The familial risk of subarachnoid haemorrhage

Graham M. Teasdale,1 Joanna M. Wardlaw,3 Philip M. White,1,3 Gordon Murray,4 Evelyn M. Teasdale2 and Valerie Easton3 on behalf of the Davie Cooper Scottish Aneurysm Study Group

1University Department of Neurosurgery and 2Department of Neuroradiology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, 3University of Edinburgh, Division of Clinical Neurosciences, Western General Hospital and 4University of Edinburgh, Public Health Sciences, Medical School, Edinburgh, UK

Correspondence to: Professor J. M. Wardlaw, Division of Clinical Neurosciences, Western General Hospital, Crewe Rd, Edinburgh EH4 2XU, UK
E-mail: joanna.wardlaw@ed.ac.uk

Relatives of people with aneurysmal subarachnoid haemorrhage (SAH) may be at increased risk of SAH, but precise data on the level of risk and which relatives are most likely to be affected are lacking. We studied two samples: 5478 relatives of patients from the whole of Scotland who had a SAH in one year and 3213 relatives of patients with a SAH admitted to the West of Scotland regional neurosurgical unit 10 years previously. Overall, 2% of all relatives in each sample had a SAH. In the Scotland-wide sample, the absolute lifetime risk of SAH (from birth to 70 years) was higher for first-degree relatives [4.7%; 95% confidence interval (CI): 3.1–6.3%] than for second-degree (1.9%; 95% CI: 1.0–2.9%). In the West of Scotland sample, the lifetime risks were very similar to the Scotland-wide sample. The 10-year prospective risk for first-degree relatives alive at the time of the index patient’s SAH was 1.2% (95% CI: 0.4–2%) and for second-degree was 0.5% (95% CI: 0.1–0.8%). There was a trend for risk to be highest in families with two first-degree relatives affected and lowest with only one second-degree affected. Most living relatives of patients who suffer a SAH are at low absolute risk of a future haemorrhage; screening is inappropriate except for the few families in whom two or more first-degree relatives, i.e. index case plus one extra have been affected.

Keywords: subarachnoid haemorrhage; intracranial aneurysm; familial risk; epidemiology; screening

Abbreviations: CHI = Community Health Index; CI = confidence interval; ISD = Scottish Office Information and Statistics Division; MRA = magnetic resonance angiography; SAH = subarachnoid haemorrhage


Introduction

Subarachnoid haemorrhage (SAH) affects eight to ten per 100 000 persons per year (Linn et al., 1996). Most are due to intracranial aneurysm rupture, with 25–50% dying as a result. Most deaths are due to the initial bleed and its immediate complications (Hop et al., 1997). Consequently, there is considerable interest in the identification and treatment of aneurysms prior to rupture. It is possible that relatives of SAH patients may be at increased risk of SAH.

