Natural History and Outcome After Treatment of Unruptured Intracranial Fusiform Aneurysms

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Background and Purpose—Management of unruptured fusiform intracranial aneurysms is controversial because of the paucity of natural history data. We studied their natural history and outcome after treatment.

Methods—We reviewed our neurovascular database from January 2000 to October 2013. Inclusion criteria were unruptured, intradural fusiform aneurysms with a diameter of <2.5 cm. Criteria were developed to define atherosclerotic aneurysms. For outcome assessment, we used the modified Ranking Scale and aneurysm measurements on serial imaging. Mann–Whitney (continuous) and Fisher exact (categorical) tests were used for risk factor analysis.

Results—For nonatherosclerotic aneurysms (96 patients; 193 person-years follow-up), 1 patient died (rupture) during follow-up (mortality, 0.51% per year) and 8 patients (10%) showed aneurysm progression (risk, 1.6% per year). Risk factors for progression were maximum diameter (≥7 mm; odds ratio, 12; 95% confidence interval, 1.4–104) and symptomatic clinical presentation (odds ratio, 16; 95% confidence interval, 3.1–81.4). Of the 23 treated patients, 3 had died (mortality, 12.5%) and 3 had serious disability (modified Ranking Scale, ≥2; 12.5%). For the atherosclerotic aneurysms (25 patients; 97 person-years follow-up), 5 had died (mortality, 5.2% per year) and 13 of 20 (65%) had aneurysm progression (risk, 12% per year). When compared with patients with nonatherosclerotic aneurysms, case fatality (odds ratio, 19.2; 95% confidence interval, 1.4–192) and aneurysm progression (odds ratio, 17.8; 95% confidence interval, 5.3–56) were higher.

Conclusions—Nonatherosclerotic fusiform intradural aneurysms have a low risk of adverse outcome within the first few years after diagnosis and remain stable unless symptomatic on presentation or >7 mm in maximum diameter. High risks of treatment should be balanced against this benign natural history. Atherosclerotic aneurysms have a worse natural history and may represent a different disease entity. (Stroke. 2014;45:00-00.)

Key Words: asymptomatic diseases ■ atherosclerosis ■ fusiform aneurysm ■ natural history
Criteria were established primarily based on cerebrovascular imaging with supporting evidence from the patients’ clinical profile in patients suspected of harboring atherosclerotic aneurysms (Table 1).

Our search was conducted based on review of a prospectively recorded database of patients attending clinic and an extensive electronic search of all intracranial vascular imaging reports (computed tomographic/MR angiography and digital subtraction angiography) performed at the Toronto Western Hospital during the study period. Suitable patients were further studied with a combination of electronic chart extraction and review of relevant vascular imaging. All imaging was reviewed by 2 of the study neuroradiologists to confirm aneurysm dimensions and location. Baseline clinical characteristics, including age, sex, comorbidities, and modes of presentation, were derived from the electronic records. Symptomatic presentation was defined as the patient coming to medical attention as a direct consequence of the aneurysm, such as from mass effect, stroke/transient ischemic attack (TIA) in the vascular territory compatible with the sequence of the aneurysm, such as from mass effect, stroke/transient ischemic attack (TIA) in the vascular territory compatible with the distribution of the aneurysm, or pain directly attributable to the aneurysm. We searched records for evidence of potential risk factors for intracranial fusiform aneurysms—previous trauma, known connective tissue disease, smoking, hypertension, diabetes mellitus, and hypercholesterolemia. Aneurysm location and morphology (maximum diameter and length) were measured from the imaging at first presentation and subsequent follow-up imaging studies. Because of the uncertainty of management for this group of patients, both clinical and radiological follow-up were largely similar to follow-up of unruptured saccular aneurysms with a single yearly follow-up to determine stability followed by a 3-year scan. Patients were seen/imagined sooner if they experienced clinical events.

### Outcome Assessment

Patient outcome was assessed at baseline and at last clinical follow-up based on clinic visits. We assigned a modified Ranking Scale (mRS)4 score based on their clinic visit records at baseline and last follow-up. Natural history data were divided into clinical follow-up and radiological follow-up. These were defined as from the time of initial identification of the aneurysm until the last clinic visit/imaging study or until treatment of the aneurysm. We analyzed the clinical follow-up per patient and the radiological follow-up per aneurysm. End points for clinical follow-up were defined as death related to the aneurysm or significant clinical events related to the aneurysm resulting in a drop of >2 points in the mRS from baseline. We also specifically looked for the development of strokes/TIAs during follow-up. Radiological end points for follow-up were enlargement of the maximum diameter of the aneurysm (progression); we took a figure of >2-mm increase since last follow-up to adjust for measurement error.

