Natural history and general management of unruptured intracranial aneurysms

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After an aneurysmal subarachnoid hemorrhage, nearly half of the patients die and the half who survive suffer from irreversible cerebral damage. With increasing use of noninvasive neuroimaging techniques (for example, magnetic resonance and computerized tomography angiography), more unruptured cerebral aneurysms are found. To understand the prevalence of unruptured aneurysms in the general population, along with the risks of aneurysm formation, data on growth and rupture rates are crucial. The risk of rupture in aneurysms smaller than 10 mm is still not quite clear without a population-based prospective study. Nevertheless, a 0.5 to 2% annual risk may be a reasonable estimate. Growing aneurysms and those larger than 10 mm carry a higher rate of rupture. The management of an unruptured intracranial aneurysm should be based on a thorough understanding of the natural history of these lesions and careful evaluation of the morbidity and mortality levels associated with each treatment option.

KEY WORDS • subarachnoid hemorrhage • unruptured intracranial aneurysm
the relatively small sample size, and especially by the insufficient numbers of patients with no history of SAH (only 4%), the annual rupture rate of 1.3% was nevertheless similar to that reported in all other previously published retrospective series (1–2.3%).\textsuperscript{t8, t9} Overall, these findings may be more valuable for predicting the risk of aneurysmal bleeding in patients with an unruptured lesion who also had a history of SAH from another aneurysm that was surgically treated.

Tsutsumi, et al.\textsuperscript{45,46} reported on 62 patients with saccular, nonthrombotic, noncalcified unruptured aneurysms at locations other than the cavernous sinus, which were detected on cerebral angiography studies performed for causes other than SAH between 1976 and 1997. The 5- and 10-year cumulative risks of CT-confirmed SAH from small (<10 mm) aneurysms were 4.5 and 13.9%, respectively; from large (>10 mm) aneurysms the 5- and 10-year rupture risks were 33.5 and 55.9%, respectively. This result is similar to that reported by Juvela and colleagues for their series.

In 1998, the ISUIA investigators published a study (Part 1)\textsuperscript{16} detailing the risk of rupture and the risks associated with surgical intervention for unruptured intracranial aneurysms. The natural history of 1937 unruptured intracranial aneurysms in 1449 patients was assessed in this retrospective cohort study. The results are as follows.

In Group 1 (patients with no history of SAH from a different aneurysm; 727 individuals), the cumulative rate of rupture in lesions that were less than 10 mm in diameter at diagnosis was less than 0.05% per year, and in Group 2 (patients with a history of SAH from a different aneurysm that had been repaired successfully; 722 individuals), the rate was approximately 11 times higher (0.5%/year). The rupture rate in aneurysms that were 10 mm or more in diameter was less than 1% per year in both groups, but in Group 1 the rate was 6% in the 1st year for giant aneurysms (those ≥25 mm in diameter). The size and location of the aneurysm were independent predictors of rupture. Aneurysms 10 mm or more in diameter had a relative risk of rupture of 11.6. For posterior circulation aneurysms, the relative risk was 13.8 and 13.6 for basilar tip and vertebrobasilar locations, respectively.

Because of the exceedingly low rupture rate in the patients in Group 1 whose aneurysms were less than 10 mm in diameter, and the relatively higher morbidity and mortality rates (13.7%) associated with surgical repair, the investigators in the ISUIA\textsuperscript{16} seem to suggest that it is unlikely that surgery will reduce the rates of disability and death in patients with unruptured intracranial aneurysms smaller than 10 mm in diameter who have no history of SAH. These findings became the subject of significant controversy and impacted on neurosurgical practice in the management of unruptured intracranial aneurysms.

