Greater Rupture Risk for Familial as Compared to Sporadic Unruptured Intracranial Aneurysms

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Background and Purpose—The risk of intracranial aneurysm (IA) rupture in asymptomatic members of families who have multiple affected individuals is not known.

Methods—First-degree unaffected relatives of those with a familial history of IA who had a history of smoking or hypertension but no known IA were offered cerebral MR angiography (MRA) and followed yearly as part of a National Institute of Neurological Diseases and Stroke-funded study of familial IA (Familial Intracranial Aneurysm [FIA] Study).

Results—A total of 2874 subjects from 542 FIA Study families were enrolled. After study enrollment, MRAs were performed in 548 FIA Study family members with no known history of IA. Of these 548 subjects, 113 subjects (20.6%) had 148 IAs by MRA of whom 5 subjects had IA ≥7 mm. Two subjects with an unruptured IA by MRA/CT angiography (3-mm and 4-mm anterior communicating artery) subsequently had rupture of their IA. This represents an annual rate of 1.2 ruptures per 100 subjects (1.2% per year; 95% CI, 0.14% to 4.3% per year). None of the 435 subjects with a negative MRA have had a ruptured IA. Survival curves between the MRA-positive and -negative cohorts were significantly different (P=0.004). This rupture rate of unruptured IA in the FIA Study cohort of 1.2% per year is approximately 17 times higher than the rupture rate for subjects with an unruptured IA in the International Study of Unruptured Aneurysm Study with a matched distribution of IA size and location 0.069% per year.

Conclusions—Small unruptured IAs in patients from FIA Study families may have a higher risk of rupture than sporadic unruptured IAs of similar size, which should be considered in the management of these patients. (Stroke. 2009;40: 00-00.)

Key Words: intracranial aneurysm • familial • magnetic resonance angiography • risk of rupture • smoking

Management of unruptured intracranial aneurysms (IAs) must balance the future risk of IA rupture with the risk of surgical or endovascular intervention. Larger IAs, history of prior ruptured IA, and location of IA in the posterior circulation have been the factors most consistently associated with higher risk of rupture, although some studies have suggested increased risk in older subjects, females, smokers, those with multiple aneurysms, or subjects from Finnish and Japanese populations.1–4 In the International Study of Unruptured Intracranial Aneurysm (ISUIA), subjects with unruptured IA of 6 mm in the anterior circulation, and without prior subarachnoid hemorrhage due to another IA, had an annual rupture rate of 0.069%.1 This very low rupture rate, coupled with the risk of surgical or endovascular intervention for IA, indicates that medical management and observation is the best treatment approach for the large majority of patients with IA with these characteristics. For aneurysms in the posterior circulation and in the posterior communicating artery, the annual rupture rate is 0.5% and the optimal management is less certain.

Familial aggregation of IA indicates that the rate of aneurysm formation is higher in some families than others. This is likely due to both genetic and common environmental influences. Whether rupture rate independent of IA formation is higher in these families is an important unanswered question. We previously reported that 58 (19%) of 303 asymptomatic subjects in families enrolled in the ongoing Familial Intracranial Aneurysm (FIA) Study to that point had an unsuspected IA detected by MR angiography (MRA).5,6 We now present an updated report regarding the frequency of
unruptured IA in all FIA Study subjects screened with MRA and the prospective rupture rates of these FIA Study subjects.

**Methods**

Details of the FIA Study have been outlined elsewhere. In brief, subjects were recruited through 26 clinical centers with extensive experience in the clinical management and imaging of IAs. These centers included 41 recruitment sites located throughout North America, New Zealand, and Australia (Appendix). The FIA Study was approved by the Institutional Review Boards/ethics committees at all clinical and analytic centers and recruitment sites.

