Unruptured Intracranial Aneurysms
Incidence of Rupture and Risk Factors

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Backgrounds and Purpose—The authors evaluated the incidence of rupture of unruptured intracranial saccular aneurysm during observation.

Methods—Between January 2003 and December 2006, a total of 419 patients with 529 unruptured intracranial saccular aneurysms were observed without treatment. The mean follow-up duration was 905.3 days. Aneurysm size was measured by 3-dimensional CT angiography. Clinical and 3-dimensional CT angiography follow-up were obtained every 6 months.

Results—Nineteen aneurysms ruptured during observation resulting in a 1.4% rupture rate per year. A history of subarachnoid hemorrhage (hazard ratio, 7.3; 95% CI, 2.5 to 21.2), posterior circulation aneurysm (hazard ratio, 2.9; 95% CI, 1.1 to 8), and large size were significant independent predictors for aneurysm rupture.

Conclusions—Size, history of subarachnoid hemorrhage, and posterior circulation aneurysms were significant risk factors for prediction of rupture of unruptured intracranial saccular aneurysms. (Stroke. 2009;40:313-316.)

Key Words: natural history ■ subarachnoid hemorrhage ■ unruptured intracranial aneurysm

Decision-making for treatment of unruptured intracranial saccular aneurysm (UIA) is complex and controversial. Results of the International Study on Unruptured Intracranial Aneurysms (ISUIA)1 suggest that the natural history of UIAs may be more benign than previously considered. After results of the ISUIA were reported, many institutions felt obliged to manage patients with UIA in a more conservative fashion. In this report, we analyzed the risk factor of rupture of UIAs without treatment.

Clinical Materials and Methods
From January 2003 through December 2006, a total of 419 patients with 529 UIAs were referred to our institution. Patient information and clinical presentation is summarized in Table 1. Size of the UIAs was measured by 3-dimensional CT angiography (Sensation16, Siemens, Germany). Based on the findings of 3-dimensional CT angiography, all UIAs were classified into the following categories: small (S; 0 to 4.9 mm in diameter), medium/small (MS; 5 to 9.9 mm in diameter with small neck (0 to 3.9 mm), medium/wide (MW; 5 to 9.9 mm in diameter) with a wide neck (>4 mm), large (L; >10 mm), and giant (G; >25 mm). These aneurysms were followed by 3-dimensional CT angiography every 6 months.

Data were analyzed using the biomedical data package statistical program (Version 7.0; BMDP Statistical Software, Inc, University of California, Los Angeles, Calif). Categorical variables were compared using the Fisher exact 2-tailed test, the Pearson χ² test, or the test for determining linear trend. Continuous variables were compared among groups by using the Mann-Whitney U test or the Student t test. For life-table analysis and Cox proportional hazards regression model, each patient was followed to the time of subarachnoid hemorrhage (SAH), death due to causes other than SAH, or to the last possible follow-up contact. The average annual incidence of SAH was calculated by determining the number of first-event SAH divided by the number of person-years of follow-up. Cumulative rates of SAH were estimated using the Kaplan-Meier product-limit method.

Results
Nineteen aneurysms ruptured during the follow-up period. The annual incidence of SAH was 1.4% during observation. Incidence of rupture was strongly correlated with aneurysm size. The annual rupture rate by size classification was 0.8% (S), 1.2% (M), 7.1% (L), and 43.1% (G), respectively. Details of ruptured aneurysms under conservative observation are summarized in Table 2.

In patients with a history of SAH, the hazard ratio (HR) was 7.3 (95% CI, 2.5 to 21.2, P<0.001). Particularly in...
S-sized UIAs, 2 of 8 (25%) were associated with a history of SAH. The risk of rupture in S-sized UIAs with a history of SAH was 5.5 (95% CI, 0.9 to 32.4) compared with patients with a single S-sized UIA without SAH history ($P=0.058$). With multivariate analysis, the HR in the M-sized groups was 1.6 (95% CI, 0.4 to 6.2). In the M-sized group, the risk of rupture was not significant when compared with S-sized UIAs. The HR in the L- and G-sized groups were 12.3 (95% CI, 3.9 to 38.8) and 50 (95% CI, 12.8 to 196) compared with that for small UIAs ($P<0.001$). Posterior circulation aneurysms demonstrated a significantly higher incidence of rupture (HR, 2.9; 95% CI, 1.1 to 8; $P=0.028$) than anterior circulation aneurysms (Table 3). The cumulative risk of SAH (calculated using the Kaplan-Meier method) was 1.9% in 1 year, 3.3% in 2 years, 3.7% in 3 years, and 5.6% in 5 years.

Table 1. Characteristics of the Patient Population

<table>
<thead>
<tr>
<th>Aneurysm location, no. of patients (%)</th>
<th>No. of Patients</th>
<th>No. of Aneurysms</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>216</td>
<td>419</td>
<td>41%</td>
</tr>
<tr>
<td>ACA</td>
<td>107</td>
<td>280</td>
<td>20%</td>
</tr>
<tr>
<td>MCA</td>
<td>141</td>
<td>392</td>
<td>27%</td>
</tr>
<tr>
<td>VABA</td>
<td>65</td>
<td>529</td>
<td>12%</td>
</tr>
</tbody>
</table>

Discussion

In this study of 529 UIAs, the overall annual rupture rate was 1.4%. Our study is a single-center analysis and all 529 UIAs received biannual follow-up with precise 3-dimensional CT angiography. This result is almost the same as other previous reports. However, in the ISUIA report, patients with UIAs <7 mm in diameter without a history of SAH, the rupture rate was approximately 0.1% per year. This difference may be a result of racial differences in the patient population. Recent genetic analysis has indicated that Japanese and/or Finnish descendants have a higher potential for rupture. These facts may be related to the relatively high rupture rate.

