Risk Profile of Intracranial Aneurysms
Rupture Rate Is Not Constant After Formation

Koji Sato, MD; Yuhei Yoshimoto, MD

Background and Purpose—Management of asymptomatic unruptured intracranial aneurysms remains controversial, and recent prospective follow-up studies showed that the rupture rate of small aneurysms is very low. These results are inconsistent with the finding that the majority of ruptured aneurysms in patients with subarachnoid hemorrhage are small.

Methods—A Markov model was constructed to simulate the natural history of intracranial aneurysms. All epidemiological and statistical data obtained from the Portal Site of Official Statistics of Japan (e-Stat) were adjusted to the standardized age distribution. From the selected data of aneurysm formation, the prevalence of unruptured aneurysms was estimated as 1.45% and the incidence of subarachnoid hemorrhage calculated to be 19.7/100 000/year in the whole standardized population.

Results—The function for rupture rate constant with time was first analyzed. Selected values for annual rupture rates of 0.3%, 0.5%, 0.7%, and 1.0% showed inconsistencies in the relationship between the prevalence of unruptured aneurysm and the incidence of subarachnoid hemorrhage. Next, the function for a short period of high risk followed by a long period of low risk was considered. Annual rupture rates of 0.5%, 0.7%, and 1.0% indicated epidemiological compatibility with additional early rupture rates of 20%, 15%, and 10%, respectively.

Conclusions—This study suggests that some aneurysms bleed shortly after formation and thus are rarely detected as unruptured aneurysms. Most aneurysms without early rupture remain stable for the remainder of life through some healing process, and prophylactic treatment for incidentally identified small unruptured aneurysms has no rationale. (Stroke. 2011;42:3376-3381.)

Key Words: aneurysms ■ Markov model ■ subarachnoid hemorrhage

Incidental detection of brain abnormalities has increased in recent years with the introduction of MRI and poses various practical and ethical issues. The clinical relevance and natural course of such asymptomatic abnormalities are largely unknown and may differ markedly from those of similar symptomatic lesions. In particular, the management of asymptomatic unruptured intracranial aneurysms remains controversial, so identifying the subset of patients likely to have problems with untreated aneurysms is an important clinical issue.

The International Study of Unruptured Intracranial Aneurysms (ISUIA) showed that the size of intracranial aneurysms is a primary determinant of the likelihood of rupture and that the rupture rate of small aneurysms is very low. However, these findings of the natural history of intracranial aneurysms seem to conflict with the well-known epidemiological data that the majority of ruptured aneurysms in patients with subarachnoid hemorrhage (SAH) had diameters of <10 mm. The prevalence of unruptured aneurysms will also influence the management strategy. The prevalence in the general population combined with the annual risk of rupture should equal the incidence of SAH, so “higher prevalence” would imply “lower risk.” Previous studies used life-table analysis to calculate the lifetime risk of unruptured aneurysms. However, the clinical situation may be different from simple rupture risk analysis based on assumptions of unchanging rupture rate. Therefore, a model of the natural history must incorporate changes in the rupture rate with time.

The present study constructed a mathematical model of the natural history of unruptured aneurysms and used the model to speculate about the risk profile of intracranial aneurysms.

Methods

Standardized Population Pyramid
All statistical data used in this study were obtained from the Portal Site of Official Statistics of Japan (e-Stat, www.e-stat.go.jp). The e-Stat site, developed by the Statistics Bureau, Ministry of Internal Affairs and Communications with the collaboration of other ministries and agencies, is managed by the Incorporated Administrative Agency National Statistics Center. The Statistics Bureau and the Director-General for Policy Planning of Japan are central in the official statistical system in producing and disseminating basic official statistics and coordinating statistical work under the Statistics Act and other legislation.
In a systematic review, the prevalence of aneurysms was 2.3% for adults without specific risk factors and tended to increase with age from approximately 0% for age ≤ 19 years, 1.3% for age 20 to 39 years, 1.8% for age 40 to 59 years, and 2.2% for age 60 to 79 years. This increase was statistically significant in a weighted linear regression. Therefore, we assumed that de novo aneurysm formation did not occur at age < 20 years (0% per year) and later occurred at a constant rate (m% per year). Our previous study demonstrated that this assumption provided good simulation of the epidemiological data for intracranial aneurysms.

