Cerebrovascular disease is the third leading cause of death in the industrialized countries. The incidence of cerebral infarctions and intracerebral hemorrhage have declined during the last decades, while the incidence of primary SAH has not changed. The incidence of SAH is 7 to 20/100,000 per year depending on the study population. In more than three fourths of primary SAH cases, the cause of bleeding is rupture of an IA. The diagnostic methods and preoperative, perioperative, and postoperative management of SAH have improved significantly, but SAH patients still have a poor overall outcome. Half of the patients die, 15% are severely disabled, and only 20% to 35% have a moderate or good recovery. Those patients surviving the primary bleed are treated by open operation or by endovascular means to prevent fatal rebleeding from the IA. In unselected patient populations with ruptured IAs, both the morbidity and mortality for the operative outcome are approximately 20%. There are two routes of onset of IAs, both the morbidity and mortality for the operative outcome are approximately 20%. The operative results are totally different if IAs are treated before rupture, with a mortality of 0% to 2% and a morbidity of 4%. Successful treatment of unruptured IAs is the only way to prevent nearly all deaths caused by aneurysmal SAH. Intracranial aneurysms are reported to be present in 1% to 5% of the population, and the annual risk for rupture is estimated to be 1% to 2%. However, the identification of all individuals harboring an unruptured IA is still an unsolved problem.

The incidence of FIAs (at least two affected first-degree relatives in the same family) among SAH patients is 6% to 10%. Furthermore, as many as 10% to 17% of asymptomatic relatives in FIA families may have incidental IAs. Clustering of IAs in families could be fortuitous because of the high number of IAs in the population, or it could be caused by a combination of genetic and environmental factors. A positive family history of IAs seems to be an important risk factor for IAs and is one of the few clues for screening studies of IAs.

The aims of our study were (1) to calculate the prevalence and relative risks for unruptured IAs among families with IA case(s) compared with the general population in one geographically defined area in East Finland and (2) to identify the risk group that could benefit most from screening for IAs.

**Subjects and Methods**

The risk and prevalence of IAs in the general population were estimated from the results of all forensic autopsies performed on
Risk of Harboring an Unruptured Intracranial Aneurysm

The prospective forensic autopsy study was performed on consecutive cases to estimate the prevalence and risk of unruptured IAs in the general population. Subjects who had had previous SAH and who had been operated on for IAs (n=3) and those whose cause of death was SAH (n=12) were excluded from the study. In addition, subjects who did not live permanently in East Finland, who were badly decayed, or whose circles of Willis were damaged due to trauma (n=68) were also excluded. The circle of Willis was thoroughly examined in situ; this required spending approximately 10 to 15 minutes more time for each case than in a normal forensic autopsy study. No postmortem angiographies or saline perfusions of the circle of Willis were used to identify IAs. The greatest diameter of the IA was documented with an accuracy of 1.0 mm. All IAs ≥2 mm were registered to determine the true prevalence of IAs. The sensitivity of MRA compared with that of autopsy study is clearly lower for IAs than for surgical or angiographic findings. The sensitivity of MRA compared with that of angiographies or saline perfusions of the circle of Willis was used to identify IAs. The greatest diameter of the IA was documented with an accuracy of 1.0 mm. All IAs ≥2 mm were registered to determine the true prevalence of IAs. The sensitivity of MRA compared with that of autopsy study is clearly lower for IAs than for surgical or angiographic findings.

The number of IAs is presented in 10-year age groups, and the prevalence rates are standardized for age and sex. Standardization was done by a direct method with the total population of the provinces of Kuopio and North Karelia in 1990 used as the reference population. We calculated 95% CIs for standardized prevalence rates, as presented by Morris and Gardner. Relative risks describing the risk of IAs between the different study groups were adjusted for age and sex by the Mantel-Haenszel method.

Results

The age and sex distribution of the three study groups is presented in Table 1. For the study regarding IAs in the general population, a total of 612 consecutive forensic autopsies were included. One quarter of the patients were female (125/487). The mean age of the men was 59.1 years (range, 35.7 to 69.7 years) and of the women 57.0 years (range, 50.8 to 67.4 years). A total of 33 incidental IAs ≥2 mm were found in 27 men and in 2 women. Thirty IAs were very small (<6 mm), 2 IAs were small (7 to 14 mm), and 1 IA was large (15 to 24 mm). The group with very small IAs included 12 IAs with a size of 2 mm in 11 patients.

