Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture

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Object. The authors conducted a study to investigate the long-term natural history of unruptured intracranial aneurysms and the predictive risk factors determining subsequent rupture in a patient population in which surgical selection of cases was not performed.

Methods. One hundred forty-two patients with 181 unruptured aneurysms were followed from the 1950s until death or the occurrence of subarachnoid hemorrhage or until the years 1997 to 1998. The annual and cumulative incidence of aneurysm rupture as well as several potential risk factors predictive of rupture were studied using life-table analyses and Cox’s proportional hazards regression models including time-dependent covariates.

The median follow-up time was 19.7 years (range 0.8–38.9 years). During 2575 person-years of follow up, there were 33 first-time episodes of hemorrhage from previously unruptured aneurysms, for an average annual incidence of 1.3%. In 17 patients, hemorrhage led to death. The cumulative rate of bleeding was 10.5% at 10 years, 23% at 20 years, and 30.3% at 30 years after diagnosis. The diameter of the unruptured aneurysm (relative risk [RR] 1.11 per mm in diameter, 95% confidence interval [CI] 1–1.23, p = 0.05) and patient age at diagnosis inversely (RR 0.97 per year, 95% CI 0.93–1, p = 0.05) were significant independent predictors for a subsequent aneurysm rupture after adjustment for sex, hypertension, and aneurysm group. Active smoking status at the time of diagnosis was a significant risk factor for aneurysm rupture (RR 1.46, 95% CI 1.04–2.06, p = 0.033) after adjustment for size of the aneurysm, patient age, sex, presence of hypertension, and aneurysm group. Active smoking status as a time-dependent covariate was an even more significant risk factor for aneurysm rupture (adjusted RR 3.04, 95% CI 1.21–7.66, p = 0.02).

Conclusions. Cigarette smoking, size of the unruptured intracranial aneurysm, and age, inversely, are important factors determining risk for subsequent aneurysm rupture. The authors conclude that such unruptured aneurysms should be surgically treated regardless of their size and of a patient’s smoking status, especially in young and middle-aged adults, if this is technically possible and if the patient’s concurrent diseases are not contraindications. Cessation of smoking may also be a good alternative to surgery in older patients with small-sized aneurysms.

Keywords • subarachnoid hemorrhage • unruptured intracranial aneurysm • cigarette smoking
not represent the natural history of the disease unless it is proven that a similar risk for rupture existed for the surgically treated and excluded patients. Current knowledge of the natural history of unruptured aneurysms is based on only a few studies, with risk levels as well as risk factors being even more controversial now than previously because of the differing results published in these studies.8,10,12,18,29,32–34 Thus, the decision of how to treat patients with unruptured intracranial aneurysms varies.

Before 1979, unruptured aneurysms were not surgically treated in our clinic, which was the only neurosurgical center in Finland until the late 1960s. Preliminary results have previously been published on our long-term cohort study in patients in whom unruptured aneurysms were diagnosed before 1979.19 In the present study we report the final results, including a greater number of follow-up years and analysis of more potential risk factors for aneurysm rupture.

Clinical Material and Methods

Patient Population

Follow-up and radiological data obtained in patients with unruptured intracranial aneurysms have been collected since the 1950s in the Department of Neurosurgery, Helsinki University Central Hospital.6,8,18 The records of all patients seen at the Department of Neurosurgery between 1956 and 1978 in whom intracranial aneurysms were diagnosed were again reviewed in the late 1980s to include all patients with unruptured aneurysms in the follow-up study.18 The follow-up evaluation was also reviewed at that time for all patients with unruptured aneurysms. For detailed baseline characteristics observed in the 142 patients as well as the study’s inclusion and exclusion criteria, see the previous report.18 Patients with symptomatic aneurysms were included in the study only if SAH was excluded by examining the results of a lumbar puncture within a few days after onset of symptoms.