**Enrollment of Eligible Families and Subjects**

Probands were identified by the recruitment sites and screened to determine whether they met study eligibility. Eligible families for this study included those with one of the following: (1) at least 2 living affected siblings; (2) at least 2 affected siblings, one of whom is living and the other whose genotype could be reconstructed through the collection of closely related, living family members (ie, spouse and children); (3) 3 or more affected family members (eg, cousin, uncle, aunt), 2 of whom are alive and have living connecting relatives; and (4) 3 or more affected family members with one living affected and at least one other affected relative whose genotype could be reconstructed through the collection of closely related, living family members.

Exclusion criteria included: (1) a fusiform-shaped unruptured IA of a major intracranial trunk artery; (2) an IA that is part of an arteriovenous malformation; (3) a family history of polycystic kidney disease, Ehlers Danlos syndrome, Marfan syndrome, fibromuscular dysplasia, moyamoya disease, or sickle cell disease; or (4) failure to obtain informed consent from the patient or family members.

Two neurologists on the Verification Committee independently reviewed the subject’s records and decided whether the subject met all the inclusion and exclusion criteria. Each potential affected family member was assigned one of 4 possible phenotypes: definite, probable, possible, or not a case. Definite, probable, and possible aneurysms were defined as follows: (1) definite: medical records document IA on cerebral angiogram, operative report, or autopsy, or a noninvasive imaging report (MR or CT angiography) demonstrates an IA measuring >7 mm in diameter; (2) probable: death certificate notes an IA without supporting documentation or autopsy or notes a subarachnoid hemorrhage without mention of aneurysm, and data obtained during telephone screening are consistent with ruptured IA (severe headache or altered level of consciousness) rapidly leading to death. A noninvasive imaging study documents an IA that is <7 mm but >3 mm in diameter; and (3) possible: noninvasive imaging report documents an IA measuring between 2 and 3 mm in diameter. Death certificate notes a subarachnoid hemorrhage without supporting documentation, autopsy, or recording of headache or altered level of consciousness based on information acquired during telephone screening. Death certificate lists “aneurysm” without specifying cerebral location or accompanying subarachnoid hemorrhage. In cases of disagreement between the 2 vascular neurologists regarding phenotype, a third neurologist was used to resolve the final phenotype. Both weighted kappa values and intraclass correlation were calculated for the first 2 evaluators. For the 4 categories, the weighted kappa value was 0.81 (95% CI, 0.78 to 0.83), whereas the intraclass coefficient was 0.88 (95% CI, 0.86 to 0.90); both of these values indicate excellent agreement.

Data regarding important environmental risk factors were collected. Hypertension was defined as a history of hypertension before the diagnosis of IA. The date of diagnosis of hypertension was recorded. Blood pressure was also measured during the evaluation. History of a diagnosis of diabetes or hypercholesterolemia was recorded. Smoking history was recorded as ever (current/former)/never and, if the patient was a current or former cigarette smoker, the number of pack-years before diagnosis of IA was calculated. Use of estrogen replacement was recorded. The number of alcoholic beverages consumed per day, cups of caffeinated coffee per day, highest academic grade completed, and marital status were also noted.

**Imaging of Asymptomatic Familial Intracranial Aneurysm Study Subjects**

Because MRA is very expensive and to maximize its impact without incurring excessive cost, we prospectively limited MRA screening to those subjects in whom the likelihood of an unruptured IA would be highest. Prior studies indicated much higher rates of unruptured IA in FIA Study family members who were smokers or who had hypertension. Therefore, first-degree relatives of those affected with IA were offered screening with MRA only if they had no history of IA, were ≥30 years of age, and had a history of smoking and/or hypertension. The FIA Imaging Center at Mayo Clinic, Rochester, Minn, ensured that high-quality MRA screening studies were performed at the imaging centers at the 26 clinical centers and interpreted all imaging examinations that were performed as part of the FIA Study. All FIA Study enrolling and clinical centers were eligible to be imaging centers. The process of certification of all participating imaging centers and the imaging parameters for the standard protocol are published elsewhere. In a few instances, subjects underwent MRA locally after enrollment but before being referred for a study MRA. These images were also reviewed as noted subsequently.