In the group of families with only one affected relative, 147 first-degree relatives were studied by MRA. Men accounted for 63 of 147 cases (43%), and the mean age in men was 48.6 years (range, 31 to 70 years); the mean age in women was 50.2 years (range, 31 to 70 years). Eight unruptured IAs were found and confirmed by intra-arterial digital subtraction angiography study in 6 patients: 4 men and 2 women. One patient had three separate IAs. Six of these unruptured IAs were very small, and two IAs were small.

| TABLE 1. Total Population of North Karelia and the Province of Kuopio and Patients in Different Study Groups for Unruptured IA by Age Group and Sex and Number of Persons With IA per Stratum |
|-----------------|-----------------|-----------------|-----------------|
|                | Forensic Autopsies | Families With One Aneurysmal SAH | FIA cases |
| Population     | All IA Cases     | All IA Cases     | All IA Cases |
| Men            |                  |                  |                |
| 30-39 y        | 36 776           | 83               | 18             | 3             | 78  6        |
| 40-49 y        | 32 804           | 137              | 4              | 24            | 0  66        |
| 50-59 y        | 23 169           | 118              | 12             | 7             | 0  24        |
| 60-69 y        | 20 125           | 149              | 10             | 14            | 1  30        |
| Women          |                  |                  |                |
| 30-39 y        | 33 011           | 22               | 0              | 13            | 0  79        |
| 40-49 y        | 29 270           | 24               | 0              | 30            | 1  66        |
| 50-59 y        | 23 340           | 20               | 1              | 24            | 0  38        |
| 60-69 y        | 25 409           | 59               | 1              | 17            | 1  33        |
| Total          | 223 903          | 612              | 29             | 147           | 6  414        |

Selected Abbreviations and Acronyms

CI = confidence interval
IA = intracranial aneurysm
FIA = familial intracranial aneurysm
MRA = magnetic resonance angiography
SAH = subarachnoid hemorrhage
TABLE 2. Crude and Standardized (for Age and Sex) Prevalence Rates of Unruptured IAs in Three Different Study Populations

<table>
<thead>
<tr>
<th>Forensic autopsy population</th>
<th>n</th>
<th>Crude Prevalence, %</th>
<th>Standardized Prevalence, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAs (\geq 2) mm</td>
<td>29</td>
<td>4.7</td>
<td>3.0</td>
<td>2.1-3.6</td>
</tr>
<tr>
<td>IAs (\geq 3) mm</td>
<td>19</td>
<td>3.1</td>
<td>2.2</td>
<td>1.3-2.8</td>
</tr>
<tr>
<td>Families with one aneurysmal SAH</td>
<td>6</td>
<td>4.1</td>
<td>4.5</td>
<td>2.8-5.2</td>
</tr>
<tr>
<td>FIA cases</td>
<td>37</td>
<td>8.9</td>
<td>9.8</td>
<td>8.9-10.6</td>
</tr>
</tbody>
</table>

The crude and the age- and sex-standardized prevalence rates of IAs in the general population, in families with only one affected member, and in FIA families are shown in Table 2. The calculated relative risks are given in Table 3. We calculated the prevalence of IAs in the general population in two IA size categories: \(\geq 2\) mm, representing the higher estimate of prevalence, and \(\geq 3\) mm, representing the lower estimate. The relative risk was calculated from the IA size category of \(\geq 3\) mm.

**Discussion**

The aims of our study were to calculate the prevalence and relative risk for unruptured incidental IAs among families with IA case(s) compared with the general population in one geographically defined area and to identify the risk group that could benefit most from screening for IAs. The age limit of 30 to 70 years was selected because the incidence of aneurysmal SAH is extremely low during the first three decades of life and because life expectancy should be at least 10 years for the screening studies to be beneficial to individuals.

**Prevalence of Unruptured IAs**

The standardized prevalence of unruptured IAs in the studied population in East Finland was 2.2% to 3%. Our results agree with earlier studies on the prevalence of IAs but do not explain the high incidence of aneurysmal SAH in Finland.