Classification of Unruptured Aneurysms

The unruptured aneurysms were classified into the following groups: asymptomatic incidental aneurysms (five patients); symptomatic aneurysms (six patients); and SAH (131 patients). The latter group included patients with unruptured aneurysms in whom a prior episode of SAH had occurred and in whom only the ruptured aneurysm was clipped, with occlusion of the aneurysm confirmed by postoperative angiography. If the parent artery was clipped together with the aneurysm, the patient was excluded from the study because of the possibility that a new aneurysm would form or the chance that a preexisting aneurysm would enlarge due to an increase in hemodynamic stress in the remaining arteries.26

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

Angiographic Examination

Results of angiographic studies performed at the beginning of the follow-up period were reexamined by two neuroradiologists (M.P. and K.P.). We determined the size of each aneurysm based on its greatest diameter measured on standard angiographic projections, taking into account the level of magnification. The location, shape (round, oval, or multilobed), and orientation of all aneurysms were also recorded.

In addition, the volume of each aneurysm was estimated from its maximum longitudinal and transverse diameters. Because the shape of an aneurysm was typically a round or elongated sphere, the following formula was used: volume = 2πr(R − 1/3r), where r is its smaller radius and R its larger radius.

Follow-Up Methods

From 1996 to 1998, all patients who were alive were called to the outpatient department where they were interviewed by one of the authors (S.J.) who used a structured questionnaire. The questionnaire elicited data on height and weight; previous diseases and hospital visits; regular drug use, including analgesic medications, stimulants, and narcotics; approximate intake of coffee, beer, wine, and spirits; current and previous smoking status; and family history of intracranial aneurysms. A family history of intracranial aneurysms was defined as cases of verified aneurysms in first-degree relatives.

Alcohol consumption was recorded as grams of absolute ethanol consumed within 1 week during the total follow-up period (standard drink 12 g of alcohol). Problem drinking was assessed by means of the CAGE questionnaire described in detail elsewhere.15,17 The four CAGE questions were: 1) Have you ever felt you should cut down on your drinking? 2) Have people annoyed you by criticizing your drinking? 3) Have you ever felt bad or guilty about your drinking? 4) Have you ever had a drink first thing in the morning to steady your nerves and to get rid of a hangover (eye-opener)? The CAGE interview seeks to determine not merely the amount of alcohol consumed but also abnormal drinking behavior (for example, drinking upon waking) and alcohol-induced problems. Patients with two or more positive answers to the four questions were considered to have CAGE-positive results, which is a sensitive indicator of previous and current excessive drinking (sensitivity and specificity 80–90%).15 Cigarette smoking was categorized as follows: never a smoker, formerly a regular cigarette smoker (quit before or during follow-up study), and current cigarette smoker. The age at which the patient started smoking, duration of the habit, and the time at which he or she quit smoking were also recorded.

Of the 57 patients studied in the outpatient department, 49 had not suffered a ruptured aneurysm, and eight had suffered the rupture of a previously unruptured aneurysm. All living patients, except those four who were very old (> 80 years of age) or those with a severe, incapacitating disease, were studied in the outpatient department. In 1998, the four elderly patients were interviewed by telephone in the same manner as those interviewed in the department. Furthermore, during 1997 and 1998, question-
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The diagnosis of aneurysm rupture was based on results...
of lumbar puncture, autopsy, angiography, computerized tomography, and/or surgery. Of our 33 patients in whom rupture occurred during the follow-up period, 17 (52%) died of SAH caused by a previously verified unruptured aneurysm (14 of 30 in the prior SAH group, two patients in the symptomatic aneurysm group, and one patient in the incidental aneurysm group). In the group of patients in whom SAH had previously occurred, 12 patients died of a verified aneurysm rupture and two with bilateral unruptured MCA aneurysms died of typical SAH, which was confirmed by lumbar puncture, with the exact cause undetermined because autopsy was not performed. In addition, 53 patients in this group died of unrelated causes: 12 of coronary heart disease, 12 of cancer (seven of lung cancer), six of acute brain infarction or spontaneous intracerebral hemorrhage, six of other cardiovascular diseases, 11 of other diseases, four of traumatic injury or suicide, one of SAH due to fracture of the aneurysm clip 24 years after the first operation for the ruptured aneurysm, and one of a de novo aneurysm rupture in the MCA associated with a large intracerebral hematoma 19.8 years after diagnosis of an unruptured aneurysm in the ICA.

