Comments, Opinions, and Reviews

Familial Intracranial Aneurysms
A Review

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Background: A familial occurrence of intracranial aneurysms is defined by the presence of such aneurysms in two or more first- to third-degree family members. Families with two affected members may represent accidental aggregation. Other families show a frequency compatible with an autosomal dominant mode of inheritance. A genetic basis is also suggested by the younger average age of familial cases with a ruptured intracranial aneurysm (42.3 years versus an age range of 50–54 years for nonfamilial cases), occurrence at the same site or a mirror site in sibling pairs, occurrence in identical twins, and the association of intracranial aneurysms with genetically transmitted disorders.

Summary of Review: No reliable data are available about the occurrence of familial intracranial aneurysms among all patients with ruptured aneurysms; a frequency of 6.7% has been reported from a retrospective study, but a large part of the “familial” occurrence can be explained by fortuitous aggregation. The pathogenesis of familial intracranial aneurysms is not fully explained; a (partial) deficiency of type III collagen has been reported in sporadic, but not in familial, cases.

Clinical decision analysis shows how the risk of harboring an intracranial aneurysm and the age of the patient are the main determinants for elective screening; lifetime risk of rupture (and therefore age) and surgical risks are the determinants for neurosurgical treatment.

Conclusions: Surgical treatment is recommended for patients aged <70 years with a moderate or low surgical risk, and screening (preferably by intra-arterial digital subtraction angiography) is recommended only for relatives aged 35–65 years. Magnetic resonance angiography may develop into a useful alternative for screening, but the risks of diagnostic procedures play only a minor role in the decision analysis. (Stroke 1992;23:1024–1030)

KEY WORDS • cerebral aneurysm • genetics

This review discusses the epidemiology, natural history, pathogenesis, and genetics of familial intracranial aneurysms (IAs). The risks and benefits of early detection and treatment are examined and management guidelines are given, based on clinical decision analysis.

Epidemiology
Numerous case reports and case series describe families with two or more patients having IAs, ruptured or unruptured.1–5 The occurrence of familial IAs in the general population has not been systematically studied, not even among patients with subarachnoid hemorrhage (SAH). The prevalence of unruptured IAs in general has been estimated from findings in autopsy studies in which the brain was routinely examined; prevalence ranges from 1% at age 35 years to 8% at age 65.6 A retrospective series of reanalyzed angiograms yielded a much lower prevalence rate of approximately 0.5%,7 but these angiograms were mostly made for other reasons and many IAs may have been missed because of insufficient projections.

In a series of 485 SAH patients, Norrgard et al8 identified by means of a questionnaire survey 32 patients (6.6%) with a first- to third-degree relative who had a SAH. The number of relatives at risk and the method of confirming the diagnosis in these relatives were not reported. On the basis of chance alone, one would expect 5.6% of the patients to have at least one first- to third-degree relative with SAH; this estimate assumes 17.5 relatives per SAH patient, a 1% prevalence rate of IAs, a 1% annual rate of IA rupture, and a mean age of 40 years.8 Thus, it seems likely that many “familial IAs” are just accidental aggregations. On the other hand, there is much less doubt about the underlying predisposition in families with three or more cases of SAH and a relatively young age of IA rupture.1,3–5

Natural History
The main clinical characteristic of familial IA is the young age at the time of rupture, 42.3 years (39.6 years for men and 44.6 years for women), in contrast with an average age of 50–54 years for rupture of nonfamilial IAs.1,3–5 This can be explained either by the development of IAs at a younger age or by their higher tendency to rupture because the vessel wall is weaker. No differ-
ence in the sex ratio between familial and nonfamilial IAs has been found. More than one IA is found in 20% of both nonfamilial and familial cases. However, multiplicity varies considerably from family to family; in one retrospective study it was as high as 53%. Even familial IAs seldom occur under the age of 20 years. So far, only seven such patients have been reported, the youngest being 4 years old, 5, 11-15 which must be taken into account in decisions about elective screening.

