How to manage the patient with a family history of aneurysmal subarachnoid haemorrhage

P. M. White
Consultant Neuroradiologist
Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Crewe Road, Edinburgh, EH4 2XU, UK; E-mail: pmw@skull.dcn.ed.ac.uk
Practical Neurology, 2004, 4, 88-103
© 2004 Blackwell Publishing Ltd
INTRODUCTION

‘The truth is rarely pure and never simple’. So said Oscar Wilde, and this is certainly the case for individuals with an unruptured intracranial aneurysm or a family history of aneurysmal subarachnoid haemorrhage (SAH). Before you can counsel these people, it is first necessary for the clinician to have a grasp of this complex area because once you have told the patient something it cannot be untold. You might subsequently expand on the information imparted, but you cannot remove it – correct or incorrect – from the patient’s mind (Fuller 2001). In this article I will summarize the relevant knowledge, and offer some advice, on management in this rather fraught area of medicine.

WHAT IS THE FREQUENCY OF INTRACRANIAL ANEURYSMS IN THE GENERAL POPULATION?

What is anyone’s risk of harbouring an aneurysm, after all incidental aneurysms are commonly found at autopsy? Rinkel et al. identified autopsy studies where the prevalence of unruptured aneurysms ranged from 0.4% to 3.6% for retro and prospective studies, respectively, and in retro and prospective angiography studies from 3.7% to 6%, respectively (Rinkel et al. 1998). More recent studies are more in line with the higher figures from the prospective studies (Kojima et al. 1998; Ronkainen et al. 1998). In a higher-risk group of patients, because they had already ruptured an aneurysm, 20–25% had at least one unruptured aneurysm on angiography (Lozano & Leblanc 1987). So approximately one in 20 of the population aged over 30 harbour an unruptured aneurysm. However, it is important to remember that, with an aneurysmal SAH incidence of about 8 per 100 000 per annum (Wardlaw & White 2000), clearly only a very small proportion of these aneurysms actually rupture (about 0.1–0.2% pa).

ARE SPECIFIC GROUPS AT PARTICULARLY HIGH RISK OF INTRACRANIAL ANEURYSMS?

The risk factors for SAH and for having an unruptured intracranial aneurysm are very similar (Table 1). In addition, several genetic conditions are associated with intracranial aneurysms, although these represent less than 10% of all cases:
- 10–15% of patients with adult polycystic kidney disease (ADPKD) (Rinkel et al.1998), particularly if there is a family history of aneurysms and/or SAH (Hughes et al. 1996; Ruggieri et al. 1994);
- type IV Ehlers–Danlos syndrome (Schievink et al. 1990);
- possibly pseudoxanthoma elasticum (Munyer & Margulis 1981), although this has been refuted (van den Berg et al. 1999);
- hereditary haemorrhagic telangiectasia (Roman et al. 1978);
- neurofibromatosis type I (Mulvihill et al. 1990; Morooka & Waga 1991);
- alpha1-antitrypsin deficiency (Schievink et al. 1996).

Marfan’s syndrome was thought to be associated with aneurysms but a detailed study of 135 patients (mean age 21 years) found no evidence

There are several stages of assessment and management to consider:
- What is an individual’s risk of harbouring an aneurysm?
- How best to detect an aneurysm without exposing the patient to unnecessary stress or risk?
- If an asymptomatic aneurysm is found, what is the risk of rupture?
- What treatment, if any, should be offered and what are the risks involved?

Most importantly, the risk at each stage must be weighed against the risk of not doing anything. The pros and cons of screening for aneurysms will also be briefly considered to place some of this information in context.
of a relationship (van den Berg et al. 1996), although the patients may not have been old enough for the aneurysms to have developed. In addition, aneurysmal SAH may affect several members of a family without any specific genetic ‘disease’. Familial SAH has been defined inconsistently, so here I mean a family in which two or more close blood relatives (first or second degree) have a history of aneurysmal SAH without any other known heritable disease (first-degree relatives = parents, siblings, children; second degree = grandparents, grandchildren, aunts and uncles, nieces and nephews; third degree = cousins, great grandparents, great grandchildren).

It has been suggested that many cases of familial intracranial aneurysms might simply represent accidental aggregation (ter Berg et al. 1992); on the basis of chance alone, each SAH patient has a 5.6% possibility of having a first- to third-degree relative also affected by SAH (ter Berg et al. 1992), and the proportion of SAH patients with third-degree relatives who had had an SAH is the same as the proportion with SAH in the control population (De Braekeleer et al. 1996).

