Natural history of unruptured intracranial aneurysms: a long-term follow-up study

Seppo Juvela, M.D., Matti Porras, M.D., and Olli Heiskanen, M.D.

Department of Neurosurgery, Helsinki University Central Hospital, Helsinki, Finland

To investigate the natural history of unruptured aneurysms and predictive risk factors determining subsequent rupture, the authors followed 142 patients with 181 unruptured aneurysms until death or subarachnoid hemorrhage intervened, or for at least 10 years after the unruptured aneurysm was diagnosed. Six patients had a symptomatic aneurysm, five had an incidentally discovered aneurysm, and 131 had multiple aneurysms, of which the ruptured lesion was clipped at the beginning of the follow-up study. The median follow-up time was 13.9 years (range 0.8 to 30.0 years). During 1944 patient-years of follow-up study there were 27 first episodes of hemorrhage from a previously unruptured aneurysm, giving an average annual rupture incidence of 1.4%. Fourteen of these bleeding episodes were fatal. The cumulative rate of bleeding was 10% at 10 years, 26% at 20 years, and 32% at 30 years after the diagnosis.

The only predictor for the rupture was the size of the aneurysm (p = 0.036). However, in patients with multiple aneurysms (the main subgroup) the only variable that tended to predict rupture was the age of the patient: risk of rupture was inversely associated with age (p = 0.080). The median diameter of the aneurysms was 4 mm at the beginning of the follow-up period, both in those with and those without a later hemorrhage. During the angiographic monitoring period, a ruptured aneurysm significantly (p < 0.001) increased in size in 17 patients with hemorrhage but aneurysms did not increase significantly in 14 patients without hemorrhage. In addition, a new aneurysm was found in six of 31 patients. The authors conclude that an unruptured aneurysm should be operated on, irrespective of its size, if it is technically possible and the patient’s age and concurrent diseases are not contraindications to surgery.

Key Words • unruptured intracranial aneurysm • subarachnoid hemorrhage • natural history

In spite of recent improvements in surgical and medical management of aneurysmal subarachnoid hemorrhage (SAH), the overall mortality rate for this disease is still high (about 40% to 50%). The high mortality and morbidity rates are attributed mainly to brain damage due to a severe initial bleed, early rebleeding, and delayed cerebral ischemia. Most operations for cerebral aneurysms are performed to prevent rebleeding in patients in good clinical condition and only a minority of patients undergo removal of a space-occupying hematoma to improve outcome. Incidentally identified aneurysms, as well as unruptured aneurysms in patients with multiple aneurysms, are operated on when discovered with quite a low risk, thus the high mortality and morbidity rates associated with a possible severe initial bleed can be eliminated by preventive surgical intervention. However, the natural history of unruptured intracranial aneurysms and the risk factors for rupture are poorly understood due to a lack of studies with sufficient numbers of patients and follow-up years. Current knowledge of the natural history of unruptured aneurysms is based on only a few studies, and questions about the risk and risk factors of aneurysm rupture are still open.

Before 1979, unruptured aneurysms were not operated on in our clinic. In the present long-term study, patients with unruptured aneurysms diagnosed before 1979 were followed to better define the natural history of an unruptured aneurysm and the risk factors predicting rupture.

Clinical Material and Methods

Patient Population

The records of the patients with a diagnosis of intracranial aneurysm who were managed at the Department of Neurosurgery, Helsinki University Central Hospital, between 1956 and 1978 were reviewed. During that time, only ruptured aneurysms underwent surgery.

All patients with a conservatively treated ruptured aneurysm were excluded from this study. Patients with mycotic or fusiform atherosclerotic aneurysms were also excluded, as well as those with an uncommon intracavernous carotid artery aneurysm, which is associated with minimal risk of rupture. Patients with
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Symptomatic aneurysms were included in the study only if SAH was excluded by a lumbar puncture within a few days after the onset of symptoms.

Classification of Unruptured Aneurysms

Unruptured aneurysms were classified as follows: asymptomatic incidentally discovered aneurysms (five patients); symptomatic aneurysms (six patients); and multiple aneurysms in SAH patients with only the ruptured aneurysm clipped, the occlusion of the aneurysm being confirmed by postoperative angiography (131 patients). If the parent artery was clipped together with the aneurysm, the patient was excluded from the study because of the possibility of formation of a new aneurysm or the chance of enlargement of a pre-existing aneurysm due to an increase in hemodynamic stress in the remaining arteries.20,21

Symptomatic aneurysms caused a cranial nerve deficit due to space-occupying effects in five patients and one in one patient was related to cerebral infarction, possibly due to aneurysm embolus. Cerebral angiography in five patients with asymptomatic incidentally discovered aneurysms was performed for reasons unrelated to the aneurysm, such as chronic headache, nausea, dizziness, and visual disorders.

