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Affected Twins in the Familial Intracranial Aneurysm Study

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Abstract
Background and Purpose: Very few cases of intracranial aneurysms (IAs) in twins have been reported. Previous work has suggested that vulnerability to IA formation is heritable. Twin studies provide an opportunity to evaluate the impact of genetics on IA characteristics, including IA location. We therefore sought to examine IA location concordance, multiplicity, and rupture status within affected twin-pairs. ***Methods:*** The Familial Intracranial Aneurysm study was a multicenter study whose goal was to identify genetic and other risk factors for formation and rupture of IAs. The study required at least three affected family members or an affected sibling pair for inclusion. Subjects with fusiform aneurysms, an IA associated with an AVM, 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 were excluded. Twin-pairs were identified by birth date and were classified as monozygotic (MZ) or dizygotic (DZ) through DNA marker genotypes. In addition to zygosity, we evaluated twin-pairs by smoking status, major arterial territory of IAs, and rupture status. Location concordance was defined as the presence of an IA in the same arterial distribution (ICA, MCA, ACA, and vertebrobasilar), irrespective of laterality, in both members of a twin-pair. The Fisher exact test was used for comparisons between MZ and DZ twin-pairs. ***Results:*** A total of 16 affected twin-pairs were identified. Location concordance was observed in 8 of 11 MZ twin-pairs but in only 1 of 5 DZ twin-pairs ($p = 0.08$). Three MZ subjects had unknown IA locations and comprised the three instances of MZ discordance. Six of the 11 MZ twin-pairs and none of the 5 DZ twin-pairs had IAs in the ICA distribution ($p =$

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0.03). Multiple IAs were observed in 11 of 22 MZ and 5 of 10 DZ twin-pairs. Thirteen (13) of the 32 subjects had an IA rupture, including 10 of 22 MZ twins. ***Conclusions:*** We found that arterial location concordance was greater in MZ than DZ twins, which suggests a genetic influence upon aneurysm location. The 16 twin-pairs in the present study are nearly the total of affected twin-pairs that have been reported in the literature to date. Further studies are needed to determine the impact of genetics in the formation and rupture of IAs.

Introduction

Genetic and environmental factors have been implicated in intracranial aneurysm (IA) formation [1]. Previous work has suggested that vulnerability to IA formation is heritable [2, 3]. Twin studies provide an opportunity to evaluate the impact of genetics on IA characteristics, including IA location. A few cases of IAs in twins have been reported in the literature [4], and risk factor profiles and other clinical characteristics are often absent in these reports. While genetic SAHs appear rare [5, 6], an understanding of the genetic contributions to IA formation and rupture may help improve the understanding of the underlying pathophysiology and stratify risk. We sought to examine the similarity of IA location ('location concordance'), IA multiplicity, and rupture status within affected twin-pairs in a large family based IA study.

Methods

The Familial Intracranial Aneurysm (FIA) study was a multicenter international study whose goal was to identify genetic and other risk factors for IA formation and rupture. The FIA study was approved by the Institutional Review Boards/Ethics Committees of all recruitment and analytic sites.

The detailed FIA study methodology has been published previously [7]. Families with multiple affected members were enrolled and completed a detailed evaluation. At least three affected family members or an affected sibling pair were required for inclusion in the study. Subjects with fusiform aneurysms, an IA associated with an AVM, 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, were excluded.

A verification committee of study neurologists reviewed the medical records. Two study neurologists independently reviewed the records and any discrepancy was settled by a third neurologist. For those subjects undergoing FIA study imaging, study neuroradiologists independently reviewed the images and any discrepancy was resolved by a third neuroradiologist. Each case was phenotyped as definite, probable, possible, or not a case. Definite was defined as an IA on angiography, operative report, autopsy, or an IA greater than 7 mm on a noninvasive imaging report (MRA or CTA). Probable was defined as a death certificate mentioning probable IA or mentioning subarachnoid hemorrhage (SAH) without an aneurysm and a phone screen consistent with a ruptured IA, or noninvasive imaging demonstrating an IA less than 7 mm but greater than 3 mm. Possible was defined as noninvasive imaging demonstrating an IA between 2 and 3 mm or if SAH was documented in the death certificate without any supporting documentation or if the death certificate listed 'aneurysm' without specifying cerebral location or an accompanying SAH. If there was no evidence for a possible IA, the phenotype was not a case.

