Incidence of Recurrent Subarachnoid Hemorrhage After Clipping for Ruptured Intracranial Aneurysms

Marieke J.H. Wermer, MD; Paut Greebe, RN; Ale Algra, MD, FAHA; Gabriël J.E. Rinkel, MD, FAHA

Background and Purpose—Because intracranial aneurysms develop during life, patients with subarachnoid hemorrhage (SAH) and successfully occluded aneurysms are at risk for a recurrence. We studied the incidence of and risk factors for recurrent SAH in patients who regained independence after SAH and in whom all aneurysms were occluded by means of clipping.

Methods—From a cohort of patients with SAH admitted between 1985 and 2001, we included those patients who were discharged home or to a rehabilitation facility. We interviewed these patients about new episodes of SAH. We retrieved all medical records and radiographs in case of reported recurrences. If patients had died, we retrieved the cause of death. We analyzed the incidence of and risk factors for recurrent SAH by Kaplan-Meier curves and Cox regression analysis.

Results—Of 752 patients with 6016 follow-up years (mean follow up 8.0 years), 18 had a recurrence. In the first 10 years after the initial SAH, the cumulative incidence of recurrent SAH was 3.2% (95% confidence interval [CI], 1.5% to 4.9%) and the incidence rate 286 of 100 000 patient-years (95% CI, 160 to 472 per 100 000). Risk factors were smoking (hazard ratio [HR], 6.5; 95% CI, 1.7 to 24.0), age (HR, 0.5 per 10 years; 95% CI, 0.3 to 0.8) and multiple aneurysms at the time of the initial SAH (HR, 5.5; 95% CI, 2.2 to 14.1).

Conclusions—After SAH, the incidence of a recurrence within the first 10 years is 22 (12 to 38) times higher than expected in populations with comparable age and sex. Whether this increased risk justifies screening for recurrent aneurysms in patients with a history of SAH requires further study. (Stroke. 2005;36:2394-2399.)

Key Words: cerebral aneurysm ■ epidemiology ■ subarachnoid hemorrhage

The prevalence of intracranial aneurysms under the age of 20 is very low and increases thereafter.1 This suggests that aneurysms are not congenital but develop during life. The development of aneurysms during life and the presence of multiple aneurysms in up to 30% of patients with subarachnoid hemorrhage (SAH) indicate that patients who have had an aneurysm are at risk for developing new aneurysms.2

In patients with SAH and clipping of all detected aneurysms, new aneurysms can develop at a new location (de novo) or at the clip site (regrowth).3-7 In addition, some aneurysms might have been missed at the angiogram at the time of the SAH. The International Study of Unruptured Intracranial Aneurysms (ISUIA) study showed that the rupture risk of small unruptured aneurysms in patients with a previous SAH from another aneurysm is higher than in patients with similar aneurysms but without a history of SAH.8 The ongoing development of aneurysms and higher rupture risks after a previous episode of SAH suggest that patients with a history of SAH are at considerable risk of a new SAH.

We performed a long-term follow-up study in a large cohort of patients who regained independence after SAH and in whom all detected aneurysms had been occluded by means of clipping. We determined the incidence of and the risk factors for a recurrent episode of SAH.

Methods

Patients
From a database of patients admitted to the University Medical Center Utrecht with SAH, we selected all patients admitted between 1985 and 2001 who met the following inclusion criteria: (1) subarachnoid hemorrhage confirmed by computed tomography (CT) or lumbar puncture; (2) presence of a saccular aneurysm confirmed by conventional angiography or CT-angiography; (3) clipping of the ruptured aneurysm and all additional aneurysms; (4) age at time of SAH ≥20 years; and (5) discharge to home or a rehabilitation facility. Patients who were discharged to a nursing home and patients with one or more aneurysms left untreated were not included.

Follow Up
After approval of the ethical committee of our hospital, we contacted the general practitioner of all eligible patients to know if the patient was still alive. If patients had died, we asked for the date and the cause of death. If a patient had died in a hospital or other facility, we reviewed the medical records. Subsequently, we sent a letter to all patients who were still alive. In this letter, patients 70 years of age or
younger were invited to the outpatient clinic. For patients older than 70 years, we announced a telephone call. If a patient had no phone number or an ex-directory one, we sent another letter asking the patient to contact us. At the outpatient clinic or during the telephone interview, we asked the patients about new episodes of SAH. For all patients, we retrieved data on sex, age, family history of intracranial aneurysms, smoking habits, alcohol use, history of hypertension, and number of aneurysms at the time of the initial SAH.

