Risk Factors for Multiple Intracranial Aneurysms

Seppo Juvela, MD, PhD

Background and Purpose—The presence of multiple intracranial aneurysms may be a sign of significant risk factors for aneurysm formation that differ from those factors that increase risk for aneurysm rupture. Only 2 studies concern independent risk factors for multiple aneurysms, and the results are in part controversial. This study was designed to identify independent risk factors for multiple intracranial aneurysms in patients with subarachnoid hemorrhage.

Methods—Of 266 patients with aneurysmal subarachnoid hemorrhage (139 men and 127 women, aged 15 to 60 years), 80 (30%) had multiple intracranial aneurysms. The prevalence of several health-related habits, previous diseases, and medications of these patients were compared by multiple logistic regression between those with single and those with multiple aneurysms.

Results—On the basis of multivariate statistics, only regular cigarette smoking at any time was a significant risk factor for the presence of multiple aneurysms. The odds ratio (OR) of smoking for multiple aneurysms was 2.10 (95% CI, 1.06 to 4.13) after adjustment for age and sex. After additional adjustment for hypertension, the risk was 2.06 (95% CI, 1.04 to 4.07). Of other variables, only age (OR, 1.02 per year; 95% CI, 1.00 to 1.05; \(P = 0.09\)) and female sex (OR, 1.60; 95% CI, 0.90 to 2.85; \(P = 0.11\)) showed a tendency to increase the risk for multiple aneurysms after adjustment for smoking. On the other hand, patients with hypertension had significantly (\(P = 0.029\)) more aneurysms (1.61 ± 1.04) than did those without (1.37 ± 0.68), although they did not more frequently have multiple aneurysms.

Conclusions—Cigarette smoking and possibly also age and female sex seem to be risk factors for multiple intracranial aneurysms in patients of working age who have suffered a subarachnoid hemorrhage. Patients with hypertension seem to have more aneurysms than those without. (Stroke. 2000;31:392-397.)

Key Words: cerebral aneurysm ▪ cigarette smoking ▪ hypertension ▪ sex ▪ subarachnoid hemorrhage
aneurysm group and 3 in the multiple aneurysm group) were unilateral carotid angiographies because of an emergency operation of space-occupying hematoma. Neuropathological autopsy was done later to reveal unruptured aneurysms and mechanism of death. To avoid bias, patients with a poor condition and prognosis were also included in the study because multiple intracranial aneurysms have been associated with a less favorable outcome than single-aneurysm cases after SAH. In those who died after SAH, autopsies were done in 90% (43 of 48) of those with a single aneurysm and in 86% (19 of 22) of those with multiple aneurysms. In those who died without autopsy, angiography showed the locations of their aneurysms. Not all moribund patients underwent 4-vessel angiography, but they were regularly autopsied if they died without a complete angiographic study and were of working age. The proportion of patients with multiple aneurysms was high (30%) compared with those of most previous studies. Patients and their family members were personally interviewed by use of a structured questionnaire. If patients died soon after admission or were confused, unconscious, or dysphasic, only their family members or fellow workers were interviewed. Data were not obtained from the patients themselves in 54 cases; data came from both patients and family members for the other 212 cases. None of the patients or their relatives refused an interview. The interviews of patients and their relatives were done before the performance of angiography and/or autopsy to decrease the possibility of bias. The questionnaire elicited data on the exact time of disease onset; the height and weight of the patient; previous diseases and hospital visits; recent drug use, including analgesics, stimulants, and narcotics; recent intake of coffee, beer, wine, and spirits; and current and previous smoking status. Information on all patients was also collected from the previous medical records of other hospitals and from general practitioners to confirm data on patients’ diseases, medications, and blood pressure values.

Body mass index (BMI), calculated as weight/(height)² (kg/m²), was used as the index of relative weight. Patients were considered to have definite hypertension if their blood pressure readings had repeatedly exceeded 160 mm Hg systolic or 95 mm Hg diastolic before the illness or if they used antihypertensive medication.

Recent alcohol consumption was recorded as grams of absolute ethanol consumed within the previous 24 hours and during the previous week before onset of the hemorrhage (standard drink = 12 g of alcohol). Because for alcohol intake underestimation is more likely than overestimation, and although the values reported by patients and relatives were quite similar during the careful interviews, the larger amounts reported in these cases were used in analyses. Problem drinking was assessed by use of the CAGE questionnaire (Have you ever felt you should Cut down on your drinking? Have people Annoyed you by criticizing your drinking? Have you ever felt bad or Guilty about your drinking? 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 questionnaire relates not merely to amount of alcohol consumed but to abnormal drinking behavior (eg, drinking on waking) and alcohol-induced problems.

