Approximately 3% of the population develop saccular intracranial aneurysms (sIAs) during lifetime at the forks of intracranial arteries. Most sIAs do not rupture and are too small to cause any neurological symptoms by compression. If diagnosed during life, most unruptured sIAs are incidental findings in neuroimaging for other reasons or screening for familial sIAs. Approximately 95% of aneurysmal subarachnoid hemorrhages (SAH) are caused by the rupture of the sIA wall (sIA–SAH), the third most frequent form of stroke affecting the working age population. The annual incidence has been reported to be 4 to 7 per 100,000 worldwide, possibly higher in Finland and Japan. The sIA disease is a complex trait, affected by age, female sex, smoking, hypertension, and excess drinking, and at least 10% of sIA–SAH patients belong to sIA families.

The formation of new (de novo) sIAs in angiographic follow-up of sIA disease carriers is reported in many series, with incidences from 0.3% to 4.4% per year in our literature search. Cohort sizes and numbers of de novo sIAs and follow-up protocols and times vary. Of the known sIA risk factors, only smoking has been repeatedly associated with the de novo sIA formation (Table 1).

The Kuopio Intracranial Aneurysm Database (http://www.uef.fi/ns) contains 4414 sIA patients admitted to Kuopio University Hospital from its Eastern Finnish catchment population. We studied the incidence and risk factors for de novo sIA formation in 1419 sIA patients with ≥5 years of angiographic follow-up, a total follow-up of 18,526 patient-years. There were 42 patients with a total of 56 de novo sIAs, diagnosed in a median of 11.7 years after the first sIA diagnosis. The cumulative incidence of de novo sIAs was 0.23% per patient-year and that of subarachnoid hemorrhage from a ruptured de novo sIA 0.05% per patient-year. The risk of de novo sIA discovery per patient-year increased with younger age at the first sIA diagnosis: 2.2% in the patients aged <20 years and 0.46% in the patients aged between 20 and 39 years. In Cox regression analysis, smoking history and younger age at the first sIA diagnosis significantly associated with de novo sIA formation, but female sex, multiple sIAs, and sIA family did not.

Patients aged <40 years at the first sIA diagnosis are in a significant risk of developing de novo sIAs, and they should be scheduled for long-term angiographic follow-up. Smoking increases the risk of de novo sIA formation, suggesting long-term follow-up for smokers. Antismoking efforts are highly recommended for sIA patients.

KEY WORDS: aneurysm, ruptured • follow-up studies • intracranial aneurysm • risk factors • subarachnoid hemorrhage
Table 1. Case Series of De Novo IA Formation Published Since 2000