Identification of the ruptured aneurysm in all patients with multiple aneurysms was based on a clear statement of signs of rupture in the surgical record. Other evidence for rupture of one particular aneurysm in patients with multiple aneurysms was as follows: the greater size of the ruptured aneurysm than the unruptured aneurysm in 10 patients; the size and secondary sac of the aneurysm in 69 patients; intracerebral hematoma in connection with the aneurysm in 38 patients; and oculomotor palsy and size of an aneurysm associated with an internal carotid artery aneurysm in 14 patients. Patients with SAH and two or more aneurysms of equal size but without angiographic evidence or symptoms indicating which aneurysm had bled were treated conservatively before 1979, and therefore excluded from this study.

Angiographic Examination

Angiograms performed at the beginning of the follow-up period and also during subsequent monitoring in 31 patients were re-examined by a neuroradiologist (M.P.). The size of an aneurysm was based on its greatest diameter measured in standard angiographic projections, taking into account the magnification. The location, shape (round, oval, or multilobed), and direction of the aneurysm were also recorded. In addition, the volume of an aneurysm was estimated from its maximum longitudinal and transverse diameters; since an aneurysm is typically round or ellipsoidal, the following formula was used: volume = \(2\pi r^2 (R - \frac{r}{2})\), where \(r\) is the smaller radius and \(R\) is the larger radius of the aneurysm.

Follow-Up Methods

During 1988 and 1989, follow-up evaluation was accomplished primarily by questionnaires and by a telephone interview with the patients or close relatives, as required. Information on all patients was also collected from the medical records of other (local and central) hospitals and general practitioners in order to check diseases, medications, and blood pressure (BP) values of the patients. Autopsy reports and official death certificates of deceased patients were examined. There was 100% follow-up evaluation.

Blood Pressure Recording

Blood pressures were recorded before the diagnosis and during the follow-up evaluation, excluding the values of the patients with multiple aneurysms within 3 months after SAH, because SAH may secondarily increase BP. In patients with multiple BP measurements, the values in the first and last quarter of the follow-up period were averaged. A BP measurement was missing in only one patient at the end of the follow-up period.

Mean arterial BP was calculated from the formula: diastolic BP + (systolic BP - diastolic BP)/3. Definite hypertension was defined either as a systolic pressure repeatedly greater than 160 mm Hg or diastolic pressure greater than 95 mm Hg, or as use of antihypertensive medication.

Statistical Analysis

Categorical variables were compared by Fisher’s exact or chi-squared tests. Continuous variables were compared between groups by the Mann-Whitney U test, Student’s t-test, analysis of variance (ANOVA), or the Kruskal-Wallis one-way ANOVA with multiple simultaneous pairwise comparisons; within groups, the Wilcoxon signed rank test was employed. Univariate association of continuous variables (patient age, aneurysm size, and interval from diagnosis to SAH) were tested using the Spearman rank correlation coefficients (r). The possible confounding effect of patient age on BP was tested by analysis of covariance.

For life-table analysis and the Cox proportional-hazards regression model, each patient was followed to SAH, to death from a cause other than SAH, or to the last contact which was at least 10 years in those without SAH or death. Average annual incidence of SAH was calculated by the number of first events of SAH divided by number of follow-up patient years. The cumulative rates of SAH were estimated by the Kaplan-Meier product-limit method, and the curves of different groups were compared by the log-rank test.

The Cox proportional-hazards model with a forward stepwise-regression procedure (using the BMDP statistical package*) was used to determine the significance of several variables in predicting future aneurysm rupture. These variables, known at the beginning of the follow-up study, were as follows: patient age and sex; size (maximum diameter and volume), location, and direction of the largest unruptured aneurysm in each patient; number of unruptured aneurysms; aneurysm

* BMDP statistical software supplied by the University of California, Berkeley, California.
group (symptomatic, incidental, and multiple); definite hypertension occurrence and administration of anti-hypertensive medication; and BP (systolic, diastolic, mean values) at entry into the study. Blood pressures were also tested as time-dependent covariates during the follow-up period. The assumption about proportionality was checked. Test for significance was based on changes in the log (partial) likelihood. The Wald's test was used for hypothesis testing when patient age and sex were adjusted. A two-tailed \( p \) value below 0.05 was considered to indicate statistical significance.

Results

**Study Group and Follow-Up Period**

This series included 142 patients (66 men and 76 women) with 181 unruptured intracranial aneurysms. Of the 142 patients, 109 had one unruptured aneurysm, 27 had two aneurysms, and six had three aneurysms. The patients' median age at the beginning of the follow-up period was 41.9 years (range 14.6 to 60.7 years). Patients with a symptomatic aneurysm were older (median age 51.0 years, range 37.1 to 57.3 years) than those with multiple aneurysms (median age 41.7 years, range 14.6 to 60.7 years) or incidental aneurysm (median age 39.5 years, range 24.6 to 60.6 years) (\( p < 0.05 \), between patients with symptomatic aneurysm vs. others and vs. patients with multiple aneurysms).