Since the first report of SAH in several members of a family (O’Brien et al., 1942), at least 10 studies have examined the occurrence of haemorrhage and/or the prevalence of unruptured aneurysms amongst relatives of SAH patients and included some indication of the closeness of relative (Table 1) (Norrgard et al., 1987; Bromberg et al., 1995; Schievink et al., 1995; Wang et al., 1995; De Braekeleer et al., 1996; Ronkainen et al., 1997; Raaymakers and MARS Study Group, 1999; Gaist et al., 2000; Okamoto et al., 2003; Wills et al., 2003). The list includes mostly large studies and highlights some methodological differences and problems in such studies. Study methods varied: some were retrospective—studying families of patients who had their SAH in a defined prior time period (Norrgard et al., 1987; Schievink et al., 1995; De Braekeleer et al., 1996; Ronkainen et al., 1997), five were prospective, i.e. studying families of patients presenting in the study period (Bromberg et al., 1995; Wang et al., 1995; Raaymakers and MARS Study Group, 1999; Okamoto et al., 2003; Wills et al., 2003), three were case-controlled (Wang et al., 1995; De Braekeleer et al., 1996; Okamoto et al., 2003), and others observed a population (Gaist et al., 2000). Seven were of patients with a SAH admitted to hospital (Norrgard et al., 1987; Bromberg et al., 1995; De Braekeleer et al., 1996; Ronkainen et al., 1997; Raaymakers and MARS Study Group, 1999; Gaist et al., 2000; Okamoto et al., 2003; Wills et al., 2003), two were...
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of index subjects</th>
<th>City/country</th>
<th>Number of relatives surveyed</th>
<th>Number of relatives with SAH</th>
<th>% with SAH</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norrgard et al., 1987</td>
<td>485</td>
<td>Umea, Sweden</td>
<td>1352 (siblings only)</td>
<td>22</td>
<td>4.7</td>
<td>Siblings only surveyed – average six per index case</td>
</tr>
<tr>
<td>Wang et al., 1995</td>
<td>149/171†</td>
<td>Washington, USA</td>
<td>N/S</td>
<td>18</td>
<td>11.4</td>
<td>OR for SAH in 1° relative = 1.8, 2° = 2.4; P = NS</td>
</tr>
<tr>
<td>Shievink et al., 1995</td>
<td>76/81†</td>
<td>Rochester, USA</td>
<td>N/S</td>
<td>11</td>
<td>1.8</td>
<td>RR of SAH in 1° relative = 4.14 (2.06–7.4), 2° = 1.6 compared with general population</td>
</tr>
<tr>
<td>Bromberg et al., 1995</td>
<td>163</td>
<td>Utrecht, Netherlands</td>
<td>1290</td>
<td>10 + 7*</td>
<td>1%</td>
<td>RR of SAH in 1° relative = 4.7, 2° = 2.1, 3° = 1.1 compared with general population</td>
</tr>
<tr>
<td>De Braekeleer et al., 1996</td>
<td>533 ( +1599 controls)</td>
<td>Quebec, Canada</td>
<td>N/S</td>
<td>48</td>
<td>77</td>
<td>RR of SAH in 1° relative = 6.6 (95% CI 2–21) definite and 2.7 (95% CI 1.4–5.5) possible SAH</td>
</tr>
<tr>
<td>Ronkainen et al., 1997†</td>
<td>91</td>
<td>Kuopio, E. Finland</td>
<td>←716 relatives in total (1°, 2° and 3°) → 76 ←37 → 10.6+</td>
<td>Risk of having unruptured aneurysm in 1° or 2° relative 4× higher than general population +23 (3.7%) 1° relative had an unruptured aneurysm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raaymakers and MARS Study Group, 1999†</td>
<td>160/193</td>
<td>Utrecht, Netherlands</td>
<td>626</td>
<td>4</td>
<td>0.6</td>
<td>SI 2.9 (95% CI 1.9–4.6), 4.5 for 77% cases admitted to neurosurgical unit</td>
</tr>
<tr>
<td>Gait et al., 2000</td>
<td>6175</td>
<td>Denmark (1977–1995)</td>
<td>14 781</td>
<td>19</td>
<td>0.1</td>
<td>OR for SAH in 1° relatives = 4.0</td>
</tr>
<tr>
<td>Okamoto et al., 2003</td>
<td>200</td>
<td>Nagoya, Japan</td>
<td>N/S</td>
<td>29</td>
<td>/</td>
<td>Genetic study; 27 cases per affected family</td>
</tr>
<tr>
<td>Wills et al., 2003</td>
<td>346</td>
<td>Kuopio, Helsinki, Finland</td>
<td>N/S</td>
<td>359</td>
<td>51</td>
<td></td>
</tr>
</tbody>
</table>

*Definite + possible SAH; †number surveyed/total sample available; †included relatives with SAH or unruptured aneurysm; †screened relatives of patients admitted to neurosurgical unit with MRA; + = % of all relatives, not just first degree; N/S = not stated; OR = odds ratio; RR = relative risk; SI = standardized incidence compared with general population. 1° = first-degree; 2° = second-degree; 3° = third-degree. / = data not sought.
Familial risk of SAH

Methods and participants

The project was conducted jointly by the Neurosciences Departments in Glasgow and Edinburgh and involved all Scottish regions and hospitals, and virtually all general practices. Approval was obtained from:

(i) the Multicentre Research Ethics Committee for Scotland (MREC);
(ii) the local Research Ethics Committees of all Area Health Boards;
(iii) the Scottish Office Information and Statistics Division (ISD) Privacy Advisory Committee;
(iv) the Directors of Public Health in Scotland for access to the Community Health Index (CHI), which holds the address of all patients registered with general practitioners;
(v) the National Health Service Central Registry (NHSCR) for access to death certificates;
(vi) each consultant recorded as having responsibility for patients with a SAH for inclusion of their patients in the study;
(vii) the patients’ general practitioners.
(viii) the patients themselves or next of kin.