One patient harboring an enlarged incidental ICA aneurysm died of a verified aneurysm rupture with rebleeding, and two patients with symptomatic ICA aneurysms died of typical SAH confirmed by lumbar puncture. In addition, two patients in the symptomatic aneurysm group died of other diseases. One patient in the incidental aneurysm group died of a spontaneous hypertensive intracerebral hemorrhage. A second patient in the same group died of a de novo aneurysm rupture in the MCA associated with a large intracerebral hematoma; this death occurred 13.4 years after an unruptured ICA aneurysm had been diagnosed. The neuropathological cause of these two deaths was confirmed at autopsy.

### TABLE 1

Baseline characteristics obtained in patients at the beginning of the follow up*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ruptured Aneurysm</th>
<th>Unruptured Aneurysm</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>33 (23%)</td>
<td>109 (77%)</td>
<td>142</td>
</tr>
<tr>
<td>Women</td>
<td>22 (29%)</td>
<td>54 (71%)</td>
<td>76 (54%)</td>
</tr>
<tr>
<td>Age (yrs)†</td>
<td>36.8</td>
<td>43.6</td>
<td>41.9</td>
</tr>
<tr>
<td>Median (range)</td>
<td>22.6–57.6</td>
<td>14.6–60.7</td>
<td>14.6–60.7</td>
</tr>
<tr>
<td>Aneurysm diameter (mm)§</td>
<td>5.6 ± 4.9</td>
<td>4.9 ± 3.2</td>
<td>5.1 ± 3.7</td>
</tr>
<tr>
<td>Smoking status‡</td>
<td>5 (22%)</td>
<td>14 (56%)</td>
<td>19 (51%)</td>
</tr>
<tr>
<td>Never a smoker</td>
<td>7 (18%)</td>
<td>31 (82%)</td>
<td>38 (123%)</td>
</tr>
<tr>
<td>Quit before FU§</td>
<td>7 (100%)</td>
<td>15 (66%)</td>
<td>22 (78%)</td>
</tr>
<tr>
<td>Quit during FU†</td>
<td>0 (0%)</td>
<td>11 (100%)</td>
<td>11 (123%)</td>
</tr>
<tr>
<td>Current smoker§</td>
<td>20 (100%)</td>
<td>39 (66%)</td>
<td>59 (123%)</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td>138 ± 21</td>
<td>140 ± 18</td>
<td>140 ± 19</td>
</tr>
<tr>
<td>Definite hypertension</td>
<td>5 (22%)</td>
<td>18 (78%)</td>
<td>23 (16%)</td>
</tr>
<tr>
<td>Alcohol consumption (g/wk, n = 95)</td>
<td>199 ± 173</td>
<td>106 ± 179</td>
<td>121 ± 180</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>190 (0–450)</td>
<td>8 (0–1000)</td>
<td>20 (0–1000)</td>
</tr>
<tr>
<td>CAGE-positive result</td>
<td>6 (21%)</td>
<td>23 (79%)</td>
<td>29 (111)</td>
</tr>
<tr>
<td>Family history of aneurysms</td>
<td>3 (33%)</td>
<td>6 (67%)</td>
<td>9 (94)</td>
</tr>
</tbody>
</table>

* ACA = anterior cerebral artery; ACoA = anterior communicating artery; A1 = pericallosal artery; BT = basilar tip; FU = follow up; n = number of patients with available data; SCA = superior cerebellar artery.
† p = 0.0014, significant inverse association between age at beginning of follow up and subsequent rupture.
‡ p = 0.052, test for linear trend for association between aneurysm size and cigarette-smoking groups determined at the outset of the follow-up period.
§ p = 0.0058, significant association between smoking status and aneurysm rupture divided by person-years of follow up. Smoking data were missing in 19 patients.