Two experienced neuroradiologists at the FIA Imaging Center at the Mayo Clinic reviewed all screening MRAs, and cases were adjudicated to define the level of certainty of aneurysm presence as outlined. Some patients had independently undergone MR or CT angiography for their standard clinical care. These studies were also reviewed in a blinded manner by the 2 neuroradiologists. After the imaging findings were interpreted by the 2 readers as concordant, the results were forwarded to the Coordinating Center at the University of Cincinnati. Cases requiring adjudication included those for which the first reader detected an aneurysm that was not identified by the second reader, aneurysms detected by both readers but at different anatomic sites, or aneurysms identified by both readers in which the maximal measurement differed by >1 mm. In these cases, a consensus interpretation by the 2 readers was completed. If a consensus adjudication could not be successfully accomplished, then an additional blinded interpretation by a third experienced neuroradiologist was performed, which was required in 5 instances of the 522 subjects with prospectively obtained MRAs.

**Follow-Up of Familial Intracranial Aneurysm Study Subjects**

Once a year, a medical information update and quality-of-life form were obtained from each FIA Study participant. This form provides a means of maintaining contact with participants as well as collecting information concerning any deaths, rupture of IA, or new cases of IA that may have occurred since completion of the Family History Questionnaire. All documented ruptures of IA underwent a detailed medical review and rephenootyping by the study Verification Committee.

**Statistical Methods**

Kaplan-Meier curves were calculated to estimate the rates of rupture in those subjects who had an unruptured IA (positive MRA group) and those who had a negative MRA. In these analyses, patients who underwent surgical clipping or endovascular coiling as well as those subjects who died from other causes or were lost to follow-up were censored at the time of intervention, death, or last known follow-up. The log-rank tests were computed to test for differences in the rates of rupture between the positive and negative MRA groups.

**Results**

The FIA Study enrolled 2874 subjects from 542 families. Of the 542 families, 441 families met strict eligibility criteria for inclusion in the primary analyses and eligible subjects from these families were offered MRA. Of the 2874 subjects, 1094
had a definite, probable, or possible IA on entry or during course of study (Table 1; Figure). At entry into the study, 498 living FIA Study subjects had a prior unruptured IA diagnosed by prior MRA, CT angiography, or intra-arterial angiography (Table 1). Distribution of the number of unruptured IAs among the 498 subjects are as follows: one IA, 321; 2 IAs, 113; 3 IAs, 36; 4 IAs, 16; 5 IAs, 5; 6 IAs, 6; and 7 IAs, one. Of the 787 unruptured IAs, 402 had prior clipping, 100 had prior coiling, 4 had wrapping or other procedure, 12 had unknown management, and 269 had been managed medically (185 subjects).

After study enrollment, study MRAs were performed in 541 FIA Study family members with no known history of IA. An additional 7 FIA Study subjects underwent a nonstudy MRA after study enrollment. Of these 548 subjects, 113 subjects (19.7%) had 148 IAs by MRA. Table 2 compares the presence of potential risk factors in the 113 subjects with an unruptured IA diagnosed after study enrollment with the 435 subjects who did not have an IA by study MRA. Subjects with an unruptured IA were more likely to be female, to have smoked more cigarettes, and less likely to have completed high school.

Of the 113 subjects, 72 had an IA of 2 to 3 mm, 36 had an IA of 4 to 6 mm, and 5 had an IA of ≥7 mm. Of these 113 subjects, 11 had clipping/coiling of all of their unruptured IA, including 3 of the 5 subjects with an IA of ≥7 mm. This includes one patient who had clipping of 7 aneurysms, one who had clipping of 2 aneurysms, 6 who had clipping of one aneurysm, and 3 who had coiling of one aneurysm. Two subjects with an unruptured IA by MRA/CT angiography (3-mm anterior communicating artery and 4-mm anterior communicating artery) subsequently had rupture of their IA.