The ISD (http://www.isdscotland.org) is a central records office which records data on all hospital admissions, discharges and diagnoses, and the cause of all deaths occurring whether in or out of hospital.

Two sample populations were identified: (i) a Scotland-wide sample; and (ii) a West of Scotland sample. The Scotland-wide sample consisted of index cases identified through the ISD as having had a SAH between 1 July 1994 and 30 June 1995. This sample provided index cases across the whole country, whether or not the patient had been admitted to hospital (i.e. those dying outside or failing to reach hospital were included). The West of Scotland sample was obtained from a database compiled prospectively in the West of Scotland Regional Department of Neuroradiology, Glasgow, of all patients admitted to the Regional Neurosurgical Unit with SAH in 1986 and 1987. This sample provided index cases in whom the diagnosis of SAH was known to have been established with a high degree of certainty by CT scanning or lumbar puncture, and an opportunity to study the prospective risk in the subsequent 10-year period for their relatives who were alive in 1986/87.

In the Scotland-wide sample, initially we identified 1530 episodes from ISD records using quite broad International Classification of Disease (ICD) codes for SAH (431) and also codes for sudden death (798.5, 7989, 6749) with a potential diagnosis of SAH in the index year. For patients coded as sudden death, we checked the death certificates for any evidence that the death could have been SAH and excluded the patient if the cause was not SAH. Because the ISD codes each hospital admission individually, we removed entries for transfers between hospitals for the same disease episode and readmissions after discharge for complications of the same disease episode in order to identify individual disease episodes. After eliminating multiple hospital episodes per patient and using more specific codes for aneurysmal SAH (ICD 9430, 431, 4329, 4373), 1039 true index cases remained. The West of Scotland Neuroradiology database identified 370 patients admitted to the West of Scotland Regional Unit with a final diagnosis of SAH in 1986 and 1987.

For each patient, the diagnosis of SAH (on ISD code) was validated by comparison with the original records at the hospital where the patient was admitted for positive confirmation of the diagnosis of SAH (including identifying results of a CT scan showing blood in the subarachnoid space, CSF examination showing xanthochromia using a validated laboratory technique, an angiogram showing an intracranial aneurysm, or post mortem findings). The diagnosis was confirmed by consulting the patients’ general practitioners for further details of the final diagnosis (e.g. documentation of an operation to treat an aneurysm in a hospital discharge letter). Patients in whom we were unable to confirm the diagnosis of SAH by this process were excluded.

The current address of the index patient or next of kin was obtained using a predefined systematic search strategy and interrogating medical records, the Community Health Index and the NHS Central Registry. The patients’ general practitioners were also contacted to seek reasons that it might not be appropriate to approach the patient (if alive) or the next of kin if the patient had died.

From the Scotland-wide sample, 428 out of 1039 (41%) of the apparently eligible index cases were not approached because of:

(i) inability to trace a correct address through central records, general practitioner or CHI (238 cases);
(ii) not a SAH on review of hospital and general practice records (ISD coding error—90 cases);
(iii) advice from the GP that contact was not appropriate for reasons of patient sensitivity (59 cases);
(iv) miscellaneous other reasons (e.g. the patient moving with no forwarding address or the SAH being traumatic and not aneurysmal—41 cases).

In the West of Scotland population, 103 out of 370 (28%) were not contacted, the main reasons being a failure to trace them (59 cases) or advice from the GP that contact was inappropriate (16 cases), not a SAH (10 cases), and miscellaneous other reasons as above (18 cases). In other words, a similar proportion of the two populations were not contactable because of incorrect contact details (22% in the Scotland-wide sample and 20% in the West of Scotland population).