The total follow-up period after diagnosis comprised 1944 patient-years, an average of 13.7 years per patient (median 13.9 years, range 0.8 to 30.0 years); 130 patients were followed for at least 5 years, 109 for at least 10 years, 59 for at least 15 years, 19 for at least 20 years, and seven for at least 25 years (Fig. 1). The follow-up time did not differ significantly between aneurysm categories, although patients with a symptomatic aneurysm were followed for a somewhat shorter period than the others due to their greater age (Table 1).

**Location and Size of Aneurysms at Start of Follow-Up Period**

The location of the ruptured aneurysm in the 131 patients with multiple aneurysms was as follows: 41 arose from the internal carotid artery; 31 from the anterior communicating artery; three from the pericallosal artery; one from the anterior cerebral artery; and 55 from the middle cerebral artery. The median greatest diameter of the ruptured aneurysms was 10 mm (mean 10.3 mm, range 4 to 28 mm); 50% of these aneurysms were 7 to 13 mm in diameter.

The location of all unruptured aneurysms and the size of the largest unruptured aneurysm in the separate groups are shown in Table 1. The most common sites of unruptured aneurysms were in the internal carotid and middle cerebral arteries. The median greatest diameter of 181 unruptured aneurysms was 4 mm (mean 4.7 mm, range 2 to 26 mm) and that of the largest aneurysm in each patient was 4 mm (mean 5.1 mm, ranging from 2 to 26 mm). The diameters of the largest aneurysm in the six patients with a symptomatic aneurysm and the five patients with an incidental aneurysm were significantly greater than in those with mul-

![Kaplan-Meier curves showing cumulative rates of subarachnoid hemorrhage (SAH) according to aneurysm group and all patients together. The curves did not differ significantly by group. Multiple = patients with multiple aneurysms, of which the ruptured one was clipped; symptomatic = patients with unruptured symptomatic aneurysm; incidental = patients with incidentally discovered unruptured aneurysm; all = all patients. Arrowheads indicate the last censored observation in the symptomatic and incidental aneurysm groups.](image-url)
Natural history of unruptured aneurysms

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Follow-up time, and size and location of unruptured aneurysms in three aneurysm groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Incidental</td>
</tr>
<tr>
<td>no. of cases</td>
<td>5</td>
</tr>
<tr>
<td>follow-up time (yrs)</td>
<td>16.5</td>
</tr>
<tr>
<td>range</td>
<td>3.8–17.3</td>
</tr>
<tr>
<td>size of largest aneurysm (mm)</td>
<td>8.0±</td>
</tr>
<tr>
<td>range</td>
<td>5–25</td>
</tr>
<tr>
<td>location of aneurysms</td>
<td>ICA</td>
</tr>
<tr>
<td>no. of cases</td>
<td>5 (1)</td>
</tr>
<tr>
<td>ACA + A2</td>
<td>3</td>
</tr>
<tr>
<td>ACA + A2</td>
<td>0</td>
</tr>
<tr>
<td>ACA + A2</td>
<td>0</td>
</tr>
<tr>
<td>ACA + bas</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

* The number of aneurysms with later rupture is shown in parentheses. Size = maximum diameter of the largest aneurysm in each patient. ICA = internal carotid artery; MCA = middle cerebral artery; ACA = anterior cerebral artery; A2 = pericallosal artery; ACAo = anterior communicating artery; bas = basilar tip; SCA = superior cerebellar artery. Significance of difference: *p < 0.05, *p < 0.01 for the difference in aneurysm size compared to patients with multiple aneurysms by the Kruskal-Wallis one-way analysis of variance.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Blood pressures at the beginning and end of follow-up period in three aneurysm groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>Incidental</td>
</tr>
<tr>
<td>no. of cases</td>
<td>5</td>
</tr>
<tr>
<td>BP at entry</td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>136 ± 18</td>
</tr>
<tr>
<td>diastolic</td>
<td>83 ± 7</td>
</tr>
<tr>
<td>mean</td>
<td>101 ± 10</td>
</tr>
<tr>
<td>BP at end of study</td>
<td></td>
</tr>
<tr>
<td>systolic</td>
<td>142 ± 23</td>
</tr>
<tr>
<td>diastolic</td>
<td>86 ± 13</td>
</tr>
<tr>
<td>mean</td>
<td>105 ± 16</td>
</tr>
</tbody>
</table>

* Blood pressure (BP) values are expressed as means ± standard deviations. Values are averaged from multiple measurements at the beginning and the end of follow-up evaluation: mean = diastolic BP + (systolic BP − diastolic BP)/3.

† Data not available for one patient.

Multiple aneurysms (Kruskal-Wallis test statistic = 19.13, df = 2, p = 0.0001 for overall comparison between groups; adjusted p < 0.01 for difference between symptomatic and multiple aneurysms and p < 0.05 for difference between incident and multiple aneurysms) (Table 1). The median volume of the largest aneurysm in each patient was 21 cm³ (range 4 to 4155 cm³).

