The case for family screening for intracranial aneurysms

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Given that relatives of patients with intracranial aneurysms (IAs) or subarachnoid hemorrhage have a greater risk of harboring an aneurysm, family screening has become a common practice in neurosurgery. Unclear data exist regarding who should be screened and at what age and interval screening should occur. Multiple factors including the natural history of IAs, the risk of treatment, the cost of screening, and the psychosocial impact of finding an aneurysm should be taken into account when family screening is considered. In this paper, the authors review the current literature regarding risk factors and natural history of sporadic and familial aneurysms. Based on these data the authors assess current recommendations for screening and propose their own recommendations.

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Key Words • familial aneurysm • intracranial aneurysm • family screening • subarachnoid hemorrhage

Studies have shown that relatives of patients with SAH or IAs have a greater risk of harboring an aneurysm.6,10,12,71,83,86 Screening family members of patients with IAs has been a common practice in neurosurgery. However, the benefit and cost-effectiveness of this preventive measure remain uncertain. Questions regarding the age at which screening should begin and the length of the screening interval also remain unanswered. With the recent advances and the widespread use of brain imaging studies, neurosurgeons will be increasingly confronted with this problem. The high morbidity and mortality rate of an SAH is the main reason for screening and treating IAs in family members. However, this should be weighed against the complications of the treatment, the psychosocial impact from IA detection, and the cost of prevention.

Natural History of Aneurysms

According to the WHO criteria for screening, the natural history of a disease should be adequately understood before screening is considered.62 Classically, the natural history of a disease should be devastating enough to justify the risk and cost of screening and treatment. This is partly why it is recommended to screen for diseases such as breast, colorectal, and cervical cancer. There have been conflicting reports in the literature over the natural history of IAs. The ISUIA is a landmark study that enrolled patients in the US, Canada, and Europe for prospective assessment of unruptured aneurysms.35,91 This study found that the annual risk of rupture was as low as 0.05% for aneurysms smaller than 10 mm compared with 1% for those larger than 10 mm. It also reported a 5-year cumulative risk of SAH of 0%, 2.6%, 14.5%, and 40% for circulation aneurysms < 7, 7–12, 13–24, and ≥ 25 mm, respectively. Posterior circulation aneurysms had a 2.5%, 14.5%, 18.4%, and 50% rupture rate for the same size categories, respectively. The case fatality rate of an SAH approached 66%, and the 5-year survival rate was 89% for the entire cohort. The study also reported a combined morbidity and mortality rate as high as 13.7% for surgical clipping and 9.3% for endovascular therapy, thus equaling or even exceeding the risk of rupture of IAs. However, there have been reports questioning the methodology of the ISUIA study and whether selection and indication biases may have led to the low observed annual rate of rupture and the high rate of complications of treatment.29,68,70 In addition, many reports have challenged the findings of this study, reporting an annual risk of rupture greater than 1% for IAs.41,71,84,88 A recent Finnish study that enrolled 142 patients with unruptured IAs for a median follow-up of 19.7 years found an average annual incidence of SAH of 1.3%.41 The cumulative rate of bleeding was 10.5% at 10 years, 23% at 20 years, and 30.3% at 30 years after diagnosis, findings all substantially higher than those reported in the ISUIA study. Similarly, in a recent large Japanese study that followed 374 patients with small IAs (< 5 mm), the annual rate of bleeding was 0.34% for single aneurysms, 0.95% for multiple aneurysms, and 0.54% overall.80 Some studies also report that small aneurysms do rupture and that the vast majority of SAH results from aneurysms smaller than 10 mm.4,29,20,23 In a retrospective study by Forget and col-

Abbreviations used in this paper: ADPKD = autosomal dominant polycystic kidney disease; FIA = Familial Intracranial Aneurysm; IA = intracranial aneurysm; ISUIA = International Study of Unruptured Intracranial Aneurysms; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage.
Aneurysms,\textsuperscript{26} 85.6\% of all aneurysms presenting with rupture were less than 10 mm. Along similar lines, aneurysms $\leq 5$ mm accounted for almost 65\% of all ruptured aneurysms in a recent study from Hong Kong.\textsuperscript{48} It is hard to reconcile the results of these studies with the findings of the ISUIA, which complicates any consideration for screening for IAs in family members of an affected patient.