The authors normalized the prevalence rate of 0.65% for unruptured aneurysms. Nearly 80% of these intact lesions were smaller than 10 mm in their greatest diameter. The authors normalized the prevalence rate of 0.65 to 1.3% because only 53% of the patients underwent complete angiography studies. A simple mathematical reasoning based on the population of North America (250 million people during the years 1970–1980) and the prevalence rate yields 1.625 to 3.25 million people who harbored an unruptured aneurysm during that time period. It has been reported that 28,000 aneurysmal SAHs occurred yearly during the same period,\textsuperscript{26,35} during which the annual rupture rate ranged from 0.9 to 1.7%. Eighty percent of the 28,000 (or 22,500) aneurysmal SAHs occurred in lesions smaller than 10 mm, which indicated a 0.72 to 1.36% annual rupture rate for this group. In contrast, a 0.05% annual rupture rate, as reported in the ISUIA for aneurysms smaller than 10 mm, would yield a prevalence of 45 million unruptured small aneurysms (22,500/
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0.0005). Forty-five million represents approximately 18% of the population of the US and Canada between 1970 and 1980. In Part 1 of the ISUIA, 67% of aneurysms smaller than 10 mm were larger than 5 mm. This means that approximately 12% of the population (18% × 67%) will have an MR-detected cerebral aneurysm less than 5 mm in diameter.90 Certainly, the discovery of unruptured aneurysms of any size is much less frequent than this number, even in a busy MR imaging center. The 1 to 2% risk of SAH, however, would be in closer agreement with the results reported by Juvela, et al.,25 and Tsutsumi, et al.46

Risk Factors for Aneurysm Rupture

Size of Aneurysms in Stable Compared With Growing Lesions. In the ISUIA it has been pointed out that the size and location of aneurysms were independent predictors of rupture. In Group 1, aneurysms that were 25 mm or more in diameter had a rupture rate of 6% in the 1st year.16 Juvela and colleagues21,22,24 observed that aneurysms that ruptured at a later time had more often increased significantly in size (≥ 1 mm) than the largest aneurysms in patients without bleeding.

Locations of Aneurysms. In ISUIA Group 1, the relative risk of rupture was 13.8 for aneurysms at the basilar tip and 13.6 for those in the vertebrobasilar or posterior cerebral artery distribution, compared with other locations. For posterior communicating artery aneurysms, the relative risk of rupture was 8.0. In Group 2, the relative risk of rupture was 5.1 for aneurysms at the basilar tip. Asari and Ohmoto21 found that aneurysms of the vertebrobasilar and middle cerebral arteries have a statistically higher probability of subsequent bleeding.

Shape of Aneurysms. Few reports address the relationship between the risk of rupture and the shape (multilobed or with daughter domes) of unruptured aneurysms. Asari and Ohmoto21 reported that SAH occurred in seven of 22 multilobed aneurysms and in two of 50 single-lobed ones. Multilobed lesions have a significantly higher risk of hemorrhage than do single-lobed unruptured aneurysms. Wiberg, et al.,41 and Sampaio, et al.,42 reported similar findings in their small, retrospective aneurysm series.

Age and Sex of Patients. Female sex seems to be a risk factor affecting both aneurysm formation and growth.22 There were two peaks in the prevalence of aneurysms in women (at 40–49 and 60–69 years of age) reported by Iwamoto, et al.,17 in a series of 1230 consecutive autopsy procedures. This corresponds to the finding that spontaneous SAH occurs most commonly in patients who are between 40 and 60 years of age. There is an approximately 1.6-fold female predominance in the prevalence of aneurysms.93 Interestingly, among men the prevalence of aneurysms remained unchanged across the range of age groups.17

Cigarette Smoking (Active Compared With Former Smokers). There is evidence that cigarette smoking may hasten the growth of preexisting aneurysms,23 although the mechanism of this remains unknown. Some observations, however, indicate that a change in the ratio of elastase/alpha-1-antitrypsin in the plasma and arterial wall in cigarette smokers (that is, increased elastase activity and/or decreased alpha-1-antitrypsin) may contribute either to aneurysm formation or to SAH.24 The faster the growth, the more likely rupture may be.22

Families With Intracranial Aneurysms and History of Rupture. In families with two or more first-degree members, especially siblings and mother-daughter pairs, or two first- and second-degree members with SAH, the risk that other relatives will harbor unruptured intracranial aneurysms is approximately 9 to 11%, which is higher than in the general population.27,40

Genetic Conditions. The presence of ADPKD is associated with a 15% prevalence9 of cerebral aneurysms. Patients with Type IV Ehlers–Danlos syndrome, hereditary hemorrhagic telangiectasia, neurofibromatosis Type 1, alpha-1-antitrypsin deficiency, Kluneberl syndrome, tuberous sclerosis, Noonan syndrome, and alpha-glucosidase deficiency have all been shown to have a higher incidence of intracranial aneurysms compared with the general population.