Recurrent Subarachnoid Hemorrhage

For patients who reported new episodes of SAH, we retrieved all medical data from the hospital where patients had been treated and reviewed all CT scans of the brain and all angiograms of the intracranial vessels of the initial episode if available and of the recurrence. New episodes of SAH were defined as SAH proven by CT, lumbar puncture, or autopsy after treatment of all aneurysms that had been found at the time of the initial SAH. On basis of surgery reports, CT scans and angiograms, autopsy reports, or—if patients died before CT-angiography could be performed—by a pattern of hemorrhage on CT highly suggestive for the site of rupture, we categorized patients into: (1) aneurysm located at a site remote from the original clipped aneurysm, (2) aneurysm located at the same site as the original clipped aneurysm, or as (3) unclassified if patients died before CT-angiography could be performed and the site of rupture could not be derived from the hemorrhage pattern. The aneurysms at other sites than the clip were subdivided in (1) de novo (aneurysm not visible on the initial CT-angiogram at the time of the SAH); (2) additional (aneurysm visible in retrospect but not identified on the initial CT-angiogram); or (3) possible de novo (when the CT-angiogram at time of SAH was not available for review, but the aneurysm was not described in the radiology report). The aneurysms located at the clip were classified as (1) regrowth (postoperative angiogram showed complete clipping of the aneurysm); (2) remnant (postoperative angiogram showed incomplete clipping of the aneurysm); or (3) possible regrowth (when no postoperative angiogram was performed).

Patients with a history suggestive of aneurysmal rupture but without confirmation of the diagnosis because they had died before reaching hospital were classified as sudden death probably as a result of recurrent SAH. A history was classified as suggestive for aneurysmal rupture if we had an eyewitness account of a sudden severe headache before onset of coma. Patients with sudden loss of consciousness not proceeded by acute headache or patients who were found dead were not classified as suggestive for aneurysmal rupture.

Data Analysis

The risk for recurrent SAH was assessed by survival analysis. We calculated the incidence rate per 100,000 patient-years and the cumulative incidence at 5, 10, and 15 years with corresponding 95% confidence intervals (CIs) for recurrent SAH and sudden death probable as a result of recurrent SAH combined and for recurrent SAH separately. If patients had died during the follow-up period, were lost to follow up, or were admitted to a nursing home, they were censored at that point of time.

We calculated incidence rate ratios with corresponding 95% CIs by dividing the incidence rate in our population by a population-based incidence rate of SAH. This population incidence rate was derived from a population in Australia and New Zealand with a comparable age and sex distribution was 13 per 100,000. In the population-based study, the incidence rate derived from a population in Australia and New Zealand with a comparable age and sex distribution was 13 per 100,000. The risk of a subarachnoid hemorrhage in our population was 13 per 100,000. In the population-based study, the incidence rate derived from a population in Australia and New Zealand with a comparable age and sex distribution was 13 per 100,000. The risk of a subarachnoid hemorrhage in our population was therefore 22 (95% CI, 12 to 38) times higher compared with the population based incidence (Table 2).9

The cumulative incidence of new episodes in the first 10 years after the index SAH was 3.2% (95% CI, 2.8% to 5.3%). Adjustments were made for differences in sex distribution. We used Cox regression to calculate hazard ratios (HRs) and corresponding 95% CIs of baseline characteristics associated with the risk of recurrent SAH. Again, we performed the analyses for recurrent SAH and sudden death probable as a result of recurrent SAH combined and for recurrent SAH separately. The following factors were included in the analyses: age at time of SAH (categorical per 10 years), sex, smoking (dichotomous current vs former plus never smokers and categorical), family history of intracranial aneurysms (defined as one or more first-degree relative[s] with a verified aneurysm or a history suggestive of SAH), history of hypertension (dichotomous), and number of aneurysms at the time of SAH (dichotomous: one versus multiple). We performed univariate Cox regression analysis for all risk factors and multivariate Cox regression analysis with forward selection of variables with probability values <0.20 in the univariate analysis.

Results

Patients

Between 1985 and 2001, 930 patients survived after SAH and were successfully treated for the ruptured aneurysm. One hundred fifty-four did not meet the inclusion criteria (Figure 1). Of the 776 remaining patients, 24 (3%) could not be contacted. The total follow up of the 752 patients included in the study was 6016 years with a mean period of follow up of 8.0 years (range, 0.2 to 20.1 years). During the follow-up period, 107 patients had died. In 10 patients, the cause of death was a recurrent SAH. Seven patients died suddenly before reaching the hospital, of whom 2 had a history suggestive of SAH. Other causes of death were cancer (21); cardiovascular disease (19); infectious diseases (9); other causes, including dementia, trauma, renal failure (14); or unknown (27). In addition, during follow up, 23 patients were censored because they moved abroad (6) or were admitted to a nursing home (17). The baseline characteristics of the 752 patients are listed in Table 1.

