Repeated Screening for Intracranial Aneurysms in Familial Subarachnoid Hemorrhage

Marieke J.H. Wermer, MD; Gabriël J.E. Rinkel, MD, FAHA; Jan van Gijn, MD, FRCP, FRCPE

Background and Purpose—In families with ≥2 first-degree relatives with subarachnoid hemorrhage (SAH), screening for aneurysms is often recommended. The benefit of repeated screening and the interval at which screening should be performed are unknown. We studied patient compliance and the yield of repeated screening for familial intracranial aneurysms.

Methods—Relatives with familial SAH screened between 1990 and 1997 were advised to return every 5 years for follow-up screening with MR angiography. If neurosurgical clipping had been performed in the past, screening was done with CT angiography. We analyzed the results for the group as a whole and for the subgroups of relatives with and without previous aneurysms.

Results—Of 129 relatives who were advised to undergo further screening, 27 did not return, 74 had 1 repeated screening, and 28 had a second repeated screening. We detected 10 new aneurysms in 9 of the 102 screened relatives (9%), 3 of the 19 relatives with previous aneurysms (16%), and 6 of the 83 relatives without previous aneurysms (7%). One of the 9 subjects with a new aneurysm and 1 other relative had an SAH 3 years after a negative screening procedure.

Conclusions—In persons with familial occurrence of aneurysms, the motivation for repeated screening every 5 years is high and the yield is considerable, particularly in relatives who have been treated for aneurysms in the past. The occurrence of SAH <5 years after a negative screen suggests that screening may have to be repeated at shorter intervals.

Key Words: cerebral aneurysm • computed tomography • magnetic resonance angiography • subarachnoid hemorrhage

Familial clustering occurs in ≈10% of patients with subarachnoid hemorrhage (SAH).1,2 The risk of SAH in family members with ≥2 first-degree relatives with SAH or unruptured aneurysms is not exactly known. Presumably, this risk is higher than in first-degree relatives of patients with sporadic SAH, who already have a 3- to 7-fold-higher risk of SAH than the general population.3

The yield of screening in persons with ≥2 affected relatives is high; in ≈8%, an aneurysm is found.4,5 According to the guidelines of the American Heart Association, screening should be considered in such relatives.6 Because aneurysms are not congenital but develop over time, the issue of repeated screening should be considered.6,7 Repeated screening often is already performed in clinical practice, but the yield of repeated screening and the interval at which screening should be performed have never been properly assessed.

We assessed the yield of repeated screening in members of families with familial SAH by investigating the proportion of relatives who returned for repeated screening, number of newly detected aneurysms, time of detection, and characteristics of relatives with new aneurysms.

Subjects and Methods
All patients with SAH and their relatives who attend our hospital for screening are recorded in a database. We retrieved from this database all relatives who were screened for familial intracranial aneurysms between 1990 and 1997; they were all advised to undergo follow-up screening. Familial SAH was defined as ≥2 first-degree relatives (parents, siblings, children) known to have SAH or unruptured aneurysms. The advice for follow-up screening at an interval of 5 years was given to the relatives after the initial screening and was included in a letter to the family physician about the result of this initial screening. Relatives were told that they would not be invited for follow-up screening but that they had to make an appointment at the outpatient clinic at their own initiative. We did not recommend follow-up screening in relatives from ≈65 years of age because the benefit of screening at 70 years of age would probably not exceed the risk of preventive treatment.

From 1993, relatives who had not previously been treated for aneurysms were screened with MR angiography (MRA). If neurosurgical clipping had been performed in the past, screening was done with CT angiography (CTA). If an aneurysm was detected on CTA or MRA, catheter angiography was performed for confirmation of the CTA or MRA findings and for planning the optimal treatment, ie, surgical clipping or endovascular coiling. Aneurysms <4 mm in patients without previous SAH were followed up with MRA or CTA over time.
We recorded how many relatives visited our outpatient clinic for repeated screening. If relatives had not returned 6 years after the initial screening, we classified them as nonattendants. Relatives who had not returned after 5 years but had not passed the 6-year interval were classified as pending because some relatives contacted us between 5 and 6 years after the initial screening. For all relatives who had not returned for follow-up screening, we contacted the family physician to find out if the person was still alive, had had an SAH after the initial screening procedure, or had been screened elsewhere.

