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Unruptured intracranial aneurysms in the Familial Intracranial Aneurysm and International Study of Unruptured Intracranial Aneurysms cohorts: differences in multiplicity and location

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Abstract

Object—Familial predisposition is a recognized nonmodifiable risk factor for the formation and rupture of intracranial aneurysms (IAs). However, data regarding the characteristics of familial IAs are limited. The authors sought to describe familial IAs more fully, and to compare their characteristics with a large cohort of nonfamilial IAs.

Methods—The Familial Intracranial Aneurysm (FIA) study is a multicenter international study with the goal of identifying genetic and other risk factors for formation and rupture of IAs in a highly enriched population. The authors compared the FIA study cohort with the International Study of Unruptured Intracranial Aneurysms (ISUIA) cohort with regard to patient demographic data, IA location, and IA multiplicity. To improve comparability, all patients in the ISUIA who had a family history of IAs or subarachnoid hemorrhage were excluded, as well as all patients in both cohorts who had a ruptured IA prior to study entry.

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This study was preliminarily presented as a platform presentation at the 2011 International Stroke Conference in Los Angeles, California. It has not been otherwise published.

Results—Of 983 patients enrolled in the FIA study with definite or probable IAs, 511 met the inclusion criteria for this analysis. Of the 4059 patients in the ISUIA study, 983 had a previous IA rupture and 657 of the remainder had a positive family history, leaving 2419 individuals in the analysis. Multiplicity was more common in the FIA patients (35.6% vs 27.9%, $p < 0.001$). The FIA patients had a higher proportion of IAs located in the middle cerebral artery (28.6% vs 24.9%), whereas ISUIA patients had a higher proportion of posterior communicating artery IAs (13.7% vs 8.2%, $p = 0.016$).

Conclusions—Heritable structural vulnerability may account for differences in IA multiplicity and location. Important investigations into the underlying genetic mechanisms of IA formation are ongoing.

Keywords

intracranial aneurysm; epidemiological study; genetics; vascular disorders

WHEREAS the prevalence of unruptured IAs is approximately 1%–2% in the general population,[9,13] the incidence of SAH is only approximately 10 per 100,000 per year.[7] This suggests that the vast majority of IAs do not rupture and that identifying those at highest risk is important in defining the optimal management after the diagnosis of unruptured IA. Familial predisposition is known to be an important nonmodifiable risk factor for the formation and rupture of IAs,[11] but no large studies have compared characteristics of patients with familial and nonfamilial IA in heterogeneous populations. An understanding of genetic influences on IA characteristics could impact future approaches to management and prevention. Thus, we sought to compare the characteristics of familial and nonfamilial IAs by using 2 large, multinational cohorts.

Methods

Study Design

The FIA study is a multicenter international study with 41 recruitment sites in the US, Canada, Australia, and New Zealand, as outlined in detail elsewhere.[3] The FIA study, approved by the institutional review boards/ethics committees at all participating sites, commenced enrollment in late 2002 with the goal of identifying genetic and other risk factors for the formation and rupture of IAs.

Families with multiple affected members are enrolled, and a detailed evaluation consisting of medical record review and telephone screening is completed. At least 3 affected family members or an affected sibling pair are required for inclusion in the study. Patients with fusiform IAs (an IA associated with an intracranial arteriovenous malformation) or a family history of conditions known to predispose to IA formation, such as polycystic kidney disease, Ehlers-Danlos syndrome, Marfan syndrome, fibromuscular dysplasia, or moyamoya syndrome are excluded. Patients are also excluded if informed consent cannot be obtained.

A verification committee, consisting of study neurologists from the University of Cincinnati and the Mayo Clinic, reviews all medical records. Two study neurologists independently review the records, and any discrepancy is adjudicated by a third neurologist. For patients who undergo FIA study imaging, two neuroradiologists at the Study Imaging Center at Mayo Clinic in Rochester, Minnesota, independently review the images, and any discrepancy that cannot be resolved by consensus is settled by a third neuroradiologist. Each reported IA is phenotyped as either “definite”—an IA on angiography, operative report, autopsy, or an IA ≥ 7 mm on a noninvasive imaging report (MRA or CTA); “probable”—IA between 3 and 7 mm seen on noninvasive imaging; “possible”—IA between 2 and 3 mm

seen on noninvasive imaging; or "not a case." Only the definite and probable phenotypes are included in the current analysis.

