Screening for brain aneurysm in the Familial Intracranial Aneurysm study: frequency and predictors of lesion detection


FOR THE FAMILIAL INTRACRANIAL ANEURYSM (FIA) INVESTIGATORS

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Object. Approximately 20% of patients with an intracranial saccular aneurysm report a family history of intracranial aneurysm (IA) or subarachnoid hemorrhage. A better understanding of predictors of aneurysm detection in familial IA may allow more targeted aneurysm screening strategies.

Methods. The Familial Intracranial Aneurysm (FIA) study is a multicenter study, in which the primary objective is to define the susceptibility genes related to the formation of IA. First-degree relatives (FDRs) of those affected with IA are offered screening with magnetic resonance (MR) angiography if they were previously unaffected, are ≥ 30 years of age, and have a history of smoking and/or hypertension. Independent predictors of aneurysm detection on MR angiography were determined using the generalized estimated logistic equation version of logistic regression.

Results. Among the first 303 patients screened with MR angiography, 58 (19.1%) had at least 1 IA, including 24% of women and 11.7% of men. Ten (17.2%) of 58 affected patients had multiple aneurysms. Independent predictors of aneurysm detection included female sex (odds ratio [OR] 2.46, p = 0.001), pack-years of cigarette smoking (OR 3.24 for 20 pack-years of cigarette smoking compared with never having smoked, p < 0.001), and duration of hypertension (OR 1.26 comparing those with 10 years of hypertension to those with no hypertension, p = 0.006).

Conclusions. In the FIA study, among the affected patients’ FDRs who are > 30 years of age, those who are women or who have a history of smoking or hypertension are at increased risk of suffering an IA and should be strongly considered for screening. (DOI: 10.3171/JNS/2008/108/6/1132)

KEY WORDS • familial aneurysm • genetics • intracranial aneurysm • magnetic resonance angiography • screening study

Intracranial saccular aneurysms are acquired lesions, accounting for ~ 80% of all nontraumatic SAHs. Several uncommon heritable disorders are associated with brain aneurysms, including autosomal-dominant polycystic kidney disease, Marfan syndrome, Ehlers–Danlos syndrome Type IV, hereditary hemorrhagic telangiectasia, pseudoxanthoma elasticum, multiple endocrine neoplasia Type I, and neurofibromatosis Type 1. Outside of these rare heritable disorders, population-based and nonpopulation-based data suggest that there is an increased occurrence of IA and SAH in first- and second-degree relatives of those with SAH, with the highest risk being noted in siblings. Selected factors such as older age, female sex, history of hypertension, higher lipid levels, and elevated blood glucose have been suggested to increase the possibility of aneurysm detection in this setting.

To clarify further the occurrence of IA detection on brain MR angiography screening in families with several members affected, we report the initial results of MR angiography screening of FDRs—siblings, parents, and children—of those affected with an IA in a multicenter study of familial IA. We also report the predictors of IA detection on brain MR angiography among these FDRs.

Abbreviations used in this paper: ACoA = anterior communicating artery; CT = computed tomography; DICOM = Digital Information and Communications in Medicine; DS = digital subtraction; FDR = first-degree relative; FIA = Familial Intracranial Aneurysm; IA = intracranial aneurysm; ICA = internal carotid artery; MCA = middle cerebral artery; MR = magnetic resonance; OphA = ophthalmic artery; OR = odds ratio; PCoA = posterior communicating artery; SAH = subarachnoid hemorrhage.
Clinical Materials and Methods

The FIA study is an international, multicenter study including 26 clinical centers, which represents 41 recruitment sites in North America, New Zealand, and Australia. The study was approved by the institutional review board/ethics committee at each of the study centers and recruitment sites.

Families with multiple members in whom IAs were diagnosed were enrolled to identify the chromosomal regions associated with an increased risk of IA and to determine the effects of environmental factors on the expression of genes within these regions. Individuals with either ruptured or unruptured IAs were considered to have the phenotype. Patients were excluded if they had a fusiform IA; an intranidal aneurysm with an arteriovenous malformation; a family history of polycystic kidney disease, Ehlers–Danlos syndrome, Marfan syndrome, fibromuscular dysplasia, or moyamoya syndrome; or if informed consent could not be obtained from the patient or family members.

Detailed medical records and the information acquired by telephone screening of probands and family members with a reported history of IA or SAH were reviewed by the Verification Committee. Two neurologists independently reviewed the records and determined if the participant met all the inclusion and exclusion criteria. In cases of disagreement, a third neurologist was consulted.