Numerous factors are associated with a higher risk of rupture of IAs. An updated metaanalysis that included 19 studies identified age $> 60$ years, aneurysm size $> 5$ mm, female sex, posterior circulation, and symptomatic aneurysms as potential risk factors for rupture of IAs.\textsuperscript{38} According to another metaanalysis, cigarette smoking, heavy alcohol consumption, hypertension, female sex, and older age are all indisputable risk factors for SAH.\textsuperscript{39} Polycystic kidney disease and a family history of SAH or IA were also suggested as substantial risk factors.

**Familial Aneurysms**

Familial aneurysms (Fig. 1), defined as 2 first-degree relatives with IAs, account for approximately 10\% of all SAHs.\textsuperscript{12,51} Differences have been described between sporadic and familial aneurysms. Familial IAs are more frequently multiple, tend to occur in the MCA, and are underrepresented in the anterior communicating artery location.\textsuperscript{14,42,47,51,70} They also rupture at a younger age compared with sporadic aneurysms.\textsuperscript{47,49,51} A few studies have shown that familial IAs are smaller than sporadic IAs.\textsuperscript{47,51} However, in a well-designed study by Ruigrok et al.\textsuperscript{70} that compared 58 patients with familial SAH to 88 patients with sporadic SAH, familial IAs were found to be larger than sporadic IAs. In this study, IAs were ruled out in all first-degree family members not only by history-taking, but with MR angiography as well. All previous studies relied on history-taking alone, which may have led to inclusion of familial IAs into the sporadic group, thus affecting data regarding size comparison.

The rate of morbidity and mortality from an SAH remains high. An aneurysmal SAH is fatal in 50\% of cases, and only a minority of those who survive return to their daily activities.\textsuperscript{32} Moreover, patients with a familial SAH have a worse outcome than those with a sporadic SAH.\textsuperscript{13} This was initially described by Bromberg et al.\textsuperscript{15} in a study that compared 29 patients with familial SAH to 125 patients with sporadic SAH. They found that 52\% of patients with familial SAH had a poor outcome compared with 37\% in the sporadic group, thus justifying familial screening. Furthermore, studies have shown that familial IAs have a greater risk of growth and rupture compared with sporadic IAs.\textsuperscript{10,55,71} The FIA study deserves a special mention in this setting. The FIA study is an international ongoing project that enrolled 475 families with multiple affected relatives with the primary goal of identifying the genes that underlie the development and rupture of IAs.\textsuperscript{41} A recently published article evaluated the risk of rupture of IAs in 113 subjects of the FIA study families.\textsuperscript{10} The annual rate of rupture of these familial IAs was 1.2\%, which is 17 times higher than the rupture rate for patients with IAs in the ISUIA study when adjusted for size and location (0.069\%). The authors concluded that familial IAs had a greater risk of rupture compared with sporadic IAs, a finding in favor of screening and treating relatives of patients with IAs. However, the findings of this study should be interpreted with caution. The authors enrolled only patients with IAs from the FIA study who were smokers and had a history of hypertension, 2 factors that have been shown to increase the risk of rupture of an aneurysm.\textsuperscript{25,58,86} Therefore, it is not clear to what extent the family history of IAs has contributed to the higher annual rate of rupture observed in the series. Moreover, this study did not include a control group (sporadic IAs), and, consequently, the annual rupture rate in the series had to be compared with that of the ISUIA study. Any conclusion drawn from this report would depend on the validity of the findings of the ISUIA study. In addition, the total number of observed SAHs in the FIA series was just 2, which greatly limits the statistical power of the study.