Table 1. No. of Enrolled Subjects With IA by Phenotype and Rupture Status

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Unruptured</th>
<th>Unknown*</th>
<th>Ruptured</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>448</td>
<td>72</td>
<td>390</td>
<td>910</td>
</tr>
<tr>
<td>Probable</td>
<td>57</td>
<td>7</td>
<td>10</td>
<td>74</td>
</tr>
<tr>
<td>Possible</td>
<td>102</td>
<td>7</td>
<td>1</td>
<td>110</td>
</tr>
<tr>
<td>Totals</td>
<td>607†</td>
<td>86</td>
<td>401‡</td>
<td>1094</td>
</tr>
</tbody>
</table>

*Medical records may have indicated clearly that an aneurysm had been clipped, coiled, or imaged by angiography, but the available medical records and phone screening did not include enough details of the patient presentation to determine whether the IA ruptured or whether other symptoms or family history prompted diagnostic evaluation and treatment.

†A total of 498 subjects had a diagnosis of unruptured IA before study entry, of which 2 had ruptures after enrollment; 113 subjects were diagnosed by MRA after study enrollment, of which 2 subsequently had ruptures. (The 4 ruptures are tallied in the “ruptured” column).

‡One subject (Subject 5 in Table 3) who was undiagnosed at study enrollment had a ruptured IA after enrollment but before opportunity for study MRA.

Figure. Flow diagram for FIA Study and MRA/CT angiography screening before (retrospective cohort) and after enrollment into the study (prospective cohort).
Table 3. FIA Study Subjects With Ruptured IAs During Prospective Follow-Up

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Diagnosis by Study MRA</th>
<th>Age at Time of Diagnosis</th>
<th>Months From Diagnosis to Rupture</th>
<th>Location</th>
<th>Size</th>
<th>Smoking Status Time of Rupture</th>
<th>No. of 1°/Total Relatives With IA</th>
<th>Pack-Years</th>
<th>Hypertension</th>
<th>Years Since Diagnosis of Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>59</td>
<td>Female</td>
<td>ACOM</td>
<td>3 mm</td>
<td>Former</td>
<td>3/3 (one ruptured)</td>
<td>31</td>
<td>Yes</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>50</td>
<td>Male</td>
<td>ACOM</td>
<td>4 mm</td>
<td>Current</td>
<td>4/6 (3 ruptured)</td>
<td>4.7</td>
<td>Yes</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>53</td>
<td>Female</td>
<td>ACOM</td>
<td>4 mm</td>
<td>Never</td>
<td>1/1 (one ruptured)</td>
<td>NA</td>
<td>Yes</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>46</td>
<td>Female</td>
<td>MCA</td>
<td>8 mm</td>
<td>Current</td>
<td>4/4 (one ruptured)</td>
<td>29</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>5*</td>
<td>No</td>
<td>65</td>
<td>Female</td>
<td>MCA</td>
<td>4 mm</td>
<td>Current</td>
<td>2/2 (2 ruptured)</td>
<td>25</td>
<td>Yes</td>
<td>23</td>
</tr>
</tbody>
</table>

*Rupture after study enrollment but before study MRA.

ACOM indicates anterior communicating artery; OPTH, ophthalmic artery aneurysm; MCA, middle cerebral artery; PCA, posterior cerebral artery.

Both of the subjects diagnosed with an unruptured IA by MRA after enrollment who had rupture of their IA (Subjects 1 and 2 in Table 3) had successful clipping of the ruptured IA. Subject 3 had a known unruptured IA before study entry and had an IA rupture 3 years after diagnosis, which was treated successfully with coiling (4-mm anterior communicating artery). Subject 4 had 2 known unruptured IAs (8-mm middle cerebral artery and 5-mm posterior cerebral artery) diagnosed before enrollment in the FIA Study and died from a ruptured IA approximately 2 years after diagnosis. Subject 5, who had enrolled in the study, had a ruptured IA before completion of study MRA (4-mm middle cerebral artery IA on angiogram after rupture). The aneurysm was successfully clipped.