Definite, probable, and possible aneurysms were defined as follows. 1) Definite: medical records document IA on cerebral angiogram, operative report, or autopsy, or a non-invasive 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 an SAH 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 non-invasive imaging study documents an IA that is < 7 mm but > 3 mm in diameter. 3) Possible: noninvasive imaging report documents an IA measuring between 2 and 3 mm in diameter.

Fig. 1. Preoperative MR angiogram (A) and DS angiogram (B) demonstrating a 2-mm ACoA aneurysm (arrows), which was successfully treated with coil embolization. Magnetic resonance angiogram (C) and DS angiogram (D) obtained in another patient of a wide-necked 2-mm aneurysm on the left M1 branch.
diameter. Death certificate notes an SAH 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 SAH.

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

The FDRs of those affected with IA were offered screening with MR angiography if they were previously unaffected, ≥30 years of age, and had a history of smoking and/or hypertension. The FIA Imaging Center at Mayo Clinic, Rochester, Minnesota, ensured that high-quality MR angiography screening studies were performed at the imaging centers and interpreted all imaging examinations that were performed as part of the FIA study. All FIA enrolling and clinical centers were eligible to be imaging centers (see Appendix). Prior to the imaging sessions for the individuals in this study, the centers underwent an accreditation process, beginning with the center performing an MR angiography study as close to a standardized sequence as appropriate, given the vendor and field strength of the MR unit. Generally accepted parameters for intracranial MR angiography imaging have been developed over time. To assist the imaging centers with the optimization of their MR angiograms, an MR physicist and MR technologist were available for consultation at the imaging center. Accredited imaging centers included General Electric, Philips, and Siemens MR systems at 1.5-, 3.0-, and 4.0-T field strengths.

The imaging parameters for the standard protocol included a scout image of choice, a 3D time-of-flight MR angiogram, and an axial T2-weighted fast spin echo sequence. The 3D time-of-flight MR angiogram typically included 3 axial slabs of 32 sections per slab with 1.4-mm-thick sections, resulting in an imaging volume that included the posterior inferior cerebellar arteries to the bifurcation of the pericallosal and callosal marginal arteries. The axial fast spin echo T2-weighted sequence was performed with 4-mm-thick sections with zero skip and included the same imaging volume as the MR angiography sequence. The fast spin echo sequence was performed to exclude giant aneurysms with such slow flow that, due to saturation effects, these lesions might not be depicted with standard MR angiography imaging. Also, this allowed evaluation of the total size of partially thrombosed aneurysms. On completing a trial of the standard protocol, the other imaging centers forwarded the study in a DICOM format to the central FIA Imaging Center. Central imaging center review of the qualifying MR angiogram was performed to determine if changes to the imaging technique were required prior to certification.

Accredited centers were eligible to obtain images in the patients and forwarded the completed studies in a blinded manner to the imaging center. When received, the DICOM-formatted studies were postprocessed by the imaging coordinator. Maximum intensity projections of the MR angiogram were created to include the right carotid, left carotid, and posterior circulations, with 10° rotations per image. Hard-copy films of the collapsed image, maximum intensity projections, and fast spin echo images were created for archival purposes.

Two experienced neuroradiologists at the imaging center reviewed all screening MR angiograms, 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 in 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 anatomical 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.

Statistical Analysis

An aneurysm was considered suitable as a case for the current analysis if the diameter was ≥2 mm based on MR angiography findings; that is, was definite, probable, or possible. A generalized estimating equation version of multiple logistic regression was used in these analyses, with aneurysm case status as the binary outcome variable. The generalized estimating equation model takes into account the lack of independence of outcomes within a family by considering the members of each family as a cluster of correlated events. Several potential risk factors were considered for possible inclusion in the model, as follows: patient age, sex, history and duration of hypertension, smoking history and pack-years of cigarette smoking, marijuana use, history and amount of alcohol use, history and amount of caffeine consumption, estrogen replacement therapy, body mass index, history of diabetes or of increased cholesterol, marital status, and educational level completed. Regression diagnostics was used to assess the final model for collinearity.