General Clinical Management of Unruptured Aneurysms

Aneurysmal SAH carries a high fatality rate. In the retrospective part of the ISUIA, 66% of the patients (83% in Group 1 and 55% in Group 2) who suffered an SAH from a previously unruptured aneurysm died.1 In the study by Juvela, et al.,23 52% of patients who sustained an aneurysm rupture during the follow-up period died. Tsutsumi and his colleagues46 reported an 86% mortality rate due to aneurysm ruptures. Ideally, the aneurysm should be secured before it ruptures. Nevertheless, given the discrepancies in the data regarding the natural history of unruptured aneurysms and their tendency to rupture,16,22–24,49,51,53 and the incidence of morbidity and mortality associated with prophylactic treatments,3,20,36,38,48 decisions regarding the management of unruptured cerebral aneurysms are challenging and have to be individualized for each patient. Because only a proportion of aneurysms actually bleed, the key to the management of unruptured lesions is first to identify patients who are at greatest risk of harboring an aneurysm, and second to determine which of those aneurysms are at greatest risk of rupture. At present, however, both the natural course of unruptured cerebral aneurysms and outcome after treatment continue to be subjects of controversy.

For example, Juvela22 advocated that patients with unruptured aneurysms, especially young and middle-aged adults, should be surgically treated regardless of the aneurysm size and patients’ smoking status. White and Wardlaw47 argue that in patients with no history of SAH the risk/benefit analysis favors treatment in individuals younger than 50 years of age for all aneurysms except those located in the anterior circulation and smaller than 7 mm in diameter. For patients older than 50 years, treatment is only favored for lesions larger than 12 mm, and possibly for posterior circulation aneurysms larger than 7 mm.

In 2000, the Stroke Council of the American Heart Association issued a scientific statement with the following recommendations for the management of unruptured intracranial aneurysms:

The treatment of small incidental intracavernous ICA aneurysms is not generally indicated. For large symptomatic intracavernous aneurysms, treatment decisions should be indi-
visualized on the basis of patient age, severity and progression of symptoms, and treatment alternatives. The higher risk of treatment and shorter life expectancy in older individuals must be considered in all patients and favors observation in older patients with asymptomatic aneurysms.

Symptomatic intradural aneurysms of all sizes should be considered for treatment, with relative urgency for the treatment of acutely symptomatic aneurysms. Symptomatic large or giant aneurysms carry higher surgical risks that require a careful analysis of individualized patient and aneurysmal risks and surgeon and center expertise.

Coexisting or remaining aneurysms of all sizes in patients with SAH due to another treated aneurysm carry a higher risk for future hemorrhage than do similar sized aneurysms without a prior SAH history and warrant consideration for treatment. Aneurysms located at the basilar apex carry a relatively high risk of rupture. Treatment decisions must take into account the patient’s age, existing medical and neurological condition, and relative risks of repair. If a decision is made for observation, re-evaluation on a periodic basis with CT/MR [angiography] or selective contrast angiography should be considered, with changes in aneurysmal size sought, although careful attention to technical factors will be required to optimize the reliability of these measures.

In consideration of the apparent low risk of hemorrhage from incidental small (<10 mm) aneurysms in patients without previous SAH, treatment rather than observation cannot be generally advocated. However, special consideration for treatment should be given to young patients in this group. Likewise, small aneurysms approaching the 10-mm diameter size, those with daughter sac formation and other unique hemodynamic features, and patients with a positive family history for aneurysms or aneurysmal SAH deserve special consideration for treatment. In those managed conservatively, periodic follow-up imaging evaluation should be considered and is necessary if a specific symptom should arise. If changes in aneurysmal size or configuration are observed, this should lead to special consideration for treatment.

Asymptomatic aneurysms of ≥10 mm in diameter warrant strong consideration for treatment, taking into account patient age, existing medical and neurological conditions, and relative risks for age at rupture.