Twin-pairs were identified in the database by birth date. Genotypic data were used to classify twin-pairs as monozygotic (MZ) or dizygotic (DZ) [8]. The present analysis included twin-pairs in which both twins were affected with IA. Demographics were recorded at the baseline interview. IA characteristics were recorded from available imaging and medical record reports.

Location concordance was defined as the presence of an IA in the same major arterial territory – internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), or vertebrobasilar – irrespective of laterality – in both members of a twin-pair. Fisher's exact test was used to test whether concordance was greater in MZ as compared with DZ twin-pairs.

Results

Using birthdates and linkage testing, we identified 36 candidate families in the overall FIA study with twins. One family with three twins (two MZ siblings and one DZ sibling) was excluded because all three siblings were unaffected. Seven twin-pairs (two MZ, five DZ) were excluded because both twins were unaffected. Five twin-pairs (one MZ, four DZ) were excluded because only one twin was affected. Six twin-pairs (two MZ, four DZ) were excluded because one twin was affected but the other twin refused a study MRA. One twin-pair (DZ) was excluded because one twin was unaffected and the other twin refused a study MRA. A total of 16 affected twin-pairs met inclusion criteria for this study. All included subjects had a definite or probable phenotype with the exception of one twin in the 5 DZ twin-pair. Patient and IA characteristics are noted in the table 1. Location concordance was observed in 8 of 11 MZ twin-pairs but only in 1 of 5 DZ twin-pairs ($p = 0.08$). Three MZ subjects had unknown IA locations; these comprised the three instances of MZ discordance. Data from twins with conclusive location results in a heritability estimate of 66%. Seven of the 11 MZ twin-pairs versus none of the five DZ twin-pairs, were concordant in the ICA distribution ($p = 0.03$). Five of the 11 MZ twin-pairs versus one of the five DZ twin-

Table 1. Characteristics of monozygotic (MZ) and dizygotic (DZ) twin-pairs at time of initial diagnosis of intracranial aneurysm (IA)

	Age	Gender	HTN	Smoking (pack-years)	IA location(s) and size	Rupture
MZ twin-pairs						
1	22	F	no	never	**L ICA** (unk), **R ICA** (6 mm)	yes (L ICA)
	22	F	no	never	**L ICA** (unk), AComm (unk)	yes (L ICA)
2	56	F	no	former (43.5)	L MCA (6 mm), **L AntChor** (unk), Bas (unk),	yes (record does
	55	F	yes	former (3.6)	**L SupHyp** (3 mm)	not indicate
					L ICA (3 mm)	which IA)
						no
3	43	F	no	current (14.5)	L ICA (7 mm), L Ophth (1.5 mm)	no
	43	F	no	current (21.8)	not specified on report	yes
4	41	M	yes	never	**R ICA** (3 mm)	no
	27	M	no	never	**R ICA** (6 mm)	yes
5	32	F	no	current (14.3)	R MCA (unk), L MCA (unk)	no
	31	F	yes	current (18)	not specified on report	yes
6	51	F	yes	never	**AComm** (7 mm)	yes
	53	F	yes	never	**AComm** (4 mm)	yes
7	54	M	no	former (25.1)	**R ICA** (7 mm), L SupCer (3 mm)	no
	53	M	no	current (21)	L MCA (17 mm), **R PComm** (5 mm), AComm (unk)	no
8	56	F	no	never	**R ICA** (8 mm), Bas (3 mm)	no
	56	F	no	never	**L ICA** (unk)	no
9	45	F	no	current (20.3)	R MCA (unk), **R PComm** (unk), **AntChor** (unk)	yes (R MCA)
	44	F	no	current (11)	**R PComm** (11 mm)	no
10	68	F	no	former (14)	**L ICA** (unk), **L MCA** (unk)	no
	66	F	no	former (34)	**L MCA** (5 mm), **L ICA** (2 mm)	no
11	50	F	no	current (17)	MCA (report does not mention side or size)	no
	42	F	no	current (20.3)	not specified on death certificate (unk)	yes
DZ twin-pairs						
1	64	F	no	never	R ICA (4.5 mm)	no
	64	F	yes	current (43)	L MCA (2 mm)	no
2	61	F	yes	former (8.7)	R ICA (8 mm), R ICA (1 mm)	no
	60	F	yes	never	AComm (15 mm)	yes
3	46	F	no	former (16.5)	**L MCA** (4 mm), **Bas** (3 mm)	yes (Bas)
	46	F	no	former (5.8)	**R MCA** (7 mm), R ACA (2.9 mm), **Bas** (0.5 mm)	no
4	44	F	no	former (2)	AComm (unk)	no
	35	F	no	current (20)	L MCA (unk)	yes
5	51	F	no	former (17.8)	L MCA (6 mm), R MCA (2 mm)	no
	51	F	yes	current (34)	AComm (3 mm), L PComm (3 mm)	no