### Statistical Analysis

Descriptive statistics were used to summarize the patient demographics, risk factors, comorbidities, presentation, and aneurysm characteristics. Comparisons between patients with atherosclerotic and nonatherosclerotic, as well as progressing and stable aneurysms, were performed using the Mann–Whitney test for continuous variables and the Fisher exact test for categorical variables. Two by two tables were used to generate odds ratios (ORs) and 95% confidence intervals (CIs). Aneurysm lengths and diameters were dichotomized based on median values for the purposes of analysis.

Survival analysis was performed for clinical outcome for the atherosclerotic and nonatherosclerotic groups (censored to death/drop in mRS>2 points or treatment) using Kaplan–Meier curves and a log-rank test was run to compare differences between the groups. Hazard
ratios were calculated using cox proportional hazards model. All tests were 2-sided, and a P value of <0.05 was considered to indicate a statistically significant association.

Data analyses were performed using a software package (IBM SPSS Statistics for Windows, version 20.0. Released 2011; IBM Corp, Armonk, NY).

Results
A total of 121 patients with 138 aneurysms fulfilled our study inclusion criteria. Baseline demographics and mode of presentation for the patient cohort are shown in Table 2. The distribution and dimensions of the nonatherosclerotic and atherosclerotic aneurysms are presented in Table 3. Of the 87 patients with incidental presentations, 46 (53%) patients underwent imaging for evaluation of headaches, 12 patients (14%) for evaluation of ischemic stroke/TIA-like symptoms in distributions remote from the aneurysm, and the remaining 29 (33%) patients for nonspecific neurological complaints, such as dizziness and tinnitus.

In comparison with nonatherosclerotic aneurysms, patients with atherosclerotic aneurysms were more likely to be men (OR, 4.2; 95% CI, 1.5–12), present with ischemic symptoms (OR, 19.6; 95% CI, 6.6–58.2) and have aneurysms located within the posterior circulation (OR, 3.1; 95% CI, 1.3–7.5), which were of larger mean diameter 11.6 mm (range, 4–24 mm) versus 7.5 mm (2–24 mm; P<0.001). Eight patients (38%) with atherosclerotic aneurysms had intramural thrombus identified on MRI, which was not significantly associated with worse clinical outcome (OR, 1.4; 95% CI, 0.2–8.6).

Natural History
For patients with nonatherosclerotic aneurysms, natural history follow-up was available in 87 patients (91%) and imaging follow-up in 82 (85%) patients with 94 aneurysms (87%). There were 193 person-years clinical follow-up (median, 12 months; range, 6–135 months) and 477 aneurysm years of imaging follow-up (median, 46; range, 6–415 months). For atherosclerotic aneurysms, complete follow-up was available in 23 patients (92%) and imaging follow-up in 22 patients (88%) with 26 aneurysms. In this group, there were 97 person-years of clinical follow-up (median, 36 months; range, 3–180 months) and 110 years of imaging follow-up (median, 36 months; range, 1–170 months).

Clinical Follow-Up
In the nonatherosclerotic patient group, 2 patients died during follow-up—1 from an unrelated pulmonary embolus and another from confirmed aneurysmal subarachnoid hemorrhage (SAH) during follow-up (rupture rate, 0.51% per year;
Table 3. Aneurysm Distribution for Atherosclerotic and Nonatherosclerotic Aneurysms

<table>
<thead>
<tr>
<th>Location</th>
<th>Nonatherosclerotic Aneurysms</th>
<th>Atherosclerotic Aneurysms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diameter, mm*</td>
<td>Length, mm*</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>28 8 (4–23) 15 (5–39)</td>
<td>4 9 (7–19) 26 (9–43.1)</td>
</tr>
<tr>
<td>ACA</td>
<td>8 5 (3–9) 7 (8–36)</td>
<td>...</td>
</tr>
<tr>
<td>MCA</td>
<td>20 5.8 (4–14) 11 (4–24)</td>
<td>3 6 (4–9) 13.5 (5–15)</td>
</tr>
<tr>
<td>Total</td>
<td>56 6 (3–23) 11 (4–39)</td>
<td>7 8 (4–19) 13.5 (5–43.1)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertebral</td>
<td>20 7 (4–9) 10 (5–20)</td>
<td>5† 11 (6–17) 18 (6–54)</td>
</tr>
<tr>
<td>PCA</td>
<td>7 7 (2–15) 9 (5–12)</td>
<td>...</td>
</tr>
<tr>
<td>Basilar</td>
<td>11 6 (3–12) 13.5 (4–30)</td>
<td>18 12 (2–24) 20 (9–47)</td>
</tr>
<tr>
<td>ACA</td>
<td>1 2</td>
<td>3</td>
</tr>
<tr>
<td>PCA</td>
<td>11 8 (3–20) 6 (6–13)</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>50 6 (2–20) 10 (3–36)</td>
<td>23 12 (2–24) 19 (6–54)</td>
</tr>
<tr>
<td>Diffuse</td>
<td>2</td>
<td>...</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; ACA, anterior cerebral artery; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; and PICA, posterior inferior cerebellar artery.