Discussion

Based on a comparison with the ISUIA Study historical controls, our data suggest that subjects with unruptured IAs in those families with familial aggregation of IA have a higher risk of aneurysm rupture than subjects with unruptured IAs who do not have a family history of IA. In the FIA Study, 3 of the 5 subjects with unruptured IAs of $\geq7$ mm identified by an MRA after study enrollment had clipping or coiling of their IA. The 2 subjects who subsequently had a ruptured IA had unruptured IAs of 3 mm and 4 mm on the baseline study MRA. Although the confidence interval around the point estimate is broad (0.14% to 4.3% per year), the annual rupture rate of IAs of $\leq6$ mm in the FIA Study subjects is approximately 17 times higher than the rupture rate for subjects with an unruptured IA in the ISUIA Study who had IAs of $\geq6$ mm and matched distribution of IA locations, 0.069% per year. Those FIA Study subjects who had the diagnosis of unruptured IA before study enrollment had a rupture rate of 0.21% per year. These latter FIA Study subjects were not prospectively identified, which may introduce bias, and also had a longer mean period of follow-up than those subjects identified after study enrollment. Thus, small unruptured IAs in patients in the FIA Study who have a positive history of smoking or hypertension may have a higher risk of rupture than patients with sporadic unruptured IAs of similar size, but that risk may lessen over time from initial diagnosis.

This information regarding rupture risk in patients with unruptured IA from the FIA Study should be considered in determining whether a more aggressive treatment approach is indicated. The ISUIA Study reported overall 30-day rates of...

(Table 2). The rupture rate for those 113 subjects diagnosed with an IA on screening was 1.2 ruptures per 100 subjects (1.2% per year; 95% CI, 0.14% to 4.3% per year). None of the 435 subjects with a negative MRA have had a ruptured IA. Using Kaplan-Meier analysis, the 2 survival distributions of MRA-positive and MRA-negative cohorts were significantly different (log-rank test, $P=0.004$).

We performed a second Kaplan-Meier analysis of the 498 subjects who had an unruptured IA before enrollment in the study. Two subjects had a ruptured IA (one subject with a 4-mm IA and one with an 8-mm IA) during 92.9 patient-years of follow-up, which represents an annual rupture rate of 0.22% per year (95% CI, 0.026% to 0.78%). The log-rank test for the differences in rupture rate between the retrospectively identified and prospectively identified subjects who had an unruptured IA before enrollment was small ($P=0.143$).
death of approximately 2% after coiling or clipping of unruptured IA. An additional 2% to 3% of patients had a modified Rankin Scale score of 3 to 5 and an additional 3% to 6% of subjects with a modified Rankin Scale score of 0 to 2 had cognitive impairment after intervention. The risk of surgical morbidity and mortality in ISUIA subjects increased with older age, larger aneurysms, and posterior circulation location of the IA. Because there is morbidity and mortality associated with interventional management of aneurysms, and because 3 of the 5 FIA Study subjects who ruptured continued to smoke after identification of the aneurysm, it remains unclear if FIA Study subjects with an unruptured IA are best treated with clipping or coiling of the IA or with observation and meticulous risk factor control. The decision-making process for an individual patient should include considerations of the patient’s age, size and location of IA, the presence and management of smoking behavior and hypertension as well as the family history.

The FIA Study illustrates the importance of MRA or CT angiography to screen for unsuspected unruptured IA in family members of FIA Study families. Twenty-one percent of first-degree relatives who underwent MRA had an IA demonstrated by imaging. One limitation of our study is that we imaged only those subjects with ≥10 pack-years of smoking or a current smoker or a history of hypertension. The rate of IA detection by MRA, and possibly the subsequent rate of IA rupture, is likely somewhat lower in those FIA Study subjects without a history of smoking or hypertension. The overall goal of the FIA Study is to identify specific genetic variants on chromosome 9p21.3, 8q11.12-12.1, and 2q33.1 that are associated with IA and prior smoking among patients with IA, we hypothesize that strong interactions between the environment and genes likely underlie development and rupture of IA. Prevention of IA rupture in the future will depend on knowing family history and genetic risk factors, aggressive modification of risk factors such as smoking and hypertension, vascular imaging of intracranial arteries in those affected family members identified to be at higher risk, objective determination of the risks associated with surgical or endovascular interventions, and use of these interventions when the cumulative risk is lower than that of medical management.