In fully reported sibling pairs, IAs occur at the same site or at mirror sites and rupture within the same decade twice as often as in randomly selected nonrelated patients with IAs. Although it has been stated that familial IAs rupture at a smaller size, size is not mentioned in the majority of reports. From data concerning unruptured IAs in general, the annual risk of rupture of familial IAs is estimated at approximately 1%. The risk of rupture of incidental IAs probably increases with size, especially when they are >10 mm in diameter. However, data were obtained from series of patients who had bled from another aneurysm and may not be generalizable. Shortly after rupture there is a decrease in IA size, followed by an increase in size of approximately 15% during the first week. On the other hand, post mortem the size may decrease by approximately one third. Even IAs <5 mm in diameter may rupture, which makes successful screening more difficult. A recent case report describes a ruptured familial IA 5 mm in diameter that was not visualized by means of intravenous digital subtraction angiography (IVDSA) 2 years earlier. Some evidence exists that IAs can rapidly increase in size, but they may also enlarge more gradually. Growth and rupture may occur soon after their formation. This can especially be the case with familial IAs.

Genetics

If not explained by accidental aggregation, occurrence of IAs can be the only familial abnormality, or it can represent only a part of a more complex hereditary syndrome. Syndromic occurrence of IAs, both familial and nonfamilial, has been reported in association with defects of collagen and elastic tissue in the vessel wall (such as Marfan's syndrome, Ehlers-Danlos syndrome type IV, pseudoxanthoma elasticum, and polycystic kidney disease) and coarctation of the aorta. In the latter two disorders the associated arterial hypertension may play a causal role in the development of IAs. With regard to nonsyndromic familial IAs, only 18 families with more than two affected members have been described to our knowledge: seven families with three, five with four, one with five, three with six, one with seven, and one with eight members. Most reports concern first- and second-degree relatives in one or two generations. An autosomal dominant mode of inheritance is most probable, but polygenic multifactorial transmission cannot be excluded. Alternatively, expression of a dominant IA gene may vary considerably from family to family. Another argument in favor of a genetic predisposition for IAs is their occurrence in identical twins yet the very low proportion of familial IAs reported during the first and second decades of life seems to contradict their genetic origin. This low rate is in agreement with that of nonfamilial IAs in the 0-20-year-old group: 1.5% in the Cooperative Study series (2,627 patients), 1.9% in the series of Patel and Richardson (3,000 patients), 4.4% in the series of Sedzimir and Robinson (1,066 patients), and 0.5% in the series of Yoshimoto et al (1,116 patients). The youngest patients reported with nonfamilial IAs are 4.8, 6, and 13 years old. IAs in the 0-2-year-old age group of nonfamilial IAs have some remarkable features that argue in favor of a congenital origin: a predilection to the development of "giant aneurysms," a remarkably peripheral localization, and an association with other congenital anomalies.

Pathogenesis

The pathogenesis of familial IAs remains the subject of considerable controversy. Their predilection for the intracranial vessels has not been clarified, other than that intracranial arteries lack vasa vasorum and have a thin tunica adventitia. Two hypotheses have been put forward to explain the development of nonfamilial IAs. The "degenerative theory" implies acquired factors such as atherosclerosis and hypertension. The second, or the "genetic theory," implies inborn defects of the arterial wall. The vessel wall shows a polymorphism with regard to both type I and type III collagen. Deficiency of type III collagen from a defect in the type III collagen gene or in its expression results in an abnormality of collagen fibers and fiber structure, which leads to abnormal extensibility of the arterial wall. Type III collagen deficiency has been reported in patients with nonfamilial IAs and may even account for 40-50% of patients with a ruptured IA. Deficiency of type III collagen is inborn and does not exclude an abnormality of the collagen gene or molecule. For instance, posttranslational modifications of the type III collagen molecule might occur, although in that case a syndrome with more widespread clinical manifestations would be expected. Anomalies of the iridocorneal angle of the eye were found by screening for (sub)clinical manifestations of a connective tissue disorder in one family with a high rate of IAs. An association of human lymphocyte antigens with both nonfamilial and familial IAs has been reported by some researchers but has not been confirmed by others. The syndrome of abdominal aortic aneurysms (AAAs) may be another manifestation of a genetically determined condition resulting in blood vessel abnormalities. Whether atherosclerosis precedes or is a consequence of aortic dilatation is unclear. One study demonstrated by means of ultrasound examination dilatation of the aorta in 29% of asymptomatic first-degree relatives of patients with AAA. In this syndrome, mutations in the gene for type III procollagen have been found, with an 11-fold increase of AAA risk among persons with an affected first-degree relative.

Once a mutation has been established in a family by means of peripheral blood samples or mucosal cells from saliva, a simple polymerase chain reaction test can
identify members with the same mutation, and this will radically change the elective screening procedure delineated below. However, the underlying biochemical defect of IAs has not been clarified, nor has its genetic background. Perhaps a relative deficiency of type III collagen is only one of several risk factors for developing an IA. In this way the degenerative and genetic theories may have to be combined.