### TABLE 2

Annual and cumulative rupture rates in relation to age, aneurysm size, and cigarette-smoking groups determined at the outset of the follow-up period*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients</th>
<th>Annual Rupture Rates (%)</th>
<th>Cumulative Rupture Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)‡</td>
<td>25 (9 of 468)</td>
<td>1.9</td>
<td>12 (31)</td>
</tr>
<tr>
<td>Prior SAH group‡</td>
<td>24 (9 of 439)</td>
<td>2.0</td>
<td>13 (32)</td>
</tr>
<tr>
<td>Diameter of unruptured aneurysm (mm)§</td>
<td>116 (23 of 1268)</td>
<td>1.1</td>
<td>9 (18)</td>
</tr>
<tr>
<td>No current cigarette smoker‖</td>
<td>53 (7 of 1176)</td>
<td>0.6</td>
<td>2 (14)</td>
</tr>
<tr>
<td>All patients†</td>
<td>142 (3 of 2575)</td>
<td>1.3</td>
<td>11 (23)</td>
</tr>
</tbody>
</table>

* Values presented parenthetically represent the number of patients with aneurysm rupture divided by person-years of follow up. Smoking data were missing in 19 patients.
† p = 0.33, log-rank test.
‡ p = 0.16, log-rank test.
§ p = 0.008, log-rank test.
‖ p = 0.016, log-rank test.

Blood Pressure Values and Hypertension

The presence of defined hypertension and BP values at the beginning of follow up were not associated with the later occurrence of SAH (Table 1). At the end of the fol-
follow-up period, eight (27%) of 30 patients with BP values greater than 160/95 mm Hg and 24 (22%) of the 111 patients in whom BP values were lower later suffered an aneurysm rupture (nonsignificant difference).

On the other hand, BP values measured at the end of follow up before SAH occurred were significantly higher in those patients whose SAH was fatal (mean pressure 111 ± 9 mm Hg) than in those with a nonfatal SAH (135 ± 15/83 ± 11 mm Hg; mean pressure 100 ± 12 mm Hg; p < 0.05). After adjustment for age, these differences remained nearly significant for systolic BP (p = 0.053) and mean arterial pressure (p = 0.079).

Aneurysm Size and Subsequent Rupture

Twenty-three (70%) of the 33 aneurysms that later ruptured were less than or equal to 6 mm in diameter (Tables 1 and 2). The proportion of aneurysm ruptures increased almost linearly by size category. In patients with multiple unruptured aneurysms in whom the onset of SAH occurred later, the largest aneurysm ruptured, except in three patients: two with two unruptured aneurysms of equal size (5 mm in diameter) and only one whose ruptured aneurysm was originally smaller (2 mm) than his largest unruptured one (4 mm). In these three patients, the ruptured aneurysm’s size had increased significantly before the onset of SAH.

The size of the aneurysm that ruptured during the follow-up period correlated with age at beginning of follow up (r = 0.392, p = 0.024); that is, those aneurysms that later ruptured were originally larger in older than in younger patients, although patient age and the size of aneurysm in the whole patient population did not correlate significantly at the beginning of follow up (r = 0.118, p = 0.16).

Prediction of Aneurysm Rupture

In univariate analyses, age as a continuous variable and cigarette smoking were significant risk factors for aneurysmal SAH as was, almost significantly, aneurysm size as a categorical variable (Tables 1 and 2). The relative risk of rupture for an aneurysm with a diameter greater than or equal to 7 mm was 2.31 (95% CI 1.10–4.88), compared with that for smaller-sized aneurysms (p = 0.028).