An information pack was devised which explained the study background and objectives, and included a request to take part in the...
study, a questionnaire booklet, clear definitions of all the descriptive and medical terms used, and a family tree template. The pack was evaluated for clarity and validity by staff members and patients with prior SAH in the Edinburgh and Glasgow patient self help groups (BASIC).

First-degree relatives were defined as parent, brother or sister, or children. Second-degree relatives were defined as grandparents, siblings of parents (i.e. uncles, aunts), or grandchildren. The questionnaires asked the index patient to provide as much information as possible about each of their first- and second-degree relatives including; date of birth (or age if not known), history of stroke or SAH (and, if so, the approximate date or age at which it had occurred) and, if deceased, the date and cause of death. A family tree template was provided to help patients give as much information as possible on all first and second degree relations, and to ensure that data were correctly entered against each relative by the study investigators.

Questionnaires were posted to the patient or next of kin if the patient was known to have died. Non-responders received a follow-up letter and, if possible, were contacted by telephone. Incomplete questionnaires were also followed up by letter or phone (if possible) to obtain as complete data as possible. The information returned from index cases was further validated by cross-checking with information held on those relatives by centralized Scottish records (ISD). The ethics regulations did not allow us to approach relatives directly.

From the 611 (64%) of the 949 correctly coded and approachable index cases in the Scotland-wide study, 305 booklets were returned (50% of those sampled, 32% overall), yielding 5478 relatives. Of the 267 booklets (72% of index cases) sent to West of Scotland families, 148 were returned (55% of those sampled, 40% overall), yielding information on 3213 relatives. Amongst the patients to whom booklets were not sent (428 in the Scotland-wide and 103 in the West of Scotland samples), 54% and 49% of patients, respectively, were dead (of any cause) compared with the 611 and 267 patients to whom booklets were sent, of whom 28% and 25%, respectively, were dead. Amongst the 611 patients in the Scotland-wide sample to whom booklets were sent, only 23% were returned from index cases known to have died (of any cause) compared with 59% from those still alive. Amongst the 370 patients in the West of Scotland sample to whom booklets were sent, only 24% were returned from index cases known to have died compared with 65% from those still alive. There was therefore a systematic bias towards better survey returns from index cases who were still alive at the time of the survey.

Booklets were checked for completeness and consistency, and entered into two identical, encrypted, password-protected, specifically designed databases—one for the Scotland-wide data and for the West of Scotland data. As we were not able to access data on patients whom we had not been able to approach (for whatever reason) or who had not returned a booklet, we had very limited information to determine whether the sample who did return booklets were different to those who did not. The only information available to us was whether the patient had died or not.

Statistical methods

Two strategies were used in the analysis: (i) one retaining all data and interpolating to account for missing data; and (ii) removing at the outset any relative with missing data, e.g. on whether alive or dead, time of death, whether or not a SAH had taken place.

To estimate the lifetime risk of SAH, observation began with the birth of the index case’s relative and ended with that relative suffering a SAH, or being censored at death from other causes, or at the end of the study period, i.e. 31 December 1999. Relatives with unknown date of birth (not even the year) had to be removed from the initial data bank of 8691 (5478 + 3213) relatives before any survival analysis could be done. This left 4117 relatives for analysis from the Scotland-wide and West of Scotland sample combined. The survival curves are based on Kaplan–Meier estimates and the hazard ratios were derived by fitting Cox proportional hazard regression models.

Results

Study populations

Amongst all the index patients, 885 out of 1406 (63%) were female, consistent with the increased risk of SAH in females.

In the Scotland-wide sample, of the 5478 relatives identified, ~half (2772) were male, and 3195 (58%) were still alive at the time of the survey; 1931 (35%) were first-degree and 3547 (65%) second-degree relatives. Age distributions were very similar in first- and second-degree relatives, but less information on age was available for second-degree relatives (34% missing compared with 8% for first-degree relatives). Ninety-five relatives (2%) had had a SAH (Table 2), of whom 56 out of 95 (59%) were first degree, 52 out of 95 (55%) were female, and 24 were still alive at the time of the survey.

