Differences in Aneurysm and Patient Characteristics Between Cohorts of Finnish and Dutch Patients With Subarachnoid Hemorrhage

Time Trends Between 1986 and 2005

Caspar E.P. van Munster, MD; Mikael von und zu Fraunberg, MD; Gabriel J.E. Rinkel, MD; Jaako Rinne, MD; Timo Koivisto, MD; Antti Ronkainen, MD

Background and Purpose—The high incidence of aneurysmal subarachnoid hemorrhage (aSAH) in Finland may be related to genetic or environmental factors, which may also influence patient and aneurysm characteristics. We compared these characteristics in 2 cohorts in Finland (Kuopio) and the Netherlands (Utrecht).

Methods—For aSAH patients in Kuopio (n = 1786) and Utrecht (n = 1788), we compared sex, age at onset, and the sites and number of aneurysms from 1986 to 2005. Five-year time trends were assessed with $\chi^2$ tests (sex distribution and the sites and number of aneurysms) and with 1-way ANOVA (age).

Results—The proportion of men in Kuopio (46.1%; 95% CI, 43.8% to 48.4%) was higher than in Utrecht (33.6%, 95% CI, 31.4% to 35.8%) and declined in Kuopio from 50.9% (95% CI, 46.3% to 55.5%) in 1986–1990 to 42.8% (95% CI, 38.0% to 47.6%) in 2001–2005. Mean ± SD age at onset was 52.4 ± 13.3 years in Kuopio and 53.3 ± 14.3 years in Utrecht. Both increased similarly over time. The most common aneurysm site in the Kuopio cohort was the middle cerebral artery (33.1%; 95% CI, 30.9% to 35.3%) and in the Utrecht cohort was the anterior communicating artery (38.0%; 95% CI, 35.5% to 40.5%). Multiple aneurysms were more frequent in Kuopio (27.8%; 95% CI, 25.1% to 29.2%) than in Utrecht (14.8%; 95% CI, 13.0% to 16.6%). Sites and proportions of multiple aneurysms did not change during 1986–2005.

Conclusions—The cohorts of aSAH patients differed with respect to age at onset and the number and sites of aneurysms. The decline in the proportion of men in Kuopio coincided with increased smoking and alcohol use in women and decreased smoking in men. The differences in aneurysm characteristics remained stable, which suggests that these factors are less influenced by environmental factors. (Stroke. 2009;40:000–000.)

Key Words: subarachnoid hemorrhage ■ aneurysm ■ sex ■ age ■ aneurysm sites ■ multiplicity ■ risk factors ■ etiology ■ hypertension ■ smoking ■ alcohol

The incidence of subarachnoid hemorrhage (SAH) in most Western countries is ~9 per 100 000 person-years, but in Finland it is ~20 per 100 000 person-years. This disparity may be explained by genetic or environmental differences between Finland and other countries. Differences in genetic or environmental factors may influence not only incidence rates but also patient and aneurysm characteristics of aneurysmal SAH (aSAH). In familial SAH, which occurs in ~10% of all patients with SAH, patients tend to have a younger age of onset, the proportion of women is smaller, aneurysms are more often multiple and large, and the most common site of rupture is the middle cerebral artery (MCA). Important modifiable risk factors are smoking, alcohol use, and hypertension. The prevalence of smoking, alcohol abuse, and hypertension in Finland has always been 1 of the highest in the world, which has resulted in high incidences of cardiovascular diseases in general. During the past few decades, several major community-based preventive programs have been established in Finland, which have been followed by a large decline in the incidence of cardiovascular diseases, including stroke. This decline has been larger than in other countries. Thus, if environmental factors influence patient and aneurysm characteristics, changes over time in environmental factors may result in changes in patient and aneurysm characteristics. We investigated whether the sex distribution, age at onset, and the sites...
and number of aneurysms differ between a cohort of aSAH patients in Finland and those in the Netherlands and whether these differences changed over time between 1986 and 2005.