**Risk Factors for Aneurysms**

**Nonmodifiable Risk Factors**

Several risk factors have been identified for harboring IAs. The strongest risk factor is a family history of IAs or SAH.\textsuperscript{46,71,83} Compared with the general population, the risk of SAH in parents, siblings, and children (first-degree relatives) of patients with SAH is 3–7 times higher.\textsuperscript{12} This risk also increases with the number of affected first-degree relatives.\textsuperscript{52} This was initially described by Bromberg et al.\textsuperscript{15} in a study that compared 29 patients with familial SAH to 125 patients with sporadic SAH. They found that 52\% of patients with familial SAH had a poor outcome compared with 37\% in the sporadic group, thus justifying familial screening. Furthermore, studies have shown that familial IAs have a greater risk of growth and rupture compared with sporadic IAs.\textsuperscript{10,55,71} The FIA study deserves a special mention in this setting. The FIA study is an international ongoing project that enrolled 475 families with multiple affected relatives with the primary goal of identifying the genes that underlie the development and rupture of IAs.\textsuperscript{41} A recently published article evaluated the risk of rupture of IAs in 113 subjects of the FIA study families.\textsuperscript{10} The annual rate of rupture of these familial IAs was 1.2\%, which is 17 times higher than the rupture rate for patients with IAs in the ISUIA study when adjusted for size and location (0.069\%). The authors concluded that familial IAs had a greater risk of rupture compared with sporadic IAs, a finding in favor of screening and treating relatives of patients with IAs. However, the findings of this study should be interpreted with caution. The authors enrolled only patients with IAs from the FIA study who were smokers and had a history of hypertension, 2 factors that have been shown to increase the risk of rupture of an aneurysm.\textsuperscript{25,58,86} Therefore, it is not clear to what extent the family history of IAs has contributed to the higher annual rate of rupture observed in the series. Moreover, this study did not include a control group (sporadic IAs), and, consequently, the annual rupture rate in the series had to be compared with that of the ISUIA study. Any conclusion drawn from this report would depend on the validity of the findings of the ISUIA study. In addition, the total number of observed SAHs in the FIA series was just 2, which greatly limits the statistical power of the study.
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relatives. The prevalence of IAs is 2.3% in the general population, 4% in people with 1 affected first-degree relative, and 8% in those with 2 affected first-degree relatives. In a recent large study by Bor et al., which assessed the risk of SAH in 130,373 relatives of 5282 patients with SAH, the odds ratio of SAH was 2.15 for individuals with 1 affected first-degree relative and as high as 51 for those with 2 affected first-degree relatives. In a series of 626 first-degree relatives of patients with sporadic SAH, Raaymakers found that the risk of harboring an IA is 4%, which is twice the risk of the general population. The risk for first-degree relatives was further increased when the affected patient was young and harbored multiple aneurysms. The risk of IAs was 4 times higher in siblings compared with children of affected patients. This finding, also reported in other studies, can be explained by an autosomal recessive inheritance mode for genes implicated in the development of IAs. The fact that the prevalence of IAs increases with age is another plausible explanation for this finding, reflecting the elapsed time that is required to develop an IA. In another study by Raaymakers et al. that enrolled relatives of patients with familial SAH, the risk of harboring an aneurysm was 8% in first-degree relatives. This prevalence is 4 times higher than the prevalence in the general population. The familial occurrence of aneurysms has prompted researchers to identify the genes underlying the development of IAs. There have been some reports on a potential linkage of familial IAs on chromosomes 1p, 7, and 19. We hope that the FIA study will help identify the genetic basis of IAs.