Hypertension

Blood pressures did not significantly differ according to aneurysm group either at the beginning or at the end of follow-up evaluation (Table 2). Thirty-five patients (25%) received antihypertensive therapy during the follow-up period. Blood pressure was repeatedly increased (systolic BP > 160/diastolic BP > 95 mm Hg) in 17 patients (12%) at entry to the follow-up study and in 29 patients (20%) at the end of the follow-up period.

Incidence of Aneurysm Rupture

During the follow-up period of 1944 patient-years, 27 (19%) of the 142 patients suffered a SAH, giving an approximate annual incidence of 1.4%. The number of patients with later SAH did not differ significantly between the aneurysm groups (Table 1 and Fig. 1). The average annual incidence of SAH by group was 3.6% for symptomatic aneurysms, 1.5% for incidentally discovered aneurysms, and 1.3% for multiple aneurysms.

The median time between diagnosis and subsequent rupture of aneurysm was 9.6 years (mean 9.4 years, range 1.2 to 23.1 years), and the median time of follow-up evaluation in those without SAH was as follows: 15.3 years (mean 16.2 years, range 10.0 to 30.0 years) for those who were alive and 9.0 years (mean 10.8 years, range 0.8 to 26.0 years) for those who died from unrelated causes.

The risk of bleeding from an unruptured aneurysm was nearly constant over the three decades following diagnosis (Fig. 1). During the first decade after diagnosis, there were 14 first events of SAH within 1279 patient-years, yielding an incidence of 1.1% per year. In addition, 19 patients died within the first decade from causes unrelated to aneurysm. During the second decade, 12 of 109 patients suffered SAH within a follow-up period of 590 patient-years (2.0% per year) and nine patients died from unrelated causes. During the third decade, there was one patient with SAH among 19 patients within the follow-up period of 75 patient-years (1.3% per year) and four patients died of unrelated causes. At the end of the follow-up period, 83 patients were still alive without SAH from unruptured aneurysm.

The cumulative rates of SAH by aneurysm group are shown in Fig. 1. The cumulative probability of SAH did not differ significantly (p = 0.29) by aneurysm group, but the number of patients was small in the groups of symptomatic and incidentally aneurysms. The cumulative rate of bleeding in the entire patient population was 10.0% (95% confidence interval 4.8% to 15.3%) at 10 years, 25.6% (15.9% to 35.4%) at 20 years, and 32.4% (16.0% to 48.8%) at 30 years after the diagnosis of unruptured aneurysm.

Patients With Aneurysm Rupture

The diagnosis was based on lumbar puncture, angiography, and/or surgery in those who survived after SAH. Of the 27 patients, 14 (52%) died due to SAH caused by previously unruptured aneurysm (11 of 24 in the multiple aneurysm group, both of the two in the symptomatic aneurysm group, and the one patient in the incidental aneurysm group).

In the multiple aneurysm group, nine patients died of verified aneurysm rupture, and two patients with bilateral unruptured middle cerebral artery aneurysms...
died of typical SAH confirmed by lumbar puncture; however, the exact cause was not proven because an autopsy was not performed. In addition, 30 patients in this aneurysm group died from the following causes: nine of coronary heart disease, seven of cancer, 11 of other diseases, two due to trauma or suicide, and one of SAH due to fracture of the aneurysm clip 24 years after the first operation for the ruptured aneurysm.

One patient with an incidental internal carotid artery aneurysm died of aneurysm rupture, confirmed by angiography and autopsy, and two patients with a symptomatic internal carotid artery aneurysm died from a typical SAH, which was verified by lumbar puncture. In addition, death from other diseases was noted in two patients in the symptomatic aneurysm group (one due to myocardial infarct and the other due to pulmonary embolus) but none in the incidental aneurysm group.

Patients who later suffered SAH were younger (median 36.8 years, range 22.6 to 57.6 years) than those who did not have an SAH (median 42.7 years, range 14.6 to 60.7 years) (p = 0.053). This difference was even more marked in patients with multiple aneurysms (median 36.1 years, range 22.6 to 57.6 years vs. a median 42.6 years, range 14.6 to 60.7 years; p = 0.021). Women suffered SAH twice as often as men (19 of 76 or 25% vs. eight of 66 or 12%; p = 0.057), but the fatality rate after SAH was similar in men (four of eight) and women (10 of 19). On the other hand, men died of unrelated causes more than twice as often as women (22 of 66 or 33% vs. 10 of 76 or 13%). Therefore, the curves of the cumulative probability of SAH did not differ significantly according to sex (p = 0.11).

