Editorial

Unruptured aneurysms

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For the ISUIA Investigators

We read with interest the paper by Juvela, et al., the abstract of which appears on page 57. The Helsinki group has produced interesting natural history information about this cohort of 141 patients with unruptured intracranial aneurysms who were identified between 1956 and 1978. The aforementioned paper provided additional follow-up information to supplement that presented in the prior natural history paper from 1993, but only 57 patients were available for continued follow-up review over the past 7 years.

It is important to point out that 135 of the 141 patients in this cohort have a history of subarachnoid hemorrhage (SAH) from another aneurysm (referred to as Group 2 patients in the International Study of Unruptured Intracranial Aneurysms [ISUIA]), so the study by Juvela, et al., essentially involves only that subgroup of patients. In the ISUIA, the rupture rates for Group 2 patients with small unruptured intracranial aneurysms were considerably higher than for Group 1 patients (those with no history of SAH from another aneurysm). The rupture rates in Group 2 patients with small unruptured intracranial aneurysms in the ISUIA study (0.5%/year) and the overall Group 2 rupture rates (approximately 0.65%/year) are entirely compatible with the rupture rates of 1.3% per year reported by Juvela, et al., given the large confidence intervals (CIs) associated with the small cohort of patients in their study. It is not possible to make a judgment about rupture rates for subgroups of symptomatic Group 2 patients or Group 1 compared with Group 2 patients in the Juvela study because the authors have provided data on only five patients in one group and six in another.

Although the authors have stated that their retrospectively selected cohort provides a less biased sample than the cohort produced by the ISUIA, it is clear that the mix of patients in whom unruptured intracranial aneurysms were identified 30 to 50 years ago in Helsinki, Finland, before the advent of computerized tomography (CT) and magnetic resonance technology, is very different from the mix being seen in medical centers across North America and Europe today.

Prospective identification of patients with unruptured intracranial aneurysms across North America and Europe in our study indicates that the majority of patients who are treated surgically or nonsurgically are Group 1 patients, whereas the Juvela study provides a cohort that is composed of 96% Group 2 patients, which is not representative of those with unruptured intracranial aneurysms who are seen in the modern era. In addition, substantial potential referral bias is inherent in a single-center study with a small sample size. Concern over this possibility with our own single-center data was one of the driving forces that led to the development of the ISUIA. It is also clear that all of the SAH endpoints that occurred before 1975 would involve diagnosis without the benefits of cross-sectional imaging techniques (that is, CT scanning).

The authors’ assumption in the discussion that the retrospective natural history component of the ISUIA involved approximately one patient per center per year is not accurate, as has been previously reported. The ISUIA started out with approximately 34 centers, which were allowed to enter patients retrospectively only as far back as all hard copies of their arteriograms were saved in that center. For most North American centers, for instance, this dictated that they could enter patients retrospectively from only a few years ago. Nevertheless, the largest number of patients entered retrospectively by a single center exceeded the number in the Juvela study.

Regarding risk factors for bleeds of unruptured intracranial aneurysms, the assumption by Juvela, et al., that risk factors were not analyzed for Group 1 and Group 2 patients together is also inaccurate. Analyses were performed both ways, and while doing so, it became clear that aneurysm size and location had very different impacts on future rupture for aneurysms in Group 1 compared with Group 2. It is not possible to make such a determination with the cohort presented by Juvela, et al., because only 11 Group 1 patients were included in that cohort. The ISUIA data provided evidence that rupture rates were higher among Group 2 patients, and, although aneurysm size was a major predictor for future rupture among Group 1 patients, we could not say without a doubt that it was a risk factor for future rupture among Group 2 patients. Although Juvela, et al., suggest that aneurysm size is a risk factor for future rupture in their Group 2 cohort, the level of significance is very marginal, as it is for other risk factors presented.