Patients with ≥2 positive answers to the 4 questions in the CAGE interview were considered CAGE positive, which is a sensitive indicator of previous and current excessive drinking (sensitivity and specificity of 80% to 90%). Smoking was categorized as follows: never a smoker; a former regular cigarette smoker (all had smoked >3 years and quit >1 year before SAH); and current cigarette smoker, with 10 and 20 cigarettes per day as cutoff points. The erythrocyte mean cell volume (MCV) (normal range, 80 to 96 fL) and γ-glutamyltransferase (GGT) (normal range, 0 to 44 U/L) were used as laboratory markers of alcohol intake because they were routinely available for most patients soon after admission to hospital. Besides heavy drinking, cigarette smoking has also been shown to raise MCV values.

The data were analyzed with the biomedical data package statistical programs (BMDP Statistical Software Inc, version 1993, release 7.0). Categorical variables were compared by Fisher’s exact 2-tailed test, the Pearson χ² test, or the test for linear trend. Continuous variables, which are expressed as mean±SD or as median with the 25th and 75th percentiles (when the distribution was skewed), were compared between groups by Student’s t test or the Mann-Whitney U test. Univariate association of continuous variables was tested with the Spearman rank correlation coefficients (r).

Univariate and multivariate odds ratios (ORs) with 95% CI were calculated by logistic regression (maximum likelihood method). Stepwise logistic regression (P<0.1 for enter limit and P>0.15 for remove limit) was used to test differences in the prevalence of variables between patients with single or multiple aneurysms. Variables tested were as follows: sex, age, BMI, history of hypertension, diabetes mellitus, and hyperlipidemia, previous cardiovascular (stenocardia or myocardial infarction) and cerebrovascular disease (transient ischemic attack or minor cerebral infarction), amount of alcohol consumed within 24 hours and during 1 week before SAH, CAGE positiveness, current and former heavy drinking, and alcohol-induced problems. A 2-tailed P value <0.05 was considered statistically significant.

### Results

Of 266 patients with a total of 382 aneurysms, 186 had a single aneurysm, and 80 had multiple aneurysms; 54 had 2 aneurysms, 20 had 3 aneurysms, and 6 had 4 to 6 aneurysms. Baseline characteristics and patients’ previous diseases are shown by presence of multiple aneurysms in Table 1, and hypertension, smoking status, and alcohol consumption by sex and presence of multiple aneurysms are shown in Table 2. No significant differences existed in baseline characteristics, previous diseases, or health habits between patients with either single or multiple aneurysms. Patients with multiple aneurysms were nonsignificantly more often women, more often had hypertension (especially women), or were older than those with a single aneurysm. Only 12% (3 of 25) of patients aged ≤30 years had multiple aneurysms, but ≥30% of older patients had multiple aneurysms irrespective of age limits. There were tendencies for male patients with multiple aneurysms to have used more alcohol within 24 hours.
and 1 week (P=0.07) before SAH than male patients with a single aneurysm. The former group also had significantly (P<0.01) higher levels of both MCV and GGT than the latter, which supports data on their heavier alcohol consumption.

Current smoking or regular smoking at any time was not significantly more common in male patients with multiple aneurysms than those with a single aneurysm, but in both male groups, smoking, especially heavy smoking, was very common. In female patients, those with multiple aneurysms had smoked cigarettes regularly at any time more often (P=0.088) but had used less alcohol (P=0.078) within 24 hours before SAH than had those with a single aneurysm.

Duration of smoking in patients with multiple aneurysms (24±9 years) was similar to that in those with a single aneurysm (22±10 years). In men, the corresponding time periods were 26±8 and 23±10 years and in women 21±8 and 20±8 years. Cigarette smoking measured in pack-years followed the same pattern (data not shown).

Cigarette smoking and alcohol consumption were significantly more common in men than in women (P<0.01 for all alcohol and smoking variables). Cigarette smoking status correlated with all alcohol variables (r, ranging from 0.256 to 0.493; P<0.001) and also was inversely correlated with age (r=0.163, P=0.008). Those having smoked at any time were significantly (P<0.013) younger (43.5±9.7 versus 47.0±11.3 years) than others, as were current smokers (43.6±9.7 versus 46.4±11.2 years; P=0.033). Men were significantly (P=0.038) younger than women (43.3±10.3 versus 45.8±10.2 years). As expected, patients with hypertension were significantly (P<0.0001) older than those without (50.4±7.4 versus 42.4±10.6 years). Hypertension did not, however, correlate with either cigarette smoking or sex.

