Editorial

Assessing the constancy of intracranial aneurysm growth rates

Gavin Britz, M.D.
H. Richard Winn, M.D.

Cerebrovascular Center, Duke University Medical Center, Durham, North Carolina; and Department of Neurosurgery, Mount Sinai School of Medicine, New York

Despite ongoing natural history studies, the natural history of unruptured cerebral aneurysms, including patterns of growth, remains undefined. Elucidating this growth pattern may allow physicians to determine if specific periods of risk occur or if the risk to the patient is constant. Two possibilities exist for the pattern of aneurysm growth: linear (constant) or episodic with periods of growth separated by periods without. Linear growth would theoretically be associated with a constant predictable risk based on the growth rate, which occasionally could be rapid, whereas episodic growth might be associated with periods of unpredictable increased or decreased risk. It has been assumed that cerebral aneurysms have linear growth, and the authors of the proceeding article have tested this hypothesis by evaluating the plausibility of a constant growth rate for intracranial aneurysms via mathematical modeling. They tested the plausibility of a constant growth rate by comparing hypothetical cohorts of patients with different initial mean constant lesion growth rates and the population-based incidence of subarachnoid hemorrhage (SAH). The authors found that even within a hypothetical cohort with a growth rate that most closely resembled the incidence rates in the actual population, the specific incidence rates in the model differed substantially from those in the observed population data. They therefore concluded that the actual growth process must be episodic. This conclusion should be interpreted with caution as biological behavior is seldom accurately predicted with mathematical modeling. An aneurysm is a complex active biological structure and not simply a balloon that obeys the Laplace Law. Constant biological changes are occurring at all times within the aneurysm wall and can be related to flow or molecular changes that are not clearly understood. Not all aneurysms are equal and some may indeed have constant slow growth whereas others may be more unstable and associated with episodic growth based on factors that are currently unknown.

Regarding the limitations of the paper by Koffijberg and colleagues, as with other mathematical modeling studies, assumptions are made that can hinder a conclusive argument. This is particularly true if multiple assumptions are made despite the authors’ arguments to the contrary. The first assumption to be addressed concerns the multiplicity of aneurysms not influencing the results. Although the authors stated that the International Study of Unruptured Intracranial Aneurysms did not show an increased risk of SAH with multiple aneurysms, which was also demonstrated by Juvela et al., and therefore will not affect the results of their own study, it must be remembered that many other studies have shown that multiple aneurysms do increase the risk of SAH in patients. In 1974 Mount and Brissman reviewed 158 cases of unruptured multiple aneurysms and found a bleeding rate of at least 10% per year in patients with multiple aneurysms. Wiebers and associates have also noted that unruptured lesions that are part of multiple aneurysm constellations can have a greater propensity to rupture than solitary aneurysms, and this hypothesis was supported by data from Winn et al. The Finnish data also support the concept that patients with multiple aneurysms have a higher likelihood of rupture of an unruptured intracranial aneurysm. Heiskanen and Marttila have reported on 84 patients with multiple aneurysms in whom a ruptured lesion was definitely identified and treated at surgery. Of these 84 patients, 8 had a recurrent hemorrhage from the unruptured aneurysm during follow-up periods ranging from 4 months to 11 years with a rupture rate of > 1% per year. Heiskanen has also reported on a 10-year follow-up in 61 patients with unruptured intracranial aneurysms who had undergone surgery for a prior ruptured aneurysm and with a lesion rupture rate of > 1% per year. Japanese data also support an increased risk of hemorrhage in patients with multiple aneurysms, with Yasui and associates demonstrating an annual rupture rate of 6.8% for multiple aneurysms and 1.9% for single ones. Therefore, if the latter argument holds true, it would significantly change the results of the study by Koffijberg et al., as up to 30% of patients have multiple aneurysms.

The second assumption that must be addressed is in regards to ignoring the age-related mortality rate and its insignificance. This factor may not be as insignificant as the authors suggest. In the recent International Study of Unruptured Intracranial Aneurysms data, a patient’s age was especially important because, although it does not affect rupture rates, it has a substantial effect on surgical morbidity and mortality rates, which would significantly affect the results of their analysis. The third assumption that needs to be addressed regards ignoring the association between growth and rupture risk. This factor is significant as growth does not always equal rupture, and there are no direct clinical data that prove that growth really equates with rupture. Insufficient data...
exist in the literature to conclusively document a relationship between aneurysm growth and risk of rupture, and therefore, any speculation of its minimal affects on the modeling must be considered with caution. In regards to the fourth assumption of a decreasing aneurysm size affecting the results, we agree with the authors that the effect of a decreasing aneurysm size is probably negligible, although it is interesting that in bed-rested patients, cerebral angiograms obtained 6 months after aneurysmal SAH revealed a decrease in the size of ruptured aneurysms in 30%. Moreover, the authors failed to highlight another significant assumption: they compared simulation with population-based data on SAH incidence rates and assumed that these were correct data. Population-based data are often significantly flawed, and therefore, the foundation of the comparison may be flawed.

In summary, Koffijberg and associates have demonstrated mathematically that aneurysms appear to have episodic growth and rupture rather than constant growth; however, as delineated above, the conclusions must be taken with reservations as mathematics is not biology. The truth is probably that each aneurysm is different based on the genetic makeup of an individual, specific flow dynamics to the aneurysm and a specific cascade of inflammatory and molecular changes occurring in the aneurysm wall that are related to flow and genetics and cause some aneurysms to remain stable, others to have linear growth, and others to have episodic growth.

Response

HENDRIK KOFFIJBERG, PH.D.
ERIK BUSKENS, M.D., PH.D.
ALE ALGRA, M.D., PH.D.
MARIJKE J. H. WERMER, M.D., PH.D.
GABRIEL J. E. RINKEL, M.D.

We appreciate the thoughtful and detailed comments on our article. Furthermore, we fully agree with Drs. Britz and Winn that not all intracranial aneurysms are equal. Some aneurysms can exhibit constant growth, whereas others display episodic growth, possibly at different growth rates. In fact, the main point of our article is a constant growth rate for (all) intracranial aneurysms, in general, is unlikely. The actual growth process is likely to be episodic, at least for some aneurysms.

The main critique of Drs. Britz and Winn focuses on several assumptions in our model. Although we agree that assumptions may hinder a conclusive argument and that each additional assumption may weaken the overall conclusion to an unknown degree, there are several points on which we disagree with the commentators. With respect to the first assumption—a multiplicity of aneurysms does not influence the results—we can only conclude that it is currently unclear whether multiple aneurysms increase the risk of SAH in patients. Evidence for and against this notion can be found in the literature, as indicated by Drs. Britz and Winn. Moreover, the effect of a multiplicity can vary between regions and populations, which would partially explain the diverse findings reported in the literature. The results by Yasui and associates are likely to be valid worldwide. As Yasui and associates have stated in their discussion: “the higher incidence of