<table>
<thead>
<tr>
<th>Series</th>
<th>Year</th>
<th>Type of Study</th>
<th>IA Patients</th>
<th>Unruptured De Novo IAs</th>
<th>Ruptured De Novo IAs</th>
<th>Mean Follow-Up, y (Range)</th>
<th>Incidence of De Novo IA Patients</th>
<th>Risk Factors for De Novo IA Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juvela et al7</td>
<td>2001</td>
<td>Prospective</td>
<td>94</td>
<td>12</td>
<td>7</td>
<td>18.9 (1.2–39)</td>
<td>0.73%–0.84% per year</td>
<td>Female sex, smoking</td>
</tr>
<tr>
<td>Tsutsumi et al6</td>
<td>2001</td>
<td>Prospective</td>
<td>112</td>
<td>5</td>
<td>4</td>
<td>9.0 (3.0–21)</td>
<td>0.89% per year</td>
<td>NA</td>
</tr>
<tr>
<td>Akyüz et al10</td>
<td>2004</td>
<td>Prospective</td>
<td>136</td>
<td>2</td>
<td>0</td>
<td>3.9 (3.0–7.1)</td>
<td>0.38%</td>
<td>NA</td>
</tr>
<tr>
<td>Yoneoka et al19</td>
<td>2004</td>
<td>Retrospective</td>
<td>483</td>
<td>0</td>
<td>12</td>
<td>10.7 (2.6–24)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>van der Schaaf et al11</td>
<td>2005</td>
<td>Prospective</td>
<td>495</td>
<td>19</td>
<td>0</td>
<td>8.1 (4.4–14)</td>
<td>0.67% per year</td>
<td>NA</td>
</tr>
<tr>
<td>Wermer et al12</td>
<td>2005</td>
<td>Prospective</td>
<td>610</td>
<td>19</td>
<td>0</td>
<td>9.1 (4.4–14)</td>
<td>0.37% per year and 0.8% at 5 y</td>
<td>Multiple IAs, smoking, IA family history</td>
</tr>
<tr>
<td>Edler et al13</td>
<td>2007</td>
<td>Prospective</td>
<td>43</td>
<td>8</td>
<td>0</td>
<td>19.8 (19–20)</td>
<td>0.90%</td>
<td>NA</td>
</tr>
<tr>
<td>Kim et al14</td>
<td>2007</td>
<td>Retrospective</td>
<td>65</td>
<td>0</td>
<td>12</td>
<td>8.9 (1.0–17)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Molyneux et al15</td>
<td>2009</td>
<td>Prospective</td>
<td>2143</td>
<td>0</td>
<td>6</td>
<td>7.8 (6.0–14)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hetts et al18a</td>
<td>2011</td>
<td>Retrospective</td>
<td>83</td>
<td>8</td>
<td>1</td>
<td>5.9</td>
<td>11%</td>
<td>Multiple IAs, fusiform IA, primary treatment with parent artery occlusion</td>
</tr>
<tr>
<td>Ferns et al17</td>
<td>2011</td>
<td>Prospective</td>
<td>276</td>
<td>2</td>
<td>0</td>
<td>5.0</td>
<td>1.14% per year</td>
<td>NA</td>
</tr>
<tr>
<td>Bruneau et al19</td>
<td>2011</td>
<td>Prospective</td>
<td>20</td>
<td>6</td>
<td></td>
<td>18.0 (10–26)</td>
<td>0.84% per year</td>
<td>Multiple IAs</td>
</tr>
<tr>
<td>Plowman et al19</td>
<td>2011</td>
<td>Retrospective</td>
<td>570</td>
<td>1</td>
<td>1</td>
<td>6.1 (0.5–16)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Kemp et al20</td>
<td>2012</td>
<td>Retrospective</td>
<td>611</td>
<td>32</td>
<td>10</td>
<td>NA</td>
<td>4.4%</td>
<td>None of the tested</td>
</tr>
<tr>
<td>Lai et al21</td>
<td>2014</td>
<td>Retrospective</td>
<td>472</td>
<td>43</td>
<td>3</td>
<td>4.5 (0.5–20)</td>
<td>4.21% at 5 y and 15% at 10 y</td>
<td>Smoking, unruptured IA disease at first diagnosis</td>
</tr>
<tr>
<td>Wang et al22</td>
<td>2015</td>
<td>Retrospective</td>
<td>185</td>
<td>21</td>
<td>5</td>
<td>3.3 (0.7–18)</td>
<td>1.14% per year</td>
<td>None of the tested</td>
</tr>
<tr>
<td>Lecler et al23</td>
<td>2015</td>
<td>Prospective</td>
<td>112</td>
<td>11</td>
<td>0</td>
<td>11</td>
<td>9.1% at 10 y</td>
<td>NA</td>
</tr>
</tbody>
</table>

IA indicates intracranial aneurysm; and NA, not available.

*Pediatric patients only.

All cases of SAH diagnosed by spinal tap or computed tomography in the KUH catchment area have been acutely admitted to KUH for angiography and treatment if not moribund or aged. Cases with unruptured IA(s) and no SAH have also had neurosurgical consultation for elective occlusion. The findings were confirmed by 4-vessel catheter angiography, magnetic resonance angiography, or computed tomographic angiography. Most index sIA’s in this series have been treated microsurgically. In these cases, all sIAs seen in the operative field were clipped if technically possible. In rare cases, tiny aneurysms were found in the operative field, not seen in the preoperative angiography. These were not considered de novo sIAs but were added to our database.

Kuopio Intracranial Aneurysm Database maintains a registry on all cases of unruptured and ruptured IAs admitted to the KUH. The database is run by a full-time nurse who interviews new cases and codes variables with detailed information, including family history. The criterion for sIA family is at least 2 affected first-degree relatives. Clinical data from the hospital periods and follow-up visits are entered prospectively. Follow-up images are analyzed weekly in KUH Neurovascular Group meetings by neurovascular surgeons and neurovascular radiologists.

Figure 1. Flowchart showing the final study cohort of 1419 saccular intracranial aneurysm (sIA) patients fulfilling the inclusion criteria. KUH indicates Kuopio University Hospital.
Study Population
The cohort consisted of 1419 sIA patients from KUH sIA Database fulfilling the following criteria (Figure 1):

1. A citizen of Finland and resident of the KUH catchment area at the first diagnosis of sIA disease between January 1, 1975, and December 31, 2014.
2. Admission alive to KUH.
3. Verification of sIA(s) by angiography (computed tomographic angiography, magnetic resonance angiography, or digital subtraction angiography).
4. Angiographically verified de novo aneurysm in the follow-up, available for re-review, or
5. At least 5 years of negative angiographic (computed tomographic angiography, magnetic resonance angiography, or digital subtraction angiography) follow-up after the first sIA diagnosis.