Current smokers and previous smokers had more aneurysms (1.45±0.78 and 1.50±0.65) than did those who had never smoked regularly (1.38±0.86), but the differences were not significant. Women had nonsignificantly (P=0.36) more aneurysms than men (1.49±0.88 versus 1.39±0.71, respectively). Patients with hypertension had more aneurysms (1.61±1.04) than those without (1.37±0.68) (P=0.029, test for linear trend). The number of aneurysms also correlated with GGT values (r=0.154, P=0.016) but not with MCV or alcohol variables. Levels of GGT correlated significantly, in

### Table 2. Hypertension, Alcohol Consumption, and Cigarette Smoking by Sex in 266 Patients With SAH

<table>
<thead>
<tr>
<th></th>
<th>Men With</th>
<th></th>
<th>Women With</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single Aneurysm</td>
<td>Multiple Aneurysms</td>
<td>Single Aneurysm</td>
<td>Multiple Aneurysms</td>
</tr>
<tr>
<td>No. of patients</td>
<td>101</td>
<td>38</td>
<td>85</td>
<td>42</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>25 (25)</td>
<td>10 (26)</td>
<td>20 (24)</td>
<td>15 (36)</td>
</tr>
<tr>
<td>Cigarette smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>14 (14)</td>
<td>3 (8)</td>
<td>44 (52)</td>
<td>15 (36)</td>
</tr>
<tr>
<td>Former smokers</td>
<td>7 (7)</td>
<td>2 (5)</td>
<td>1 (1)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Current smokers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 cigarettes/day</td>
<td>4 (4)</td>
<td>1 (3)</td>
<td>7 (8)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>11–20 cigarettes/day</td>
<td>7 (7)</td>
<td>4 (11)</td>
<td>11 (13)</td>
<td>5 (12)</td>
</tr>
<tr>
<td>&gt;20 cigarettes/day</td>
<td>69 (68)</td>
<td>28 (74)</td>
<td>22 (26)</td>
<td>13 (31)</td>
</tr>
<tr>
<td>Alcohol consumption before the onset of hemorrhage, g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 24 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25th, 75th percentile</td>
<td>0, 80</td>
<td>0, 153</td>
<td>0, 60</td>
<td>0, 0</td>
</tr>
<tr>
<td>Within 1 week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>100</td>
<td>200</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>25th, 75th percentile</td>
<td>0, 300</td>
<td>25, 543</td>
<td>0, 120</td>
<td>0, 93</td>
</tr>
<tr>
<td>Heavy drinking (%)</td>
<td>26 (26)</td>
<td>13 (34)</td>
<td>11 (13)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>CAGE-positive (%)</td>
<td>26 (26)</td>
<td>13 (34)</td>
<td>12 (14)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Former heavy drinking (%)</td>
<td>10 (10)</td>
<td>1 (3)</td>
<td>3 (4)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Mean±SD MCV, fl</td>
<td>94.9±4.4</td>
<td>97.7±4.8*</td>
<td>93.5±6.6</td>
<td>92.4±7.3</td>
</tr>
<tr>
<td>Median GGT, U/L</td>
<td>24</td>
<td>39*</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>25th, 75th percentile</td>
<td>16, 44</td>
<td>23, 90</td>
<td>10, 29</td>
<td>12, 33</td>
</tr>
</tbody>
</table>

Heavy drinking indicates alcohol consumption of ≥300 g/wk during the year before hemorrhage; CAGE-positive, ≥2 positive responses to 4 questions in CAGE interview; former heavy drinking, CAGE-positive patients who used <300 g alcohol during the week previous to hemorrhage.

*P<0.01.
The risk factors for aneurysm formation may only be more augmented in the patients with multiple aneurysms.

The prevalence of multiple aneurysms has also been related to the accuracy and completeness of angiography or autopsy.3,9 Their prevalence in this study was one of the highest reported in the literature, despite restriction of the patient population to those aged ≤60 years.3,5-9 The results of this study cannot be generalized to populations aged >60 years who may have different risk factors, but the results were quite similar to those obtained by Qureshi and colleagues6 among patients with a mean age of 52 years. In the present study the greatest change in prevalence of multiple aneurysms occurred soon after the age of 30 years. Since prevalence of multiple aneurysms has not been shown to increase after age 60 years, aging also does not seem to be a risk factor for multiple aneurysms.3,5-8 Accordingly, the rate of formation of new aneurysms may be quite low after age 60 years.