Recurrent Subarachnoid Hemorrhage

A new episode of SAH had occurred in 18 (2.4%; 95% CI, 1.5% to 3.8%) of the 752 patients during the follow-up period. The incidence rate in our patients for the first 10 years after SAH was 286 per 100,000 (95% CI, 160 to 472 per 100,000). In the population-based study, the incidence rate derived from a population in Australia and New Zealand with a comparable age and sex distribution was 13 per 100,000. The risk of a subarachnoid hemorrhage in our population was therefore 22 (95% CI, 12 to 38) times higher compared with the population based incidence (Table 2).9

The cumulative incidence of new episodes in the first 10 years after the index SAH was 3.2% (95% CI, 1.5% to 4.9%) for all certain recurrences (Figure 2 and Table 2). When the 2 patients with sudden death probable as a result of SAH were included the cumulative incidence was 3.5% (95% CI, 1.8% to 5.3%).

In the 18 patients with a recurrent SAH after successful treatment, 19 recurrent aneurysms were found: 13 patients had an aneurysm located at a new location, 3 patients had an aneurysm located at the clip site from the previous operation, one patient had both an aneurysm located at a new location and an aneurysm located at the clip site, and one patient had an unclassified aneurysm. Of the 14 patients with aneurysms at a new location, the CTA or angiogram was available for review in 8 patients: 4 aneurysms were certain de novo aneurysms and 4 were classified as additional. The remaining 6 aneurysms were classified as possible de novo aneurysms. Of the 4 patients with an aneurysm at the clip site all were classified as possible regrowths.

The mean interval between the initial SAH and the recurrence was 6.5 years (range, 0.2 to 17 years). We found no recurrent SAH from a (possible) de novo or regrowth aneurysm within the first 33 months after operation.
Risk Factors for Recurrent Subarachnoid Hemorrhage

In the univariate Cox regression analysis for recurrent SAH, significant risk factors were age (HR, 0.6 per 10 years; 95% CI, 0.4 to 0.9), a verified history of familial SAH (HR, 3.8; 95% CI, 1.1 to 13.2), current smoking (HR, 4.8; 95% CI, 1.3 to 17.4), and the presence of multiple aneurysms at time of the SAH (HR, 5.7; 95% CI, 2.3 to 14.5). Gender (HR, 0.4 for men; 95% CI, 0.1 to 1.3) was not a statistically significant risk factor but had a probability value >0.2 and was therefore also included in the multivariate analysis. In the multivariate forward Cox regression analyses, current smoking (HR, 6.5; 95% CI, 1.7 to 24.0), age (HR, 0.5 per 10 years; 95% CI, 0.3 to 0.8), and the presence of multiple aneurysms at time of the SAH (HR, 5.5; 95% CI, 2.2 to 14.1) were statistically significant risk factors. In the Cox regression analysis for recurrent SAH, including sudden death probable resulting from SAH, the same risk factors were detected in both the univariate as the multivariate analysis with comparable hazard ratios in the multivariate analysis.

Discussion

We found that in patients who had recovered to an independent state after an episode of aneurysmal SAH and in whom all detected aneurysms were treated by means of clipping, the risk of a recurrence the first 10 years after treatment is 22 times higher than the risk of SAH in a healthy cohort with comparable age and sex. Independent risk factors for subse-
subarachnoid hemorrhage (SAH), including sudden death possibly resulting from SAH; IR Study Group, incidence rate in the study population; IR Population, incidence rate estimated for a population with a comparable age and sex distribution; Incidence Rate Ratio, the incidence rate observed for the study population divided by the incidence rate observed in the population-based study.

<table>
<thead>
<tr>
<th>Time After Initial SAH</th>
<th>Re-SAH (95% CI)</th>
<th>Re-SD-SAH (95% CI)</th>
<th>IR Study Group per 100 000 Patient-Years (95% CI)</th>
<th>IR Population per 100 000 Patient-Years (95% CI)</th>
<th>Incidence Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y</td>
<td>1.0% (0.3%–1.8%)</td>
<td>1.2% (0.4%–2.1%)</td>
<td>207 (63–426)</td>
<td>13 (10–18)</td>
<td>16 (7–34)</td>
</tr>
<tr>
<td>10 y</td>
<td>3.2% (1.5%–4.9%)</td>
<td>3.5% (1.8%–5.3%)</td>
<td>286 (160–472)</td>
<td>13 (10–18)</td>
<td>22 (12–38)</td>
</tr>
<tr>
<td>15 y</td>
<td>4.6% (1.9%–7.2%)</td>
<td>4.9% (2.2%–7.6%)</td>
<td>287 (167–460)</td>
<td>13 (10–18)</td>
<td>22 (13–38)</td>
</tr>
</tbody>
</table>