Without factoring in cigarette smoking as a variable, the Cox model with a stepwise procedure revealed that significant risk factors for aneurysm rupture were patient age inversely and maximum diameter of the largest aneurysm. These risk factors as continuous variables were also significant after adjustment for sex, aneurysm group (prior SAH group compared with others), and hypertension (Table 3). Aneurysm volume was significant for prediction of rupture, similar to that of diameter.

Thereafter, the Cox stepwise procedure was used to analyze health-related habits because these data were incomplete in some patients. Data were missing, for instance, on smoking status in 19 (13%) of the 142 patients; five had died of SAH and 14 of other causes. Cigarette smoking at diagnosis was a significant risk factor for later-onset aneurysmal SAH; the significance of aneurysm size also became greater, although age was no longer a significant risk factor when compared with relative risks calculated when this habit was not a factor. These risk factors also remained significant after adjustments for sex, presence of hypertension, and aneurysm group (Table 4). Alcohol consumption and CAGE-positive status were not predictive, independently of other variables, of the later onset of aneurysm rupture.

Time-dependent systolic, diastolic, or mean BP values were not associated with risk of SAH, either when analyzed separately or when combined with initial size of aneurysm and with age, which were fixed covariates. On the
Aneurysms seem to be acquired degenerative lesions that develop as a result of hemodynamic stress, but they may sometimes be familial (approximately 10% of cases) or associated with connective tissue diseases. Many factors may 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 in collagen Type III, asymmetry of the circle of Willis, cerebral arteriovenous malformations, viral infections, pituitary tumors, and certain human leukocyte antigen–associated factors. Indisputable modifiable risk factors for SAH seem to be limited to cigarette smoking, alcohol consumption, and, to a lesser extent, hypertension. Although age, female sex, and hypertension may be direct risk factors for the formation of an aneurysm, the association of these factors with rupture of the aneurysm itself is unlikely. In addition, history of SAH has been suggested to increase the risk of rupture of a previously known unruptured aneurysm. Therefore, it is important to control the relative risks from significant rupture-related risk factors by these potential confounding factors to determine the significant independent risk factors.

In this study, the presence of a family history of cerebral aneurysms did not increase the risk for rupture of intact intracranial aneurysms. The prevalence of family history cases was high and comparable with that reported in a previously published Finnish study despite exclusion of possible but unverified cases. This high prevalence could be at least partly explained by a relatively large family size of patients with a family history of aneurysms (range five–12, median seven siblings) and by the fact that five of nine patients with a family history of aneurysms lived in East Finland, where the prevalence of familial intracranial aneurysms has been shown to be high.

Patient Age and Aneurysm Size as Risk Factors

Based on our data, the size of aneurysm, patient age inversely, and status as a current cigarette smoker were independent predictors for subsequent aneurysm rupture. The relative risk from cigarette smoking, tested as a time-dependent covariate, increased if the patient continued smoking during the follow-up period. These three risk factors were also significant after adjustment for sex, hypertension, and aneurysm group.

In the retrospective part of the ISUIA and in the study reported by Wiebers, et al., the significant predictor for rupture was size of the aneurysm, with the critical diameter being 10 mm. In the ISUIA study, the risk of rupture of an intact aneurysm less than 10 mm in diameter in patients with no history of SAH (Group 1) was as low as 0.05% per year. The risk of rupture for similar aneurysms in patients with a history of treated ruptured aneurysm (Group 2) was also quite low (0.5% per year). The risk of rupture of larger aneurysms was approximately 1% per year in both groups. The risk of rupture of small aneurysms in ISUIA Group 2 patients was, however, similar to that in patients in the present study who were older than 50 years of age at the time at which the aneurysm was diagnosed.