Before this study, only 2 studies used multivariate statistics to reveal independent risk factors for multiple intracranial aneurysms.6,5 Østegaard and Hog5 found that hypertension and female sex were independent risk factors for multiple aneurysms in a population of 737 aneurysm patients (719 patients had SAH), of which 18% had multiple aneurysms. They likely did not use routine 4-vessel angiography, and they did not estimate the effect of cigarette smoking as a risk factor. In addition, patients who had elevated blood pressure values or left ventricular hypertrophy after the aneurysm rupture were considered to have chronic hypertension, although at least some of those findings may be due to stress caused by SAH. Qureshi et al6 found that cigarette smoking and female sex were independent risk factors for multiple aneurysms in a population of 419 aneurysm patients (298 patients had SAH), of which 30% had multiple aneurysms. In their study, the number of aneurysms was also greater in any-time smokers than in never-smokers. That analyses of patients with ruptured or unruptured aneurysms separately did not affect these results suggests that smoking and female sex, but not hypertension, are risk factors for aneurysm formation.

In this study univariate statistics revealed no significant risk factors for multiple aneurysms, although many factors such as cigarette smoking, female sex, age, and hypertension tended to be associated with multiple aneurysms. An increase in sample size might have led to significant differences. However, because cigarette smoking correlated negatively with 2 other possible risk factors (age and female sex), multivariate analysis was able to show a significant role of cigarette smoking as a risk factor. Cigarette smoking correlated with male sex and inversely with age. Alcohol consumption and cigarette smoking in Finland are known to be more frequent among men than among women, with both these habits decreasing with age.10,11 In addition, female patients were older than male patients, and patients with hypertension were older than those without.

Cigarette smoking has been shown to increase risk for SAH in several cohort and case-control studies,10-13,19 but the mechanism by which smoking increases this risk has been unknown. Cigarette smoking also seems to be a very impor-

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**TABLE 3. Multivariate ORs of Multiple Intracranial Aneurysms in 266 Patients With SAH**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>2.10 (1.06–4.13)*</td>
<td>2.06 (1.04–4.07)*</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.02 (1.00–1.05)†</td>
<td>1.02 (0.99–1.05)</td>
</tr>
<tr>
<td>Women</td>
<td>1.60 (0.90–2.85)</td>
<td>1.60 (0.90–2.84)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>...</td>
<td>1.19 (0.64–2.23)</td>
</tr>
</tbody>
</table>

ORs are adjusted for other variables in models. Numbers in parentheses indicate 95% CI.

*P<0.05.
†P=0.094.

addition to alcohol variables, with hypertension, BMI, smoking variables, and male sex.

Multiple logistic regression showed that only regular cigarette smoking at any time was a significant risk factor for presence of multiple intracranial aneurysms after adjustment for age, sex, and hypertension, although the univariate OR of smoking was not significant (1.56; 95% CI, 0.85 to 2.88) (Table 3). Additional adjustment for the source of information on health-related habits yielded a risk of smoking for multiple aneurysms that was similar to the risk without this adjustment (OR, 2.06; 95% CI, 1.04 to 4.07). Of other variables, only age (P=0.094) and female sex (P=0.11) showed a tendency toward increased risk for multiple aneurysms after adjustment for smoking. Current smokers had a risk of 1.98 (95% CI, 1.00 to 3.94; P=0.051) and previous smokers a risk of 3.33 (95% CI, 0.96 to 11.56; P=0.057) for multiple aneurysms compared with nonsmokers after adjustment for age, sex, and hypertension.

**Discussion**

On the basis of these findings, cigarette smoking and possibly also female sex and age seem to be risk factors for multiple intracranial aneurysms in patients with aneurysmal SAH aged ≤60 years.

Indisputable modifiable risk factors for SAH seem to be only cigarette smoking, alcohol consumption, and, to a lesser extent, hypertension.10-13 Many other factors may also increase risk for aneurysm formation or SAH, mainly through unknown mechanisms. These include atherosclerosis, female sex, aging, use of oral contraceptives, arterial deficiency in collagen type III, asymmetry of the circle of Willis, cerebral arteriovenous malformations, viral infections, pituitary tumors, and certain HLA-associated factors.14,15 Although aging, female sex, and hypertension may be risk factors for aneurysm formation, their association with the rupture of the aneurysm itself is unlikely.16-18