Since 1987, 10 studies have examined the prevalence of unruptured aneurysms and/or SAH amongst relatives of patients with SAH (Table 2). The relative risk for SAH in relatives compared with the background population was 2.9–6.6 for first-degree relatives and 1.6–2.1 for second degree. Whilst these relative risks appear large, it is important to remember the small absolute number of relatives affected: only 156/21054 (0.74%) first-degree relatives were themselves affected by SAH. In our Scottish study (in press) the risk of SAH among family members over the decade after the index case had their SAH was 1.2% for first-degree and 0.5% for second-degree relatives (some 12 and 5 times, respectively, the background population SAH risk) (Wardlaw et al., in press).

Familial intracranial aneurysms may have distinguishing biological features, including: rupture at a younger age (most frequently in the fifth decade compared to the sixth decade for sporadic SAH) (Bromberg et al. 1995); worse clinical outcome; and an increased prevalence of middle cerebral artery aneurysms (Kojima et al. 1998; Bromberg et al. 1995). There may be a younger age of rupture in subsequent generations, implying ‘anticipation’ (International Subarachnoid Aneurysm Trial 2002) but familial aneurysms may also have a predilection towards rupture in the same decade in individuals of the same family, particularly in siblings (Leblanc 1997).

Approximately one in 20 of the population aged over 30 harbour an unruptured aneurysm.
<table>
<thead>
<tr>
<th>STUDY</th>
<th>NUMBER OF INDEX SUBJECTS</th>
<th>LOCATION</th>
<th>NUMBER OF RELATIVES SURVEYED</th>
<th>NUMBER OF RELATIVES WITH SAH</th>
<th>% 1° WITH SAH</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1°</td>
<td>2°</td>
<td>3°</td>
<td>1°</td>
</tr>
<tr>
<td>Norrgard 1987</td>
<td>485</td>
<td>Umea, Sweden (sibs only)</td>
<td>1352</td>
<td>/</td>
<td>/</td>
<td>22</td>
</tr>
<tr>
<td>Wang 1995</td>
<td>149/171†</td>
<td>Washington, USA</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
<td>18</td>
</tr>
<tr>
<td>Schievink 1995</td>
<td>76/81†</td>
<td>Rochester, USA</td>
<td>608</td>
<td>N/S</td>
<td>N/S</td>
<td>11</td>
</tr>
<tr>
<td>Bromberg 1995</td>
<td>163</td>
<td>Utrecht, Netherlands</td>
<td>1290</td>
<td>3588</td>
<td>N/S</td>
<td>10 + 7‡</td>
</tr>
<tr>
<td>de Braekeleer 1996</td>
<td>533 (+ 1599 controls)</td>
<td>Quebec, Canada</td>
<td>N/S</td>
<td>N/S</td>
<td>N/S</td>
<td>48</td>
</tr>
<tr>
<td>Ronkainen§ 1997</td>
<td>91</td>
<td>Kuopio, Finland (1°, 2° and 3°)</td>
<td>716 relatives in total → (2° and 3°)</td>
<td>76</td>
<td>37 relatives in total →</td>
<td>10.6§</td>
</tr>
<tr>
<td>Raaymakers 1999</td>
<td>160</td>
<td>Utrecht, Netherlands</td>
<td>626</td>
<td>/</td>
<td>/</td>
<td>4</td>
</tr>
<tr>
<td>Gaist 2000</td>
<td>6175</td>
<td>Denmark (1977–95)</td>
<td>14781</td>
<td>/</td>
<td>/</td>
<td>19</td>
</tr>
<tr>
<td>Davie Cooper Study</td>
<td>453</td>
<td>Scotland</td>
<td>3023</td>
<td>5668</td>
<td>87</td>
<td>65</td>
</tr>
<tr>
<td>Okamoto 2003</td>
<td>200</td>
<td>Japan</td>
<td>N/S</td>
<td>/</td>
<td>/</td>
<td>29</td>
</tr>
</tbody>
</table>

*Wardlaw in press.
†number surveyed/total sample available.
‡definite + possible SAH.
§relatives with SAH or aneurysm.
¶% of all relatives not just first degree.
OR, odds ratio; RR, relative risk; N/S = not stated
/ = no data.
WHICH RELATIVES ARE MOST FREQUENTLY AFFECTED BY SAH?

In families with more than one person with SAH, the most frequent relationship is index patient to sibling, followed by index patient to parent (Wardlaw & White 2000). However, a parent was affected in only 29% so in less than one-third of affected families was there a clear warning of the potential for SAH from a previous generation. Interestingly, one study found a much stronger familial link to maternal SAH than to paternal or sibling SAH (Okamoto et al. 2003) and in another study, the slightly more commonly affected first-degree relatives were also parents (38%) rather than siblings (33%) (Wardlaw, in press). Only our Scottish study has prospectively investigated the interaction between the type of relationship and involvement of more than one family member (with SAH) on the risk of SAH to the other family members (Table 3). Here, there was a hierarchy of ascending risk from a second-degree relative and no other family members affected (0.3% cumulative lifetime SAH risk) to the highest risk in a member of a family with at least two first-degree relatives affected (7% cumulative lifetime SAH risk) (Wardlaw in press).