In the FIA study, IA location classifications are ICA, MCA, ACA, ACoA, PCoA, OA, BA tip, other BA and VA, and "other" (the location of which is described in a text field). Aneurysm sizes are stratified as < 7 mm, 7–12 mm, 13–24 mm, ≥ 25 mm, and unknown.

Comparison With ISUIA

The ISUIA is an international, multicenter study with sites in the US, Canada, and Europe, whose aims include the prospective assessment of the risk of IA rupture in patients whose lesions are managed conservatively, and the morbidity and mortality rates associated with surgical or endovascular management for unruptured IAs. Inclusion requires at least 1 unruptured IA documented on conventional cerebral angiography reviewed by study neuroradiologists at the ISUIA Coordinating Center at Mayo Clinic, Rochester, Minnesota. A detailed description of the methods has been previously reported.[15]

Location classifications for the ISUIA are similar to those used by the FIA study, except that the ISUIA separates cavernous ICA and OA from other ICAs, and the ISUIA does not have separate categories for ACA and ACoA. Therefore, for the present analysis, IAs in the ICA, cavernous ICA, and OA were combined into a single group, and IAs in the ACA and ACoA were combined into a single group.

We compared the FIA cohort with the ISUIA cohort with regard to demographic data and IA characteristics. The lead investigators of the ISUIA were involved with the present work to ensure consistent interpretation of data items. To improve comparability, we excluded all ISUIA patients with a family history of IA or SAH as well as all patients in both cohorts who had a ruptured IA prior to study entry. Aneurysms < 2 mm were not included. In comparing location and size between 2 groups, each patient's largest IA was used, irrespective of imaging or surgical technique.

Statistical Analysis

In univariate analyses, we used the Student t-test for age, the 2-tailed Fisher exact test for dichotomized variables, and the chi-square test for variables with multiple categories. We performed a separate univariate analysis for patients with multiple IAs.

Results

In the FIA study, 1094 enrolled patients had IAs, of which 983 were definite or probable phenotypes. We excluded 472 patients from the analysis: 396 had a ruptured IA prior to study entry, 74 had unknown rupture status, 1 patient's IA was on an arteriovenous malformation feeding artery, and the IA location for 1 patient was unknown. The remaining 511 patients with unruptured IAs were included in the analysis. Of the 4059 patients in the ISUIA study, 983 had a previous IA rupture and 657 of the remainder had a family history of IAs or SAH, leaving 2419 patients in the analysis.

Table 1 presents the baseline characteristics of patients from the 2 cohorts. Compared with the ISUIA patients, participants in the FIA study were of similar age. The FIA cohort had a higher proportion of women, a lower proportion of non-Hispanic white patients, and a higher proportion of patients with multiple IAs. With regard to IA location, the FIA cohort had a slightly higher proportion of IAs in the MCA, whereas the ISUIA cohort had a higher proportion of IAs in the PCoA. A higher proportion of patients in the FIA reported a history of hypertension. The FIA patients reported less alcohol consumption but more caffeinated beverage consumption than those in the ISUIA. Proportions of patients who never smoked

were similar in both cohorts, although more participants in the FIA study were former smokers.

The size of the largest IA for each patient in the 2 cohorts is shown in Table 2. A substantial portion (21.7%) of patients in the FIA had an unknown IA size, whereas there were no unknown IA sizes in the ISUIA. The patients in the FIA study tended to have smaller IAs than did those in the ISUIA (50.3% vs 34% with IAs < 7 mm).

A univariate analysis of risk factors for patients with multiple IAs is shown in Table 3. The results of the comparison between patients in the FIA who had multiple IAs and those in the ISUIA who had multiple IAs are essentially the same as for the cohorts as a whole, in that the FIA cohort had higher proportions of women, a lower proportion of non-Hispanic white patients, a higher proportion of individuals with a history of hypertension, a higher proportion of former smokers, less alcohol consumption, and more caffeinated beverage consumption. The location of the largest IA in patients with multiple IAs was not significantly different between the 2 cohorts.