Size of the aneurysm, posterior circulation aneurysms, and a history of SAH were independent predictors for subsequent SAH. This was also prominent in the S-sized UIAs associated with a ruptured aneurysm, in which the risk of rupture was 5.5 times higher than those aneurysms that were not associated with a ruptured aneurysm. This result was similar to the ISUIA report. Patients in the ISUIA Group 2 had higher rupture rates than those in Group 1. The probability of rupture may be different between these 2 groups. According to these data, when a patient has an UIA associated with a ruptured aneurysm, even if that aneurysm is small in diameter, we should recommend treatment.

It is well known that the risk of rupture in larger-sized aneurysms is high. In a recent meta-analysis, risk of rupture tends to increase by size. In our series, aneurysms between 5 and 9.9 mm did not have a significantly increased risk of rupture compared with that for S-sized UIAs. UIAs larger than 10 mm in diameter (L- and G-sized) demonstrated a higher probability of rupture than in the S-sized group. Thus, aggressive treatment for L- or G-sized aneurysms should be recommended. Regarding aneurysm location, the HR of rupture for anterior cerebral artery and middle cerebral artery aneurysms were 0.6 (95% CI, 0.12 to 2.7) and 0.8 (95% CI, 0.2 to 2.7), respectively, compared with that for internal carotid artery aneurysms in a multivariate analysis. There were no significant differences among these aneurysms. Risk of rupture in posterior circulation aneurysms was significantly higher than that of anterior circulation aneurysms (HR, 2.9; 95% CI, 1.1 to 8). We did not observe a statistically significant influence of location of the aneurysm, but the limited data and outcome events preclude definite conclusions on these topics. Multiplicity did not have a significantly increased risk of rupture compared with that for single UIAs. However, 7 of 11 <10 mm aneurysms, which ruptured, occurred in patients with multiple aneurysms.

Referral bias exists in this study. Our hospital is one of the largest referral centers for intracranial aneurysms in our country. It is unclear how these factors involved in the treatment decision have influenced the results of this study. It is almost impossible in modern medicine to conduct a pure natural history study without treatment. Selection bias is never completely eliminated from this type of analysis.
Conclusion
Size, history of SAH, and posterior circulation aneurysms were significant risk factors for prediction of rupture of UIAs. However, one should note that size of the UIA alone should not be applied for the final decision of the treatment of UIAs.

Acknowledgments
We thank Naoya Kunigane, RT, for 3-dimensional CT angiography measurement.

Disclosures
None.

References
Table 3. Risks Associated With Size, History of SAH, Multiplicity, Sex, and Location of UIA

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of SAHs</th>
<th>No. of Aneurysms</th>
<th>Annual Rupture Rate</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size of aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 mm</td>
<td>8</td>
<td>392</td>
<td>0.8%</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>5–9.9 mm</td>
<td>3</td>
<td>108</td>
<td>1.2%</td>
<td>1.6 (0.4–6.2)</td>
<td>0.369</td>
</tr>
<tr>
<td>10–24.9 mm</td>
<td>5</td>
<td>24</td>
<td>7.1%</td>
<td>12.3 (3.9–38.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>&gt;25 mm</td>
<td>3</td>
<td>5</td>
<td>43.1%</td>
<td>50 (12.8–196)</td>
<td>0.000</td>
</tr>
<tr>
<td>Location of aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>7</td>
<td>216</td>
<td>1.4%</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>2</td>
<td>107</td>
<td>0.9%</td>
<td>0.6 (0.12–2.9)</td>
<td>0.266</td>
</tr>
<tr>
<td>MCA</td>
<td>4</td>
<td>141</td>
<td>1.1%</td>
<td>0.8 (0.2–2.7)</td>
<td>0.713</td>
</tr>
<tr>
<td>VABA</td>
<td>6</td>
<td>65</td>
<td>3.1%</td>
<td>2.5 (0.8–7.6)</td>
<td>0.120</td>
</tr>
<tr>
<td>Anterior circulation aneurysms</td>
<td>16</td>
<td>464</td>
<td>1.2%</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Posterior circulation aneurysms</td>
<td>3</td>
<td>65</td>
<td>3.1%</td>
<td>2.9 (1.1–8)</td>
<td>0.028</td>
</tr>
<tr>
<td>History of SAH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13</td>
<td>510</td>
<td>1.1%</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>19</td>
<td>8.0%</td>
<td>7.3 (2.5–21.2)</td>
<td>0.000</td>
</tr>
<tr>
<td>History of SAH in small-sized aneurysms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>379</td>
<td>0.6%</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>13</td>
<td>4.5%</td>
<td>5.5 (0.9–32.4)</td>
<td>0.058</td>
</tr>
<tr>
<td>Multiplicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single aneurysm</td>
<td>8</td>
<td>298</td>
<td>1.1%</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Multiple aneurysm</td>
<td>11</td>
<td>231</td>
<td>1.9%</td>
<td>1.6</td>
<td>0.353</td>
</tr>
</tbody>
</table>

Interval indicates duration from date which was first found aneurysm to rupture date; ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; VABA, vertebrobasilar artery.
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Stroke. 2009;40:313-316; originally published online October 9, 2008;
doi: 10.1161/STROKEAHA.108.521674

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