Although one can make the case, as the ISUIA investigators did in their recent paper, that the retrospective na-
ture of the ISUIA cohort provides potential for bias, it does not suffer from bias created by single medical center populations or small sample size. In addition, virtually all of the evidence collected subsequently to assess more completely a possible bias in the ISUIA retrospectively selected cohort indicates that the amount of bias is remarkably low. The argument that dangerous aneurysms are being surgically treated is not supported by a comparison of surgically and nonsurgically treated patients in the prospectively chosen ISUIA cohort, which shows that the two groups are almost identical. We assert that this reflects a lack of consensus about the management of patients with unruptured intracranial aneurysms. All aneurysm size categories, locations, and other baseline characteristics, including the patients’ smoking status, were well represented in surgically and nonsurgically treated groups, including the retrospectively chosen cohort. The baseline characteristics of patients in this retrospectively selected cohort were compared with the only available population-based cohort with intracranial aneurysms from Rochester, Minnesota, and remarkably similar characteristics were confirmed in these two cohorts. Additionally, in approximately 10 of our 60 centers between 0% and 20% of patients with unruptured aneurysms underwent operations during the retrospective and prospective portions of the study. The rupture rate for small (<10 mm) unruptured intracranial aneurysms among Group 1 patients entered from those centers was 0%.

We are especially concerned about the conclusion by Juvela, et al., that all unruptured intracranial aneurysms should be surgically treated. Although we agree that younger patients (<45 years old) are better surgical candidates, it is unsound to take data from this single-center small cohort involving Group 2 patients identified before the CT era and extrapolate it to all patients with unruptured aneurysms identified currently. Their conclusion also does not reflect a realistic understanding of the operative morbidity and mortality rates associated with repair of these lesions.

So far, compared with operative morbidity and mortality rates in most of the leading medical centers in North America and Europe, including Helsinki, the ISUIA has yielded overall 1-year operative morbidity and mortality rates of approximately 15.7% in Group 1 and 13.1% in Group 2. Even if surgical morbidity and mortality rates are found to be half this for patients with small (<10 mm) unruptured intracranial aneurysms, the most comprehensive rupture rate data available at this point indicate that one would be taking more than a lifetime of rupture risk in operating on these patients. Even with overall rupture rates of 1% per year, the patient assumes 13 to 15 years worth of risk related to the surgical treatment.

It is noteworthy, however, that Juvela, et al., have become more conservative in their recommendations over the 7-year interval since their last natural history paper, saying that surgery is advisable if patient age and technical factors allow and that procedures should be performed only by experienced surgeons to decrease associated morbidity and mortality levels. Further, in their recent publication, they are more strict about age criteria, suggesting that surgery be considered in younger patients (<50 years old) and that smoking cessation may be an alternative approach to treating unruptured aneurysms. Perhaps surgery in this group of patients is not being generally recommended.

A subsequent paper by Tsutsumi, et al.,6 regarding the risk of rupture from incidental cerebral aneurysms also deserves comment. Although the findings in their study confirmed the overwhelming importance of aneurysm size in determining natural history rupture rates among Group 1 patients with unruptured intracranial aneurysms, the absolute rates were higher than those reported in the ISUIA. It is important to note that although these natural history findings are of interest, they are based on follow-up review of a total of only 62 patients, in whom there were ruptures in five of six individuals with aneurysms 10 mm or larger in diameter, and three of 56 patients with aneurysms smaller than 10 mm in diameter. This is a single-center study from Japan that is subject not only to the potential referral and treatment bias associated with a single-center series (as opposed to different patterns over 30–60 centers) but also the unavoidable difficulties encountered with small numbers of patients, which make the CIs for the rupture rates wide enough to be compatible with those reported from the ISUIA.3 As the authors note, the mean age of the cohort in their paper is 70.8 years compared with mean ages of 50 to 55 years among surgically and nonsurgically treated patients in the ISUIA. The three ruptures that occurred in patients with aneurysms smaller than 10 mm in diameter involved patients who were 68, 71, and 84 years old.

The other very important point that needs to be considered is the possibility that natural history rupture rates could be different in this population based in part on genetic factors. Only 1% of the ISUIA cohort was of Asian descent. Several population-based comparisons have indicated higher incidence rates of SAH in Japan compared with populations in North America and Europe, and there are compelling reasons to believe that genetic factors are important determinants of aneurysm development and rupture.2 We are pleased to learn that the findings in the ISUIA have prompted a similar study in the Japanese population.

References