Literature Search
PubMed was searched for de novo IA case series published since 2000 (Table 1) with the following terms: aneurysm, de novo, formation, and intracranial.

Statistical Analysis
Univariate analyses were performed using the Mann–Whitney U test or the \( \chi^2 \) test, as appropriate. Kaplan–Meier curves were plotted, and log-rank test was used in the univariate analysis. Multivariate analyses were performed using the Cox regression with variables showing significant association in the univariate analyses. The date of the imaging study confirming the first de novo sIA formation was used as the occurrence time in the incidence calculations and time-to-event variable calculation in Cox regression.

Ethical Aspects
The study was approved by the Ethics Committee of the KUH. Data fusion from the national registries were performed with the approval from Ministry of Social Affairs and Health of Finland.

Results

Study Cohort
The final study cohort consisted of 1419 patients (1107 ruptured; 312 unruptured) with the first sIA diagnosis between 1975 and 2014. They had at least 1 follow-up angiography between 1975 and October 2015, with a median follow-up time to the last angiography of 11.0 years (total, 18,526 patient-years). In overall, 56 de novo sIAs were angiographically diagnosed in 42 patients in a median of 11.7 years (range, 0.7–30) from the first sIA diagnosis (Table 2).

Characteristics of 42 Patients With De Novo sIAs
In univariate analyses, the 42 patients with de novo sIAs and the remaining 1377 differed significantly in 4 aspects at the first sIA diagnosis (Table 2): age (median, 39 versus 51 years); history of smoking (60% versus 27%); familial sIA disease (30% versus 17%); and the site distribution of the primary sIA(s). Instead, the prevalence of hypertension was equal (31% versus 33%; Table 2). Of the 42 patients, 9 presented with SAH from a ruptured de novo sIA in a median time of 10.3 years from the primary sIA diagnosis. Of the 42 patients, 12 developed multiple de novo sIAs (Table 2).

Characteristics of 56 De Novo sIAs
The 9 ruptured de novo sIAs, reaching the median size of 7.5 mm (Table 3) in a median of 11.2 years, did not present any particular feature that would distinguish them from the 1066
ruptured primary sIAs (data not shown). Only 1 of the 353 primarily unruptured patients later experienced SAH from a ruptured de novo sIA. The 47 unruptured de novo sIAs, reaching the median size of 3 mm in a median of 12.1 years, did not differ from the primary unruptured sIAs in the 312 patients either (data not shown).

Incidence of De Novo sIAs

The overall discovery rate for de novo patients was 0.2% at 5 years and 2.0% at 10 years. Overall discovery rate for de novo sIAs was 0.3% per patient-year and for multiple de novo sIAs 0.06% per patient-year. The overall cumulative discovery rate for de novo patients was 0.23% per patient-year, 0.12% for nonsmokers and 0.6% for the patients with a smoking history. The cumulative incidence decreased by age at the first sIA diagnosis: 2.2% for the patients aged <20 years; 0.46% for 21 to 40 years; 0.19% for 41 to 60 years; and 0.02% for >60 years. The cumulative incidence for SAH from a ruptured de novo sIA was 0.05% per patient-year.

Table 3. Characteristics of 56 De Novo Saccular Intracranial Aneurysms in 42 Patients

<table>
<thead>
<tr>
<th>Location, n (%)</th>
<th>All</th>
<th>Ruptured</th>
<th>Unruptured</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA</td>
<td>13 (23)</td>
<td>0</td>
<td>13 (28)</td>
</tr>
<tr>
<td>MCA</td>
<td>21 (38)</td>
<td>2 (22)</td>
<td>19 (40)</td>
</tr>
<tr>
<td>ACA</td>
<td>1 (2)</td>
<td>1 (11)</td>
<td>0</td>
</tr>
<tr>
<td>ACom</td>
<td>10 (18)</td>
<td>4 (44)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>VA</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BA</td>
<td>6 (11)</td>
<td>1 (11)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>PICA</td>
<td>5 (9)</td>
<td>1 (11)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Median size, mm (range)</td>
<td>3 (1–61)</td>
<td>7.5 (3–61)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Irregular shape, n (%)</td>
<td>11 (20)</td>
<td>8 (89)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

ACA indicates anterior cerebral artery; ACom, anterior communicating artery; BA, basilar artery; ICA, internal carotid artery; MCA, middle cerebral artery; PICA, posterior inferior cerebellar artery; and VA, vertebral artery.