Medical check-up of the brain is supported by the Ministry of Health, Labor and Welfare of Japan and is now widely available nationwide. This examination includes high-resolution brain MRI and MR angiography to identify occult brain abnormalities in healthy people. The scientific advantage of the brain check-up is that it covers healthy adults without significant risk factors, thus providing valuable data with low bias. In a study of 7345 adults (age range, 30–90 years; mean, 53.5 years) who underwent a physical check-up including brain MRI and MR angiography, the frequency of unruptured aneurysms was 2.0% overall and 2.9% in subjects aged ≥ 60 years. The Japanese national program of health checks is aimed at workers in the middle age group, so subjects aged < 40 years and > 70 years were both underrepresented. This truncation could lead to bias, but the prevalence of aneurysms is expected to be much lower in the younger age group and probably higher in the elderly group.

The Markov model was used to simulate events in intracranial aneurysms over time, including de novo formation and rupture. The present model was defined by a set number of discrete health states (Figure 2): well without aneurysm (An [−]), well with unruptured aneurysm (An [+]), post-SAH state with repaired aneurysm (post-SAH), and dead. Transitions between states were assumed to occur at the beginning of each yearly cycle. The analysis was continued until all individuals in the hypothetical cohort died of aneurysmal SAH or other causes.

During the yearly cycle, subjects with no aneurysm (An [−]) might survive with or without de novo aneurysm formation or die of causes other than SAH. Subjects with unruptured aneurysm (An [+]) might survive without developing SAH, develop SAH, or die of causes other than SAH. If the unruptured aneurysm did not rupture, the state of An (+) in the Markov model remains in the same state in the next cycle. All patients who developed aneurysmal SAH would undergo surgical or endovascular repair of the aneurysm and then die or survive with repaired aneurysm. The mortality rate of SAH was assumed to be 50%, and other subjects survived with or without disability (50%). For simplicity, the assumptions were made that aneurysms persist for life and the proportion that disappears is negligible and that aneurysm treatment permanently abolished the risk of SAH. In succeeding years, survivors were assumed to have the same death rate as the general population.

Prevalence of Unruptured Aneurysm

Estimates for the prevalence of intracranial aneurysms vary widely. In a systematic review, the prevalence of aneurysms was 2.3% for
prevalence of unruptured aneurysms was calculated in the standardized population. Sensitivity was analyzed by varying the values for de novo formation within the clinically reasonable range of 0.01% to 0.10% annual de novo aneurysm formation over the age of 20 years with different rupture rates, and the prevalence of unruptured aneurysms was calculated from the Markov model for specific ages or age groups as well as the whole population as shown in the Table. The prevalence of unruptured aneurysms is mainly determined by the rate of de novo aneurysm formation, and the effects of changes in rupture rate within the clinically reasonable range (0.5%–1.0%) are relatively small on the prevalence of unruptured aneurysms. The reported prevalences from both meta-analysis3 and brain check-up data7 correspond with annual formation rates in the 0.06% to 0.08% range. The prevalence of unruptured aneurysms was estimated as 1.45% in the whole standardized population based on the selected value of 0.07% annual de novo formation with annual rupture rate of 0.7%.

**Incidence of SAH**

The crude death rate from SAH in Japan was 11.6/100 000/year in 2005 (e-Stat). Approximately 65% to 85% of cases of spontaneous SAH originate from aneurysms.8,9 Assuming that aneurysmal rupture accounts for 75% of SAH-related deaths and that the death rate of aneurysmal rupture is 50%,8 the crude occurrence rate of SAH is calculated to be 17.4/100 000/year. The e-Stat database provides further data of the age group-specific annual death rate from SAH in 2005. Similar conversion of these values to the standardized population indicates that the adjusted rate of annual SAH in the standardized population is 19.7/100 000/year.

**Results**

**Constant Rupture Rate Models**

The mathematical model was first used to analyze the function for rupture rate remaining constant with time (Figure...
Selected values for rupture rate were 0.3%, 0.5%, 0.7%, 1.0%, and 1.3% per year. The relationships between the prevalence of unruptured aneurysms and annual SAH incidence are shown in Figure 4 based on the assumption of unchanging rupture rate. The annual rate of aneurysm formation in subjects aged ≥20 years varied from 0.01% to 0.10%. As expected, both the prevalence and SAH incidence increased with higher rate of de novo formation, and the linear relationship between 2 variables was confirmed. The shaded circle indicates the “compatible zone” with the epidemiological data. The “compatible zone” represents a circle centered at the values of unruptured aneurysm prevalence of 1.45% and SAH incidence of 19.7/100 000/year, whereas all other lines of 0.3% to 1.0% pass below the compatible zone.

