Incidence, Locations, and Longitudinal Course of Silent Microbleeds in Moyamoya Disease
A Prospective T2*-Weighted MRI Study

Satoshi Kuroda, MD, PhD; Daina Kashiwazaki, MD; Tatsuya Ishikawa, MD, PhD; Naoki Nakayama, MD, PhD; Kiyohiro Houkin, MD, PhD

Background and Purpose—Clinical significance of silent microbleeds is unknown in moyamoya disease. This study was aimed to clarify the incidence, locations, and longitudinal course.

Methods—This prospective cohort study included 78 nontreated patients with moyamoya disease. The incidence and locations of silent microbleeds were evaluated on T2*-weighted MRI. MR examinations were repeated every 6 or 12 months during a mean follow-up period of 43.1 months.

Results—T2*-weighted MRI identified silent microbleeds in 17 (29.3%) of 58 adult patients with moyamoya disease, but in none of 20 pediatric patients. During follow-up periods, de novo silent microbleeds developed in 4 (6.9%) of 58 adult patients. Hemorrhagic stroke occurred in 4 patients (6.9%), all of whom had silent microbleeds on initial examination. The presence of silent microbleeds was a significant predictor for subsequent hemorrhagic stroke in adult moyamoya disease (P<0.001).

Conclusions—Careful and long-term follow-up of silent microbleeds would be essential to improve their outcome in adult patients with moyamoya disease.

Key Words: microbleeds ■ moyamoya disease ■ MRI ■ outcome

Moyamoya disease is characterized by progressive occlusion of the supraclinoid internal carotid artery and its main branches, resulting in the formation of moyamoya vessels at the base of the brain.1 The majority of pediatric patients develop transient ischemic attack and ischemic stroke, whereas about half of adult patients develop intracranial bleeding.1 The moyamoya vessels may rupture because of persistent hemodynamic stress, thus intracranial bleeding occurs in the basal ganglia, thalamus, and periventricular region.2,1

According to recent studies, silent microbleeds are identified on T2*-weighted MRI in moyamoya disease.4–6 They are found in the basal ganglia, thalamus, and periventricular region, where intracranial bleeding often occurs.4–6 They may predict subsequent hemorrhagic stroke.6 However, the information on their clinical significance is still limited. Especially, none of previous studies could disclose actual features of silent microbleeds, because the majority of subjects in these studies had already undergone surgical revascularization before initial MR examination.4–6 Therefore, this study enrolled nontreated patients and prospectively assessed the incidence, locations, and longitudinal course of silent microbleeds in moyamoya disease.

Methods
This prospective cohort study included 78 patients who were admitted to our hospital because of moyamoya disease between November 2003 and October 2011. All met the guideline for the diagnosis set by the Research Committee on Moyamoya Disease of the Ministry of Health, Labor and Welfare of Japan. There were 18 males and 60 females. There were 20 children and 58 adults. The mean ages were 10.1±5.6 and 46.6±14.0 years in pediatric and adult patients, respectively. All pediatric patients developed transient ischemic attack or ischemic stroke. In adult patients, clinical diagnosis included asymptomatic in 20, transient ischemic attack or ischemic stroke in 27, and intracranial bleeding in 11.

MR imaging was performed before surgery, using a 1.5-Tesla scanner, as reported previously.1 The involved hemisphere with impaired reactivity to acetazolamide was considered as the candidate for surgical revascularization. Totally 46 patients underwent surgical revascularization after initial examinations.7 All patients were followed up in the outpatient clinic. Both MRI and magnetic resonance angiography were repeated every 6 or 12 months. Hypertension was noted in 10 adult patients. None of them received antplatelets and anticoagulants.

Continuous data were expressed as mean±SD. Categorical data were compared by using χ² test. Cumulative hemorrhagic stroke-free survival rate was compared between 2 groups with the Kaplan-Meier method and Cox-Mantel log-rank statistics. Multivariate analysis using the Cox proportional hazards model determined the joint effect of multiple variables on hemorrhagic stroke over time. Differences were considered statistically significant when P value was <0.05.

Results
No silent microbleeds were detected in 20 pediatric patients, whereas silent microbleeds were detected in 17 (29.3%) of
58 adult patients. Of these 17 patients, 11 had 1 silent microbleed and the other 6 had >2 silent microbleeds (total number of silent microbleeds = 27). Silent microbleeds were found in the basal ganglia, thalamus, and periventricular white matter. There were no significant differences in clinical variables between patients with silent microbleeds and those without. Silent microbleeds were found in 5 (25.0%) of 20 asymptomatic patients, in 6 (22.2%) of 27 ischemic-type patients, and in 6 (54.5%) of 11 hemorrhagic-type patients. The incidence of silent microbleeds did not differ among them, although the incidence of silent microbleeds in hemorrhagic-type patients was higher ($P=0.121$).