We classified the newly developed aneurysms as de novo (aneurysm located at a site that previously showed no abnormalities), regrowth (aneurysm located at the site of an originally treated aneurysm), or additional (in relatives with previous aneurysms in whom the second aneurysm was seen in retrospect but had not been identified on initial screening with MRA or CTA). We constructed pedigree trees for all families. The characteristics of relatives with new aneurysms in terms of degree of kinship, age, sex, and previous SAH or unruptured aneurysms were compared with those of relatives without aneurysms detected on repeated screening. We calculated proportions and relative risks with corresponding confidence intervals for the group as a whole and for the subgroups with and without previous aneurysms (ruptured or unruptured).

Results
In total, 129 relatives in 26 families with familial SAH had been advised to undergo follow-up screening every 5 years. Of these 129 relatives, 102 (79%; 42 men, 60 women) from 19 families actually returned for repeated screening. The mean age of the those screened at the time of the initial contact was 37 years (range, 18 to 62 years). The mean number of relatives per family was 5 (range, 1 to 17). Of the 102 relatives, 57 were siblings of affected relatives, 33 were children, 10 had an affected parent and an affected sibling, 1 was a parent, and 1 had an affected parent and an affected child. One relative was known to have autosomal dominant polycystic kidney disease. Nineteen relatives had been treated for aneurysms in the past, 11 after SAH and 8 for an asymptomatic aneurysm. Seventy-four relatives had a single follow-up investigation; 28 had 2 follow-up screens. The total follow-up time between the initial screen and the first follow-up screen was 552.3 years (5.4 years per relative). The total follow-up time between the first and second repeated screens was 104.3 years (3.7 years per relative). Of the 27 relatives who had not returned, 8 were pending. All 27 relatives were found to be alive; 1 of them had been screened in a hospital closer to her residence, reportedly with normal results. Twenty-six had no SAH after the initial screening; for 1 relative, this information was lacking. The characteristics of the relatives who did not return for screening were similar to those of the patients who did return except that only 1 of the 27 nonattendants had been treated for an aneurysm in the past.

New Aneurysms Detected With Screening
At follow-up screening, we detected 10 aneurysms in 9 of the 102 repeatedly screened family members (9%). Of the 10 detected aneurysms, 3 were treated with coiling and 3 with clipping. No complications occurred during treatment, and all treated patients had a good recovery. The remaining 4 aneurysms were <4 mm and are followed up over time. In all patients, the angiogram performed after the positive screening confirmed the findings on MRA or CTA. In the patient with 2 new aneurysms, the second was initially not detected on CTA but was found on the angiogram performed for the other new aneurysm (Table 1, patient 7). The number of relatives needed to screen per 5 years to find 1 aneurysm was 13. The characteristics of the 9 subjects and the newly developed aneurysms are shown in Table 1.

Relatives Without Previous History of SAH or Unruptured Aneurysms
Six of the 10 new aneurysms were found in 6 of the 83 relatives without previous aneurysms (7%). In 3 patients, a new aneurysm was detected at the first follow-up investigation in 3 patients and at the second in 3 patients. One of the aneurysms detected at the second visit was in retrospect visible on the MRA 5 years before but not on the initial MRA; in the interval, it had grown from 4 to 9 mm. In another patient, an aneurysm found on the first follow-up screen could in retrospect be identified on the initial MRA; this aneurysm had grown from 5 to 7 mm over a period of 6 years.