Blood pressures differed slightly at both the beginning and the end of follow-up evaluation between those with SAH and those without SAH. Mean ± standard deviation systolic/diastolic BP values were 137 ± 21/82 ± 10 mm Hg for those with SAH and 140 ± 18/86 ± 10 mm Hg for those without SAH in the beginning of the follow-up period (p = 0.042 for the difference between diastolic BPs). Corresponding values were 140 ± 15/86 ± 11 mm Hg and 146 ± 17/89 ± 10 mm Hg at the end of follow-up study. In patients with multiple aneurysms, BP's differed more clearly. At the start of the follow-up evaluation, the mean BP was 137 ± 22/81 ± 10 mm Hg for patients with SAH and 140 ± 18/86 ± 9 mm Hg for patients without SAH (p = 0.030 for the difference between diastolic BPs), and at the end of follow-up evaluation, the corresponding BP's were 138 ± 15/86 ± 12 mm Hg and 146 ± 17/89 ± 9 mm Hg (p = 0.044 for difference between systolic pressures). However, the mean arterial BP did not differ according to the occurrence of SAH, and the observed lower BP's in those with a later SAH were explicable simply by the effect of age because these differences disappeared after adjustment by age. Blood pressures were very significantly associated with age. Systolic BP during the entire study period and diastolic BP at the entry into the follow-up study were related to age (p < 0.01), but diastolic BP at the end of follow-up evaluation was no longer associated significantly with age. The presence of defined hypertension at the beginning of follow-up evaluation was not associated with later SAH. Six (14%) of 42 patients with hypertension and 21 (21%) of the 100 patients without hypertension had SAH during the follow-up period.

On the other hand, BP's at the end of follow-up evaluation before SAH were significantly higher in those with a fatal SAH (mean BP 147 ± 11/91 ± 8 mm Hg, mean pressure 110 ± 9 mm Hg) than in those with a nonfatal SAH (mean BP 133 ± 16/81 ± 12 mm Hg, mean pressure 98 ± 13 mm Hg) (p < 0.05). These differences, however, did not reach significance after adjustment by age.

### Size of Aneurysm vs. Subsequent Rupture

The maximum diameter of the largest aneurysm did not differ at the beginning of the follow-up period between those who later suffered SAH and those who did not (mean 6.0 ± 5.3 mm, median 4.0 mm, range 2 to 25 mm vs. mean 4.9 ± 3.2 mm, median 4.0 mm, range 2 to 26 mm, respectively; p = 0.76). In patients with multiple aneurysms, the difference was even less (mean 4.8 ± 3.1 mm, median 4.0 mm, range 2 to 12 mm for those with later SAH vs. mean 4.4 ± 1.9 mm, median 4.0 mm, range 2 to 12 mm for those without later SAH; p = 0.86). In patients with incidental or symptomatic aneurysms, aneurysm size did not reach significance, possibly because of the small number of patients (mean 16.0 ± 9.5 mm, median 17.0 mm, range 6 to 25 mm for those with rupture and mean 11.5 ± 7.6 mm, median 9.0 mm, range 5 to 26 mm for those without rupture; p = 0.35). Fatal SAH was not associated with the size of the aneurysm in the beginning of follow-up evaluation.

Because 18 (67%) of the 27 aneurysms that later ruptured were 6 mm or less in diameter, the size of the lesion did not seem to predict rupture (Table 3). On the other hand, the proportion of aneurysm ruptures increased almost constantly according to size category (test for linear trend, p = 0.030 in the entire patient population and p = 0.038 in the group with multiple aneurysms). In patients with multiple unruptured aneurysms and a later SAH, generally the largest lesion ruptured except in three patients who each had two unruptured aneurysms of equal size (< 5 mm in diameter).

### Table 3

<table>
<thead>
<tr>
<th>Aneurysm Size (mm)</th>
<th>Incidental Aneurysms</th>
<th>Symptomatic Aneurysms</th>
<th>Multiple Aneurysms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aneurysms Ruptures</td>
<td>Aneurysms Ruptures</td>
<td>Aneurysms Ruptures</td>
</tr>
<tr>
<td>2-6</td>
<td>2 (+3)</td>
<td>2 (+1)</td>
<td>111 (+34)</td>
</tr>
<tr>
<td>7-9</td>
<td>1</td>
<td>0 (+1)</td>
<td>15</td>
</tr>
<tr>
<td>10-15</td>
<td>1</td>
<td>0 (+1)</td>
<td>5</td>
</tr>
<tr>
<td>16-20</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>21-26</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>26-36</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

* The number of second and third aneurysms in patients with multiple unruptured aneurysms is given in parentheses.
Natural history of unruptured aneurysms

Aneurysm size was not associated with the interval between discovery of the aneurysm and its rupture (r = 0.053, p = 0.79 for all patients with SAH and r = 0.275, p = 0.19 for those with SAH in multiple aneurysm group); that is, there was not even a trend to associate increased aneurysm size and a decreased period to rupture. Additionally, the size of aneurysms did not correlate with age at the beginning of the follow-up study (r = 0.096, p = 0.26).