Independent Risk Factors for De Novo sIA Formation

In the multivariate Cox regression analysis, history of smoking (hazard ratio [HR], 5.61), age at the first sIA diagnosis (HR, 0.96 per year), and the anterior cerebral artery location of the primary sIA (HR, 0.19) independently associated with de novo sIA formation. The HR decreased by age at the first sIA diagnosis: HR, 27.4 for <20 years; HR, 8.63 for 20 to 40 years; HR, 5.32 (not significant) for 41 to 60 years; and with >60 years as a reference. Instead, sIA family and primarily unruptured sIA disease were not independent risk factors (Figure 2; Table 4).

Discussion

We analyzed the incidence and risk factors for de novo sIA formation, to our knowledge, in the largest population-based cohort. Incidence of de novo formation was significantly higher for younger sIA patients and for sIA patients with a history of smoking (Figure 2).

Previous studies of de novo IA formation report incidences from 0.15% to 1.14% per follow-up year (Table 1). Two studies with the longest follow-up times reported 0.84% and 0.90% per year, much higher than 0.23% in our study. One explanation is younger age at the first IA diagnosis: a mean of 38 years for the 94 Finnish patients (mean follow-up, 18.9 years) by Juvela et al and 42 years for the 43 Swedish patients (mean follow-up, 19.8 years) by Edner and Almqvist. In our series, with a median follow-up time of 11 years, the incidence was as much as 2.2% for the 20 patients aged <20 years and 0.46% for the 288 patients aged 20 to 39 years at the first sIA diagnosis. In the prospective study by Wermer et al, with a mean follow-up of 9.1 years, 57% patients with de novo sIAs were <40 years at the first sIA diagnosis. In the pediatric series of 59 Finnish patients, followed up for a median of 34 years after the first IA diagnosis at an age <19 years by Koroknay-Pál et al, the incidence for de novo IA formation was 1.9% per follow-up year, in line with our results. In a follow-up study of 84 pediatric patients with 114 IAs, 8.4% developed new or enlarging aneurysms in a mean follow-up of 5.9 years.

Of 17 previous studies with a total of 181 unruptured and 60 ruptured de novo IAs (Table 1), only 4 reported any risk...
Factors for de novo IA formation: smoking,7,12,21 female sex,14 multiple IA disease,5,18 family history of IA,12 and unruptured IA at first diagnosis.21 In our study with 47 unruptured and 9 ruptured de novo sIAs history of smoking and younger age at the first sIA diagnosis independently associated with de novo sIA formation. In the pediatric series by Koroknay-Pál et al,29 smoking was the only significant risk factor for de novo IA formation.

Of the 9 ruptured de novo sIAs, 8 developed in the 1066 patients with sA–SAH at first diagnosis, and only 1 in the 353 primarily unruptured sIA patients. There was no significant difference in the distribution of sex or prevalence of family history for sIA disease, hypertension, or smoking in ruptured and unruptured de novo sIA patients. The incidence of SAH from a ruptured de novo sIA was 50/100,000, clearly higher than the incidence of SAH (4–7/100,000) in general population.

This study has several strengths that are derived from the Scandinavian healthcare system. Finland is divided into exclusive catchment areas for the 5 university hospitals, allowing cohorts that are unselected and minimally biased. Accurate population statistics and stable population ensure that few patients are lost to follow-up. We studied angiographically verified sIAs and de novo sIAs only, whereas many series may have included other forms of IAs than saccular ones. The weakness of our study is that we had to exclude 20 possible de novo carriers (Figure 1) because of missing angiographies or their low diagnostic accuracy. This is a potential source for bias toward underestimation of de novo sIA formation rate. The selection of patients into long-term follow-up based on an individual assessment rather than the use of a rigid follow-up protocol is another potential source of bias. Because of a relatively small number of end events in the Cox regression, the results should be interpreted cautiously and externally validated, preferably in multiple independent cohorts.

Conclusions
Patients aged <40 years at the first sIA diagnosis are in a significant risk of developing de novo sIAs, and they should be scheduled for long-term angiographic follow-up, for example, at 5-year intervals. Smoking increases the risk of de novo sIA formation, and long-term follow-up should be considered for smokers. Antismoking efforts are highly recommended for sIA patients.

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Disclosures
None.

References


De Novo Aneurysm Formation in Carriers of Saccular Intracranial Aneurysm Disease in Eastern Finland

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