HOW BEST TO DETECT AN ANEURYSM?

The gold standard is an intra-arterial digital subtraction angiogram (IADSA) with selective cerebral arterial injections and multiple projections, particularly using the 3D DSA technique (Fig. 1). However, IADSA is invasive, costly, and not without risk of a permanent neurological complication. In patients with SAH, suspected aneurysm or arteriovenous malformation, this risk was 0.07% (Cloft et al. 1999). Non-invasive tests, such as magnetic resonance angiography (MRA), dynamic spiral CT Angiography (CTA) and transcranial Doppler sonography (TCDS) (Fig. 2) are attractive for detecting asymptomatic intracranial aneurysms but they have to be extremely accurate to replace IADSA. So how accurate are they?

Analysis of accuracy per patient rather than per aneurysm is of more clinical relevance to ‘screening’ an individual for aneurysms. Most studies reported apparently excellent results but were in patients with a recent SAH so the aneurysm prevalence was high (Table 4) (White et al. 2000). As a result the sensitivities, specificities and predictive values must be interpreted with caution, particularly if one is extrapolating to using the non-invasive test in a low aneurysm prevalence population where far more positive test results will be false positives. Crucially, the results for non-invasive imaging methods are significantly poorer for aneurysms < 5 mm in size, which constitute as many as one-third of aneurysms in asymptomatic patients (Kojima et al. 1998) (Fig. 3). Sensitivities are in the order of 35%, 57% and 35% for aneurysms < 5 mm diameter for MRA, CTA and TCDS, respectively (White et al. 2001; White et al. 2001) ICA aneurysms are even harder to detect (White et al. 2000, 2001). Ultrasound has the advantage of the lowest capital cost, and portability, and with contrast agents and 3-D imaging the accuracy may improve towards the level of CTA/MRA (Wardlaw & White 2000). Unfortunately, about 10% of patients will not have an adequate bone window and the technique is operator dependent.

Table 3

<table>
<thead>
<tr>
<th>FAMILY HISTORY OF SAH</th>
<th>NUMBER OF SAH EVENTS OCCURRING</th>
<th>CUMULATIVE SAH RISK (BIRTH TO 70 YEARS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One second-degree relative with SAH</td>
<td>6</td>
<td>0.3%</td>
</tr>
<tr>
<td>One first-degree relative</td>
<td>7</td>
<td>0.8%</td>
</tr>
<tr>
<td>No first but at least two second-degree relatives</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>One first and at least one second-degree relative</td>
<td>2</td>
<td>2%</td>
</tr>
<tr>
<td>At least two first-degree relatives</td>
<td>4</td>
<td>7%</td>
</tr>
</tbody>
</table>

Analysis based on 3213 relatives of 148 index cases.

Risk prior to 30 years of age is extremely low.

For comparison, the background population risk of SAH is ~0.06% per decade.
**Figure 1** (a) Imaging of a large anterior communicating artery aneurysm (arrow) with standard 2D intra-arterial digital subtraction angiography (IADSA). By comparison, the 3D IADSA image (b) demonstrates the detailed anatomy of the aneurysm, particularly the neck, far more clearly. Note additional right middle carotid artery aneurysm.

**Figure 2** (a) Right terminal carotid bifurcation aneurysm (arrow) demonstrated on 2D intra-arterial digital subtraction angiography (b) MRA – Maximum Intensity Projection (MIP) and (c) CTA MIP images. This was a ruptured aneurysm and the associated haematoma results in marked T1 breakthrough effect on the MRA MIP image – highlighting the location of the aneurysm. This effect (or the blood distribution on CT) is one reason why diagnostic accuracy studies on SAH patients cannot be readily extrapolated into the screening context.
More recently there have been further studies of non-invasive imaging tests vs. IADSA (White et al. 2001a; White et al. 2001b; Okahara et al. 2002; Chung et al. 1999; Jager et al. 2000; Metens et al. 2000; Suzuki et al. 2003; Pedersen et al. 2001) and a CTA meta-analysis was published in 2002 (Chappell et al. 2003). These later studies have in general been of better quality although there was still a marked preponderance of patients with SAH rather than asymptomatic unruptured aneurysms. The sensitivities and specificities were similar to those in the earlier systematic review. Two small studies suggest that dynamic contrast MRA (rapid MRA during an intravenous injection of gadolinium) may be more accurate than time of flight MRA (Metens et al. 2000; Suzuki et al. 2003), but they do suffer from the methodological problems of the early time-of-flight MRA studies and might be over-optimistic. Two studies, which looked at the effect of observer experience on aneurysm detection found, not surprisingly, that experts detected substantially more aneurysms, and more reliably, than less experienced observers (Okahara et al. 2002; White et al. 2003).