IAs in bold type denote location concordance within twin-pairs.

ICA territory: ICA = Internal carotid artery; PComm = posterior communicating artery; Ophth = ophthalmic artery; AntChor = anterior choroidal artery; SupHyp = superior hypophyseal artery.

MCA territory: MCA = Middle cerebral artery.

ACA territory: ACA = Anterior cerebral artery; AComm = anterior communicating artery.

Vertebrobasilar territory: Bas = Basilar tip; SupCer = superior cerebellar artery.

CTA = CT angiogram; unk = unknown.

pairs, had exact matches of IA location and laterality. Age, gender, hypertensive status, smoking behavior, IA location and size, and rupture status of affected twins are shown in the table 1.

Discussion

We found that location concordance was greater in MZ than DZ twins in twin-pairs in which both twins are affected. Our previous work has demonstrated that IA location concordance is greater in several territories when probands are compared with their own affected first-degree relatives than with a randomly selected comparison family, which suggests that anatomic vulnerability might be heritable. The present paper extends this work by comparing the MZ and DZ twins.

Efforts to identify genes associated with IA formation have been modestly successful. Genome-wide association studies have demonstrated associations between multiple loci and IA formation [8–15], although the effect sizes of these common SNPs are modest. This suggests that there are likely many common variants of modest effect contributing to IA risk. These studies did not stratify by IA location.

Very few affected IA twin pairs have been reported in the literature [4, 5, 16], with high location concordance rates in those studies, which report IA locations. Most affected twin-pairs have both suffered an SAH. A study of the Nordic Twin Cohort found 6 instances (5 MZ) of concordant SAH in nearly 80,000 twin-pairs, of which ~30% were MZ. IA locations were not reported [5]. The reasons why so few cases have been reported are unclear.

The 16 twin-pairs in the present study are nearly the total of affected twin-pairs that have been reported in the literature to date, with the advantages of genetic confirmation of zygosity and risk factor profiles. However, this study has several limitations: it is small and IA locations were unknown for three MZ twins. The small sample size also limits our ability to comment on the contribution of environmental risk factors such as smoking on IA formation. Because this was a cross-sectional study and IA can develop over time, we only included twin-pairs with both twins affected; this limits the analysis of genetic contribution to IA location. In addition, phenotype verification in the FIA study was largely based on reports rather than images, so that independent verification of IA location by the study team was not possible. We cannot comment on IA development over time. We also cannot comment on IA anatomic or hemodynamic characteristics.

IA formation is a complex process. An improved understanding of the genetic component of IA formation could result in improved identification of at-risk individuals.

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