Re-SAH indicates cumulative incidence recurrent subarachnoid hemorrhage; Re-SD-SAH, cumulative incidence recurrent subarachnoid hemorrhage, including sudden death probably resulting from SAH; IR Study Group, incidence rate in the study population; IR Population, incidence rate derived from a population in Australia and New Zealand with a comparable age and sex distribution; Incidence Rate Ratio, the incidence rate observed for the study population divided by the incidence rate observed in the population-based study.

We compared the incidence of recurrent SAH in our study with a large population-based study on the incidence of SAH in Australia and New Zealand.9 We chose this study as comparison because it is a recent study with over 1.7 million patient-years of follow up and data are reported for men and women separately in different age groups. The SAH incidence in this study was comparable with an incidence study performed between 1978 and 1980 in The Netherlands and with the incidence of SAH found in a meta-analysis of 15 studies from populations other than Finland and Japan.12,13 In Finland and Japan, the SAH incidences are higher than in other countries (around 20 per 100 000 patient-years).13–15 In our study, the incidence of recurrent SAH was 286 per 100 000. Thus, even if we compare our incidence of recurrences with relatively high incidences of SAH as in Finland.
or Japan, the difference between the incidence in the population and the incidence of recurrent SAH is impressive and is included within the limits of the confidence interval of our estimate (incidence rate ratio, 22; 95% CI, 12 to 38).

There are some limitations of our study that need to be acknowledged. Although the number of patients lost to follow up in our study was very small (3%), we did not have follow up for all patients. Furthermore, in 27 patients, the exact cause of death was unknown, and an additional 5 patients died suddenly of unknown cause. If some or all of these patients would have had a subarachnoid hemorrhage, the actual recurrence rate is higher than the one observed in our study. Conversely, if none of the patients who were lost to follow up had a recurrence, we have slightly overestimated the rate of recurrent SAH by not including the follow-up years of these patients.

In 4 patients, the recurrence was caused by an aneurysm at the clip site. Unfortunately, a postoperative angiogram was not performed in these patients. In some patients, the aneurysm might have been incompletely clipped. Even after surgery by experienced neurosurgeons, neck remnants are found in nearly 10% of the cases. We therefore cannot exclude that some patients had small remnants of the initial ruptured aneurysm.

We excluded patients who were discharged to a nursing home because consent for follow up in these patients is in general hard to obtain because most of these patients have severe cognitive deficits. Moreover, from a clinical point of view, the risk of recurrence is less relevant for such patients. Our results therefore apply only to patients discharged home or to a rehabilitation center, which will in general be a younger population than the patients discharged to a nursing home. Whether our results can be generalized to coiled patients is unclear. One can assume that the formation rate and rupture risk of de novo aneurysms in coiled patients is comparable with that in clipped patients. The number of regrowth aneurysms or remnants caused by impaction of coils, however, may be higher than by clipping and therefore these patients are possibly even at a higher risk of a recurrence.

The high risk of a recurrent SAH indicates that having an SAH is not a single event in a lifetime. New aneurysms have previously been found in up to 16% of the patients with a history of SAH. Screening for aneurysms in these patients might be effective, but screening also has disadvantages. Screening carries the risks of angiography and preventive treatment, especially in older patients. In addition, not all aneurysms will be treated, and the knowledge of having an untreated aneurysm has a negative effect on the quality of life of these patients. Moreover, screening also has psychosocial consequences. Thus, whether a regular screening program for detection of new aneurysms is beneficial for patients who survived after treatment for SAH requires careful weighing of the pros and cons, for example, in a decision analysis.

Acknowledgments

This study was supported by an established clinical investigator grant from the Netherlands Heart Foundation to G.J.E.R. (grant D98.014) and a grant from the Netherlands Organization for Scientific Research/ZonMw (grant 945-02-007).

References


Incidence of Recurrent Subarachnoid Hemorrhage After Clipping for Ruptured Intracranial Aneurysms
Marieke J.H. Wermer, Paut Greebe, Ale Algra and Gabriël J.E. Rinkel

Stroke. 2005;36:2394-2399; originally published online October 6, 2005;
doi: 10.1161/01.STR.0000185686.28035.d2

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/36/11/2394

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/