Discussion

With more than 3000 participants, this study is the largest multinational descriptive comparison of familial and nonfamilial IAs. We found that patients with a strong familial predisposition for IA are more likely to have multiple IAs, more likely to have an IA in the MCA territory, and less likely to have IA in the PCoA territory. Previous work has established several risk factors for IA rupture, including family history,[2] larger IA size, location in the posterior circulation or PCoA sites, and history of rupture.[15] Whether IA multiplicity is a risk factor for rupture is more controversial,[14] but it has been suggested in both retrospective[6] and prospective[15] studies.

In previous smaller series of ruptured and unruptured familial IAs, the most common site for familial IAs was the MCA distribution,[8,10] which is similar to our study. The proportion of multiple familial and nonfamilial IAs in these studies was 22%–25%. Investigators in a large eastern Finnish study recently reported on 148 familial and 385 nonfamilial patients with unruptured IAs and found that familial patients were more likely to have multiple IAs (32% vs 25%),[5] which is similar to our findings. The most common sites for IA in both familial and nonfamilial patients were MCA (specifically MCA bifurcation) followed by ICA. The proportion of men (44%) was higher in the Finnish study than in either the FIA or ISUIA.[5] The degree to which Finnish genetic homogeneity accounts for the differences observed between that cohort and our multinational one is unclear.

Ongoing efforts to define specific genes associated with IA formation have yielded some noteworthy findings.[12] Recent genome-wide association studies have identified several loci associated with IA,[1,4,16] although associations have been relatively modest. In all likelihood IA formation is related to multiple genetic and environmental risk factors. However, there has been no gene association with multiplicity or location of IA.

There are several limitations to this study. The FIA and ISUIA are different studies with different goals. The FIA is concerned primarily with identifying genetic risk factors for IA formation and rupture via genotyping, whereas the ISUIA is concerned with prospectively identifying patients with unruptured IAs to assess for long-term outcomes, both in those treated conservatively and in those receiving surgical or endovascular management of their lesions. To that end, whereas every patient with IAs in the ISUIA had a conventional angiogram reviewed centrally, in the FIA study there were often no images to review but rather reports, such as operative, CTA or MRA, conventional angiography, or autopsy. The IA size was therefore available for every patient in the ISUIA but was missing for a

substantial proportion of patients in the FIA study. We thus cannot make a definitive statement regarding IA size differences between the 2 studies. Although one might expect that the false-positive rate for multiple IAs would be higher in the FIA study given the potential for CTA or MRA overcall of IAs, including only “definite” and “probable” phenotypes in this analysis serves to allay this concern. Another limitation of this analysis is that the FIA and ISUIA were not population based, and patients enrolled in these studies might not represent the broader IA population. Another caveat in interpreting these results is that there were significant underlying baseline population differences between the 2 cohorts. Finally, although the differences in IA location were statistically significant between the 2 groups, it is unclear if this difference is clinically meaningful.

Conclusions

Identifying and interrupting the biological pathways leading to IA formation and rupture remains a significant challenge. The present epidemiological work suggests that, even in a genetically and geographically heterogeneous population, some differences in IA characteristics may exist between familial and nonfamilial patients. A possible explanation for these findings is that familial patients have underlying biologically conferred vulnerability. Although the exact nature of the interplay between genetics and environment in IA formation remains uncertain, the importance of ongoing investigations into the underlying genetic mechanisms of IA formation is clear.

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Abbreviations used in this paper

ACA	anterior cerebral artery
ACoA	anterior communicating artery
BA	basilar artery
CTA	CT angiography
FIA	Familial Intracranial Aneurysm
IA	intracranial aneurysm
ICA	internal carotid artery
ISUIA	International Study of Unruptured Intracranial Aneurysms
MCA	middle cerebral artery
MRA	MR angiography
OA	ophthalmic artery
PCoA	posterior communicating artery
SAH	subarachnoid hemorrhage
VA	vertebral artery