**IF AN ASYMPTOMATIC ANEURYSM IS FOUND WHAT IS ITS RISK OF RUPTURE?**

The best available data on rupture risk are summarised in Table 5. A systematic review by Rinkel et al. found an overall annual rupture rate of 1.9% (Rinkel et al. 1998). Aneurysms were twice as likely to rupture in women than in men and the risk of rupture increased with age. Symptomatic aneurysms were significantly more likely to rupture than incidental or additional (asymptomatic) aneurysms (6.5% vs. 0.8% vs. 1.4%, respectively). Posterior circulation and large (> 10 mm) aneurysms were significantly more likely to rupture. In a logistic regression model, the only factor significantly related to aneurysm rupture was the size of the aneurysm – 7 mm or larger aneurysms had a relative risk of rupture of 2.24 compared with smaller aneurysms (Juvela et al. 1993). Virtually all patients in this study had had a previous SAH. In the

**Figure 3** (a) Left terminal carotid bifurcation aneurysm (arrow) on 2D intra-arterial digital subtraction angiography. (b) Although the terminal carotid is irregular in appearance, the very small aneurysm cannot be readily appreciated on the MRA MIP image and even the base image (c) does not clearly demonstrate the aneurysm – illustrating the problems of detecting very small aneurysms with non-invasive imaging methods. However, the aneurysm was detected on transcranial Doppler sonography – arrowed ‘An’ (d).
Table 4  Sensitivity and specificity of non-invasive tests for intracranial aneurysms (White et al. 2000)

<table>
<thead>
<tr>
<th></th>
<th>MRA (PP)*</th>
<th>CTA (PP)†</th>
<th>TCDS (PP)‡</th>
<th>MRA (PA)§</th>
<th>CTA (PA)¶</th>
<th>TCDS (PA)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>87</td>
<td>92</td>
<td>–</td>
<td>87</td>
<td>90</td>
<td>82</td>
</tr>
<tr>
<td>Specificity</td>
<td>92</td>
<td>94</td>
<td>–</td>
<td>95</td>
<td>86</td>
<td>95</td>
</tr>
</tbody>
</table>

*926 subjects in 20 studies; †677 subjects in 16 studies; ‡No studies reported data per patient; §1596 aneurysms in 926 subjects; ¶1582 aneurysms in 677 subjects; **97 aneurysms in 162 subjects.

PP, identification of a patient as having or not having an aneurysm; PA, identification of an individual aneurysm correctly; MRA, magnetic resonance angiography; CTA, computerized tomography angiography; TCDS, transcranial Doppler sonography.

Table 5  Summary of data on annual risk of rupture of unruptured aneurysms

<table>
<thead>
<tr>
<th></th>
<th>INTERNATIONAL STUDY OF UNRUPTURED INTRACRANIAL ANEURYSMS &amp; INVESTIGATORS 1998 (RETROSPECTIVE)</th>
<th>INTERNATIONAL STUDY OF UNRUPTURED INTRACRANIAL ANEURYSMS &amp; INVESTIGATORS 2003 (PROSPECTIVE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>95</td>
<td>1449</td>
</tr>
<tr>
<td>No. of aneurysms</td>
<td>–</td>
<td>193</td>
</tr>
<tr>
<td>Duration of follow-up (patient years)</td>
<td>(mean of mean follow-ups 5.5, range 2.1–13.7 years)</td>
<td>12023</td>
</tr>
<tr>
<td>Number ruptured</td>
<td>75</td>
<td>32</td>
</tr>
<tr>
<td>Overall rupture rate (% pa)</td>
<td>1.9</td>
<td>0.27</td>
</tr>
<tr>
<td>Rupture rate</td>
<td>&lt; 10 mm: 0.7</td>
<td>&lt; 7 mm all sites no prior SAH ~0.07</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 mm: 4.0</td>
<td>&lt; 7 mm all sites prior SAH ~0.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 7 mm all sites patients ~0.1†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 7 mm ~0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 7 mm ~2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;0.36 all sizes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5–5% per decade</td>
</tr>
<tr>
<td>Cumulative aneurysm rupture rate (from Juvela et al. 1993)</td>
<td>10% per decade</td>
<td>0.5–5% per decade</td>
</tr>
<tr>
<td>Incidental aneurysm rupture rate</td>
<td>6.5</td>
<td>data not extractable</td>
</tr>
<tr>
<td>Asymptomatic aneurysm rupture rate</td>
<td>0.8 but 7/8 ruptures in aneurysms &gt; 10 mm</td>
<td>data not extractable</td>
</tr>
<tr>
<td>Asymptomatic aneurysm rupture rate</td>
<td>1.4</td>
<td>&lt; 7 mm ~0.07</td>
</tr>
<tr>
<td>Posterior circulation aneurysm rupture rate</td>
<td>6.5</td>
<td>&gt; 7 mm ~2.1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20–39: 0</td>
<td>&gt;0.36 all sizes</td>
</tr>
<tr>
<td></td>
<td>40–59: 3.5</td>
<td>0.5 (≤ 7 mm) – 10% (≥ 24 mm)</td>
</tr>
<tr>
<td></td>
<td>60–79: 5.7</td>
<td>data not extractable</td>
</tr>
</tbody>
</table>