**Screening for Occult Intracranial Aneurysms in Patients With a Family History of Aneurysmal SAH**

In 1999, a prospective study conducted by the Magnetic Resonance Angiography in Relatives of Patients with Subarachnoid Hemorrhage Study Group revealed the benefits and risks of screening for aneurysms in first-degree relatives of patients with sporadic SAH.27 In this study a prevalence rate of 4% was found for unruptured aneurysms. The prevalence reflects that in the general population, calculated from available data. Based on the estimated annual risks of rupture of 0.46% for lesions less than 5 mm in maximal diameter, 0.95% for aneurysms between 5 and 12 mm, and 6.8% for those larger than 12 mm, the number of relatives who would need to be screened to prevent one SAH on a lifetime basis was 149, and 298 would have to be screened to prevent one fatal SAH. Therefore, implementation of a screening program for the first-degree relatives of patients with sporadic SAH was not recommended. Although the investigators in this study may have underestimated the prevalence of unruptured aneurysms because MR angiography was performed on 1.5-tesla MR imaging systems with time-of-flight technique, the sensitivity of this method was 80%.22

Nevertheless, in families with two or more first-degree members, especially siblings and mother-daughter pairs, or two first- and second-degree members with SAH, the risk that other relatives will harbor unruptured intracranial aneurysms is approximately 9 to 11%.37,40 This is much higher than the prevalence in the general population, and therefore it has been advocated that these family members be screened. The modalities of MR imaging, MR angiography, and CT angiography provide adequate noninvasive options for screening. The optimal patient age at which screening should be performed is not known. It has been reported that SAH occurs at a younger age in subsequent generations.6 In siblings with SAH, aneurysmal rupture occurs within the same decade of life significantly more often than it does in randomly selected pairs of patients with SAH.28,41 It therefore seems reasonable to start screening first-degree relatives, especially siblings, in families with two or more affected members at a younger age than that at which the patients suffered their SAH. Nevertheless, cost-effectiveness has not been evaluated in clinical studies and screening should be considered on an individual basis.4

**Prevalence of Aneurysms in Patients With ADPKD**

Approximately 500,000 individuals in the US carry a mutant gene for ADPKD, making it one of the most common inherited disorders.24 In patients with ADPKD, this disorder is associated with an increased prevalence of cerebral aneurysms and increased risk of SAH. The clinical literature on the prevalence of asymptomatic aneurysms in patients with ADPKD reports a rate of 14 to 16% at autopsy and on conventional angiography studies.7 There is an absence of population-based data on the rates of aneurysm rupture specifically in patients with ADPKD. Nevertheless, the mean age at rupture in patients with ADPKD is between 35 and 40 years,9,11,29 that is, 10 to 20 years earlier than in patients with sporadic SAH. This indicates that ADPKD per se is a risk factor for aneurysm rupture. Using decision analysis, a statistical technique that aids in making decisions that involve competing risks and benefits, Butler, et al.,7 demonstrated that an MR angiography screening strategy increased the life expectancy in young patients with ADPKD and reduced the financial impact of this disorder on society.

**Monitoring de Novo Aneurysms**

The annual rate of new aneurysm formation in patients treated for aneurysmal SAH is reported be as high as 1.8%, especially in those with a history of multiple lesions.28 Follow-up duration in this study was 4.4 ± 1.6 years. During 1789 patient-years of follow up in 89 patients with unruptured aneurysms, Juvela22 found 19 de novo aneurysms in 15 patients, of which two lesions caused SAH. The probability of de novo aneurysm formation was 0.84% per year. A similar annual rate, 0.89%, was reported by Tsutsumi, et al.38 The cumulative risk becomes significant after 9 to 10 years. These findings support the rationale for late (10-year) angiographic follow-up review in patients with aneurysms that have been treated surgically or endovascularly. In addition, female sex and active smoking were the significant independent risk factors for new aneurysm formation.22 Cessation of
smoking is very important for patients with unruptured aneurysms and possibly also for those with a history of SAH.

CONCLUSIONS

The natural history of unruptured intracranial aneurysms, especially small lesions, is still not quite clear and may be difficult to define without a population-based prospective study. Nevertheless, a 0.5 to 2% annual risk of rupture in aneurysms smaller than 10 mm may be a reasonable estimate. Aneurysms growing in size and larger than 10 mm carry a higher rate of rupture, and their management therefore should be more aggressive. The use of MR angiography or CT angiography screening for aneurysm in patients with ADPKD or in family members with two or more first-degree relatives presenting with aneurysmal SAH is warranted.

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