Prediction of Aneurysm Rupture

The Cox model with a stepwise procedure revealed that the only independent variable of significant prognostic value was the size (maximum diameter) of the largest aneurysm, which was directly associated with the risk of rupture (p = 0.036). The volume of an aneurysm had a similar significance in prediction of rupture. Patients whose largest aneurysm was at least 7 mm in diameter had a relative risk of 2.24 (95% confidence interval 1.01 to 4.99, p = 0.043) for aneurysm rupture compared to those with smaller aneurysms. The corresponding age and sex-adjusted relative risk was 2.18 (range 0.97 to 4.89, p = 0.060).

There were no significant prognostic factors for rupture in the group with multiple aneurysms. The only variable with some value was the patient’s age at entry into the follow-up study (p = 0.080): the younger patients had a higher risk of rupture than the older ones. Time-dependent systolic, diastolic, or mean BP’s were not associated with risk of SAH, when they were analyzed separately, or combined with the initial size of aneurysm and age, which were fixed covariates.

Growth of Aneurysms During Follow-Up Period

During the follow-up period, angiography was performed in 31 patients, including bilateral carotid angiography in 23, unilateral carotid angiography in seven, and four-vessel angiography in one. The mean time between angiograms was 9 years (median 8.5 years, range 0.8 to 23.0 years), yielding a total of 279 angiogram-follow-up years. The median age of the patients at first angiography was 34.3 years (range 22.6 to 54.1 years) and that at second angiography was 44.7 years (range 30.1 to 61.8 years). These patients were significantly (p < 0.001) younger than those who were not followed by angiography. Among the 31 patients, the angiograms were obtained because of SAH in 17 and to check the cerebral arteries in patients without SAH in 14.

The size of the largest aneurysm (which had ruptured) in patients with SAH increased significantly (p < 0.001); this was not so in those without SAH (Table 4). All 17 ruptured aneurysms had increased in size compared with only two of the largest aneurysms in 14 patients without SAH (p < 0.001). The second largest aneurysm in those with SAH had also increased in size in five of seven patients with multiple unruptured aneurysms (p = 0.063). Only one of the second largest aneurysms in six patients without SAH had enlarged. In addition, one incidentally found aneurysm reduced in size from 26 to 8 mm, likely due to intra-aneurysmal thrombus formation.

### Table 4

<table>
<thead>
<tr>
<th>Feature</th>
<th>Aneurysm Rupture</th>
<th>No Aneurysm Rupture</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>median aneurysm diameter (mm)</td>
<td>4.2 (2-25)</td>
<td>4.5 (2-26)</td>
</tr>
<tr>
<td>at start of study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>at end of study</td>
<td>10 (6-33)</td>
<td>5 (2-20)</td>
</tr>
<tr>
<td>increase in size</td>
<td>5 (1-17)</td>
<td>0 (-18-44)</td>
</tr>
<tr>
<td>mean follow-up time (yrs)</td>
<td>9.1 (1.2-17.3)</td>
<td>8.9 (0.8-23.0)</td>
</tr>
<tr>
<td>median relative change in size/yr</td>
<td>0.16 (0.01-3.47)</td>
<td>0 (-0.1-0.1)</td>
</tr>
</tbody>
</table>

* Ranges are given in parentheses. Aneurysm size = largest diameter. Follow-up time = time between angiograms. Relative change in size = change in size/size at the beginning of follow-up period divided by follow-up time.

† Significant differences between rupture groups (p < 0.001).
‡ In one patient an aneurysm 26 mm in diameter decreased in size.

Aneurysm growth was not found to be associated significantly with sex, BP, aneurysm size, or patient age at the beginning of the study, or time of angiographic monitoring. On the other hand, age at the time of follow-up angiography correlated inversely with increase in aneurysm size (r = -0.323, p = 0.076).

Ruptured aneurysms were measured at autopsy before fixation in four patients who died of SAH and who had not had an angiographic study. In all four patients, the size of aneurysm was increased (from 2 to 10 mm, from 6 to 20 mm, and from 2 to 8 mm). In only two of the seven autopsies on those who died of unrelated causes was the unruptured aneurysm measured: in one patient the estimated size was the same as on the primary angiogram (5 mm) and in another the aneurysm had increased from 5 to 10 mm.

The size of ruptured aneurysms measured by angiography (17 cases) or at autopsy (four cases) was as follows: less than 7 mm in four patients, 7 to 9 mm in five, 10 to 15 mm in nine, 16 to 20 mm in one, and greater than 20 mm in two. The largest aneurysm was less than 7 mm in diameter in 12 of 16 patients without aneurysm rupture.

Fatal SAH was not associated with the size of the ruptured aneurysm observed by angiography or at autopsy. However, if those ruptured aneurysms measured only at autopsy were estimated to be at least 50% greater before death, then mortality was significantly (p < 0.05) associated with aneurysm size although the growth rate of an aneurysm during the follow-up period did not.