Subjects and Methods

Patients

We retrieved data for patients from prospectively collected databases from cerebrovascular centers in Finland (Kuopio University Hospital) and the Netherlands (University Medical Centre Utrecht) who had been admitted from 1986 through 2005. Other inclusion criteria were SAH confirmed by either computed tomography or lumbar puncture and aneurysm confirmed by computed tomography angiography (CTA), digital subtraction angiography (DSA), or an aneurysmal pattern of hemorrhage for those patients who did not undergo DSA in the early years of the study period because of their poor clinical condition. Patients with negative CTA or DSA findings were excluded. The subset of patients without DSA or CTA data were included only in the analyses of patient characteristics, not in those for aneurysm characteristics. The catchment area of the Kuopio hospital was very strictly defined and covered a stable population of 850,000 inhabitants. For the Utrecht hospital, the catchment area has enlarged during the study period.

We retrieved data on year of SAH, sex, age at onset, and sites and number of aneurysms. Year of SAH was categorized in subgroups of 5 years. For age-specific analysis of the sex distribution and the distribution of the sites and number of aneurysms, age at onset was stratified in groups of 10 years and those <25 years or >85 years. Sites of aneurysm were categorized into the internal carotid artery, MCA, anterior communicating artery (AComA), distal anterior cerebral artery, posterior communicating artery, and vertebrobasilar artery (including the posterior cerebral artery). The number of aneurysms was grouped into single and multiple. This study was approved by the ethics committees of both hospitals.

Analysis

To compare characteristics between Kuopio and Utrecht, we calculated per-center proportions with corresponding 95% CIs for sex distribution and overall sex- and age-specific sites and number of aneurysms. For overall and sex-specific mean age at onset, we calculated standard deviations and used an independent-sample t-test to determine significance. Analyses of sex distribution and the distribution of the sites and number of aneurysms per age group were done with a χ² test. Also, a χ² test was used to determine whether the characteristics changed during the 5-year periods. For mean age at onset, this was done on a per-year basis by 1-way ANOVA. P<0.05 was defined as significant.

Results

A total of 3574 patients were included, 1786 patients from the Kuopio database and 1788 from the Utrecht database. The numbers of patients were equally distributed among the 5-year periods in Kuopio but increased in Utrecht from 250 to 581 between 1986 to 1990 and 2001 to 2005 (Table 1). For all patients from Kuopio, aneurysm characteristics were available, and corresponding data were available for 1489 (83.3%) patients from Utrecht (Table 2). When we restricted the analysis to patients with proven aneurysms, the results were essentially the same.

Sex Distribution

In Kuopio, 824 (46.1%; 95% CI, 43.8% to 48.4%) patients were men; in Utrecht, there were 601 men (33.6%; 95% CI, 31.4% to 35.8%; Table 1). In Kuopio, males were in the minority starting within the age group 46 to 55 years, whereas in Utrecht, the sex distribution was the same in all age groups. In Kuopio, the proportion of men declined from 50.9% (95% CI, 46.3% to 55.5%) in 1986 to 1990 to 42.8% (95% CI, 38.0% to 37.6%) in 2001 to 2005 (P=0.053; Figure 1). Sex distribution remained stable over time in Utrecht (P=0.200; Figure 2).