The ISUIA Group 2 patients were significantly younger

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**TABLE 3**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>diameter of unruptured aneurysm (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–6</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>7–9</td>
<td>2.13 (0.86–5.25)</td>
<td>2.57 (0.97–6.81)</td>
</tr>
<tr>
<td>10–26</td>
<td>2.66 (0.92–7.70)</td>
<td>3.38 (1.05–10.93)†</td>
</tr>
<tr>
<td>continuous (per mm)</td>
<td>1.08 (1.00–1.18)</td>
<td>1.11 (1.00–1.23)†</td>
</tr>
<tr>
<td>age (yrs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;31</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>31–40</td>
<td>0.76 (0.32–1.80)</td>
<td>0.56 (0.22–1.44)</td>
</tr>
<tr>
<td>41–50</td>
<td>0.46 (0.18–1.19)</td>
<td>0.33 (0.12–0.91)†</td>
</tr>
<tr>
<td>&gt;50</td>
<td>0.46 (0.14–1.50)</td>
<td>0.37 (0.11–1.25)</td>
</tr>
<tr>
<td>continuous (per year)</td>
<td>0.97 (0.94–1.01)</td>
<td>0.97 (0.93–1.00)†</td>
</tr>
</tbody>
</table>

* In multivariate analysis, relative risks were adjusted for the other variables and additionally for the aneurysm group (prior SAH group compared with others), sex, and hypertension.
† p < 0.05.
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and harbored smaller aneurysms than those in Group 1. However, these groups were not combined when conducting risk factor analyses; therefore, the investigators did not determine whether age and aneurysm group, in addition to aneurysm size, would also be significant risk factors. The groups were analyzed separately, and age was, contrary to our own observations, directly associated with the risk of rupture in Group 2 patients. However, contrary to general expectations, patients in the prospective part of the ISUIA were clearly older than those in the prospective part, although medical and surgical treatment have become significantly more active during the last 30 years, with older patients in poorer condition being examined and treated more actively in recent times. Thus, in the case of nonselection, patients in the prospective arm of the study should have been significantly older than those in the retrospective study.

In the ISUIA, a total of 1449 patients with 12,023 follow-up years in the retrospective study were collected from 53 centers during a period of 22 years. This means that fewer than 30 patients from each center or approximately one patient per center per year were enrolled. For comparison, in the present study we enrolled approximately nine patients with an unruptured aneurysm annually in the 1970s. Thus, the prospective part of the ISUIA study must have included only a small fraction of the total patient population with unruptured aneurysms treated in the participating centers at that time.

Retrospective cohort studies may yield considerably biased results if follow-up data are not complete, and the vast majority of patients cannot be enrolled in the study; findings for such a cohort cannot represent the actual natural history of a disease. Several reasons exist for exclusion of patients: death or departure to a different location, treatment of ruptured or unruptured aneurysms at another institution, unwillingness to take part in a study, or impatience with follow up. Cigarette smokers have been cited as being less likely to participate in medical studies.

During the 1970s and 1980s, the surgical treatment of unruptured aneurysms was increasingly performed in most neurosurgical centers, leading to a considerable selection of the patients in the retrospective cohorts. Very likely, younger adults with unruptured aneurysms have more often undergone surgery soon after diagnosis than have the elderly, leading to exclusion of young people from follow-up studies. Contrary to the results of the ISUIA, our younger patients were at greater risk than older patients, as was reported in two other recent studies, especially regarding patients with a secured ruptured aneurysm. Significantly increased risk of rupture of vertebrobasilar aneurysms in patients compared with those with aneurysms located at other sites can probably be explained by the lesser extent of surgical selection in cases of vertebrobasilar aneurysms. In another recent study with a sizable patient population and a long follow-up period (1464 patient years), only 234 of 885 patients with unruptured aneurysms could be followed to determine the later risk of rupture, because selection was influenced mainly by surgical treatment of the unruptured aneurysm and death due to underlying disease. The fate of 126 patients remained totally unknown. In that study, the approximate annual risk rate for aneurysm rupture was 2.5%, a value somewhat higher than that reported in other studies. The presence of multiple unruptured aneurysms was a significant factor predictive of later rupture, but aneurysm size was not measured.