Early High Rupture Rate Models

To resolve this incompatibility, we considered the function with a short period of high risk followed by a low-risk period of long duration. An example of the temporal profile of such models indicates that the early high-risk period extends for several weeks to months and then the risk falls gradually to reach a steady values below 1.0%/year (Figure 3, middle). Our Markov model was based on a yearly cycle, and both aneurysm-related and unrelated events were assumed to occur at the beginning of the cycle so that the curve can be approximated in this model to a time profile with relatively high and constant risk during the first year followed by lower risk, which continues for the remainder of life (Figure 3, lower). This simple model of rupture rate could be approximated from curves with initial high risk falling within 1 year. These simulations showed the high rupture risk during the first year ranged up to 20%, and risk after 1 year was 0.3%, 0.5%, 0.7%, and 1.0% per year (Figure 5). The annual rate of aneurysm formation varied from 0.01% to 0.10%. The lines without an early high rupture rate (lowest lines) did not cross the compatible zone in all models. Annual rupture rates of 0.5%, 0.7%, and 1.0% reached and crossed the center of the compatible zone assuming early rupture rates of 20%, 15%, and 10% within the first year, respectively. Assumption of an annual rupture rate of 0.3% required a much higher early rupture rate (>20%) for compatibility with the known epidemiology.

Discussion

Natural History of Intracranial Aneurysms

Recent prospective follow-up studies have suggested that small aneurysms carry very low risks of rupture. The prevalence of aneurysms and the risk of rupture should approximate the incidence of SAH, but the general population...
does not seem to harbor enough unruptured aneurysms to account for the observed incidence of SAH. Furthermore, most ruptured aneurysms seen in daily clinical practice are small,\textsuperscript{2,3} so there is a discrepancy between the etiologic data and the size of ruptured aneurysms. One hypothesis explaining these observations is that certain aneurysms may decrease in size after rupture.\textsuperscript{11} However, aneurysm measurements after rupture, whereas some grew further postrupture. Our present study suggested that some aneurysms bleed very shortly after formation. Aneurysms that do not rupture in this early period may form in people of any age and go through a comparatively brief high-risk period. Aneurysms not seem to harbor enough unruptured aneurysms to account for the observed incidence of SAH. Furthermore, most ruptured aneurysms seen in daily clinical practice are small,\textsuperscript{2,3} so there is a discrepancy between the etiologic data and the size of ruptured aneurysms. One hypothesis explaining these observations is that certain aneurysms may decrease in size after rupture.\textsuperscript{11} However, aneurysm measurements after rupture, whereas some grew further postrupture. Our present study suggested that certain aneurysms bleed very shortly after formation. Aneurysms that do not rupture in this early period may form in people of any age and go through a comparatively brief high-risk period. Aneurysms that do not rupture in this early period may carry a reduced risk of hemorrhage.\textsuperscript{13}

Histological study of intracranial aneurysms has revealed that ruptured and unruptured aneurysms have different natures.\textsuperscript{14} In approximately half of small ruptured aneurysms, almost the whole specimen is replaced by hyaline-like structures without a collagen layer or vascular smooth muscle cells. These findings may be the result of acute stretching of the aneurysm wall. In contrast, in most incidentally found, unruptured aneurysms, the walls have a dense collagen layer and vascular smooth muscle cells.\textsuperscript{15} One possible mechanism is that individual aneurysms pass through some healing process after formation and so are strengthened after an initial period of fragility.

**Minor Leak or De Novo Aneurysm Formation**

Aneurysmal SAH is frequently preceded by an episode of sudden headache, termed “warning leak,” and the incidence ranges from 19\% to 59\%.\textsuperscript{16–18} The majority of episodes occurred within 1 month before rupture. Such headaches are considered to represent minor bleeding into the subarachnoid space, but we postulated that some may be associated with vascular pain due to acute stretching caused by de novo aneurysm formation or expansion of pre-existing aneurysms. In either case, the preceding headache corresponds well with the aneurysmal SAH process occurring several weeks before the symptomatic SAH. The risk profile with early high risk is similar to the observations of a high bleeding rate after oculomotor nerve palsy of acute onset caused by internal carotid artery aneurysm without SAH.\textsuperscript{19} The time profile required for the repair process of the aneurysm wall might possibly be similar to the post-SAH rebleeding rate,\textsuperscript{20} although the risk after rupture would be higher. We think that a period of a few days to a few months is likely, which fits with the time distribution of pre-SAH headaches\textsuperscript{16,17} and with the post-SAH rehemorrhage rate, which decreases with the interval from onset.\textsuperscript{20}