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TABLE 1

Baseline characteristics of patients with IAs*

Characteristic	FIA Cohort	ISUIA Cohort	p Value
no. of pts	511	2419	
mean age in yrs at study entry	55.0 ± 11.5	55.4 ± 12.6	0.510
no. of women (%)	417 (81.6)	1758 (72.7)	<0.001
no. of white, non-Hispanic pts (%)	438 (85.7)	2222 (91.9)	<0.001
unruptured IA frequency (%)			<0.001
single	329 (64.4)	1743 (72.1)	
multiple	182 (35.6)	674 (27.9)	
total no. of unruptured IAs	791	3380	
location of largest IA (%)			0.016
ICA, cavernous ICA, OA	194 (38.0)	873 (36.1)	
ACoA, ACA	75 (14.7)	323 (13.4)	
MCA	146 (28.6)	603 (24.9)	
PCoA	42 (8.2)	332 (13.7)	
BA tip	34 (6.7)	173 (7.2)	
VBA (other than BA tip)	20 (3.9)	115 (4.8)	
no. w/ history of hypertension (%)	252 (49.3)	1022 (42.3)	0.004
cigarette smoking (%)			0.001
never smoked	103 (20.2)	598 (24.7)	
former smoker	217 (42.5)	814 (33.7)	
current smoker	191 (37.4)	997 (41.2)	
unknown	0 (0.0)	10 (0.4)	
alcoholic drinks, avg no./day (%)			<0.001
never drinks	320 (62.6)	913 (37.7)	
<1	80 (15.7)	943 (39.0)	
1–2	81 (15.9)	374 (15.5)	
3–5	11 (2.2)	121 (5.0)	
6–8	5 (1.0)	30 (1.2)	
≥9	11 (2.2)	18 (0.7)	
unknown	3 (0.6)	20 (0.8)	
caffeine drinks, avg no./day (%)			<0.001
none	30 (5.9)	307 (12.7)	
<1	24 (4.7)	544 (22.5)	
1–2	137 (26.8)	661 (27.3)	
3–4	140 (27.4)	598 (24.7)	
≥5	179 (35.0)	302 (12.5)	
unknown	1 (0.2)	7 (0.3)	

*The mean age is expressed ± SD. Abbreviations: avg = average; pts = patients; VBA = vertebrobasilar artery.

TABLE 2

Size of largest IA in the 2 cohorts

Characteristic	FIA Cohort	ISUIA Cohort	p Value
no. of pts	511	2419	
size of IA			<0.001
<7 mm (%)	257 (50.3)	822 (34.0)	
7–12 mm (%)	111 (21.7)	901 (37.3)	
13–24 mm (%)	26 (5.1)	536 (22.2)	
≥25 mm (%)	6 (1.2)	160 (6.6)	
unknown (%)	111 (21.7)	0 (0.0)	

TABLE 3

Risk factors for multiple IAs

Factor	FIA	ISUIA	p Value
no. of pts	182	674	
mean age in yrs at study entry	56.4 ± 11.5	55.6 ± 11.7	0.412
no. of women (%)	160 (87.9)	531 (78.8)	0.006
no. white, non-Hispanic pts (%)	154 (84.6)	617 (91.5)	0.006
total no. of unruptured IAs	462	1637	
location of largest IA (%)			0.473
ICA, cavernous ICA, OA	73 (40.1)	269 (39.9)	
ACoA, ACA	17 (9.3)	74 (11.0)	
MCA	53 (29.1)	183 (27.2)	
PCoA	19 (10.4)	82 (12.2)	
BA tip	11 (6.0)	50 (7.4)	
VBA (other than BA tip)	9 (4.9)	16 (2.4)	
no. w/ history of hypertension (%)	102 (56.0)	269 (39.9)	<0.001
cigarette smoking (%)			0.002
never smoked	28 (15.4)	129 (19.1)	
former smoker	91 (50.0)	234 (34.7)	
current smoker	63 (34.6)	308 (45.7)	
unknown	0 (0.0)	3 (0.5)	
alcoholic drinks, avg no./day (%)			<0.001
never drinks	109 (59.9)	262 (38.9)	
<1	24 (13.2)	261 (38.7)	
1–2	37 (20.3)	95 (14.1)	
3–5	4 (2.2)	37 (5.5)	
6–8	2 (1.1)	9 (1.3)	
≥9	5 (2.7)	5 (0.7)	
unknown	1 (0.5)	5 (0.7)	
caffeine drinks, avg no./day (%)			<0.001
none	13 (7.1)	81 (12.0)	
<1	8 (4.4)	125 (18.6)	
1–2	44 (24.2)	192 (28.5)	
3–4	48 (26.4)	182 (27.0)	
≥5	69 (37.9)	91 (13.5)	
unknown	0 (0.0)	3 (0.5)	