Female sex and older age are 2 important nonmodifiable risk factors for IAs in both sporadic and familial cases, according to multiple reports. A recent meta-analysis by Vlak et al. that included 68 studies with 94,912 participants (1450 had IAs) from 21 countries identified female sex, older age, family history of IAs, and ADPKD as risk factors for harboring aneurysms. Autosomal dominant polycystic kidney disease is a known strong risk factor for IAs, although it accounts for less than 1% of all SAHs. Intracranial aneurysms are found in 10–15% of patients with ADPKD. The prevalence of IAs can even reach 23.3% in ADPKD patients older than 60 years. Intracranial aneurysms in this population occur most commonly in the MCA and tend to be smaller than those in patients without ADPKD. A positive family history for IAs or SAH is a substantial risk factor for aneurysms in the ADPKD population. A recent study estimated that the risk of IAs in patients with ADPKD and a positive family history for SAH is twice that of patients with ADPKD but no such family history. Irazabal et al. have recently published the results of a 20-year follow-up series of 38 patients with ADPKD harboring aneurysms. This study showed that the risk of growth and rupture of IAs in patients with ADPKD were not higher compared with those without ADPKD. This finding solidifies the recommendations of the American Heart Association (2000) that routine screening for this population is not recommended.

A rare disease, Ehlers-Danlos Type IV, is an inherited collagen defect disorder that is strongly associated with saccular or fusiform IAs. It is advocated not to screen these patients using invasive methods such as catheter-based angiography due to the fragility of the vessel walls that greatly increases the rate of complication of treatment. In 2 other genetic disorders, Marfan disease and neurofibromatosis, surveys and autopsy studies have not shown an association with IAs.

It is debated whether acromegaly predisposes to aneurysm formation. However, a recent study by Manara et al. found that 17.3% of patients with acromegaly harbored IAs. Interestingly, the presence of IAs correlated with growth hormone serum values at the time of diagnosis.

Sickle cell anemia patients appear to be predisposed to IAs. According to a meta-analysis, these aneurysms occur at a young age, tend to be multiple, and arise in the posterior circulation. The proposed pathogenesis involves endothelial injury over the entire cerebral circulation initiated by sickled cells, which could explain why IAs tend to be multiple in this population. Physicians should therefore keep in mind this predisposition when dealing with a patient with sickle cell anemia who complains of headaches or other neurological symptoms. Routine screening of this population does not appear warranted at this time and should be reserved for those with high clinical suspicion of IAs.

There have been numerous reports regarding the association between IAs and aortic coarctation. In this group, IAs tend to occur and rupture at a young age (average 25 years), with an annual rate of rupture as high as 4.8%. Finally, in a recent case-control study that compared 61 patients with bicuspid aortic valve to 291 controls, the frequency of IAs was significantly higher in the bicuspid valve group (9.8% had an IA). More studies are needed to confirm this finding.

Modifiable Risk Factors

Smoking and arterial hypertension are definite risk factors for IAs as demonstrated by several studies in different populations. In a study by Wermer et al. that assessed the risk of new aneurysm formation after an SAH, active smoking and hypertension were important risk factors for IA formation and growth with a hazard ratio of 3.8 and 2.3, respectively. Although heavy alcohol consumption has been shown to increase the risk of SAH, it does not predispose to aneurysm formation and growth. The increased risk of SAH in these patients may be the result of transient increases in blood pressure. Atherosclerosis does not appear to be associated with IAs according to the recently published meta-analysis by Vlak and colleagues.

Screening for IAs

Screening for Familial IAs

The decision as to whether to screen for IAs in relatives of patients with aneurysms should take into account several factors, including the frequency and natural history of IAs, the cost of screening, the safety and efficacy of treatment, the patient’s age, comorbidities, preferences, and the psychosocial impact of finding an aneurysm. Given that no randomized controlled trials have assessed
the efficacy of screening for IAs, the quality of evidence supporting any recommendation in this regard is very low and only Grade 2C recommendations (“weak recommendation, low quality or very low-quality evidence”) can be made according to the grading system of the American College of Chest Physicians.20