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Kuopio</th>
<th>Utrecht</th>
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<tbody>
<tr>
<td></td>
<td>n (% (95% CI))</td>
<td>n (% (95% CI))</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>824 (46.1 (43.8–48.4))</td>
<td>601 (33.6 (31.4–35.8))</td>
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<tr>
<td>1986–1990</td>
<td>232 (50.9 (46.3–55.5))</td>
<td>87 (34.8 (28.9–40.7))</td>
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<tr>
<td>1991–1995</td>
<td>216 (47.3 (42.8–52.0))</td>
<td>156 (37.5 (32.8–42.2))</td>
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<tr>
<td>1996–2000</td>
<td>200 (43.3 (38.8–47.8))</td>
<td>169 (31.2 (27.3–35.1))</td>
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<tr>
<td>2001–2005</td>
<td>176 (42.8 (38.0–47.6))</td>
<td>189 (32.5 (28.7–36.3))</td>
</tr>
<tr>
<td>Age groups, n and % men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>23 (56.1 (39.8–71.5))</td>
<td>21 (50.0 (34.2–65.8))</td>
</tr>
<tr>
<td>26–35</td>
<td>87 (62.1 (54.1–70.2))</td>
<td>45 (33.8 (25.8–41.9))</td>
</tr>
<tr>
<td>36–45</td>
<td>224 (57.4 (52.5–52.3))</td>
<td>111 (30.8 (26.1–35.6))</td>
</tr>
<tr>
<td>46–55</td>
<td>224 (47.9 (43.3–52.4))</td>
<td>165 (34.7 (30.5–39.0))</td>
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<tr>
<td>56–65</td>
<td>177 (41.5 (36.8–46.1))</td>
<td>144 (35.3 (30.7–39.9))</td>
</tr>
<tr>
<td>66–75</td>
<td>74 (29.5 (23.8–35.1))</td>
<td>85 (33.1 (27.3–38.8))</td>
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<tr>
<td>76–85</td>
<td>14 (20.9 (11.9–32.6))</td>
<td>27 (26.0 (17.5–34.4))</td>
</tr>
<tr>
<td>&gt;86</td>
<td>1 (50.0 (1.3–98.7))</td>
<td>3 (33.3 (7.5–70.1))</td>
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<tr>
<td>Mean age at onset, years (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>52.4 (13.3)</td>
<td>53.3 (14.3)</td>
</tr>
<tr>
<td>Men</td>
<td>49.3 (12.4)</td>
<td>52.8 (14.3)</td>
</tr>
<tr>
<td>Women</td>
<td>55.2 (13.4)</td>
<td>53.6 (14.3)</td>
</tr>
</tbody>
</table>
Sex distribution per age group seemed to have changed over time only in the age group 26 to 35 years. For this age group, there was a trend toward a greater proportion of women for both Kuopio (P = 0.039) and Utrecht (P = 0.043), but the numbers of patients were small (140 in Kuopio and 133 in Utrecht).

**Age at Onset**
Overall mean age at onset was slightly lower in Kuopio (52.4 years; SD = 13.3 years) than in Utrecht (53.3 years; SD = 14.3 years; P value for difference = 0.051). For men separately, mean age at onset was statistically significantly (P < 0.001) lower in Kuopio (49.3 years; SD = 12.4 years) than in Utrecht (52.8 years; SD = 14.3 years). In contrast, the age at onset for women was statistically significantly higher (P = 0.01) in Kuopio (55.2 years; SD = 13.4 years) than in Utrecht (53.6 years; SD = 14.3 years).

In both hospitals, there was a statistically significant (P < 0.001) increase in mean age at onset between 1986 and 2005: in Kuopio from 50.1 (SD = 13.3) to 55.0 (SD = 13.0) years and in Utrecht from 50.2 (SD = 14.0) to 55.4 (SD = 14.1) years. This increase was mainly due to an increased proportion of the age group 66 to 85 years (in Kuopio, 13.2% to 21.7% and in Utrecht, 13.6% to 22.5%) and a decrease of patients in the age group 26 to 45 years (in Kuopio, 35.1% to 21.7% and in Utrecht, 37.2% to 21.7%). When stratified for sex, both men and women showed a significant increase in age over time at both hospitals (P < 0.001).

**Sites**
The distribution of sites of aneurysms was different between Kuopio and Utrecht (Table 2). In Kuopio, MCA aneurysms were the most frequent (33.1%; 95% CI, 30.9% to 35.3%) followed by AComA aneurysms (31.5%; 95% CI, 29.3% to 33.6%). In Utrecht, the most frequent were AComA aneurysms (38.0%; 95% CI, 35.5% to 40.5%) followed by MCA aneurysms (21.0%; 95% CI, 18.9% to 23.1%). When stratified for sex, the proportion of MCA aneurysms in Kuopio was greatest for women; for men this was the AComA aneurysm. In Utrecht, AComA aneurysms were the most common for both sexes (Table 2). When stratified for age, in Kuopio MCA aneurysms were the most frequent in the age groups 36 to 45 (36.4%), 46 to 55 (35.9%), and 56 to 65 (36.6%) years; in the other age groups, AComA aneurysms