Of the 3213 relatives identified in the West of Scotland sample, 1656 (52%) were male, 1968 (61%) were still alive at the time of the survey, 1092 (34%) were first-degree relatives and 2121 (66%) were second-degree relatives. Fifty-seven relatives (2%) had had a SAH (Table 2), of whom 54% were first degree, 32 out of 57 (56%) were female and 10 were still alive at the time of the survey. At the time the West of Scotland index patients suffered their SAH in 1986/87, 2606 (81%) of the relatives had been alive. Over the next 10 years, 20 relatives (0.8%) suffered a SAH, of whom 12 died (five due to the SAH, three due to a stroke or other cerebrovascular incident not thought to be a SAH, and four from other causes). Information on the date of birth was available for 15 out of 20; these could be used in the estimates of 10-year prospective risk.

Survival analysis

The estimates of lifetime risk of SAH obtained from the two samples are shown in Table 3. Retaining as much information as possible, the estimated relative hazard of having a SAH in their lifetime for first-degree versus second-degree relatives in the Scotland-wide sample was 2.29 [95% confidence interval (CI): 1.36–3.87]. Using only cases with complete data yielded very similar estimates; thus, only those results based on retaining all possible information are reported in Table 3. The corresponding result using all available data from the West of Scotland sample for first-degree versus second-degree relatives was 2.43 (95% CI: 1.01–5.87). There was no
statistically significant effect of gender on the risk of SAH in either analysis, although the confidence intervals were wide.

Retaining as much information as possible in the Scotland-wide sample, the estimated absolute risk of SAH from birth to age of 70 years was 4.7% (95% CI: 3.1–6.3%) for first-degree relatives and 1.9% (95% CI: 1.0–2.9%) for second-degree relatives. For the West of Scotland survey, the data for first-degree relatives were 4.2% (95% CI: 2.2–6.1%) and for second-degree relatives 2.3% (95% CI: 0.8–3.9%). Very similar estimates were obtained using only cases with complete data.

The estimates of absolute lifetime risk come from a survival analysis where deaths from other causes are censored. These estimates of lifetime risk do not have a simple direct interpretation, and relatively less weight should be placed on these analyses than on the estimated relative hazard for first-degree relatives compared with second-degree relatives and estimates of absolute prospective 10-year risk.

### Prospective 10-year risk of SAH

Using data from the West of Scotland sample, the estimated absolute 10-year prospective risk of SAH for a first-degree relative was 1.2% (95% CI: 0.4–2.0%); the corresponding figure for a second-degree relative was 0.5% (95% CI: 0.1–0.8%) (Table 4). These figures can be compared with the widely quoted figure for incidence of SAH in the general population of 8–10 per 100 000 per year (Linn et al., 1996) or ~0.1% prospective 10-year risk. Thus, in a first-degree relative, the risk is increased ~12-fold and, in a second-degree relative, 5-fold compared with the general population (although the absolute risk remains low).

### Involvement of multiple family members

The West of Scotland population was used to investigate further whether, in families with more than one member with SAH, any particular kinship was more frequent than others (Table 4). The families in which the index case in 1986/87 was the first known SAH (first group) were compared with families in which a member had already suffered a SAH before 1986/87 (second group). Within the first group, first-degree and second-degree relatives were compared. Amongst the second group, comparisons were made between the families with at least two first-degree relatives having a SAH, and those with one first-degree and at least one second-degree and, finally, those with no first-degree relative involved but at least two second-degree relatives with SAH. There was an ascending absolute risk of SAH (Table 4), lowest for people with only one second-degree relative affected (0.3%) and highest for people with at least two first-degree relatives involved (7.1%), i.e. a 20-fold increase. However, the confidence intervals were wide and none of the differences were statistically significant. Thirty families were involved in these calculations, in six of which three or more members had had a SAH. These families contained a very small proportion of the total number of relatives.

### Age of relative

Table 5 shows the age at occurrence of SAH among the relatives for whom data of birth or age at death were known from both the Scotland-wide and West of Scotland samples.

