Defining the Natural History of Unruptured Aneurysms

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Despite advances in neurosurgical technique, neuroanesthesia, and neurocritical care and the evolution of endovascular therapy, aneurysmal subarachnoid hemorrhage (SAH) continues to be associated with poor outcome in a majority of patients. The 30-day mortality rate for SAH approaches 50%, and nearly one half of survivors suffer major neurologic morbidity. These dismal outcomes are especially significant since SAH affects a younger cohort than ischemic stroke, and the impact is magnified in terms of lost quality life-years. On the basis of an annual incidence of 10/100,000, it is estimated that nearly 30,000 Americans will have an aneurysmal SAH each year. Although prevention of SAH would seem to be the most effective strategy for reducing morbidity, the optimal management of patients with unruptured cerebral aneurysms remains controversial and requires a precise assessment of the risks for various treatment strategies and accurate knowledge of the natural history of the disease process.

Unfortunately, the natural history of unruptured cerebral aneurysms is poorly understood. Until recently, few systematic studies have enrolled a sufficient number of patients for follow-up, and larger retrospective population analyses were done prior to the advent of current imaging modalities. Five years ago, the first phase of the International Study of Unruptured Intracranial Aneurysms (ISUIA) study provided a retrospective analysis of previously identified patients with unruptured cerebral aneurysms not receiving treatment, as well as a temporal snapshot of a cohort of patients followed prospectively over a 4-year period. The study reported what many considered to be remarkably low rates of aneurysm rupture (especially for aneurysms <10 mm in diameter) and a remarkably high rate of complications for surgical treatment, thus prompting a longer-term prospective analysis.

In the second ISUIA study, >4000 patients were enrolled over a 7-year time period from >60 centers in the United States, Canada, and Europe. To date, this study represents the most significant contribution to the knowledge of the natural history of unruptured aneurysms. Among the patients studied, 1692 did not have aneurysm treatment (natural history group), 1917 had microsurgical procedures (clipping), and 451 had endovascular therapy (coiling). These cohorts were divided into 2 groups: group 1 were patients who had no prior history of aneurysmal SAH, and group 2 were patients with a history of prior aneurysmal SAH.

The ISUIA prospective study similarly demonstrated an exceptionally low 5-year cumulative risk of hemorrhage for small aneurysms; the 5-year cumulative rupture rates for anterior circulation aneurysms in group 1 (no prior SAH) patients were 0% (aneurysms 3 to 7 mm), 2.6% (7 to 12 mm), 14.5% (13 to 24 mm), and 40% (≥25 mm). Posterior circulation aneurysms (including posterior communicating artery aneurysms) in group 1 patients had 5-year rupture rates of 2.5%, 14.5%, 18.4%, and 50%, respectively, for the same size categories. Aneurysm rupture rates did not significantly differ between group 1 and group 2, except for a slightly higher rupture rate in <7 mm aneurysms for group 2. By multivariate analysis using proportional hazards methodology, statistically significant predictors of increased risks of hemorrhage included larger aneurysm size and 2 locations (tip of basilar artery and posterior communicating artery). Patient age was not significant when included in the multivariate model.

Morbidity and mortality for microsurgical and endovascular treatment was lower than that reported in the earlier ISUIA study, but higher than in previous retrospective or prospective reports. For combined major morbidity and mortality, there was no significant outcome difference between surgical (10.1% to 12.6%) and endovascular (7.1% to 9.8%) therapy. Age, aneurysm size, prior stroke, and aneurysmal mass effect were associated with worse outcome for surgery, whereas aneurysm size and posterior circulation portended poor outcome with coiling. Only about one half of coiled aneurysms were completely obliterated.

