate of hemorrhage onset as well as the originally limited numbers of patients with moyamoya disease, poor understanding of the clinical course of rebleeding, correct surgical management, and long-term outcome. We present here the results of an overall survey of patients with hemorrhagic moyamoya disease in a district of Miyagi Prefecture in Japan and examine their clinical course, efficacy of revascularization surgery, and long-term outcome.

Methods—This study included 28 moyamoya patients with episodes of intracranial hemorrhage between 1976 and 1988. The mean follow-up period was 14.2 years. There were 4 males and 24 females, aged 7 to 69 years (mean 39.2 years). Cerebral angiography and CT scans were performed for all patients. Surgical treatment was performed in 19 patients (67.9%), and 10 patients (35.7%) underwent revascularization surgery. We observed the clinical course of all 28 patients. We also studied the relationship between the efficacy of surgical treatment and long-term outcome.

Results—Five of the 28 patients (17.9%) died of the initial intracranial hemorrhage, and 2 patients died of other causes. Rebleeding occurred in 6 of the remaining 21 patients (28.6%). The interval to rebleeding ranged from 2 to 20 years (mean 7.3 years). Of these 6 patients, 4 died of rebleeding. Rebleeding was observed in 1 of 8 patients who underwent bypass surgery and in 5 of 13 patients who did not, which suggested that rebleeding was less likely to occur in patients who had undergone bypass surgery. However, there was no significant difference in rebleeding ratio or mortality between patients with and those without revascularization surgery ($P>0.05$).

Conclusions—In this study, we compiled the results of meticulous follow-up conducted over the past 10 years for patients with hemorrhagic moyamoya disease. Because hemorrhagic moyamoya disease is known for its high rate of mortality at the time of rebleeding and often causes rebleeding long after the initial episode (as much as 20 years later), implementation of long-term preventive measures for rebleeding is necessary. This suggests that a long-term prospective study of a large number of patients with hemorrhagic moyamoya disease is required to determine whether bypass surgery prevents rebleeding of hemorrhagic moyamoya disease. (Stroke. 1999;30:2272-2276.)

Key Words: cerebral revascularization ■ intracerebral hemorrhage ■ moyamoya disease

Since Suzuki first reported “moyamoya” disease in 1969,1 the number of patients with diagnosed moyamoya disease in Japan, where the disease is most frequently observed, has reached approximately 3900. Many articles concerning its diagnosis, pathological examination, treatment, and prognosis have appeared. Revascularization surgery for moyamoya disease caused by intracranial internal carotid artery occlusion is believed to prevent cerebral ischemic attacks by improving cerebral blood flow,2–5 and bypass surgery is actively performed for patients who have the disease after an ischemic attack. On the other hand, the frequency of onset of moyamoya disease with intracranial hemorrhage is reported to be 26.2%. The cause of hemorrhage is said to be failure of moyamoya blood vessels resulting from hemodynamic stress.6 Because improvement of cerebral circulatory metabolism was minimal and no preventive effect on rebleeding was recognized in the literature, many neurosurgeons have been performing conservative treatment.7 However, as a...
result of progress made by recent studies of cerebral circulatory metabolism in understanding the pathology of moyamoya disease, an increasing number of neurosurgeons are performing bypass surgery for patients with hemorrhagic moyamoya disease, on the assumption that decrease in hemorrhagic stress on moyamoya blood vessels will lead to prevention of rebleeding. Nevertheless, with the limited number of cases and short period of observation of clinical course, measures to prevent rebleeding in patients with moyamoya disease have yet not been established. The study by Suzuki and Takaku in Miyagi Prefecture, which has a population of 2.35 million. Since then, we have registered all the patients with the disease in this region and followed them. We present here results of an overall survey of patients with hemorrhagic moyamoya disease in a district of Miyagi Prefecture in Japan and examine their clinical course, efficacy of revascularization surgery, and long-term outcome. This study represents part of a therapeutic survey of hemorrhagic moyamoya disease, and we examined the preventive effect of bypass surgery on rebleeding based on its results.