Amongst 1908 relatives in the West of Scotland data with known date of birth, adding age to the Cox proportional hazards regression model showed the effect of age to be highly significant ($P < 0.001$). However, this entire analysis is based on only 15 instances of SAH amongst relatives, as any relatives without a known date of birth did not contribute to the regression analysis, and so it is not possible to establish the exact relationship between age and risk.

---

**Table 2** Number of relatives who suffered a SAH in Scotland and West of Scotland samples according to relationship to index patient

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of index patients</th>
<th>Number of index patients with affected relatives</th>
<th>Number (%) of affected relatives and relationships to index patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Parent not sibling</td>
<td>Sibling not parent</td>
</tr>
<tr>
<td>Scotland-wide</td>
<td>305</td>
<td>78</td>
<td>95 (26%)</td>
</tr>
<tr>
<td>West of Scotland wide</td>
<td>148</td>
<td>39</td>
<td>57 (19%)</td>
</tr>
</tbody>
</table>

**Table 3** Estimate of risk (with 95% CIs) of occurrence of a SAH in a member of a family of a patient with a SAH

<table>
<thead>
<tr>
<th>Relative risk of SAH</th>
<th>Scotland-wide sample</th>
<th>West of Scotland sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree versus second-degree relationship</td>
<td>2.29 (1.36–3.87)</td>
<td>2.43 (1.01–5.87)</td>
</tr>
<tr>
<td>Lifetime (70 year) risk of SAH</td>
<td>First-degree</td>
<td>4.7% (3.1–6.3%)</td>
</tr>
<tr>
<td></td>
<td>Second-degree</td>
<td>1.9% (1.0–2.9%)</td>
</tr>
<tr>
<td>10-year prospective risk</td>
<td>First-degree</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Second-degree</td>
<td>–</td>
</tr>
</tbody>
</table>

---
Validation of the patient’s history by ISD

Amongst 8961 relatives, ISD were able to identify 37% as having had a hospital admission in Scotland for any reason or who had died. Thus, of 152 relatives identified by the index patient’s family history as having had a SAH, 34 were confirmed by ISD and 118 were not. In 96 out of 118 (81%), the SAH had occurred before 1981 (when record linkage began) or had no date of SAH and thus could have been prior to 1981. Twenty-two SAHs (according to the patient history) occurred after 1981, but were not confirmed by ISD (in most cases because the relative could not be matched to central data).

Discussion

The main finding from our study is the low absolute risk of SAH among the relatives of patients who have suffered a SAH. Overall, 2% of relatives in both study samples had an SAH. For most first-degree relatives, our best estimate of the absolute risk is in the region of 1% per decade above the age of 20, with an upper 95% confidence limit of 2%. This low absolute risk, although some ten times more than in the general population, coupled with the uncertainty about the merits of intervention on an unruptured aneurysm (Raaymakers et al., 1998; Wiebers et al., 2003), does not support routine screening of the intracranial vasculature of family members of most patients with a SAH. The exception may be the occasional instances where someone already has two affected first-degree relatives for whom we found the risk to be greatest, as in previous work (Bromberg et al., 1995). In these patients, the optimum age to start, and the frequency of, screening are uncertain, although a recent study suggested repeated screening every five years in patients at high risk (Wermer et al., 2003).

Table 4 Ten-year prospective risk estimate (%) of SAH by relationship to index case amongst 2601 relatives alive and SAH-free at the time of the Index SAH

<table>
<thead>
<tr>
<th>Number of events</th>
<th>Risk of SAH over 10 years (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>People with at least two first-degree relatives (including the index case) who have had a SAH.</td>
<td>4</td>
<td>7.1</td>
</tr>
<tr>
<td>People with one first-degree relative and at least one other second-degree relative (the index case) who have had a SAH</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>People with no first-degree relative with a SAH, but with at least two second-degree relatives who have had a SAH</td>
<td>1</td>
<td>1.1</td>
</tr>
<tr>
<td>People with one first-degree relative (the index case), but no other first- or second-degree relative affected by SAH</td>
<td>7</td>
<td>0.8</td>
</tr>
<tr>
<td>People with only one second-degree relative</td>
<td>6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Table 5 Occurrence of SAH in relatives of different ages at the time that another family member has a SAH