It is generally advocated to screen for IAs in all individuals with 2 or more affected first-degree relatives because of the high frequency of IAs in this group.67,69 As previously mentioned, the prevalence of aneurysms is 8%–10% in first-degree relatives of patients with familial IAs, which is 4–5 times higher than the risk of the general population.60,73 Familial aneurysms also rupture more frequently, and the resultant SAH has a worse prognosis compared with sporadic cases.19,13 Moreover, the risk of IAs can be as high as 19% in first-degree relatives who are older than 30 years and have a history of smoking and hypertension, according to a recent report by Brown et al.68 from the FIA study. This finding delineates the high yield of screening a high-risk population that was identified solely on the basis of personal and family history.17

Bor et al.6 used a Markov model and Monte Carlo simulations to assess the cost-effectiveness of screening individuals with 2 or more first-degree relatives with SAH. Screening was found to be cost effective, with an optimal strategy of screening individuals from age 20 to 80 every 7 years (with a cost-effectiveness threshold of $29,200 per quality-adjusted life year). A Japanese study using a Markov model also showed that screening relatives of patients with familial IAs was cost effective with an incremental cost-effectiveness ratio of $37,400 per quality-adjusted life-year.62 However, it is worth noting that these theoretical studies are potentially prone to bias due to the limitations of the data used to build the model, including the assumed incidence, natural history, and risk of treatment of IAs. Although there is a consensus among experts to recommend screening for patients with 2 affected first-degree relatives,69 the underlying evidence is still limited and only a Grade 2C recommendation for screening can be made in this group.

**Screening for Sporadic IAs**

According to the recommendations of the American Heart Association (2000), screening should not be offered to individuals with only 1 affected first-degree relative (SAH or IA).3 This recommendation was based mainly on the results of the study by the “Magnetic Resonance Angiography in Relatives of Patients with Subarachnoid Hemorrhage Study Group” (1999).52 This group prospectively assessed the benefits and risks of screening for and operating on aneurysms in first-degree relatives of patients with sporadic SAH. They found that screening increased the life expectancy by 4 weeks per person screened at the expense of 19 years of decreased function per person screened. Using a Markov model, they demonstrated that to prevent 1 SAH, 149 relatives would need to be screened. To prevent 1 fatal SAH, 298 relatives would need to be screened. The authors concluded that screening first-degree relatives of patients with sporadic SAH was not warranted. However, it should be noted that patients in this series were only offered open surgery for treatment of their aneurysms. No patient was treated with endovascular procedures.

Studies have shown that endovascular treatment of IAs has a lower rate of morbidity and mortality than surgical clipping.7,31,35,57 A recent large study by Brinjikji et al.2 that assessed the outcome of treatment of unruptured IAs in the US between 2001 and 2008 stated that endovascular coiling is associated with less morbidity (14% vs 49%) and mortality (1.2% vs 6.0%) than surgical clipping. Benes et al.17 also reported a remarkable 1.5% combined morbidity and mortality at 6 months for endovascular coiling of IAs. Similarly, in centers with ample expertise in treating aneurysms, open surgery is associated with a very low complication rate. In a study by Aghakhani et al.1 the 1-year morbidity rate for surgical clipping of unruptured IAs was 2.2%. For aneurysms smaller than 10 mm in patients younger than 65 years old, the morbidity rate was just 0.56%. Likewise, Peerless and colleagues36 reported a morbidity rate of 3.3% for surgical clipping of basilar aneurysms. These rates of complications are lower than the rate that was reported in the study by the “Magnetic Resonance Angiography in Relatives of Patients with Subarachnoid Hemorrhage Study Group” where 11 of 18 patients had postoperative sequelae. Therefore, a firm conclusion cannot be drawn from this study regarding the effectiveness of screening individuals with a single affected first-degree relative. The quality and quantity of evidence are both very limited and support only a Grade 2C recommendation against screening in this group.