**TABLE 1. Location of Aneurysms and Characteristics of Patients With Newly Detected Aneurysms**

<table>
<thead>
<tr>
<th>No</th>
<th>Birth year</th>
<th>Sex</th>
<th>History of SAH or UA</th>
<th>Degree of Kinship</th>
<th>Year of Initial Screen</th>
<th>Result</th>
<th>Year of First Follow-Up</th>
<th>Result</th>
<th>Year of Second Follow-Up</th>
<th>Result</th>
<th>Aneurysm Classification</th>
<th>Size, mm</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1945</td>
<td>F</td>
<td>No</td>
<td>Sib + child</td>
<td>1993</td>
<td>Negative</td>
<td>1997</td>
<td>Negative</td>
<td>P com A</td>
<td>De novo*</td>
<td>9×5</td>
<td>Coiling</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1945</td>
<td>F</td>
<td>No</td>
<td>Sib</td>
<td>1995</td>
<td>Negative</td>
<td>2001</td>
<td>MCA A</td>
<td>...</td>
<td>De novo</td>
<td>7</td>
<td>Coiling</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1972</td>
<td>F</td>
<td>No</td>
<td>Child</td>
<td>1990</td>
<td>Negative</td>
<td>1995</td>
<td>Negative</td>
<td>Basilar A</td>
<td>De novo</td>
<td>3</td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>4†</td>
<td>1957</td>
<td>F</td>
<td>No</td>
<td>Sib</td>
<td>1995</td>
<td>Negative</td>
<td>2000</td>
<td>Negative</td>
<td>MCA A</td>
<td>De novo</td>
<td>2</td>
<td>Clipping</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1950</td>
<td>F</td>
<td>No</td>
<td>Sib</td>
<td>1995</td>
<td>Negative</td>
<td>2003</td>
<td>MCA A</td>
<td>...</td>
<td>De novo</td>
<td>3</td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1949</td>
<td>M</td>
<td>No</td>
<td>Sib</td>
<td>1995</td>
<td>Negative</td>
<td>2000</td>
<td>P com A</td>
<td>...</td>
<td>De novo</td>
<td>4</td>
<td>Clipping</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1956</td>
<td>F</td>
<td>UA</td>
<td>Sib</td>
<td>1996</td>
<td>4 MCA A</td>
<td>2001</td>
<td>A com A</td>
<td>Additional</td>
<td>3×4</td>
<td>Follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clipping</td>
</tr>
<tr>
<td>8</td>
<td>1949</td>
<td>F</td>
<td>SAH</td>
<td>Sib</td>
<td>1993 SAH</td>
<td>A com A</td>
<td>2001</td>
<td>ICA A</td>
<td>...</td>
<td>De novo</td>
<td>5</td>
<td>Coiling</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1929</td>
<td>M</td>
<td>SAH</td>
<td>Sib</td>
<td>1980 SAH</td>
<td>MCA A</td>
<td>1993</td>
<td>MCA A</td>
<td>Negative</td>
<td>Regrowth</td>
<td>15</td>
<td>Clipping</td>
<td></td>
</tr>
</tbody>
</table>

UA indicates unruptured aneurysm; Sib, sibling; P com A, aneurysm of the communicating posterior cerebral artery; MCA A, aneurysm of the middle cerebral artery; Basilar A, aneurysm of the basilar artery; A com A, aneurysm of the communicating anterior cerebral artery; and ICA A, aneurysm of the internal carotid artery.

†Patient 4 had an SAH in 1998 from an aneurysm of the anterior communicating artery despite negative screening in 1995 (Figure 1).
Intracranial Aneurysms

Risk Factors for Development of New Familial Aneurysms

A history of ruptured or unruptured aneurysms was associated with a relatively high risk of the development of new aneurysms. A new aneurysm developed in 3 of the 19 relatives (16%) with previous aneurysms and 6 of the 83 relatives (7%) without previous aneurysms. Women had a higher risk than men for developing aneurysms, and siblings had a higher risk than children and parents (Table 2).

Discussion

We found that the yield of repeated screening for familial intracranial aneurysms is high; new aneurysms were detected in 16% of the relatives with previous aneurysms and in 7% of the relatives without previous aneurysms, mostly within 5 years. In addition, 2 relatives had an SAH in the 5-year interval between 1 screening procedure: 1 from a newly developed aneurysm and 1 from an additional aneurysm that was missed on the initial angiogram and the first follow-up screen. These results indicate that persons with aneurysms had a high risk for the development of new aneurysms. There was trend for an increased risk of new aneurysm formation in relatives with a previous aneurysm, women, siblings, and relatives between 40 and 60 years of age, but these results were not statistically significant. Because we had no data on smoking habits and hypertension in most of the relatives, we were not able to assess the impact of these risk factors in our study.

Seventy-nine percent of the relatives who were advised to return for follow-up screening actually returned. This proportion is high. We could not find attendance rates of comparable screening programs in other medical fields. One explanation for the high compliance might be pressure on the relatives from other family members. The motive for the nonattendance remains unknown because we considered it unethical to contact them and ask why they did not return for screening.