Subjects and Methods

Patients
This study included 111 moyamoya patients seen from 1976 to 1988 and was based on cerebral angiography performed at 18 institutions participating in the Miyagi Stroke Study Group. All patients were followed up for >10 years, from onset until 1998. Patients with pseudo-moyamoya disease or other systemic diseases were excluded. Intracranial lesions caused by moyamoya disease were all confirmed by CT scans. Of these 111 patients, 28 (25.2%) presented with intracranial hemorrhage. There were 4 males and 24 females (sex ratio 1:6) aged 7 to 69 years (mean 39.2 years). Five patients were aged <19 years and 23 were >20 years (Figures 1 and 2, Table 1). The clinical course, therapeutic methods, and long-term outcome of these 28 patients were investigated.

Types of Hemorrhagic Episodes
Types of hemorrhage in the above 28 patients included 7 intracerebral hemorrhages, 10 intraventricular hemorrhages, 6 intracerebral hemorrhages with intraventricular hemorrhage, and 5 subarachnoid hemorrhages (Table 2). Five of the 28 patients (17.9%) died of hemorrhage at first admission (Table 3).

Surgical Treatment
Eighteen of the 28 hemorrhagic moyamoya patients were transferred to 4 major facilities with neurosurgical departments, where they underwent surgical treatment, including ventricular drainage in 6, hematoma evacuation in 1, and arteriovenous malformation shunting in 2 patients. Of these patients, 10 (35.7%) underwent revascularization surgery for 16 hemispheres: 7 patients with encephalo-duro-arterio-synangiosis (EDAS), 1 hemisphere in 1 patient with encephalo-myo-synangiosis (EMS), 1 hemisphere in 1 patient with STA-MCA anastomosis, and 2 hemispheres in 1 patient with STA-MCA anastomosis combined with EDAS (Table 2). All the patients were followed up from 1976 to 1998, over a period ranging from 10 to 22 years (mean 14.2 years). The 7 patients who died at first admission were excluded.

Results
Rebleeding
Excluding the 7 patients who died at first admission, 6 of the remaining 21 patients (28.6%), including 1 male and 5 females, suffered rebleeding. The interval from the initial episode of rebleeding ranged from 2 to 20 years (mean 7.3 years): <2 years for 2 patients, from 2 to 5 years for 2, from 10 to 20 years for 1, and at 20 years for 1. Rebleeding tended to increase within 5 years after the first hemorrhagic episode (Figure 3). Patient age ranged from 49 to 67 years (mean 54.3 years). Types of rebleeding were as follows: 3 intracerebral
hemorrhages, 2 intraventricular hemorrhages, and 1 subarachnoid hemorrhage (Table 4). Five of the 6 rebleeding patients (83.3%) died during hospitalization. The mortality of rebleeding was significantly higher than that of first bleeding (17.9%) (Table 3).

**TABLE 2. Summary of 28 Patients With Intracranial Hemorrhage**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, y</th>
<th>Onset</th>
<th>Symptom</th>
<th>ADL on Discharge</th>
<th>Follow-Up Results</th>
<th>Treatment</th>
<th>Rebleeding</th>
<th>Interval of Rebleeding, y</th>
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<td>40</td>
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<td>E</td>
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<td></td>
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<tr>
<td>3</td>
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<td>46</td>
<td>1983</td>
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<td>Clipping, L EDAS</td>
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<td>43</td>
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<td>E</td>
<td>R STA-MCA anastomosis</td>
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<td></td>
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<td>ICH</td>
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<tr>
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<td>ICH</td>
<td>E</td>
<td>E</td>
<td>R EMS</td>
<td></td>
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</tr>
</tbody>
</table>

IVH indicates intraventricular hemorrhage; SAH, subarachnoid hemorrhage; ICH, intracranial hemorrhage; ADL, activities of daily living; E, excellent; G, good; F, fair; P, poor; D, died; EDAS, encephalo-duro-arterio-synangiosis; VPS, ventriculo-peritoneal shunt; STA-MCA, superficial temporal artery–middle cerebral artery; AN, aneurysm; CVD, continuous ventricular drainage; removal, removal of cerebral hematoma; and EMS, encephalo-myo-synangiosis.