**Psychosocial Implications of Screening for Aneurysms**

The psychosocial effects of screening for aneurysms are often underrecognized and underestimated by physicians. A study by Wermer et al.28 that assessed the psychosocial effects of screening for IAs revealed that 44% of patients that screened positive reduced their work and 66% experienced changes in self-esteem, future outlook, or relationships. These patients also had a reduced quality of life compared with the general population. Similar effects were noted in less than 10% of those who screened negative. Conversely, Bossuyt and colleagues’ found that the levels of anxiety and depression were not affected by the invitation to screen for IAs in 980 first-degree relatives of patients with SAH. Beyond the psychosocial impact, some patients also experience a financial burden, suffering difficulties in getting affordable life, disability, and health insurance coverage. With the new prospective health care system, this last aspect would not be an issue in the near future, at least in the US. The importance of counseling and dissemination of information in these patients cannot be overstressed.

**How to Screen**

It is recommended to screen family members using noninvasive brain imaging studies. Computed tomography angiography and MR angiography can reliably detect IAs even as small as 3 mm in diameter.33,48 Sensitivity rates for both techniques range from 80% to 99% according to multiple reports.33,44,56,74,85,97 Magnetic resonance angiography offers the advantage of being a contrast-free
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and radiation-free technique, making it the preferred modality in many centers, especially when repetitive screening is needed. The age at which screening should begin is unknown. Siblings tend to present with SAH in the same decade.\textsuperscript{42,46,72} Similarly, aneurysms tend to rupture within the same decade in members of the same family,\textsuperscript{46,72} supporting the argument that screening should be started years before the age at which the aneurysm ruptured or was discovered in a family member. In children, an anticipation phenomenon has been noted, with children developing IAs at a younger age than their parents.\textsuperscript{14,81} Because IAs are not congenital and develop during life, repeated screening should be considered especially in children of the affected patient. As such, aneurysms have been found in 7% of individuals with a family history of IAs who initially screened negative.\textsuperscript{87} Although uncommon, aneurysms can form and rupture within a 5-year screening interval.\textsuperscript{76} Thus, patients should be counseled that screening and treatment do not totally eliminate the risk of an SAH.

We recommend screening all individuals with 2 affected first-degree relatives because of the high frequency of IAs in this group. The interval for screening should be around 5 years. We also recommend screening patients who have 1 affected first-degree relative only if they possess other risk factors for harboring IAs. In other terms, screening is offered to first-degree relatives who have 3 or more of the following factors that increase the risk of finding an aneurysm: female sex, older age, active smoking, arterial hypertension, siblings of the affected patient, and relatives of a patient harboring multiple aneurysms at a young age.

Screening a high-risk group would undoubtedly increase the frequency of detected IAs. The high yield of such an approach has been demonstrated in the previously discussed report by Brown et al.\textsuperscript{16} in the FIA study. If screening is negative, no further screening is required in this group.

Given that IAs are uncommon before the age of 18 years, we recommend screening children of high-risk families starting at the age of 18 with an interval of 5 years. Patients older than 70 years and those with a short life expectancy should not be offered screening regardless of the number of affected relatives.

The suggested recommendations are limited by the quality and quantity of evidence available, and future trials, although unlikely to happen, are needed to assess the efficacy and cost-effectiveness of screening for IAs. Our recommendations are summarized in Figure 2.

Fig. 2. Flow chart of screening for IAs in family members of an affected patient.
Conclusions

There is a consensus among experts to screen for IAs in individuals who have 2 or more affected first-degree relatives. It is not clear if screening relatives of a patient with a sporadic IA or SAH is justified. Only randomized controlled trials with long periods of follow-up can confirm whether screening for IAs in family members of an affected patient is beneficial. When screening is proposed, physicians should counsel patients about the frequency, natural history, and risk of treatment of IAs. Patients should also be aware of the socioeconomic repercussions of finding an aneurysm such as potential lifestyle changes and insurance coverage issues.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References


N. Chalouhi et al.

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71. Rinkel GJ, Djibuti M, Algra A, van Gijn J: Prevalence and
risk of rupture of intracranial aneurysms: a systematic review. 
*Stroke* **29**:251–256, 1998

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