Results

The MR angiography screening was performed in 303 patients, and of these 58 (19.1%) had at least 1 aneurysm (Fig. 1). Overall, 71 aneurysms were detected, with multiple lesions being detected in 10 (17.2%) of 58 patients: 1 had 4 IAs, 1 had 3 lesions, and 8 had 2. The characteristics of those with and without an IA detected on MR angiography are summarized in Table 1. Women had an IA on MR angiography in 44 (24%) of 183 screening studies, compared with 14 (11.7%) of 120 studies obtained in men. Those in whom an IA was detected had a mean age of 53.7 years compared with 50.4 years for those with negative findings on MR angiography. A history of current or prior
cigarette smoking was present in 90% of those with IAs compared with 72% without lesions. The mean number of pack-years of cigarette smoking was 27.4 in those with an IA, compared with 17.8 in those without an IA. The duration of hypertension was 6.5 years in those with an IA, compared with 4.4 years in those without an IA.

Numerous factors were evaluated as potential predictors of IA detection on MR angiography screening. In the univariate analysis, history of cigarette smoking and pack-years of cigarette smoking were predictors of IA detection, and a higher level of education and having graduated from high school were associated with a decreased risk (Table 2). In a multivariate analysis, independent predictors of detection of IA included female sex (OR 2.46), pack-years of cigarette smoking (OR 3.24 for 20 pack-years of cigarette smoking compared with never having smoked), and duration of hypertension (OR 1.26 when comparing those with 10 years of hypertension to those with no hypertension; Table 3).

The characteristics of the lesions detected (71 IAs among 58 patients) are summarized in Table 4. Most of the aneurysms were small: 2 IAs were \( \leq 7 \) mm in maximal diameter; 19 were 4–6 mm; and 50 were 2–3 mm. Aneurysms arose most commonly on the ICA, with 31 such lesions (8 OphA, and 23 other ICA), followed in frequency by the MCA (20), PCoA (8), anterior cerebral artery (7), ACoA (3), and other locations (2).

During a mean follow-up period of 10 months (through September 1, 2006), of the 58 patients in whom aneurysms were detected, 10 patients (17%) underwent some form of surgical or endovascular intervention for 11 aneurysms (Table 5). Overall, among the 58 patients followed for a mean of 10 months, through September 1, 2006, 1 rupture occurred in a 3-mm ACoA aneurysm 15 months after enrollment. Giv-
It is apparent that there is an increased risk of IA detection among FDRs of patients presenting with an IA. The degree of this increased risk, and in particular, predictors of an increased possibility of IA detection, are not clear. The results of our study suggest that, in the FIA cohort among families with at least 2 members suffering from a brain aneurysm, in the FDRs of those affected there is a relatively high risk of aneurysm detection on MR angiography screening. Overall, aneurysms were detected in 19.1% of these “high-risk” FDRs, a risk that was even higher in women than in men. This compares to a frequency of detection in the general population of 1–2%. It is noteworthy that, in this research study, to increase the cost-effectiveness of the MR angiography screening, only FDRs who were < 7 mm in diameter, the rupture risk was 2% per year.

Discussion

It is apparent that there is an increased risk of IA detection among FDRs of patients presenting with an IA. The degree of this increased risk, and in particular, predictors of an increased possibility of IA detection, are not clear. The results of our study suggest that, in the FIA cohort among families with at least 2 members suffering from a brain aneurysm, in the FDRs of those affected there is a relatively high risk of aneurysm detection on MR angiography screening. Overall, aneurysms were detected in 19.1% of these “high-risk” FDRs, a risk that was even higher in women than in men. This compares to a frequency of detection in the general population of 1–2%. It is noteworthy that, in this research study, to increase the cost-effectiveness of the MR angiography screening, only FDRs who were < 7 mm in diameter, the rupture risk was 2% per year.

TABLE 3
Multivariate analysis of selected factors as potential predictors of aneurysms detected on MR angiography screening*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>SE</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>log (pack-years of cigarette smoking)</td>
<td>3.24† (1.81–5.79)</td>
<td>0.072</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sex</td>
<td>2.46§ (1.46–4.54)</td>
<td>0.290</td>
<td>0.001</td>
</tr>
<tr>
<td>duration of hypertension</td>
<td>1.26§ (1.07–1.49)</td>
<td>0.009</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* CI = confidence interval.
† Odds ratio for 20 pack-years of cigarette smoking compared to never having smoked.
§ Odds ratio for females compared to males.