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**Table 2. Aneurysm Characteristics**

| Sites | Kuopio (n=1786) | | | | | | Utrecht (n=1489) | | | |
|-------|----------------|---|---|---|---|---|---|---|---|---|---|---|
|       | Men (% 95%CI) | Women (% 95%CI) | Overall (% 95%CI) | Men (% 95%CI) | Women (% 95%CI) | Overall (% 95%CI) |
| AComA | 39.2 (35.9–2.5) | 24.8 (22.1–27.6) | 31.5 (29.3–33.6) | 46.6 (42.2–51.0) | 33.8 (30.9–36.7) | 38.0 (35.5–40.5) |
| MCA   | 33.0 (29.8–6.2) | 33.2 (30.2–36.1) | 33.1 (30.9–35.3) | 19.4 (15.9–22.9) | 21.7 (19.1–24.3) | 21.0 (18.9–23.0) |
| PCOMA | 6.8 (5.2–8.7) | 17.2 (14.8–9.5) | 12.4 (10.8–13.9) | 11.9 (9.0–14.7) | 19.8 (17.3–22.3) | 17.2 (15.3–19.1) |
| ICA   | 7.4 (5.7–9.4) | 8.7 (7.0–10.7) | 8.1 (6.9–9.5) | 7.4 (5.2–10.1) | 9.9 (8.1–11.9) | 9.1 (7.7–10.6) |
| DACA  | 5.7 (4.2–7.5) | 5.6 (4.2–7.3) | 5.7 (4.6–6.8) | 1.4 (0.6–2.9) | 3.6 (2.5–5.0) | 2.9 (2.1–3.9) |
| VBA   | 7.9 (6.2–9.9) | 10.5 (8.6–12.4) | 9.3 (8.0–10.7) | 13.3 (10.3–16.3) | 11.2 (9.3–13.2) | 11.9 (10.2–13.5) |
| Multiple aneurysms | 26.2 (23.2–29.2) | 28.0 (25.1–30.8) | 27.2 (25.1–29.2) | 11.2 (8.5–14.0) | 16.6 (14.3–18.9) | 14.8 (13.0–16.6) |

CI: Confidence interval; AComA: Anterior communicating artery; MCA: Middle cerebral artery; PCOMA: Posterior communicating artery; ICA: Internal carotid artery; DACA: Distal anterior cerebral artery; VBA: Vertebrobasilar artery

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**Figure 1.** Sex distribution over time in Kuopio.
were the most common. For the Utrecht cohort, the AComA was the most prevalent site for all age groups (ranging from 29.0% to 40.6%). The distribution of sites did not change significantly from 1986 to 2005 in Kuopio ($P=0.267$) or Utrecht ($P=0.337$; Figure 3).

Number of Aneurysms
The proportion of patients with multiple aneurysms was higher in the Kuopio (27.2%; 95% CI, 25.1% to 29.2%) than in the Utrecht (14.8%; 95% CI, 13.0% to 16.6%; Table 2) cohort. In Kuopio, multiple aneurysms were as frequent in men (26.2%; 95% CI, 23.2% to 29.2%) as in women (28.0%; 95% CI, 25.1% to 30.8%). In Utrecht multiple aneurysms were more frequent in women (16.6% (95% CI, 14.3% to 18.9%) than in men (11.2%; 95% CI, 8.5% to 14.0%). When stratified by age group, no significant differences were found in Kuopio or Utrecht.

In Kuopio the distribution of the number of aneurysms remained stable during the study period ($P=0.158$; Figure 4). In Utrecht the proportion of patients with multiple aneurysms increased from 8.8% (95% CI, 5.2% to 13.7%) in 1986 to 1990 to 17.0% (95% CI, 13.7% to 20.2%) in 2001 to 2005 ($P=0.023$; Figure 4). The proportion of multiple aneurysms remained higher in Kuopio during the study period.

Discussion
A main finding of our study was that the preponderance of female patients was less marked in Kuopio than in Utrecht. In the early years, the sex distribution in Kuopio was equal; at the end of the study period, however, there was a slight female preponderance, but even at that time the female preponderance was less than that in Utrecht. Second, patients in Kuopio were younger than in Utrecht, and this difference did not change during the study period. Third, MCA aneurysms and multiple aneurysms were more common in Kuopio than in Utrecht.

In a recent review on the incidence of SAH, a female preponderance was found in all regions where incidence studies had been performed. In other studies in Scandinavia, a female preponderance was also found; in a study from Sweden in the period 1987 to 2002, women outnumbered men, and during this period a decline in incidence was found for both women and men. In other regions of Finland, incidence was also higher in women than in men, and no...
increase was found in female incidence in the period 1972 to 1991. During the study period, a female preponderance emerged in the Kuopio region.