<table>
<thead>
<tr>
<th>Band</th>
<th>Number of relatives’ years free of SAH</th>
<th>Number of relatives with SAH</th>
<th>% events in ‘at risk’ relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scottish-wide sample</td>
<td>91–100 years</td>
<td>211</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>81–90 years</td>
<td>1868</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>71–80 years</td>
<td>5653</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>61–70 years</td>
<td>10 726</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>51–60 years</td>
<td>16 186</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>41–50 years</td>
<td>21 207</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>31–40 years</td>
<td>26 337</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>21–30 years</td>
<td>31 796</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>11–20 years</td>
<td>35 781</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1–10 years</td>
<td>38 996</td>
<td>0</td>
</tr>
<tr>
<td>West of Scotland sample</td>
<td>91–100 years</td>
<td>105</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>81–90 years</td>
<td>870</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>71–80 years</td>
<td>2657</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>61–70 years</td>
<td>5191</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>51–60 years</td>
<td>7917</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>41–50 years</td>
<td>10 257</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>31–40 years</td>
<td>13 498</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21–30 years</td>
<td>16 980</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>11–20 years</td>
<td>20 017</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1–10 years</td>
<td>22 283</td>
<td>0</td>
</tr>
</tbody>
</table>
Strengths

The strengths of our study include: the large number of first- and second-degree relatives surveyed (8691); the careful validation of the accuracy of the SAH diagnosis in patients and relatives where possible; the large number of SAH events found amongst relatives (152, 2%); the inclusion of index cases admitted as well as not admitted to hospital; the prospective 10 year sample; and the striking similarity in the results obtained from our two populations despite them being identified in different ways.

No previous study has used two different approaches to identify two separate samples of relatives from the same overall population. Moreover, none has examined the 10-year prospective risk in living relatives, as well as the lifetime risk. The extremely close comparability of the findings in a survey of all patients diagnosed as having suffered a SAH in a specified time period in Scotland, and in a group admitted to the West of Scotland Regional Neurosurgical Unit, each collected independently and separately in time by 10 years is evidence of the robustness of our findings.

Limitations

The major limitations of our study concern the proportion of index cases who could not be traced or did not respond, and the limited detail available from patients about their relatives. These factors led to information being obtained from only 32% of families from the Scotland-wide survey and 40% of those in the West of Scotland survey (of those initially identified from record coding as possible or probable SAH), although 50% and 55%, respectively, of those actually sent questionnaires. This opens up the potential for bias between the features of families responding and those not surveyed. However, apart from the larger proportion of index patients who had died amongst those not sent questionnaires and amongst those failing to return questionnaires of those sent, we had little information (due to the Data Protection Act) on non-responders to be able to determine whether non-responders were systematically different to responders. We doubt, however, that this produced a major distortion of results. It is likely that any such bias would be for families with more than one member involved to have a higher response rate.

Another limitation concerns the validity and accuracy of the information obtained from respondents on pedigrees and the identification of haemorrhages among relatives. Family histories are not always reliable (Greebe et al., 1997), although we did attempt to overcome difficulties in previous studies by providing a family tree template and telephoneing for further information if the questionnaire was ambiguous. We were limited in how much central tracing of relatives or direct contact with relatives we could do by recent changes in the Data Protection Act. Information on first-degree relatives may be more accurate than for second-degree.

It is likely that all these biases would overestimate risk. The ‘true’ risk, therefore, may be even lower than our estimate.

It was not possible to obtain details of what type of SAH (aneurysmal/non-aneurysmal) the relatives had had; it was clear during the process of refining and testing the questionnaire that requesting this degree of detail might actually impede patient’s willingness to provide any information about their relatives. A final problem was that even by sampling a whole country with good centralized records, the sample of relatives identified with SAH was small, limiting the analyses that we could do to explore associations with degree of relative, age and gender.