Appendix: List of FIA Study Clinical Sites and Key Investigators

University of Alabama at Birmingham: W. Fisher (Principal Investigator [PI]), H. Forson, coordinator; Clinical Trials Research Unit, University of Auckland and Auckland City Hospital, New Zealand: C. Anderson (PI), E. Mee (PI), C. Howe, coordinator, S. Vos, coordinator; Royal Perth Hospital, Sir Charles Gairdner Hospital, Royal Adelaide Hospital, Royal Melbourne Hospital, Alfred Hospital, Westmead Hospital, Royal North Shore Hospital, Royal Prince Alfred Hospital, Australia: C. Anderson (PI), G. Hankey (PI), N. Knuckey (PI), J. Laidlaw (PI), P. Reilly (PI), N. Dorsch (PI), M. Morgan (PI), M. Besser (PI), J. Rosenfeld (PI), K. Athanasiadis, coordinator, A. Claxton, coordinator, V. Dunne, coordinator, J. Griffith, coordinator, J. Davidson, coordinator, S. Pope, coordinator, Amanda Froelich, coordinator; Brigham & Women’s Hospital: A. Day (PI), R. Brach, coordinator; University of Cincinnati: D. Woo (co-PI), M. Zuccarello (co-PI), A. Ringer (co-PI), H. Yeh (co-PI), K. Franklin, coordinator; Cleveland Clinic Foundation: P. Ramussen (PI), D. Andrews-Hinders, coordinator, T. Wheler, coordinator; Columbia University: E. S. Connolly (PI), R. Sacco (co-PI), D. LaMonica, coordinator; University of Florida: S. B. Lewis (PI), A. Royster, coordinator; Indianapolis Neurosurgical Group: T. Payne (PI), N. Mifiacl, coordinator; Johns Hopkins: K. Murphy (PI), K. Katsura, coordinator; Massachusetts General Hospital: C. Ogilvy (PI), D. Buckley, coordinator, J. Manansala, coordinator; London Health Science Center Research Inc: G. Ferguson (PI), C. Mayer, coordinator, J. Peacock, coordinator; Notre Dame Hospital: G. Rouleau (PI), A. Desjarlais, coordinator; University of Maryland: E. F. Aldrich (PI), C. Aldrich, coordinator, C. Byard, coordinator; Mayo Clinic: R. D. Brown (PI), L. Jaeger, coordinator; University of Michigan: L. Morgenstern (PI), M. Concannon, coordinator; New Jersey Medical School: A.I. Qureshi (PI), P. Harris-Ln, coordinator; Northwestern University: H. Batjer (PI), G. Joven, S. Thompson, coordinator; University of Ottawa: M. T. Richard (PI), A. Hopper (PI); University of Pittsburgh: A. B. Kassam (PI), K. Lee, coordinator, University of California, San Francisco: C. Johnston (PI), K. Katsura, coordinator; University of Southern California: S. Giannotta (PI), D. Fishback, coordinator; Stanford University Medical Center: G. Steinberg (PI), D. Llu, coordinator, M. Coburn, coordinator; University of Texas at Houston: M. Malkoff (PI), A. Wojner, coordinator; University of Virginia: N. Kassel (PI), B. Worrall (co-PI), G. Radakovic, coordinator; University of Washington: D. Tirschwell (PI), P. Tanzi, coordinator; Washington University: C. Derdeyn (PI), M. Catanzaro, coordinator; University of Manitoba (Winnipeg), A. Kaufmann (PI), D. Gladish, coordinator.

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Disclosures
None.
References
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