TABLE 2. Relative Risk for the Development of New Aneurysms or Aneurysms Detected After Growth in Subgroups of Relatives

<table>
<thead>
<tr>
<th>Subgroup of Relatives</th>
<th>Relatives, n</th>
<th>Relatives With New Aneurysms, n (%) [95% CI]</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous aneurysm</td>
<td>83</td>
<td>6 (7) [CI 3–16]</td>
<td>Reference</td>
</tr>
<tr>
<td>Previous aneurysm</td>
<td>19</td>
<td>3 (16) [CI 4–40]</td>
<td>2.2 (0.6–8.0)</td>
</tr>
<tr>
<td>Children*</td>
<td>44</td>
<td>2 (5)</td>
<td>Reference</td>
</tr>
<tr>
<td>Siblings*</td>
<td>67</td>
<td>7 (10)</td>
<td>2.3 (0.5–10.6)</td>
</tr>
<tr>
<td>Parents*</td>
<td>2</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>Men</td>
<td>42</td>
<td>2 (5)</td>
<td>Reference</td>
</tr>
<tr>
<td>Women</td>
<td>60</td>
<td>7 (12)</td>
<td>2.6 (0.6–11.8)</td>
</tr>
<tr>
<td>Age &lt;40 y†</td>
<td>60</td>
<td>4 (7)</td>
<td>Reference</td>
</tr>
<tr>
<td>Age 40–60 y</td>
<td>40</td>
<td>5 (13)</td>
<td>1.9 (0.5–6.6)</td>
</tr>
<tr>
<td>Age &gt;60 y</td>
<td>2</td>
<td>0</td>
<td>...</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.
*Cumulative number because relatives can be classified into >1 category.
†Age at initial screening.
In our study, we tried to avoid any bias. All relatives were informed and treated the same way, and only 1 nonattendant was partly lost to follow-up (We knew she was alive but had no information on whether she had a SAH after the initial screening). In addition, relatives of a large number of families were screened, which increases the generalizability of the results.

This is the first study to assess the yield of repeated screening in a large series of subjects with ≥2 first-degree relatives with SAH or unruptured aneurysms. Three decision analyses have been performed on the issue of screening for familial aneurysms, but none has specifically or properly addressed repeated screening in persons with ≥2 affected first-degree relatives.8–10

Screening for aneurysms carries benefits and risks. Screening can prevent new episodes of SAH but can lead to disability and death from preventive treatment. With the ongoing improvement in MRA and CTA techniques, more small aneurysms will be detected that will often not be treated but followed up over time. The knowledge of having an untreated aneurysm will negatively influence quality of life.11 On the other hand, with the advent of endovascular treatment, many unruptured aneurysms can now be treated with relatively low risk of complications.12 The outcome after sporadic SAH is still very poor and probably is even worse in familial cases.13 Until now, no population-based clinical study has assessed the risk and benefits or the cost-effectiveness of repeated screening in familial SAH. The high yield of repeated screening in this study is a factor in favor of screening and indicates that repeated screening should be considered for every relative in familial SAH.

The appropriate interval at which repeated screening should be performed has not yet been established. It is often assumed that aneurysms need some years to develop. In our study, 2 relatives were admitted for SAH within 3 years after a negative screening. Others have reported a member of a family with intracranial aneurysms in whom SAH occurred only 2 years after a negative angiography.14 These 3 examples show that screening at an interval of 5 years is not sufficient to detect all new familial aneurysms. In some families, screening may have to be performed at intervals shorter than an arbitrary period of 5 years. The follow-up interval may have to be tailored to individual relatives according not only to the family but also to individual risk factors. Smoking, hypertension, and female sex are important risk factors for the growth and development of intracranial aneurysms.15 Although we are not yet able to identify all characteristic features indicating high risk of rapid aneurysm formation, individual risk factors should be taken into account in determining the interval of repeated screening.

We conclude that repeated screening for familial intracranial aneurysms has a high yield, especially in relatives with previous SAH. The attendance for repeated screening is high. The interval at which screening should be performed remains uncertain and may have to be tailored according to phenotype, genotype, and additional risk factors.

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