*Median (range).
†Vertebral/basilar.

Table 4, patient 8). There were no other aneurysm-related clinical events or significant changes on the mRS scale during clinical follow-up. In the atherosclerotic patient group, there were 7 deaths, 5 aneurysm related (2 from rupture and 3 from ischemic stroke), with a mortality rate of 5.2% per year. A further 3 patients experienced additional TIAs during follow-up and another had a nonfatal SAH, leading to an overall significant aneurysm-related clinical event rate of 9.3% per year. Kaplan–Meier survival curves for both groups are shown in Figure 2. The hazard ratio for atherosclerotic aneurysms versus nonatherosclerotic aneurysms was 0.06 (95% CI, 0.007–0.46).

Aneurysm Follow-Up
In the nonatherosclerotic group, 8 patients (9.8%) showed evidence of aneurysm growth, with an overall risk of aneurysm progression of 1.6% per year. Significant risk factors for aneurysm progression in this group (Table 2) were symptomatic presentation (OR, 16; 95% CI, 3.1–81.4) and maximum aneurysm diameter (OR, 12.2; 1.4–104.4) > 7 mm (median).

The duration of imaging follow-up in these 8 patients was similar to the overall population (median, 50 months). These patients are presented in Table 4. There was no predilection for aneurysm site and 6 of the 8 patients underwent treatment for their aneurysm after enlargement. Of the 2 patients who were not treated, a 44-year-old man died from an unrelated pulmonary embolus and the second patient (described above) died from a SAH 1 week before scheduled treatment.

By contrast, 13 (65%) patients in the atherosclerotic group demonstrated progressive aneurysm enlargement on follow-up (OR, 10; 95% CI, 3.4–29.3) with the overall risk of aneurysm progression of 12% per year. In both groups, no patients with aneurysms <7 mm at presentation enlarged on subsequent follow-up.

Surgical and Endovascular Treatment
Twenty-three patients (24%) underwent aneurysm treatment (15 surgical and 8 endovascular). Ten (43%) of these patients were symptomatic at presentation: 5 with mass effect leading to neurological symptoms, 4 with stroke/TIAs, and 1 patient with occipitocervical pain caused by previous vertebral dissection. In terms of surgical treatment, 9 patients underwent vessel trapping/occlusion and concurrent bypass. In patients who underwent endovascular treatment, 6 patients were treated with proximal occlusion of the parent vessel and 2 patients underwent stent-assisted coiling of their aneurysm.

There were a total of 3 deaths (12.5%) in patients who underwent treatment. One patient (55-year-old woman) who had an occluded bypass after partial trapping of her large terminal internal carotid artery aneurysm, refused further treatment despite continuing enlargement of the aneurysm and died from a SAH 2 years after her treatment. Three patients

Table 4. Details of Patients With Nonatherosclerotic Aneurysms That Enlarged During Follow-Up

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age/Sex</th>
<th>Aneurysm Location</th>
<th>Length, mm</th>
<th>Diameter, mm</th>
<th>Presenting Symptoms</th>
<th>Treatment After Enlargement</th>
<th>Outcome (mRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50/F</td>
<td>RT vertebral</td>
<td>12</td>
<td>8</td>
<td>SAH*</td>
<td>E: occlusion</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>52/M</td>
<td>RT paracclinoid</td>
<td>20</td>
<td>16</td>
<td>CN palsy</td>
<td>S: bypass</td>
<td>2†</td>
</tr>
<tr>
<td>3</td>
<td>37/M</td>
<td>RT PICA</td>
<td>10</td>
<td>15</td>
<td>Mass effect</td>
<td>S: bypass</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>31/F</td>
<td>LT MCA</td>
<td>7</td>
<td>8</td>
<td>Incidental</td>
<td>S: bypass</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>52/F</td>
<td>RT supraclinoid</td>
<td>17</td>
<td>23</td>
<td>CN palsy</td>
<td>S: clipping</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>58/F</td>
<td>LT paracclinoid</td>
<td>7</td>
<td>13</td>
<td>Incidental</td>
<td>E: coiling</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>44/M</td>
<td>Basilar</td>
<td>19</td>
<td>11</td>
<td>Stroke</td>
<td>None</td>
<td>6‡</td>
</tr>
<tr>
<td>8</td>
<td>69/M</td>
<td>LT PCA</td>
<td>36</td>
<td>15</td>
<td>Incidental</td>
<td>None</td>
<td>6§</td>
</tr>
</tbody>
</table>

CN indicates cranial nerve; F, female; LT, left; M, male; MCA, middle cerebral artery; mRS, modified Ranking Scale; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; RT, right; and SAH, subarachnoid hemorrhage.