*Additional data to that published in the systematic review were kindly supplied by Dr Gabriel Rinkel to allow calculation of duration of follow up. The paper by Juvela et al. 1993 contributed 28% of the patients to the systematic review but almost half the patient-years of follow up.
†No difference in rates between groups for larger aneurysms.
The rupture rate is much higher than the combined overall figure for the subgroups of posterior circulation aneurysms > 7 mm and for anterior circulation aneurysms > 12 mm.
same size. Of no direct concern to this article, in

...with anterior circulation aneurysms of the

...uncinatic) aneurysms was 3–3.2 compared

...posterior circulation (including posterior com-

...higher risk for larger anterior circulation aneu-

...anterior circulation aneurysms < 7 mm, but substantially

...negligible rupture risk for anterior circulation aneu-

...occurred of an aneurysm < 10 mm in diameter

...only 1/12 aneurysmal ruptures

...systematic review (Rinkel et al. 1998). This 0.05% risk is in

...thin rupture risk of 0.05% per annum for small aneurysms (< 10 mm
diameter) in patients who had not had an SAH previously, and of 0.5% per annum for large

...the re-calculation of the rupture risk of 0.1% for aneurysms < 10 mm

...Rinkel’s systematic review (Rinkel et al. 1998). In the patients that had not previously

...SAH, only 1/12 aneurysmal ruptures occurred of an aneurysm < 10 mm in diameter

...the SAH group for larger aneurysms (International Study of Unruptured

...ruptures in the no prior SAH group were of aneurysms < 7 mm

...with anterior circulation aneurysms), compared with 7/10 in those with prior SAH.

...It is worth noting that aneurysms < 2 mm were arbitrarily excluded from ISUIA, though these
can rupture.

WHAT TREATMENT, IF ANY, SHOULD BE OFFERED AND WHAT ARE THE RISKS INVOLVED?

Whether any treatment for an asymptomatic aneurysm should be offered or not depends
critically on the balance between the long-term rupture risk (i.e. untreated natural history risk) vs.
the immediate treatment risk. Both of these risks in turn depend on the age, gender and lifestyle factors of the individual patient.

Treatment risks

Aneurysms are treated by surgical clipping or by interventional neuroradiology – coiling.
A systematic review of surgical treatment for unruptured aneurysms identified 61 studies
between 1966 and 1996, but only eight were prospective and unfortunately, in virtually all,
the neurosurgeon performing the operation was also the observer of outcome (Raaymakers et al. 1998). Permanent morbidity occurred in
10.9% of patients and the case fatality was 2.6%. The lowest morbidity and mortality was found
with small anterior circulation aneurysms (case fatality 0.8%, morbidity 1.9%), and the high-
est with large posterior fossa aneurysms (case fatality 9.6%, morbidity 38%). The lack of in-
dependent outcome assessment and the effect of publication bias must have underestimated
the surgical risk. The prospective arm of ISUIA (Fig. 4) found the surgery-related case fatality
at 1 year was 2.7% in patients with no prior SAH and 0.6% in patients who had previously
suffered SAH. Morbidity was the same at 10% (International Study of Unruptured Intracranial
Aneurysms & Investigators 2003). Age was the only independent predictor of outcome:
surgery-related morbidity and mortality at one year was about five times higher in those
> 64 years of age compared with patients < 45 years of age (International Study of Unrup-
tured Intracranial Aneurysms & Investigators 1998).

The effectiveness and risks of aneurysm coiling in unruptured aneurysms are less certain because the technique is newer and still developing. Guigliemi detachable coils (GDC) were introduced in 1991 and revolutionised the endovascular treatment of intracranial aneurysms (Guiglielmi et al. 1991) (Fig. 5). Systematic reviews of aneurysm coiling have identified 48 studies (all observational, mostly retrospective) including 1383 patients – but these were predominantly of ruptured aneurysms (Brilstra et al. 1999). Permanent complications (death/disability) occurred in 3.7%. However, only 54% of aneurysms were completely occluded after one procedure, although 88% were substantially (> 90%) coiled (Brilstra et al. 1999).

