Sex-Related Clustering of Intracranial Aneurysms Within Families

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Background and Purpose—Family history is an important risk factor for intracranial aneurysms (ICA), but the pattern of inheritance is unsettled. If ICA within families would cluster according to sex, this may have implications for risk prediction and screening advice within families. We assessed the relationship between the sex of probands and their affected first-degree relatives (FDRs) within families with ICA.

Methods—We used data from our prospectively collected database of families with known familial ICA. We calculated relative risks for a female affected proband having a female affected FDR as compared with a male affected proband having female affected FDR with corresponding 95% confidence intervals.

Results—We included 148 families with 376 affected FDR. For a female proband the relative risk for having a female affected FDR compared with a male proband having an affected female FDR was 1.2 (95% confidence interval, 1.0–1.6).

Conclusions—The clustering of ICA within families is greater in women than in men, with an excess of affected female FDR in female probands. However, because this excess is modest, our findings indicate that sex is not a relevant factor in risk prediction or screening advice in families with ICA. (Stroke. 2015;46:00-00. DOI: 10.1161/STROKEAHA.115.008798.)

Key Words: intracranial aneurysm subarachnoid hemorrhage

A positive family history is an important risk factor for aneurysmal subarachnoid hemorrhage (aSAH) and intracranial aneurysms (ICA), with familial clustering occurring in ≈10% of patients with aSAH.1 Serial screening for ICA is recommended for individuals with 2 affected first-degree relatives (FDRs).2 Sex is another risk factor with a higher prevalence of ICA and higher incidence of aSAH in women than in men.3,4 Whether the clustering of ICA within families occurs according to sex is unknown. Such sex-related clustering may have implications for risk prediction and screening advice within families. Therefore, we determined the relationship between the sex of affected probands and the sex of affected FDR within families with ICA.

Methods

Study Population

From the prospectively collected database of a consecutive series of families with familial ICA at the Department of Neurology and Neurosurgery of the University Medical Center Utrecht, we used all available information from April 1993 up to January 2014. A positive family history was defined as ≥2 affected FDR (parents, siblings, and children) with definite or probable aSAH1 or unruptured ICA. The episodes of aSAH were defined on the basis of history and if available on medical records that were retrieved from our or other hospitals. Unruptured ICA had to be diagnosed by computed tomography, MR, or conventional angiography. Patients with autosomal-dominant polycystic kidney disease were excluded (n=4).

Data Collection

We constructed pedigrees and determined the affected proband and the affected FDR of the proband for each family. The affected proband was defined as the first family member diagnosed with aSAH or unruptured ICA based on family history. Affected FDRs of the families were stratified according to sex of the proband and were grouped according to their relation to proband.

Data Analysis

To assess the relationship of the sex of affected probands and the sex of affected FDR within families, we calculated relative risks (RRs) with corresponding 95% confidence intervals for a female affected proband having a female affected FDR as compared with a male affected proband having female affected FDR. In addition, we calculated RR and 95% confidence interval for the subset of probands and FDR with aSAH, thus excluding those probands and FDR with unruptured ICA. By that we assessed whether larger clustering of aSAH and ICA within families in women as compared with men might have been influenced by a larger proportion of women undergoing screening as compared with men. Both analyses were performed for all affected FDR together but also by subdividing the affected FDR according to their type of family relation to the proband, being parents, siblings, or children.

Results

We included 148 families with a total of 376 FDR of whom 148 were designated as affected probands and the remaining 228 family members as affected FDR. Of the 148 probands, 107 were women (72.3%) and 142 had an episode of aSAH. Of the 228 affected FDR, 153 were women (67.1%), 148 had aSAH, and 80 unruptured ICA.
**Table 1. Relationship Between the Sex of Affected Probands and the Sex of Affected First-Degree Relatives Within Families With Intracranial Aneurysm**

<table>
<thead>
<tr>
<th>Relative</th>
<th>Female (n=172)</th>
<th>Male (n=56)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother</td>
<td>14/16 (88%)</td>
<td>2/2 (100%)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Siblings</td>
<td>66/95 (69%)</td>
<td>17/32 (53%)</td>
<td>1.3 (0.9–2.0)</td>
</tr>
<tr>
<td>Sister</td>
<td>41/61 (67%)</td>
<td>13/22 (59%)</td>
<td>1.1 (0.8–1.9)</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daughter</td>
<td>121/172 (70%)</td>
<td>32/56 (57%)</td>
<td>1.2 (1.0–1.6)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and RR, relative risk.

For a female proband the RR for having a female affected FDR as compared with a male proband having a female affected FDR was 1.2 (95% confidence interval, 1.0–1.6; Table 1). When including only probands and FDR who had aSAH the RR is comparable: RR 1.2 (95% confidence interval, 1.0–1.8; Table 2). The RRs of the analyses subdividing the affected FDR according to their type of family relation to the proband were also comparable although no longer statistically significant (Tables 1 and 2).

**Discussion**

Our results show a sex-related clustering within families with ICA with affected female probands having a higher risk of having female affected FDR as compared with male probands having female affected FDR.

We found 1 previous Finnish study showing no effect of sex on the transmission but also no preponderance of female patients within the 126 families analyzed. As in other populations such a preponderance of female patients within families exists this may explain that no effect of sex on the transmission was found in the Finnish.

Our observed sex-related clustering within families with ICA may be influenced by female hormone levels, alone or by interaction with genetic risk factors. Because hypertension is a risk factor for both sporadic and familial aSAH and heritability for hypertension through the female line has been described, hypertension might also contribute to the sex-related clustering. We are not able to study the contribution of hypertension to the observed sex-related interactions because we have no systematically collected information on hypertension in our probands and FDR.

The strength of this study was the large number of families analyzed all included from a single center. Our study also has limitations that need to be addressed. First, details on family history may be inaccurate because part of the information about family history was obtained from patients or relatives and the accuracy of self-reporting of a familial history of aSAH is not optimal. However, the potential imprecision in reporting family history is unlikely to be related to the sex of the proband. Second, women may be more likely to undergo screening than men, which could potentially have led to an over-representation of women with unruptured ICA identified at screening. However, we excluded that such an over-representation of women influenced our findings, because we found comparable results by only including probands and FDR with aSAH and thus excluding those with unruptured ICA.

Although we found clustering of aSAH and unruptured ICA within families according to female sex, the effect is small from a clinical standpoint of view. Thus, sex is not a relevant factor in risk prediction or screening advice in families with ICA. Further studies on the interaction between environmental risk factors such as smoking and hypertension and female hormones with genetic determinants of ICA may reveal more insight into why aSAH and ICA cluster according to female sex.

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**Disclosures**

None.

**References**

multiplex Finnish families. *Stroke*. 2003;34:1370–1374. doi: 10.1161/01.STR.0000072822.35605.8B.


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