*SAH 6 mo previously.
†Worsening ophthalmoplegia from surgery.
‡Died from pulmonary embolism unrelated to aneurysm or treatment.
§SAH related to aneurysm.
(12.5%) had mild disability (mRS=2) at last follow-up (all because of treatment-related events).

Discussion

Previous studies on fusiform intracranial aneurysms have included a heterogeneous population of both ruptured and unruptured fusiform aneurysms and are limited by small numbers. To our knowledge, this is the first consecutive series describing the natural history of patients with fusiform intradural aneurysms, which distinguishes between those who are atherosclerotic and those who are not. We confirmed the poor natural history of patients with atherosclerotic, predominantly vertebrobasilar aneurysms that has previously been reported. Unique to this study are the findings that the risk of rupture or adverse clinical events is low in patients with fusiform aneurysms not associated with intracranial atherosclerosis during the first 3 years after diagnosis. In addition, the risks of aneurysmal progression also seem to be low for the majority of aneurysms not associated with atherosclerosis. In this group, patients with either symptomatic aneurysms at presentation or those with larger aneurysm diameters were more likely to progress in terms of aneurysm enlargement.

In the absence of a standard definition, we undertook to profile patients with fusiform aneurysms associated with intracranial atherosclerosis from a clinical and imaging perspective to serve as a guide to standardize this population group, which we think that has a different natural history. Limitation to this definition is the retrospective nature of the classification and a realization that there is likely to be overlap between the 2 groups of fusiform aneurysm patients. A possible explanation for the poor natural history in atherosclerotic patients is that they were more likely to be both symptomatic at presentation and to have larger aneurysms but may also reflect a different disease process within these aneurysms. The observation that symptomatic patients continued to enlarge in both groups may be a reflection of unstable growth in these cases that cause these aneurysms to come to clinical attention. In both groups, only patients with aneurysms ≥7 mm in maximum diameter are enlarged. In contrast, there was no association between the length of the fusiform segment and the risk of enlargement. The figure of 7 mm is remarkably similar to the consistent finding that saccular aneurysms >7 mm pose a higher risk of rupture for most locations and may reflect a point at which aneurysmal growth becomes more likely because of mechanical instability within the vessel wall.

Similar to the major studies of unruptured intracranial saccular aneurysms, our study has a selection bias because of the treatment of those patients considered to be at highest risk of rupture—those with progressively increasing diameters or aneurysm-related symptoms. Referral bias may also have affected our results (eg, symptomatic patients or those with larger aneurysms preferentially being referred to the clinic). Subgroup analysis of risk factors for rupture was not possible in this study because of the small numbers of index cases. We excluded giant aneurysms because of their known natural history and the difficulty of determining the exact morphology (saccular versus fusiform) once an aneurysm reaches these proportions.

The cause of fusiform aneurysms may be because of a variety of underlying pathologies affecting the vessel wall. Intramural dissection has been described as a cause for fusiform aneurysms in both the acute and the chronic stages. We think that acute dissecting intracranial aneurysms without SAH or early pseudoaneurysm formation may be managed expectantly. In the present study, 2 patients presented with sudden occipitocervical pain, and although initial angiographic workup was negative, these patients were subsequently noted to develop intracranial fusiform aneurysms at follow-up >6 months from initial presentation. Both of these aneurysms remained stable and asymptomatic for serial follow-ups.

Because of their morphology, the treatment required to exclude or repair fusiform aneurysms differs from the standard therapy of saccular aneurysms. As shown in the current study, there is a definite risk associated with treatment of these challenging lesions, a permanent morbidity/mortality rate of up to 25%, which is similar to the findings of other studies.
This study is timely given the recent advances in endovascular flow diversion technology, which have become available and may be used as an alternative therapy for fusiform aneurysms. Given the findings of this study, careful consideration should be given to the relatively benign natural history in many of these patients before embarking on therapeutic interventions.

Conclusions
Patients presenting with fusiform intradural aneurysms should be evaluated for features suggestive of association with intracranial atherosclerosis. Unruptured fusiform aneurysms not associated with atherosclerosis that are <7 mm in maximum diameter have a low risk of rupture or becoming symptomatic during the first few years after presentation. If discovered incidentally, follow-up imaging (such as at 1 year) should be considered to determine stability. Aneurysms that are >7 mm in maximum diameter or that are symptomatic at presentation have an increased risk of progressive enlargement (and possible rupture). Aneurysms associated with intracranial atherosclerosis represent a worse prognosis and treatment remains challenging, particularly of the vertebral-basilar circulation. The significant risks of treatment associated with fusiform intradural aneurysms should be taken into consideration when evaluating their natural history.

Disclosures
None.

References
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