The re-bleeding rate from partially treated aneurysms is higher, and partial occlusion is well recognised to be more common with coiling than clipping. The technology of coils and coiling assist devices is improving all the time, so the partial occlusion rate is likely to decline.

There is only one large randomised trial that has compared coiling with clipping – the International Subarachnoid Aneurysm Trial (ISAT) – but only in ruptured aneurysms (International Subarachnoid Aneurysm Trial 2002). This demonstrated a relative risk reduction in death/dependency for coiling over clipping of 23% at one year – an absolute risk reduction of 7%. Most ISAT patients had anterior circulation aneurysms < 10 mm so the trial was not completely representative of the generality of aneurysms. However, anterior circulation aneurysms < 12 mm accounted for about 65% of the unoperated subjects and 67% of the surgically treated individuals in ISUIA (International Study of Unruptured Intracranial Aneurysms & Investigators 2003). The prospective ISUIA data on treatment outcomes are interesting although directly comparing clipping and coiling is difficult because patient characteristics differ between the cohorts. There were proportionately far more elderly patients, posterior circulation and large aneurysms (all predisposing to poorer outcome) in the endovascular cohort. Nevertheless, for those with no prior SAH the combined morbidity and mortality at 1 year was 12.6% for clipping and 9.8% for coiling – a 22% relative risk reduction. For prior SAH patients at one year the relative risk reduction was 30% (7.1% vs. 10.1%).

There is a negligible risk of rupture of anterior circulation aneurysms < 7mm in those without prior subarachnoid haemorrhage.
In unruptured aneurysms the long-term durability after treatment is of particular concern. Although the durability of surgical clipping is widely accepted, the literature on re-bleeding from a previously clipped aneurysm is actually quite scanty and nearly all the information on re-bleeding rates after coiling or clipping relates to previously ruptured aneurysms which are probably more likely to re-bleed after treatment than an unruptured aneurysm. In a purely surgical series, 17 patients presented with ruptured or symptomatic recurrences post clipping – 0.1% per annum (Lin & Fox 1989). A centre, which treated 466 patients with coiling between 1992 and 2002, found major aneurysm recurrences in 21% of treated aneurysms. Three patients re-bled from a coiled aneurysm during a mean follow-up of 31 months – a risk of approximately 0.25% (Raymond et al. 2003).

ISAT will eventually provide 5 and then 10-year follow-up, which will help resolve the issue of endovascular treatment durability.

How to assess if treatment should be offered?
The 'effective natural history risk' is the individual's life expectancy multiplied by the annual rupture risk of their aneurysm. For treatment to be worthwhile at all, the natural history risk should substantially exceed the treatment risk – after all the treatment risk is at once, whereas the untreated risk accumulates over time. As an example, a giant posterior circulation aneurysm has an annual rupture rate of 10%, but a treatment risk of 40% (International Study of Unruptured Intracranial Aneurysms & Investigators 2003). If a patient has a life expectancy of 20 years, the chance of rupture far exceeds the 40% treatment risk. On the other hand if the patient is a 71-year-old male with, for example, a 4-year life expectancy, the effective natural history risk minus the 40% treatment risk is about zero. In practice, a sensible figure in order to at least consider treating an asymptomatic unruptured aneurysm in an individual is for the effective natural history risk to exceed the treatment risk by at least 5–10 years. In patients with prior SAH, treatment of additional unruptured aneurysms will often be indicated but life expectancy, comorbidity and treatment risks must be assessed carefully on an individual basis. But other factors such as patient anxiety and implications for employment may all have an important impact on the final treatment decision.

Figure 5. Basilar tip aneurysm with false sac (*) before (a) and after coiling (b) with complete occlusion achieved. Image (c) demonstrates a three-dimensional GDC™ coil of the type commonly used as an initial coil in such procedures.
Are there other worthwhile interventions?
Stopping smoking, careful control of blood pressure, avoidance of risk factors for atherosclerosis (careful diet, regular exercise, etc.), while unproven, may help reduce both the risk of formation of aneurysms and their risk of rupture, as well as improving general health.

SCREENING FOR ANEURYSMS
Unfortunately, we cannot tell when aneurysms are going to rupture or form de novo. It is difficult to know for certain who to screen, when to screen and how often, which aneurysms to treat (or sometimes how best to treat) and which to leave alone.