Consequently, patients with suspected “warning leak” should undergo CT and sometimes lumbar puncture, but both investigations could show negative findings in the absence of subarachnoid clot. In consideration of the possible rapid expansion of the aneurysm, MR angiography or 3-dimensional CT angiography should be performed to identify de novo small or enlarged aneurysms with high risk of rupture in patients with unusual headache of acute onset with or without other symptoms.\textsuperscript{21}

**Indications for Prophylactic Treatment**

Our present study suggested that some aneurysms bleed shortly after formation and thus are never detected as unruptured aneurysms, indicating that some cases of SAH originate from recently formed rather than long-standing aneurysms.\textsuperscript{11,13} In this scenario, length bias\textsuperscript{22} ensures that most
aneurysms detected incidentally have passed into the period of low bleeding rate, whereas some aneurysms manifesting as SAH are in the early high-risk period. Therefore, we think that there is no rationale for prophylactic treatment for incidentally identified small unruptured aneurysms without symptoms.

Growth of unruptured aneurysms is really unpredictable, because the rate is reported to be 6% to 7% during a follow-up of 18 to 41 months.\textsuperscript{10,22} Although the risk of future rupture of growing aneurysms is unknown, rupture is much more likely to occur with probable fragility. Therefore, unruptured aneurysms should be treated after signs, even if slight, of enlargement or morphological change during the follow-up course.

Based on our observations, most small aneurysms without early rupture remain stable for the remainder of life, but a small number grow to a larger size. In contrast to the histological findings of small ruptured aneurysms, only 1 of 17 large ruptured aneurysms showed extensive replacement by hyaline-like structure.\textsuperscript{15} Therefore, large aneurysms causing SAH are unlikely to be recently formed. Aneurysms having grown to a large size may behave differently from small aneurysms and may remain constant with time or even carry increased risk of rupture with further enlargement. The ISUIA bleeding rate of large aneurysms is relatively high, but the treatment risk is also high. Therefore, the need for repair of such aneurysms should be carefully determined on a case-by-case basis.

Limitations
The uncertainties of statistical data and the assumptions necessary for the construction of the present mathematical model place limitations on the reliability of our conclusions. This study used highly reliable epidemiological and statistical data obtained from the recently developed official statistical system of Japan, e-Stat. We tried to minimize the amount of bias and reduced the uncertainty of data to acceptably small levels by adjusting for the standardized age distribution. However, all such sources are never free of bias.

Disclosures
None.

References
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*Stroke*. 2011;42:3376-3381; originally published online October 6, 2011;
doi: 10.1161/STROKEAHA.111.625871
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/42/12/3376

Data Supplement (unedited) at:
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頭蓋内動脈瘤のリスクの特性 — 動脈瘤形成後の破裂率は一定ではない

Koji Sato, MD; Yuhei Yoshimoto, MD
Department of Neurosurgery, Gunma University Graduate School of Medicine, Maebashi, Japan.

背景および目的：無症候性未破裂頭蓋内動脈瘤の治療につれては未だ議論の余地がある。最近の先端医療における、小動脈瘤の破壊率は非常に低いことが示されたが、この結果は未破裂動脈瘤の有病率および脳葉出血の発生率の関係において合致しなかった。次に、短期間高リスクの後に長期の低リスクとなる関数を検討した。年間破裂率0.3%、0.5%、0.7%、および1.0%は、未破裂動脈瘤の有病率および脳葉出血の発生率の関係において合致しなかった。次に、短期間高リスクの後に長期の低リスクとなる関数を検討した。年間破裂率0.3%、0.5%、0.7%、および1.0%にすると、短期間破裂率20%、15%、および10%をそれぞれ加味することにより疫学的結果と一致することが示された。

結論：本研究は、一部の動脈瘤は形成段階に出血するため、未破裂動脈瘤として検出されることでそれぞれの期間を示している。短期間破裂動脈瘤のほとんどは重要な治癒過程を経て、生涯を通じて安定し続けるため、偶然発見された未破裂小動脈瘤の予防的治療を行う根拠はない。

Stroke 2011; 42: 3376-3381