The convergence of the sex distribution in this relatively short study period could be explained by changes in female smoking habits, alcohol use, and hypertension because these are important risk factors for SAH. During the mid-1970s, major community-based programs commenced in Finland that aimed to diminish the incidence of cardiovascular diseases. As a result, the prevalence of cardiovascular risk factors changed. First, diastolic blood pressure decreased for both sexes. Second, the proportion of male daily smokers declined and the proportion of female smokers doubled. Third, between 1980 and 2005, there was a sex convergence with an increase of the proportion of female drinkers and an unchanged proportion of male drinkers. The yearly alcohol consumption is comparable between Finland and the Netherlands, but the proportion of drinkers is smaller in Finland. Also, binge drinking is often described as a distinctive drinking habit in Finland. The proportion of young female binge drinkers increased. Therefore, in Finland the high-risk profile of men decreased and that of women increased.

In the Netherlands, alcohol consumption and the incidence of hypertension remained fairly stable and smoking declined, more in men than in women. The incidence of cardiovascular diseases halved between 1970 and 2004 for both sexes. The decline for men was strongest in the age group 40 to 79 years and for women in the age group 60 to 80 years. Thus, the risk profile in the Netherlands for both men and women declined synchronously during the study period. This might explain why the sex distribution did not change in Utrecht, whereas it changed in Kuopio.

Mean age at onset of SAH increased at both centers, most probably because of aging populations or, to a lesser extent, to detection bias or a change in referral policy. However, age at onset was lower in Kuopio throughout the study period for both men and women and did not change despite changes in the prevalence of risk factors.

Because no change was found in the sites and number of aneurysms during the study period, the differences between centers are difficult to explain by smoking habits, alcohol use, and hypertension because these factors changed considerably in Finland during the study period. The differences in the sites and number of aneurysms may therefore be explained by an inherent component. The rise in multiplicity found in Utrecht can be best explained by enhanced diagnostic imaging or growing attention of the importance of searching for more aneurysms besides the ruptured one. In the first half of the study period in Utrecht, angiography of the vertebral arteries was performed only in cases of a negative carotid angiogram, a pattern of hemorrhage suggestive of a posterior circulation aneurysm, or in patients with a carotid aneurysm who were <60 years of age. Thus, additional aneurysms of the posterior circulation may have been undetected in a proportion of patients. Since 1995, however, CTA (including the posterior circulation) has been routinely performed in all patients admitted with SAH. Even in the second half of the study period, multiple aneurysms were more common in Kuopio, which can therefore no longer be explained by detection bias.

The genetic structure of the Finnish population has been described extensively as less diverse than others with different explanations, such as limited immigration and the formation of small, isolated communities in the inlands. Furthermore, the incidence of familial SAH and recessive inherited diseases is higher in Finland than in most Western countries. Genetic differences may have contributed to differences in aneurysm characteristics, rather than the changed risk factors in both countries.

A strong point of our study is the use of 2 large, prospectively collected databases of consecutive SAH patients during a 20-year period. The opportunity to compare a Finnish cohort of aSAH patients with a cohort in a country that resembles most Western countries gives a unique opportunity to investigate possible contributors to the differences. Our study also has some limitations. Data for this study were derived from 2 cohorts of patients admitted to referral centers in Kuopio and Utrecht. Because we cannot exclude detection and referral biases, the data may not be representative of “Finish” and “Dutch” patients in
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The higher proportion of patients with multiple aneurysms in Utrecht than in Kuopio and that this difference may be explained by changes in environmental factors. The younger age at onset, the higher proportion of MCA involvement, and the higher proportion of patients with multiple aneurysms in Kuopio may be related to inherent genetic differences between the Finnish and Dutch populations. Genetic studies on aneurysm characteristics may shed further light on these issues.

We conclude that a female preponderance is more marked in Utrecht than in Kuopio and that this difference may be explained by changes in environmental factors. The younger age at onset, the higher proportion of MCA involvement, and the higher proportion of patients with multiple aneurysms in Kuopio may be related to inherent genetic differences between the Finnish and Dutch populations. Genetic studies on aneurysm characteristics may shed further light on these issues.

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Disclosures

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