De Novo Aneurysms

Among 31 patients studied by follow-up angiography, seven de novo aneurysms (five in the internal carotid artery and two in the middle cerebral artery) were found in six patients (19%, three patients with SAH from another aneurysm and three without SAH). Hence, the approximate rate of formation of a new aneurysm was 2.2% per angiographic follow-up year. In the patients with multiple aneurysms, a new aneurysm was found in four (15%) of 27 patients, and the approximate annual formation rate was 1.6%. In addition, there were five patients (four with a single clipped
ruptured aneurysm and one with normal angiography) without an unruptured aneurysm at entry into the study who later suffered SAH from a new aneurysm (four in the middle cerebral artery and one in the pericallosal artery). These five patients survived after their last SAH.

The presence of de novo aneurysms did not associate with BF, patient age, or the size or growth rate of the largest aneurysm, but was directly associated (p = 0.057) with the interval between angiograms. The median time between the angiograms was 13.6 years (range 8.4 to 17.3 years) in patients with a de novo aneurysm. There were no anatomical findings (occlusion, stenosis, or hypoplasia of major arteries) that could explain the occurrence of de novo aneurysms. More women had a new aneurysm (nine of 22) than men (two of 14) (p = 0.14), which was explained by the longer angiographic follow-up time in women (mean 10.7 years, median 10.5 years, range 1.7 to 17.3 years) than in men (mean 6.2 years, median 3.0 years, range 0.8 to 23.0 years) (p < 0.01).

**Discussion**

**Prevalence of Intracranial Aneurysms**

Intracranial aneurysms in the general population have been studied mostly in autopsy series. Depending on whether the aneurysms were sought or merely noted as incidental findings, the prevalence appears to be 2% to 5% (range 0.2% to 9%).11,12,16,18,22,28 More than one-half of these aneurysms were unruptured at the patient's death. On the other hand, the size of an aneurysm is at least 30% to 60% greater before death than the size measured after death and before fixation.18 Therefore, the prevalence of small aneurysms may be greater than reported in autopsy series.

Reported frequencies of unruptured aneurysms in angiographic series are somewhat lower (1.1% to 5.6%) than in autopsy series.3,4 The variance may be explained by the age distributions of the different series as well as by racial differences.12 The incidence of multiple aneurysms depends primarily on the completeness of the diagnostic procedures and can be estimated to be at least 20% (possibly > 30%).9,11,16,29 There may also be small aneurysms observed during surgery that cannot be seen on the angiography.10

**Incidence of Subarachnoid Hemorrhage**

The incidence of SAH varies widely throughout the world, but an estimate of 10 per 100,000 per year is the generally accepted figure for western countries.10,12,22,28 The highest occurrence (> 15 per 100,000 per year) has been reported in Finland and Japan.11,12,16,25,28

Aneurysms seem to be acquired degenerative lesions as a result of hemodynamic stress and may rarely be familial or associated with connective-tissue diseases.7,21,27 Many factors may, however, increase the risk of aneurysm formation or SAH, mainly through unknown mechanisms. These include hypertension, atherosclerosis, female sex, aging, cigarette smoking, use of oral contraceptives, alcohol consumption, arterial deficiency of type III collagen, asymmetry of the circle of Willis, cerebral arteriovenous malformations, viral infections, pituitary tumors, and certain human leukocyte antigen-associated factors.7,12,26,27 Although patient age as well as arterial hypertension and sex seem to be risk factors for aneurysm formation, their association with the rupture of the aneurysm itself is less conclusive.17,22,29

**Risk of Aneurysm Rupture in Previously Unruptured Aneurysm**

The present study with 142 patients and a follow-up time of 1944 patient-years demonstrated an approximate rupture rate of 1.4% per year from previously unruptured aneurysm. This annual rupture rate is similar to earlier observations (1% to 2% per year).8,29,30 The risk of rupture, however, seems to remain almost constant over decades and the observed cumulative risk of rupture was 32% at 30 years after diagnosis. In this patient population, one-half of patients with SAH died after the bleed and this SAH-associated mortality represents 50% of all causes of death.

The risk of rupture was similar in incidentally discovered aneurysms and multiple aneurysms after clipping of the ruptured lesion. Patients with symptomatic aneurysms had somewhat higher risk of aneurysm rupture. This could be at least partly explained by the larger aneurysm size.

**Risk Factors for Aneurysm Rupture**

In the study of Wiebers, et al.,29 the only significant predictor for aneurysm rupture was the size of an aneurysm; the size also seemed to associate inversely with the time from diagnosis to rupture. None of the aneurysms smaller than 10 mm in diameter ruptured during the follow-up period of 824 patient-years. On the other hand, of the 51 aneurysms measuring 10 mm or greater in diameter, 15 ruptured during 255 patient-years of follow-up evaluation (average risk of rupture 5.9% per year), and 14 of those 15 died. These figures mean that an unruptured aneurysm 10 mm or greater in diameter has on average a greater risk of rupture than the ruptured aneurysm after 6 months from the last rupture (risk 3% per year),13 and patients with unruptured aneurysms of this size also have a worse outcome after SAH than those with an aneurysm that has previously ruptured.13 The median time from diagnosis of an unruptured aneurysm to the last rupture was less than 2 years, and SAH caused 25% of all deaths in that study.29