Several groups have applied detailed models to the screening decision-analysis process for aneurysms (MARS study Group 1999; Leblanc et al. 1994; Obuchowski et al. 1995; ter Berg et al. 1988; King et al. 1995; Kallmes et al. 1998; Crawley et al. 1999; Baba et al. 2000; Yoshimoto & Wakai 1999). The most recent studies using up-to-date information on aneurysm rupture rates, diagnostic test accuracy and treatment morbidity rates have all concluded that routine screening is not warranted. The MARS study used MRA to screen 626 asymptomatic first-degree relatives of 193 SAH patients and found 31 aneurysms in 23 relatives (4%). IADSA confirmed the presence of all 31 aneurysms, but was not performed in the other 603 relatives, so the number of aneurysms missed is unknown (MARS study Group 1999). The MARS investigators found surgery-related morbidity occurred in 11/18 operated relatives, and no ruptures occurred in the non-operated relatives with aneurysms but over what period was not stated. Overall surgery increased life expectancy by 2.5 years per operation but at the expense of 19 years of decreased function per person treated. The study investigators calculated that 298 relatives would need to be screened to prevent one fatal SAH (MARS study Group 1999). This would not be cost effective at about 12 million euros per life (MARS study Group 1999; Johnston 2000). Similar conclusions were reached in two other recent studies (Baba et al. 2000; Yoshimoto & Wakai 1999).

The stress of being screened is difficult to quantify but is not insignificant. McDonald et al. assessed reassurance after a normal echocardiogram in patients with a cardiac murmur. All those presenting with symptoms remained anxious despite the normal test result, and over half of those with an asymptomatic murmur became anxious after detection of the murmur despite the normal echocardiogram (McDonald et al. 1996). The presence of an unruptured asymptomatic aneurysm is considered to be incidental by the UK Driver and Vehicle Licensing Authority for ordinary driving licences but for heavy goods vehicle and public service vehicle licences, the licence depends on a specialist assessment of the risks on an individual patient basis. This might have considerable employment and financial implications for some patients. Furthermore, one needs to consider the effect of finding a small aneurysm where knowledge of it will generate considerable anxiety but where the simple balance of natural history vs. treatment risk does not favour treatment. Such a scenario could again have significant employment and insurance implications. Will the patient be able to cope with this situation? It may be in their best interests not to find out.

So the message here is that, in general, screening of relatives of SAH patients is inappropriate and not cost effective. So only screen for an asymptomatic aneurysm if the pre-test probability of an aneurysm in an individual is very high and if their age and any comorbidity would not militate against treatment. It is also vital to explain to the patient before screening that, if an aneurysm is detected, treatment would only be appropriate for about one half of the aneurysms found. This proportion will be even lower for patients over the age of 50.
SO WHAT SHOULD I SAY TO THE PATIENT PRESENTING TO MY CLINIC WITH A FAMILY HISTORY OF ANEURYSMAL SAH WHO IS WORRIED ABOUT HIS OR HER OWN RISK?

The first thing is to document their family history and the presence or absence of other lifestyle risk factors.

If the family history is weak
For example, if one first or second degree, or even two second-degree relatives, are affected the individual should be reassured strongly that further investigation is not indicated because there is a very low risk of SAH (lifetime risk of no more than 2–3% vs. background population risk of about 0.6%). If they are not reassured, although most are, further explanation about what is involved such as the uncertainty of non-invasive tests, the risk of treatment and possible implications on employment, driving, insurance, etc. if an aneurysm is detected, will lead many people to conclude that it is not in their interests to pursue further investigation. Investigation without a clear discussion of these facts is not in the best interests of patients, and will cause considerable anxiety.

This advice assumes that you have the benefit of a consultation without the patient having too many adverse preconceptions of their risk. If there are adverse preconceptions, then I’m afraid it is just going to be very difficult. For example, if a doctor has explained the concept of aneurysms that are discovered incidentally to a patient in terms of a time-bomb ticking away in their head and then refers them on to the regional neuroscience centre! Once a patient has heard an ill-judged phrase such as ‘time-bomb’ and then had time to worry throughout the referral process, no amount of facts and figures will reassure them. They will almost always demand treatment come what may.

If the family history is strong
If, for example, two or more first-degree relatives are affected, or there is autosomal dominant polycystic kidney disease with a family history of aneurysmal SAH, individuals are at a substantially greater risk of both harbouring an aneurysm and sustaining an SAH compared with the background population. They may merit screening for aneurysms provided they would contemplate treatment if that proves to be appropriate and their life expectancy justifies it. Again it is common sense and good medical practice not to investigate ‘just for reassurance’ without discussing first what an aneurysm means and what treatment, if indicated (and it might not be), involves. If a patient wants to consider investigation and treatment once in the full possession of these facts then it is appropriate to refer for imaging. Explain briefly what the test involves and that they will be reviewed with the result. It is worth emphasising that there is no urgency about investigation or subsequent treatment. If there are any compounding risk factors, such as smoking, emphasise the importance of modifying behaviour.