Relation to previous studies

Of previous studies (Table 1), only the national, register-based study of Gaist et al. (2000) contained more relatives (14,781), but these yielded only 19 SAH events. De Braekeleer (1996) reported on 176 relatives with a SAH from 53 index subjects, but did not specify the total number of relatives surveyed. Despite differences in study methods and difficulties in making direct comparisons, our results agree broadly with previous reports (Table 1) of an increased risk of SAH among relatives of patients with a SAH. The increase of relative risk in first-degree versus second-degree relatives was 6.6 to 2.7 (Bromberg et al., 1995) in the one previous study that compared first-degree relatives directly with second-degree relatives. Other studies compared risk amongst first-or second-degree relatives with estimates from the general population [first degree: 4.14 fold increase (Schievink, 1995) and 4.7 fold increase (De Braekeleer et al., 1996)]. Our finding that 2% of relatives had a SAH compares with previous reports of between 0.1% (Gaist et al., 2000) and 11.4% (Wang et al., 1995) of SAH patients having at least one first-degree relative with SAH, and for any relative of between 16% (Ronkainen et al., 1997) and 29.8% (De Braekeleer et al., 1996). In contrast, Gaist et al. (2000) reported an occurrence of SAH in only 0.12% of relatives. Assuming a maximum population occurrence of 0.1% per year, our data indicate a ~12-fold increase in first-degree relatives and 5-fold amongst second-degree relatives.

Our finding of an ascending risk according to the number of family members involved and the closeness of relationship is also in accord with previous studies which reported that the most frequent relationship in multiply affected members was between siblings (Wardlaw and White, 2000; Wills et al., 2003). The data we present are the first attempt to estimate the magnitude of the effect of these relationships.

Implications

Our findings do not support systematic screening of families of all patients with SAH, either from a personal or population perspective. Overall, even among first-degree relatives, at most only one in 100 is likely to suffer a SAH within the next 10 years. Such events will account for only a small minority (~0.3%) of instances of SAH in the population. Any benefit from screening and treating an unruptured aneurysm has to be balanced against the mortality and morbidity of treatment (Wiebers
et al., 2003; MARS Group, 1999; Raaymakers and MARS Study Group, 1999). In addition, future SAH could result from rupture of a new aneurysm (Wermer et al., 2003). This view is in accord with the conclusions of Raaymakers and the MARS Study Group (1999), who investigated 626 first-degree relatives of patients with SAH with magnetic resonance angiography (MRA). An aneurysm was found in 4% but, even using an estimated annual risk of rupture of 0.4% (which may be excessive), the increase in life expectancy resulting from treatment was small (0.9 years/person screened) and did not outweigh the risk of post operative sequelae.


Future research

‘Pooling’ of data from separate studies may improve the precision of the estimate of familial risk. Investigation of the merits of screening focused on families containing two or more affected members will be appropriate. The observation that some families have more than one member with SAH raises the possibility of a specific genetic factor in a small proportion of occurrences of SAH (Wills et al., 2003). Alternatively, the presence of many families with only one member with SAH may indicate a gene or genes which confer a general increase in susceptibility but require some other, possibly environmental factor, to manifest the disease.

Acknowledgements

We wish to thank the ISD, Scottish Office, the Directors of Public Health, Scotland, the NHSCR, the many consultants and general practitioners responsible for the index cases, the participants and their families for their co-operation. The study was funded by the British Brain and Spine Foundation from the funds raised by the Scottish Daily Record ‘Davie Cooper’ Appeal. We are grateful to the family of the late Davie Cooper, who was a truly inspired player for Rangers Football Club and the Scotland International Soccer Team.

References


Appendix

The members of the Davie Cooper Scottish Aneurysm Study Group are as follows:


Institute of Neurological Sciences, Glasgow
University Department of Neurosurgery
Professor G. Teasdale
Dr P. White
Ms J. Riddell
Mr K. Lindsay

Department of Neuroradiology
Dr E. Teasdale
Mr S. Sloss

Department of Clinical Neurosciences,
Professor J. Wardlaw
Dr V. Easton

Western General Hospital, Edinburgh
Dr D. Signorini
Mrs A. Leigh Brown

Public Health Sciences,
University of Edinburgh
Professor G. Murray

Medical School

Department of Neurosurgery,
Professor G. Cruickshank
University of Birmingham