**Decision Analysis**

Asymptomatic relatives in families with two or more members affected by SAH may experience great uncertainty about harboring an IA themselves. For a balanced judgment in the management of asymptomatic family members, several uncertain factors must be considered simultaneously to make the best choice from among the many diagnostic and therapeutic alternatives. Clinical decision analysis, a mixture of clinical science, mathematics, biostatistics, clinical epidemiology, and decision methodology, is increasingly applied to these kinds of complex clinical problems. Clinical decision analysis provides useful insight into the structure of a clinical problem, and it identifies the main determinants of diagnostic and therapeutic choices. It has been applied to a variety of problems, including the management of SAH, incidental IAs, and arteriovenous malformations and screening for IAs among patients with polycystic kidney disease and for familial IAs.

The process of clinical decision analysis can be divided into four stages: 1) defining the clinical problem and structuring it in a decision tree, 2) estimating probabilities and utilities (relative value judgments) for possible outcomes of diagnostic and therapeutic actions, 3) performing the requisite computations for determining the preferred course of action, including sensitivity analyses, and 4) presentation of the results in a clinically useful way. A detailed review of techniques, background, and applications is given elsewhere.

In Figure 1 the decision tree for screening an asymptomatic relative in a family with IA is shown. The tree shows the two main strategies “Do Not Screen” and “Screen Now” with intra-arterial digital subtraction angiography (IADSA). In the first strategy the patient may harbor an IA that may rupture at a certain time, resulting in death, disability, or recovery. In the absence of an IA, a new one may develop later. In the second strategy the patient undergoes IADSA, with a small risk of serious complications. An IA will be operated upon. Surgery is generally successful, but occasionally it results in death or disability. Some small IAs will remain undetected and new IAs may develop, with risk of subsequent rupture.

The dotted rectangles in Figure 1 show the two parts of the decision tree that concern the management of a
proven IA. Rectangle I depicts the natural history, and rectangle II shows surgical treatment of unruptured IAs. The decision tree is for illustrative purposes only; the numbers represent the results of life table calculations to estimate the risk of rupture and mortality from other causes.

**Early Detection of Aneurysms**

The higher the likelihood of harboring an unruptured IA, the more attractive screening will be. This likelihood depends on the age of the individual and on the relative risk of familial IAs in a given family. We estimated that if the risk of developing a familial IA is five times that in the general population, this leads to a 50% risk of harboring an IA (ruptured or unruptured) at age 80 years, as is the case in an autosomal dominant mode of inheritance with complete expression; this estimate will be used as an upper bound.8

The accuracy and the risks of the investigation depend on the screening device. Techniques that have been used in screening for familial IA include conventional cerebral angiography (CCA), IVDSA, IADSA, and high-resolution computed tomography (CT) with contrast enhancement.15,65,85-97 IADSA has higher sensitivity and specificity than IVDSA because of greater spatial resolution, fewer motion artifacts, and less superposition of cerebral vessels.98 However, formal evaluation of the test characteristics of IADSA, admittedly a difficult undertaking, has never been reported. On the other hand, IVDSA seems to be less risky than IADSA and CCA. A permanent morbidity of 0.2% and no deaths were reported after IVDSA,98 whereas CCA in patients with only mild or transient cortical territory ischemia resulted in permanent morbidity of 0.33%, 0.4%, and 1.3% and no mortality.99-101 High-resolution CT may be used as a first-line method of screening. IAs with a diameter of ≥3 mm may be detected.95-97 However, this method has a lower detection rate than IADSA for small IAs. Magnetic resonance angiography (MRA) may develop into a useful and truly noninvasive screening method in the near future. Recent MRA studies suggest that IAs as small as 3–4 mm in diameter can be detected.102,103

Of course, when it emerges from further analysis that treatment will not be beneficial in a certain patient, no method of screening is appropriate. Thus, the risks and effectiveness of neurosurgical treatment should be assessed first.