How to screen?
As most aneurysms < 5 mm in asymptomatic patients without SAH would not merit treatment, it is reasonable to screen first with CTA or MRA – provided a unit has the appropriate experience. Which test to do will depend on local availability and patient factors that make one or other the better option for that individual. However, patients must be warned of the limitations of a one-off CTA or MRA scan – a negative result does not mean they don’t have an aneurysm, just that they probably don’t have one large enough to require treatment now. Also an aneurysm could develop in the future. Whether to repeat screening examinations and if so how and when is completely unknown.

WHAT TO SAY ABOUT TREATMENT?
It is reasonable to stick to generalities at this stage. An explanation of the two treatment options available and an outline of their risks is enough. Explain that the most appropriate treatment option will depend on the site and size of any aneurysm found and possibly the patient’s age. Reiterate that for many asymptomatic aneurysms treatment is not needed. Local expertise and availability of treatment may also come into play but it is not necessary to discuss that yet. Finally, this is a complex and difficult enough field for doctors, let alone the patients. We try and provide some basic information the patients can take away and read, and frequently bring them back for a second clinic visit to go over the facts again before embarking on any investigation. If an aneurysm is identified at a site and of a size to warrant treatment, the patient should be referred to a specialist multidisciplinary neurovascular clinic, but if that is unavailable to a vascular neurosurgeon.
The role of coiling as opposed to clipping in the treatment of unruptured aneurysms is promising.

PRACTICE POINTS

• Symptomatic aneurysms are those causing SAH following rupture, or exerting symptoms by a space occupying effect (most commonly oculomotor nerve palsy produced by a posterior communicating artery aneurysm).

• Asymptomatic aneurysms are additional aneurysms found in patients with a symptomatic aneurysm, which are not responsible for the clinical presentation, or aneurysms found in patients investigated because they are at risk (of harbouring an aneurysm).

• Incidental aneurysms are those found unexpectedly in patients undergoing investigation for some other suspected problem.

• About one in 20 of the general population aged over the age of 30 harbours an unruptured asymptomatic aneurysm.

• Individuals most at risk of aneurysmal SAH are those with a family history of at least two first-degree relatives with an SAH, or patients with an underlying genetic condition – most commonly autosomal dominant polycystic kidney disease.

• The risk seems highest if at least one of the affected relatives is a sibling or mother. Lifestyle factors such as smoking, heavy alcohol consumption and hypercholesterolaemia may further increase the risk. A single relative (especially if second-degree) affected by SAH suggests a very small absolute risk of SAH to an individual without SAH.

• CT angiography and MR angiography, performed and reported by experts, can reliably detect aneurysms larger than 5 mm. These techniques are unreliable at detecting smaller aneurysms. A negative study may therefore offer false reassurance. This problem should be discussed with anyone referred for imaging to look for an asymptomatic aneurysm.

• Rupture risk depends predominantly on the site and size of an aneurysm and whether or not the patient has suffered a previous SAH. If not, small aneurysms (≤ 7 mm), particularly if anterior circulation, have an extremely low rupture risk. Other factors such as age and lifestyle factors also then need to be considered to determine overall risk. A substantial number of asymptomatic aneurysms fall into this category.

• Treatment risks rise with age and also depend on the size and site of the aneurysm. The greatest risks are with larger aneurysms, posterior circulation aneurysms and in older people (≥ 50 years). In all these groups coiling is safer than clipping – the substantially lower risk of treatment favours coiling despite the uncertainty over durability.

• Treatment risks of coiling and clipping for asymptomatic small, anterior circulation aneurysms in patients < 50 years are similar, so the unproven long-term durability of coiling is a particular issue in this group.

• In patients with no prior history of SAH, risk benefit analysis favours treatment in people < 50 years old except for those with anterior circulation aneurysms ≤ 7 mm in size (but these account for nearly 50% of the total).

• For people > 50 years, treatment is only clearly favoured for aneurysms ≥ 12 mm, and other factors such as life expectancy and coexistent conditions need to be taken into account.

• Routine screening for unruptured intracranial aneurysms in individuals with a family history of SAH is not warranted.

• Asymptomatic individuals with only one family member affected by SAH do not have a sufficiently increased risk to outweigh the risks of screening (and treatment).

• Those patients with the greatest risk of having an unruptured aneurysm, and of it then rupturing, are those aged over 30 years from families with two or more first degree relatives affected by SAH. They are perhaps at further increased risk if they have additional risk factors such as smoking and hypercholesterolaemia. Such individuals and autosomal dominant polycystic kidney disease patients with a family history of SAH should be assessed on an individual basis – taking all the relevant risk factors into account – for screening for intracranial aneurysms.

• The role of coiling as opposed to clipping in the treatment of unruptured aneurysms is promising, particularly in patients ≥ 50 years, and for posterior circulation aneurysms.
ACKNOWLEDGEMENTS

This paper was reviewed by Jan van Gijn, Utrecht, the Netherlands.

REFERENCES