**Effect of Revascularization Surgery**

Rebleeding occurred in 5 of 13 patients who underwent no revascularization surgery (38.5%). Four of the five died of rebleeding. Rebleeding occurred in 1 of 8 patients who underwent revascularization surgery (12.5%); this patient

**TABLE 3. Summary of Long-Term Outcome**

<table>
<thead>
<tr>
<th></th>
<th>Cases, n</th>
<th>Death Due to First Bleeding, n (%)</th>
<th>Death Due to Other Causes on First Admission, n</th>
<th>Follow-Up Cases, n</th>
<th>Rebleeding, n (%)</th>
<th>Death Due to Rebleeding, n</th>
<th>Death Due to Other Causes, n</th>
<th>Mortality, %</th>
<th>Survivors, n (%)</th>
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</thead>
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<tr>
<td>Without revascularization</td>
<td>18</td>
<td>4 (22.2)</td>
<td>1</td>
<td>13</td>
<td>5 (38.5)</td>
<td>4</td>
<td>1</td>
<td>38.5</td>
<td>8 (61.5)</td>
</tr>
<tr>
<td>With revascularization</td>
<td>10</td>
<td>1 (10.0)</td>
<td>1</td>
<td>8</td>
<td>1 (12.5)</td>
<td>1</td>
<td>1</td>
<td>25.0</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>5 (17.9)</td>
<td>2</td>
<td>21</td>
<td>6 (28.6)</td>
<td>5</td>
<td>2</td>
<td>33.3</td>
<td>14 (66.7)</td>
</tr>
</tbody>
</table>

The follow-up period was from 10 to 22 years (mean 14.2\(\pm\)3.5 years).

*The rebleeding, mortality, and survival rates were compared between the patient group without and that with revascularization. There was no significant difference at \(P>0.05\) (\(\chi^2\) test for independence).
also died of rebleeding. The mortality rate attributed to rebleeding did not differ between patients with and those without bypass surgery. The rebleeding ratio was 12.5% for patients with bypass surgery and lower than the 38.5% for those without bypass surgery. However, there was no significant difference in rebleeding ratio between patients with and without revascularization surgery ($P > 0.05$; $\chi^2$ test) (Table 3).

### Long-Term Outcome

Of the 21 patients, 6 (28.6%) died of rebleeding and 2 died of other causes. Fourteen patients (66.7%) attained long-term survival, including 6 patients with revascularization surgery and 8 without revascularization surgery (Figure 4). The survival rates were 75.0% and 61.5% for patients with and without revascularization surgery, respectively. There was no significant difference ($P > 0.05$, $\chi^2$ test) in survival rates between the 2 groups. The mortality rates were 25.0% and 38.5% for patients with and without revascularization surgery, respectively. In this case as well there was no significant difference between the 2 groups ($P > 0.05$, $\chi^2$ test) (Table 3).