During follow-up periods, T2*-weighted MRI did not detect any new microbleeds in pediatric patients. However, radiological and clinical events occurred in 8 (13.8%) of 58 adult patients during a mean follow-up period of 48.8 months (Table). Thus, silent microbleeds newly developed in 4 adult patients (6.9%). Two of them had silent microbleeds on initial examination, and de novo silent microbleeds were identified in the area apart from the original ones. These de novo silent microbleeds were identified in 2 asymptomatic, 1 ischemic-type, and 1 hemorrhagic-type patients. The annual incidence of de novo microbleeds was 1.7% in adult patients. Hemorrhagic stroke occurred in other 4 patients (6.9%). Their clinical diagnosis included transient ischemic attack in 2 patients, hemorrhagic stroke in 1, and asymptomatic in 1. All of these 4 patients had silent microbleeds on initial examination, but had no de novo ones during follow-up periods. Of 11 patients with single microbleeds, 3 (27.3%) developed hemorrhagic stroke. Of 6 patients with multiple microbleeds, 1 (16.7%) developed it. Their locations did not differ among them. Therefore, there were no associations with the number and location of silent microbleeds on initial examination (Table). Two of them were fatal. Another developed severe hemiparesis (Figure 1).

### Table. Clinical Data of 8 Patients With Clinical or Radiological Events During Follow-Up Periods

<table>
<thead>
<tr>
<th>Age, Sex</th>
<th>Initial Presentation</th>
<th>Silent Microbleeds</th>
<th>Surgical Treatment</th>
<th>Follow-up (mo)</th>
<th>De Novo Silent Microbleeds</th>
<th>Hemorrhagic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>36, F</td>
<td>Hemorrhagic stroke</td>
<td>Left putamen</td>
<td>Yes</td>
<td>23</td>
<td>Left periventricular white matter</td>
<td></td>
</tr>
<tr>
<td>62, F</td>
<td>Asymptomatic</td>
<td>Corpus callosum</td>
<td>None</td>
<td>6</td>
<td>Right insula, right periventricular white matter</td>
<td></td>
</tr>
<tr>
<td>51, F</td>
<td>Asymptomatic</td>
<td>None</td>
<td>None</td>
<td>8</td>
<td>Right periventricular white matter</td>
<td></td>
</tr>
<tr>
<td>29, F</td>
<td>TIA</td>
<td>None</td>
<td>None</td>
<td>32</td>
<td>Right peduncle</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age, Sex</th>
<th>Initial Presentation</th>
<th>Silent Microbleeds</th>
<th>Surgical Treatment</th>
<th>Follow-up (mo)</th>
<th>De Novo Silent Microbleeds</th>
<th>Hemorrhagic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>56, F</td>
<td>Hemorrhagic stroke</td>
<td>Right periventricular white matter</td>
<td>Yes</td>
<td>11</td>
<td>Right periventricular white matter</td>
<td></td>
</tr>
<tr>
<td>33, F</td>
<td>Asymptomatic</td>
<td>Left putamen, Bilat. periventricular white matter</td>
<td>None</td>
<td>72</td>
<td>Left putamen</td>
<td></td>
</tr>
<tr>
<td>52, F</td>
<td>TIA</td>
<td>Right thalamus</td>
<td>None</td>
<td>0.2</td>
<td>Right thalamus</td>
<td></td>
</tr>
<tr>
<td>83, M</td>
<td>TIA</td>
<td>Right periventricular white matter</td>
<td>None</td>
<td>15</td>
<td>Right periventricular white matter</td>
<td></td>
</tr>
</tbody>
</table>

Bilat indicates bilateral; and TIA, transient ischemic attack.

Figure 1. Radiological findings in a 52-year-old female who experienced transient ischemic attack attributable to moyamoya disease. Silent microbleed in the right thalamus on initial T2*-weighted MRI (A, arrowhead). Markedly dilated moyamoya vessels originating from the lenticulostriate, anterior and posterior choroidal arteries (B, arrows) and ethmoidal arteries (B, arrowhead) on right cerebral angiography. One week later, she developed right thalamic hemorrhage (C, arrow).
annual risk of hemorrhagic stroke was 1.7% in whole adult patients with moyamoya disease. The value was 6.6% in adult patients with silent microbleeds on initial T2*-weighted MRI, being significantly higher than those without (P<0.001; Figure 2).