Our patient population and results differ in some respects from those of Wiebers, et al.29 We could not find any critical diameter above which the risk of rupture increases, but did note a linear association between the risk of rupture and aneurysm size, estimated as the largest diameter or the volume. Younger patients also had a greater risk than older, especially in the group with multiple aneurysms. The difference between our results and those of Wiebers, et al., can be partly explained by the younger patient population and the longer follow-up period in our study. In addition the aneurysms were smaller in our study (median 4 mm vs. 6 mm, p < 0.01). It is also possible that older patients with a small aneurysm have a smaller risk of SAH than
Natural history of unruptured aneurysms

younger patients with an aneurysm of similar size. Our patients were approximately 15 years younger than theirs and most of our patients had multiple aneurysms; their patients had either symptomatic or incidentally discovered aneurysms without a previous SAH, and the time from diagnosis to rupture was clearly shorter than in our patients. The number of patients with incidentally discovered or symptomatic aneurysms in our study was quite small because of the strict inclusion criteria in the study. However, angiography after SAH is also the easiest way to diagnose unruptured aneurysms, and these patients probably are the most important subgroup due to their younger age.

Patients with multiple aneurysms can be considered as a definite subgroup when compared to those with a single aneurysm; multiple-aneurysm patients have been reported to be more often women, to be more often hypertensive, and to be older than those with a single aneurysm. On the other hand, some authors have reported that neither hypertension nor age are risk factors for the occurrence of multiple aneurysms. The incidence of multiple aneurysms has also been related to the accuracy and completeness of the angiography or autopsy, and it has been reported that small aneurysms may be observed during the operation that are not seen on angiography. Therefore, the presence of multiple aneurysms cannot definitely be considered evidence of weakness of the cerebral arterial walls, possibly of familial or inherited origin or as a result of hypertension, but rather due to hemodynamic stress in cerebral arteries.

Although hypertension and measured BP do not seem to be associated with the risk of aneurysm rupture, a sudden increase in systemic BP can provoke rupture of an aneurysm according to the law of Laplace. On the other hand, BP was associated significantly with mortality after SAH.

Growth Rate and Risk of Formation of an Aneurysm

All aneurysms that later ruptured had increased in size, although the growth rate varied to quite a large extent (1 to 17 mm, 1% of 347% per year). On the other hand, aneurysms that did not rupture changed little in size during the follow-up period. Alcock and Canham showed that the growth rate of an aneurysm is not consistent and can change considerably during the follow-up period. As in our study, they could not find an association between growth rate and BP, patient age, size of aneurysm, or angiographic follow-up time.

The probability of formation of a new aneurysm was approximately 2.2% per year (1.6% in the multiple-aneurysm group) in those relatively young patients (median age 34 years) who were monitored with angiography. This risk was directly associated with the interval between angiograms but not with BP. This does not, however, mean that hypertension is not correlated with the risk of aneurysm formation, because all patients with a de novo aneurysm already had an aneurysm before the formation of the new one. On the other hand, if a patient has once suffered an aneurysmal SAH, BP does not seem to correlate with the risk of future formation of an additional aneurysm. Previous studies suggest that hypertension or abnormal BP is not essential to aneurysm formation.

Assuming that the risk of rupture of an unruptured aneurysm is 1.4% per year and the rate of formation of an aneurysm is approximately 1.6% to 2.2% per year, a relatively young patient whose aneurysms have been treated successfully seems to have a risk of SAH of 22 to 31 per 100,000 per year from a de novo aneurysm during the first 10 years. This incidence of SAH is similar to that in the general adult population. Therefore, the risk of SAH may be increased as suggested by the relatively high number of new aneurysms observed in this study. The risk of a de novo aneurysm did not, however, seem to be higher in patients with multiple aneurysms than in those with an incidental aneurysm. The risk of suffering SAH from a potential de novo aneurysm seems to be so low that routine angiographic monitoring cannot be recommended to detect such lesions during subsequent decades. Occurrence of stenosis, occlusion, or hypoplasia of the internal carotid or anterior cerebral artery was not a cause of new aneurysms in any of our patients with a de novo aneurysm.

Conclusions

We conclude that an unruptured aneurysm should be operated on irrespective of its size, if it is technically possible and if the age and concurrent diseases of the patient do not increase the surgical risk. The younger the patient is, the greater is the indication for surgery of an unruptured aneurysm. Patients whose aneurysms have been clipped do not seem to have an increased risk of SAH from a new aneurysm during the first decade after the treatment compared to the general population, but this risk may increase thereafter.

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Address reprint requests to: Seppo Juvela, M.D., Department of Neurosurgery, Helsinki University Central Hospital, Topeliuksenkatu 5, SF-00260 Helsinki 26, Finland.