Although the prospective ISUIA data are a great improvement on earlier retrospective data, there are several shortcomings, and significant questions remain. We believe that these data are profoundly affected by selection bias. It is not clear why the busy academic aneurysm centers in this trial enrolled so few patients (about 10 per center per year). Based on the volume at our institution (>120 newly diagnosed unruptured aneurysms evaluated annually), centers in ISUIA may have enrolled <10% of all patients seen. No data are provided regarding the characteristics or fate of eligible patients not treated in the study.
entered into the trial. Importantly, the patients in the natural history (untreated) group were substantially different from those receiving treatment. Compared with patients with surgical or endovascular treatment, the cohort with no treatment had significantly higher incidence of prior SAH, ischemic cerebrovascular disease, intracranial hemorrhage, transient ischemic attack, hypertension and hypertension treatment, myocardial infarction, and alcohol or tobacco abuse, and had significantly lower rates of cranial nerve deficit, aneurysm mass effect, seizures, headaches, diagnosis by CT or MRI, family history of aneurysms, and use of stimulants and oral contraceptives. These broad and pervasive differences between the 2 cohorts suggest that treating physicians selected patients by undefined means, possibly identifying a category of patient at lower risk for hemorrhage for no treatment. The data concerning the relatively low rupture rates for aneurysms <12 mm run directly contrary to many previously published retrospective accounts, where the majority of ruptured aneurysms were <10 mm in size, including a substantial percentage of aneurysmal bleeds for aneurysms <7 mm.11–13 It is also not clear why cavernous internal carotid artery aneurysms (n=210, or 12.4% of untreated) were included in the ISUIA analysis, since the great majority of these lesions (especially smaller) are not located in the intradural/subarachnoid compartment and thus would not cause SAH (as shown in this study). Although 51 patients in the no-treatment group were analyzed with the primary outcome of SAH, another 36 patients with SAH in this cohort were excluded due to another (indeterminate) potential source of hemorrhage; thus, only 57% of all SAH were considered in the analysis. No analysis of aneurysm shape or configuration (eg, daughter sacs) was included in the analysis.12 Finally, the follow-up was <5 years for >50% of patients.

Complication rates noted for the treated patients in this study (1-year significant morbidity and mortality 7.1% to 12.6%) also exceed those noted in previous retrospective reports.5,9,10,14 Although selection bias might distort these findings, these data should alert physicians to the significant (and likely underestimated) risks of these procedures. On the other hand, significant advancements in technique for both microsurgical and endovascular treatment may have improved both morbidity rates and technical outcomes (eg, complete obliteration) since the epoch of the ISUIA trial.

Given these shortcomings, how are we to incorporate these data into clinical practice? The ISUIA findings do not constitute level 1 evidence and should not be taken as practice guidelines. This trial represents a prospective observation on a cohort of patients that is not necessarily representative of all patients harboring intracranial aneurysms. The true natural history of unruptured aneurysms may never be described. Consequently, these data, with identified caveats, should be incorporated into each practitioner’s global view of unruptured aneurysms and considered in light of alternative data in the decision-to-treat analysis that is done on an individual basis with every patient.

If, as the ISUIA authors contend,1 ruptured aneurysms are “different” than unruptured aneurysms, one might postulate 2 different pathogenic processes. The exact forces that lead to aneurysm formation and rupture are unknown, as are the interaction among risk factors such as hypertension, smoking, sex, family history (presumed genetic influence), and local hemodynamic forces.15 Finally, little is known about the biologic activity that occurs in the aneurysm dome, adjacent parent vessel, and the organism as a whole, as well as the effect of stagnation and thrombosis within the aneurysm.

So, where do we go from here? Perhaps these data will trigger a true population-based assessment or some type of randomized trial aimed at elucidating the risks with a greater degree of confidence, and incorporating more variables in the analysis to examine hemodynamic factors,16 the role of the aneurysm morphology,12 and genetic and proteomic influences. For clinicians, the challenge remains to identify the appropriate aneurysm patient and determine the safest therapy (including no intervention). If previous studies on hemorrhage risk are correct, then the data presented in this study would suggest that experienced cerebrovascular surgeons and neuro-interventionalists are uncommonly good at identifying who these patients are.

References

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