**Discussion**

This study prospectively investigated clinical features of silent microbleeds in patients with moyamoya disease. Silent microbleeds were detected in about 30% of adult patients. The lesions were identified in the hemorrhagic stroke-prone areas. Ishikawa et al. found them in 4 (14.8%) of 27 adult patients. They were detected in 2 (33.3%) of 6 nonoperated patients, but in 2 (9.5%) of 21 operated patients. There was a significant difference in their incidence between them. Subsequently, Kikuta et al. also reported that their incidence was 28% and 44% on 1.5- and 3.0-Tesla MR apparatus, respectively. No silent microbleeds were identified in pediatric moyamoya disease. Shorter disease periods in pediatric patients may explain no or very low incidence of silent microbleeds.

The principle finding in this study is that de novo silent microbleeds occurred even in asymptomatic patients, in patients without silent microbleeds on initial examination, or in surgically treated patients. Furthermore, hemorrhagic stroke occurred in 4 patients who had silent microbleeds on initial examination. Annual risk of hemorrhagic stroke was quite high, 6.6% in adult patients with silent microbleeds on initial examination. The value was significantly higher than those without. Intracranial hemorrhagic is still one of the most serious events that cause poor outcome in adult moyamoya disease. The present finding strongly suggests that the adult patients with silent microbleeds may carry the high risk for hemorrhagic stroke. Kikuta et al. also reported that hemorrhagic stroke occurred in totally 4 (8.0%) of 50 patients during a mean follow-up period of 16.6 months. However, their study included 23 (46%) of 50 patients who had undergone surgical revascularization before initial MR examination.

In conclusion, silent microbleeds are not rare and may predict subsequent hemorrhagic stroke in adult moyamoya patients. The incidence of de novo silent microbleeds is not small. Careful and long-term follow-up of silent microbleeds would be essential to improve their outcome in adult moyamoya disease.

**Source 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**

Incidence, Locations, and Longitudinal Course of Silent Microbleeds in Moyamoya Disease: A Prospective T2*-Weighted MRI Study
Satoshi Kuroda, Daina Kashiwazaki, Tatsuya Ishikawa, Naoki Nakayama and Kiyohiro Houkin

*Stroke*. 2013;44:516-518; originally published online December 6, 2012;
doi: 10.1161/STRKEAHA.112.678805

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/2/516

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/06/27/STROKEAHA.112.678805.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at: http://stroke.ahajournals.org//subscriptions/
もやもや病患者における無症候性微小出血の発生率、発生部位および長期的経過

前向き T2* 強調 MRI 研究

Incidence, Locations, and Longitudinal Course of Silent Microbleeds in Moyamoya Disease

A Prospective T2*-Weighted MRI Study

Satoshi Kuroda, MD, PhD; Daina Kashiwazaki, MD; Tatsuya Ishikawa, MD, PhD; Naoki Nakayama, MD, PhD; Kiyohiro Houkin, MD, PhD

Department of Neurosurgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan.

背景および目的：もやもや病における無症候性微小出血の臨床的意義は未知である。本研究では、もやもや病における無症候性微小出血の発生率、発生部位および長期的経過の解明を目的とした。

方法：無処置のもやもや病患者 78 例を本前向きコホート研究に登録した。無症候性微小出血の発生率および発生部位を T2* 強調 MRI により評価した。平均 43.1 カ月の追跡期間中、MR 検査は、6 カ月または 12 カ月ごとに繰り返し実施した。

結果：T2* 強調 MRI により、無症候性微小出血は、成人もやもや病患者 58 例中 17 例（29.3％）に特定したが、小児患者 20 例には認められなかった。追跡期間中、新規の無症候性微小出血は、成人患者 58 例中 4 例（6.9％）に発生した。出血性脳卒中は、4 例（6.9％）に発症したが、この 4 例は、すべて初回検査時に無症候性微小出血がみられた患者であった。無症候性微小出血は、成人もやもや病患者において、出血性脳卒中の続発に対する重要な予測因子であった（p < 0.001）。

結論：無症候性微小出血に対する慎重かつ長期にわたる経過観察は、成人もやもや病患者の転帰を改善する上で重要であると考えられる。

Stroke 2013; 44: 516-518

図 1 もやもや病に起因する一過性脳虚血発作を発症した 52 歳女性の画像所見。初回 T2* 強調 MRI で検出した右視床の無症候性微小出血（A, 矢尻）。右側脳血管造影により検出したレンズ核線条体動脈、前-後脈絡叢動脈（B, 矢印）、篩骨動脈（B, 矢尻）から発生し、顕著に拡張したもやもや血管。1 週間後、患者は右視床出血を発症した（C, 矢印）。