Our patients were approximately 11 to 15 years younger than those reported on in the other studies, and initially most had multiple aneurysms. Patients with multiple aneurysms can be considered a definite subgroup, unlike those with a single aneurysm, because the former are more often younger, hypertensive, or cigarette smokers. On the other hand, some authors have reported that hypertension, female sex, or age are not risk factors for multiple aneurysms. The incidence of multiple aneurysms has also been related to the accuracy and completeness of angiography or autopsy, and there may be small aneurysms observed during surgery that were not detected on angiography. Only cigarette smoking and female sex seem to be independent risk factors for multiple aneurysms. Both of these factors were taken into account in statistical models. Indeed, it seems that an approximate annual rupture risk of only 0.6% was demonstrated in nonsmokers.

The prevalence of cigarette smoking in this study, although high, was similar to that reported in previous studies. In our study, the presence of multiple unruptured aneurysms per se did not increase the risk that the aneurysm would rupture, and the same finding was reported in the ISUIA. In patients who have suffered an SAH, unruptured aneurysms are diagnosed at an earlier age, and the patient’s age at diagnosis and smoking status are likely more important than the baseline disease leading to the diagnosis.

Cigarette Smoking as Risk Factor

In several studies cigarette smoking has been shown to increase risk of sustaining SAH. In North America and Europe, the prevalence of smoking in patients who suffer SAH ranges from 45 to 75%, whereas in the general adult population it is 20 to 35%. Men and patients in younger age groups smoke more than others; this trend persists both in patients who have suffered SAH and in general populations. Approximately 40% of all cases of SAH are caused by patients’ active cigarette smok-
Although cigarette smoking is decreasing in western countries, the incidence of SAH does not necessarily change because of improved diagnostic methods and aging of populations.

Blood pressure values are generally lower in smokers than in nonsmokers, but smoking a cigarette causes an acute increase in BP for approximately 3 hours. This transient increase in BP may thus contribute to the rupture of an aneurysm. It also is possible that long-term smoking can cause formation of an aneurysm by weakening the vessel walls of cerebral arteries. Analysis of recent study findings suggests that the serum elastase/alpha 1–antitrypsin imbalance (that is, increased elastase activity and decreased alpha 1–antitrypsin activity) demonstrated in cigarette smokers may contribute either to aneurysm formation or to SAH. Our results support this concept, because unruptured aneurysms increase in size before they rupture. This significant association between cigarette smoking and the risk of subsequent rupture of the intact aneurysm strongly suggests that smoking increases the size of an unruptured lesion. Whether it can cause formation of a new aneurysm, however, remains unknown.

Surgery for Unruptured Aneurysm

If the overall annual incidence of aneurysm rupture were really as low as the 0.3% suggested in the ISUIA, the value of surgical treatment would seem to be very modest or even nonexistent, according to most calculations by King, et al. Only aneurysms larger than 10 mm in diameter may be surgically treated, and these can be associated with a higher surgery-related risk. It also seems self-evident that any kind of screening for incidental aneurysms larger than 10 mm in diameter in high-risk patients would be ineffective, because the proportion of such aneurysms is low.

According to the prospective arm of the ISUIA, the risks associated with surgically treating unruptured aneurysms are somewhat higher than previously reported. Thus, preventive surgical treatment of unruptured aneurysm should be undertaken by experienced neurosurgeons to obtain the best possible cost–benefit ratio. Our results suggest that unruptured aneurysms should be treated by surgical means regardless of size, at least in patients younger than 50 years of age. In older patients with small-sized aneurysms, cessation of smoking alone may be suitable treatment.

Conclusions

We conclude that unruptured intracranial aneurysms should be surgically treated, regardless of size, if it is technically possible, and that patient age and the presence of concurrent diseases do not increase surgery-related risk. The younger the patient, the greater the indication for surgery for such an aneurysm. Although cigarette smoking seems to increase the risk of aneurysm rupture, surgery should not be withheld in these cases, because of the devastating nature of SAH compared with success rates currently being attained in the surgical treatment of unruptured aneurysms. However, cessation of smoking may also be a good alternative to surgery.

References

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