Patients with multiple intracranial aneurysms can be considered a definite subgroup, unlike those with a single aneurysm, because the former have been reported to be more often women,5,6,8,9 hypertensive,5,8 cigarette smokers,6 or older.8 However, some authors have reported that neither hypertension,6,7 female sex,3 nor age5,6,9 is a risk factor for multiple aneurysms. Differences between SAH patients with either a single aneurysm or multiple aneurysms can also be considered risk factors for aneurysm formation, since the presence of multiple aneurysms does not seem to increase the risk of rupture of an aneurysm.16-18
tant independent risk factor for subsequent rupture of an unruptured aneurysm, irrespective of aneurysm size, sex, and age of the patient at diagnosis (S. Juvela, et al, unpublished data, 1999). It is possible that long-term smoking can cause formation of an aneurysm as well as increase its size by weakening the vessel walls of the cerebral arteries. The recent study of Baker et al suggests that a serum elastase/α2-antitrypsin imbalance or increased elastase activity of cigarette smokers may contribute to either aneurysm formation or SAH. The results of the present study and those of Qureshi et al support this concept, since cigarette smoking was indisputably an independent risk factor for multiple intracranial aneurysms and thus possibly also for aneurysm formation.

The other mechanism by which cigarette smoking may increase risk for SAH is by a transient elevation in blood pressure. Blood pressure values are generally lower in smokers than in nonsmokers, but smoking a cigarette causes an acute increase in blood pressure for 3 hours. This transient increase may contribute to the rupture of an aneurysm. The theory that cigarette smoking causes formation of aneurysms through atherosclerosis is unlikely because atherosclerosis-promoting factors such as hypertension, age, and diabetes, as well as cardiovascular and ischemic cerebrovascular diseases, did not correlate with multiple aneurysms.

Alcohol consumption has been shown to increase, independently of cigarette smoking, age, and history of hypertension, the risk for SAH, even in women. According to the present study and that of Qureshi et al, alcohol consumption was not an independent risk factor for multiple aneurysms. Thus, it is possible that alcohol intake does not cause aneurysm formation. Blood pressure levels, which are transiently increased during alcohol intake and withdrawal, may, however, prove to be an important mechanism. Such a transient increase in systemic blood pressure, together with cerebral arteriolar vasoconstriction during alcohol exposure, may contribute to rupture of an aneurysm without causing formation of an aneurysm. Use of illicit drugs may increase risk for SAH by this same mechanism, since presence of multiple aneurysms does not correlate with the use of such drugs. In this study, drug use as a risk factor for multiple aneurysms could not be estimated, since drugs are still relatively uncommon in Finland.

Although age has not been shown to be an important risk factor for multiple aneurysms, the incidence of SAH is known to increase almost linearly with age. In this study the prevalence of multiple aneurysms tended to increase with age at an approximate rate of 2% per year when smoking, sex, and hypertension were considered. The most prominent increase in prevalence was after the age of 30 years, which seemed to be a cutoff point after which the prevalence of multiple aneurysms was >30%. A study by Inagawa showed a significant (P=0.05) association between age and prevalence of multiple aneurysms only in patients aged <60 years. Prevalence increased in his series to >30% in patients aged >50 years, with the maximum prevalence of multiple aneurysms and number of aneurysms in patients aged 50 to 60 years. Because the prevalence of multiple aneurysms and number of aneurysms per patient do not seem to increase after age 60 years, it is possible that formation of new aneurysms after that age is not very common. However, elderly patients may have a higher proportion of multiple aneurysms than shown, but this could not have been verified since these patients are not routinely studied accurately and treated for unruptured aneurysms.

Although the incidence of SAH is higher in women than in men in general, its incidence among young adults is higher in men. High SAH incidences without a clear female preponderance have been reported from Finland. In this study the risk for multiple aneurysms was higher in women than in men, suggesting that women have a higher risk for aneurysm formation in Finland. Susceptibility to SAH among men in Finland might be partly contributed by their heavier smoking and drinking habits.

History of hypertension as a risk factor for SAH seems to be less crucial than for other stroke subtypes. The prevalence of hypertension among SAH patients (20% to 30%) seems to be only slightly higher than in the general population. In a prospective cohort study, hypertension (blood pressure >160/95) was a clear risk factor for SAH. After adjustment for age, sex, cigarette smoking, and alcohol consumption, history of hypertension has not been shown to increase risk for SAH in case-control studies.

Smoking and alcohol consumption have been considered to increase the risk for SAH by mechanisms other than chronic hypertension. Additionally, hypertension does not seem to increase the risk for rupture of an unruptured aneurysm. In 2 studies hypertension was considered a risk factor for multiple aneurysms. In the first study, postoperative elevated blood pressure values were considered an indication of chronic hypertension, and in the other, multiple aneurysms correlated with hypertension only in patients aged ≥55 years. In this study patients with hypertension did not more often have multiple aneurysms, but if they did, they were likely to have >2. Thus, hypertension may increase risk for aneurysm formation among people of working age who are susceptible to its formation.

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References


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