TABLE 4
Characteristics of aneurysms detected*%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Patients (%)</th>
<th>No. of Aneurysms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>size (diameter of largest aneurysm; 58 patients) max diameter (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥7</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>4–6</td>
<td>17 (29)</td>
<td></td>
</tr>
<tr>
<td>2–3</td>
<td>39 (67)</td>
<td></td>
</tr>
<tr>
<td>size (all aneurysms; 71 lesions) max diameter (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥7</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>4–6</td>
<td>19 (27)</td>
<td></td>
</tr>
<tr>
<td>2–3</td>
<td>50 (70)</td>
<td></td>
</tr>
<tr>
<td>location (all aneurysms; 71 lesions) artery of origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>31 (44)</td>
<td></td>
</tr>
<tr>
<td>OphA</td>
<td>8 (11)</td>
<td></td>
</tr>
<tr>
<td>other ICA</td>
<td>23 (32)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>20 (28)</td>
<td></td>
</tr>
<tr>
<td>PCoA</td>
<td>8 (11)</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>7 (10)</td>
<td></td>
</tr>
<tr>
<td>AC0A</td>
<td>3 (4)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>2 (3)</td>
<td></td>
</tr>
</tbody>
</table>

* ACA = anterior cerebral artery.
Screening with MR angiography for familial brain aneurysm

because only 1, a small ACoA aneurysm, hemorrhaged during the short course of follow-up.

Magnetic resonance angiography was the screening tool used for the current study. Previous data support the suggestion that this is a valid screening tool for IA. The interobserver agreement in defining IA in asymptomatic patients is excellent, and more recent advances in MR angiography have further improved this interobserver agreement, even among small aneurysms.\(^5,6\) Intraarterial cerebral arteriography remains the gold standard for aneurysm detection, but does entail a low risk of stroke and other complications. Arteriographic confirmation of the aneurysm’s presence was not required for the current study. Nevertheless, 26 of the patients did have confirmation of the aneurysm, either during coil embolization, at the time of surgical intervention, or via confirmatory arteriography or CT angiography.

The available follow-up data for the current cohort reveal 1 aneurysm rupture during a short period of follow-up (mean follow-up ~ 10 months). Considering that 1 patient among 56 with a < 7-mm aneurysm had a rupture during follow-up, this would lead to an annualized rupture rate of 2%. This is higher than the 0.1% rupture risk among all unruptured aneurysms 2–6 mm in diameter in the International Study of Unruptured Intracranial Aneurysms.\(^9\)

It is also noteworthy that another patient from a family with familial IA had an aneurysm rupture prior to MR angiography screening.

There are several limitations of the current study. Because the patients selected for screening were required to have either a history of hypertension or of cigarette smoking, these particular data arise from a group of relatively “high-risk” FDRs. Cerebral arteriography was not performed to confirm all aneurysms. It is recognized that there is an occurrence of false-positive and false-negative aneurysm detection on MR angiograms, especially for very small aneurysms. This is particularly important given that most of the aneurysms in this study were 2–3 mm in diameter. In the current study, 8 of these small aneurysms were confirmed at the time of either coil embolization (2 lesions), clip ligation (2), or arteriography (4). The overall frequency of false positives (or false negatives) in this study is unknown because arteriographic confirmation was not completed. In another familial IA screening study,\(^13\) of the 43 DS angiograms performed to confirm the MR angiography findings, 7 (16%) of 43 were negative, with the suspected IA later found to be a vessel loop. It is noteworthy that the prior study was performed > 10 years ago and that current MR angiography screening probably has a higher specificity and sensitivity,\(^5,6\) even for very small aneurysms.

Healthcare providers are faced with the need to recommend optimum screening strategies for patients who have familial IAs. Questions that follow in this circumstance include the possibility of detecting an aneurysm in the affected relatives if 2 or more members of the family are affected, and whether there are risk factors that increase the likelihood of abnormal results on the screening study. In our study the findings support the suggestion that among the FDRs of those affected, the risk of having an IA is considerable. The risk is accentuated by a history of hypertension, of cigarette smoking, and in female FDRs. These data further confirm that once an FDR of an affected patient reaches the age of 30 years, the risk of harboring a brain aneurysm is high and screening should be strongly considered, especially among women or those who either smoke or have hypertension. A key question that remains unanswered is whether the familial IAs behave differently from nonfamilial IAs. The short period of follow-up in the current study precludes definitive comment regarding long-term natural history, and that will be clarified with ongoing follow-up.

Conclusions

In familial IAs, among the affected patients’ FDRs who are > 30 years of age, those who are women or who have a history of smoking or hypertension are at increased risk of having a brain aneurysm revealed on screening MR angiography. These data further suggest that these FDRs are at particularly high risk and should be strongly considered for aneurysm screening.

Appendix

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References


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