To calculate the prevalence of IAs in the general population, we used two definitions for IA size in the forensic autopsy study material: IAs \(\geq 2\) mm and IAs \(\geq 3\) mm. The size criteria were selected because the resolution of MRA is sufficient for detecting IAs \(> 2\) to 3 mm in size and furthermore because very small IAs seem to have a low rupture rate. In autopsy studies IAs in brains in situ are 25% to 40% smaller than IAs in brains in vivo with normal blood pressure. To compare results obtained by different study methods, the sensitivity level is selected according to the less sensitive method used. After correction of the size of the of IAs found at autopsy by 25% to 40%, IAs with a size of 2 mm would be 2.5 to 2.8 mm, and IAs with a size of 3 mm would be 3.8 to 4.2 mm in an in vivo situation, respectively. Accepting this estimation, we used the larger size criteria \(\geq 3\) mm for IAs for statistical calculations.

By selecting forensic autopsy cases instead of medical autopsy cases, we were able to control the patient selection bias more easily. Indications for forensic autopsies in Finland are strictly controlled by legislation. Forensic autopsy material differs from the general population in terms of a male preponderance and a higher age, since the number of autopsies is increased in older age groups. As a result of this age and sex bias, the prevalence of IAs in the general population may be overestimated, since the number of IAs increases with age. In contrast to other aneurysm series, there is a constant male preponderance in Finland. As a result of age and sex bias, the relative risk of IA in the FIA families and in the families with only one affected member compared with the general population is likely to be underestimated.

**Relative Risk for Unruptured IA**

In a defined population in East Finland, the relative risk of unruptured IAs is 4.2 (95% CI, 2.2 to 8.0) times higher in first-degree relatives of FIA families, and in families with one affected family member it is 1.8 (95% CI, 0.7 to 4.8) times higher than in the general population. The high prevalence of IAs among FIA families is real and clearly not caused by a large number of fortuitous IAs in the general population. The impact of a genetic factor causing this clustering of IAs in certain families has not been proven but is certainly possible.

**Screening**

The ideal screening tool for IAs would be accurate, inexpensive, easily available, and safe to studied individuals. Today, MRA would be the first-choice method for this kind of large screening study. MRA methods have improved, and the resolution of MRA is good enough to detect even very small IAs without the use of contrast material. However, the disadvantages of MRA are high cost and limited availability. Consequently, it cannot be used as a screening tool to detect IAs in the general population. Screening studies for IAs among completely asymptomatic individuals without any positive family background are neither ethically nor economically acceptable. Our study results suggest the need for screening first-degree relatives in FIA families for IAs.

**Cost-effectiveness of Active Screening**

A crude estimate of the cost-effectiveness of active screening of asymptomatic first-degree relatives in FIA families in Finland...
and the impact of such screening can be roughly calculated. The incidence of SAH in Finland is 20/100,000 per year. Every year approximately 1000 new SAH cases occur in our population of just over 5 million, 10% of them familial. With an average number of five first-degree FIA family members per index case, there is a need for screening 500 asymptomatic high-risk individuals annually, with 10% yield of positive cases. Treating these 50 incidental IA patients prophylactically, we might save 5 to 10 lives. The price of one MRA study is approximately 770 US dollars per study, and therefore the annual cost of screening 500 individuals would be 385,000 US dollars. In the case of 50 positive findings, screening for IAs can be economically profitable, with a cost of 7700 US dollars annually per one positive case. Our calculation is a very simplified estimation of cost-effectiveness that includes neither the effects of angiography and operative complications nor the effects of other risk factors for IAs. However, we believe that it still provides a rough estimate of the effect of active screening of FIA families in Finland, where the incidence of aneurysmal SAH is the highest in the world.

The poor overall outcome of aneurysmal SAH has not changed during the last decades. Patients with IAs should be treated preventively before the evident rupture of the IA. FIA families with at least two affected family members form a clear risk group for incidental IAs. According to our results, first-degree relatives in FIA families are most likely to benefit from active screening of IAs, and this could save a significant number of individuals from calamitous aneurysmal SAH. Screening of the general population or of families with only one affected family member is not advocated at this time.

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