**Elective Neurosurgical Management**

The main aspects in the assessment of neurosurgical treatment of unruptured IAs are efficacy and safety. When an IA has been taken out of the circulation, one can safely assume that the risk of rupture is nil. Although failed operations have been reported (for instance, imperfect placement of the clip with subsequent rupture94), this is extremely rare. Obviously, the total benefit of surgery depends on the lifetime risk of rupture and therefore on the patient’s age and life expectancy, given a certain annual risk of rupture. This benefit is reduced by the risks of surgery, which depend mainly on size, shape, and location of the IA and on the skill of the neurosurgical team. In a retrospective case series of unruptured IAs the postoperative morbidity was related to the size of the IA: 2.3% for those <5 mm, 6.8% for those 6–15 mm, and 14% for those 16–25 mm in diameter.108 On average, the reports of neurosurgical treatment of unruptured IAs show very low mortality (0–2.5%) and morbidity (<6.5%).14,102-112 On the other hand, only very experienced centers have published their results, and good results are more likely than poor ones to be reported.

**Decision Tree**

The decision tree of Figure 1 is evaluated by inserting the estimated probabilities at each branch of a chance node and by attributing a value to each outcome. The expected utility of each strategy is computed by multiplying the probabilities of events and outcome values and adding them for each strategy. As an approximation of the expected utility, life expectancy can be used, or rather, discounted quality-adjusted life expectancy (dQALY), computed by weighting each year spent in disability with a (utility) value of 75% (62.5–87.5%) of a year spent in normal health.16 Because most patients place more value on nearby than on distant life years,113 5% (0–10%) is discounted annually. This adjustment favors conservative management.

The decision tree of Figure 1 concerns a fictitious patient, a woman aged 50 years, who has several close relatives with a definite IA. The risk that this patient harbors an unruptured (familial) IA is estimated at 11%, three (plausible range 1–5) times the risk in the general population. The annual risk of rupture of an IA is taken as 1% (0.5–2%)3,16,17,114-117 and the mortality and morbidity from rupture as 55% (50–60%) and 15% (10–20%), respectively.118 The lifetime risk of rupture (P) can be approximated by $P = 1 - (1 - r)^L$, where $r$ is the annual probability of rupture and $L$ is the life expectancy. For our patient this would amount to $1 - (1 - 0.01)^{30.8} = 26%$ (Figure 1). The annual risk of developing new IAs and a gradual increase in size are not shown in the tree, for the sake of simplicity.

Before the entire decision tree is “folded back,” one should determine the expected value of conservative and surgical treatment when the presence of an IA is certain. If there is no benefit of surgery in this comparison, then diagnostic screening can never be beneficial for a given patient. The sensitivity of the results to plausible changes in the estimates has been tested elsewhere.16,17 It appeared that the annual risk of rupture and the risk of surgical complications are the two most important factors for the treatment decision.

In strategy Do Not Screen, life expectancy of the key patient would be reduced from 30.9 to 30.6 years because of the risk of harboring an unruptured IA. Screening with IADSA results in a life expectancy of 30.8 years. Therefore, the difference between the Do Not Screen and Screen Now strategies equals 0.2 year. Discounting of later years and quality correction for disability decrease the benefit of intervention to only 0.03 dQALY. Sensitivity analysis showed that the risk of harboring an IA is a key issue in the analysis.

**Management Guidelines**

General management guidelines for the treatment of familial IAs and for screening are based on Figures 2A and 2B, respectively.9,17 Figure 2A shows for each age the break-even values of surgical mortality and morbidity, i.e., those values that result in equal dQALY for...
neurosurgical and conservative treatment. Only when the surgical mortality and morbidity are lower than the break-even value is neurosurgery recommended. For older age groups the break-even value of surgical mortality and morbidity is so low that conservative treatment is almost always preferred. Women have slightly higher break-even values because they have a higher life expectancy, resulting in a higher lifetime risk of rupture than men. When the annual risk of rupture of the IA is estimated at the low limit (0.5%), the break-even values for surgical mortality and morbidity are also lower.

Figure 2B shows the difference in dQALY between the Screen Now (with IADSA) and Do Not Screen strategies as a function of age. Screening is not beneficial in subjects <30 years of age. The benefits of surgery increase with ages above 30 years, as the risk of harboring an IA increases. Over the age of 65 years these benefits decrease steeply because the life-time risk of rupture again decreases. No additional benefit could be demonstrated for screening more than once in a lifetime. Decreasing the risks of screening by means of MRA would increase these benefits only slightly (0.02-0.05 dQALY), even when it would be a "perfect test," i.e., without complications and with 100% sensitivity and specificity, apart from having no complications. Screening can thus be recommended only for patients aged 35–65 years in whom there is an increased risk because of the familial disposition. Even then, however, the benefits of screening are quite small.

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