### Discussion

For treatment of childhood moyamoya disease, various types of revascularization surgery have been reported, and both nonanastomotic and anastomotic bypass surgeries have been demonstrated to improve cerebral circulation.2–5 Superiority of anastomotic bypass surgery to nonanastomotic bypass surgery with respect to rapid improvement of cerebral blood flow after operation has also been reported for adult moyamoya patients.2,5 However, unlike the ischemic type of moyamoya disease, prevention by surgical treatment of rebleeding in hemorrhagic moyamoya disease has not been confirmed.7–11 Although revascularization surgery appears to improve cerebral collateral circulation and to reduce the hemodynamic disturbance in moyamoya vessels, reduction of the incidence of rebleeding in hemorrhagic moyamoya patients after surgical treatment is difficult to assess due to lack of long-term postoperative follow-up data. Houkin et al9 reported no significant difference in the incidence of rebleeding for patients treated with various types of surgical revascularization over a mean 6.4 years of follow-up. However, we noted that the rebleeding ratio tended to be lower in the group of patients with bypass surgery than in the group without the surgery, as indicated by our study. Yet, there was no significant difference between them. Additionally, we found that patients undergoing bypass surgery appeared to have less rebleeding than patients in a non–bypass surgery group. Recently, Fuji et al10 reported an assessment of bypass surgery for patients with hemorrhagic moyamoya disease (a summary of the results reported by the Research Committee on Spontaneous Occlusion of the Circle of Willis of the Ministry of Health and Welfare in Japan in 1997) and concluded that there was no significant difference in the incidence of rebleeding between types of surgical treatment. The present study also found no significant prevention of rebleeding by revascularization surgery in patients with hemorrhagic moyamoya disease, although the rebleeding rate in the surgery group (11.1%) tended to be lower than that in the nonsurgery group (38.5%), even when postoperative follow-up was extended to 14.3 years. The present study showed that the prognosis of rebleeding in patients with hemorrhagic moyamoya disease was extremely poor, with 5 of 6 patients dying. Also, some patients experienced rebleeding as long as 20 years after the initial bleeding. This was not mentioned in previous reports. Therefore, the most important objective treatment for hemorrhagic moyamoya disease is long-term prevention of rebleeding. Unfortunately, even long-term follow-up for >10 years in this study also revealed no correlation between the incidence of rebleeding and surgical method. A major cause of this lack of correlation is that, in order to examine results of elaborate long-term follow-up, the area for investigation was limited to Miyagi Prefecture, which further narrowed the already-limited number of cases. As indicated by the existing reports, we consider it difficult to calculate bypass surgery’s preventive effect on rebleeding based on the past cases, taking account of various biases, such as adaptation to surgery and surgical methods.

The incidence of moyamoya disease is generally <1 in 100,000 individuals, but in Japan it is reported to be much higher. However, even with the study results available in Japan, it is difficult to prove that bypass surgery has a preventive effect on rebleeding. Prospective studies of large numbers of patients may be necessary to achieve further advances in the field of moyamoya disease. Because therapeutic methods vary depending on medical institutions, the overall characteristics of moyamoya disease and effective therapeutic strategy are difficult to assess, particularly for hemorrhagic moyamoya patients. Because patients have undergone revascularization surgery with different methods, results of the assessment of the incidence of rebleeding...
rebleeding may be unclear. Appropriate comparisons between
groups of large numbers of patients with the same therapeutic
method are thus important. Although the clinical course, surgical
management, and long-term outcome of moyamoya disease are
still unclear, despite its being considered a single entity for more
than 30 years, we can summarize the present findings for our
patients with hemorrhagic moyamoya disease as follows. (1)
Peak age of first bleeding is during the third and fourth decades
of life. (2) Rebleeding tends to be common within 7.3 years after
the first bleeding, although some cases of rebleeding occur after
a long period. In some cases, rebleeding occurred after 20 years.
(3) There is still no clear evidence that revascularization surgery
significantly prevents rebleeding in patients with hemorrhagic
moyamoya disease, even in our study, with observation per-
formed over a mean of 14.2 years. (4) A preventive effect of
bypass surgery on rebleeding is expected. However, a long-term
prospective study that targets a large number of patients is
necessary, with evaluation of cerebral circulatory metabolism.

Acknowledgments

This work was supported by grants from the Research Committee on
Spontaneous Occlusion of the Circle of Willis of the Ministry of
Health and Welfare of Japan (1999). We wish to thank Dr Su Ching
Chan for his expert help in preparation of the manuscript.

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   showing abnormal net-like vessels in base of brain. Arch Neurol. 1969;
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disease: unsatisfactory outcome in the patients presenting with intra-

   bypass surgery on rebleeding is expected. However, a long-term
   prospective study that targets a large number of patients is
   necessary, with evaluation of cerebral circulatory metabolism.

   Figure 4. Long-term outcome of hemorrhagic
   patients. Seven (25.0%) died at first admission, 5 (23.8%) died of rebleeding, and 2 died of
   other causes. Fourteen patients, including 1 with rebleeding, survived.

2276 Stroke November 1999
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Stroke. 1999;30:2272-2276
doi: 10.1161/01.STR.30.11.2272
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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