Concordance in Aneurysm Size at Time of Rupture in Familial Intracranial Aneurysms

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Background and Purpose—Intracranial aneurysm (IA) size and location are important determinants of aneurysm rupture risk. In familial IAs there is concordance of location; however, if such concordance exists for size is unknown. We analyzed the concordance of aneurysm size at time of rupture in familial IAs.

Methods—In pairs of affected relatives with aneurysmal subarachnoid hemorrhage, the ratio between the largest and the smallest aneurysm size at time of rupture was calculated. We also compared the proportion of families in which both IAs ruptured at a size < or ≥7 mm with the proportion of families in which one IA ruptured at <7 mm and another ≥7 mm. We calculated the repeatability with corresponding 95% CI for aneurysm size at time of rupture.

Results—About 130 patients from 64 families were included. Of the 68 affected pairs 18 (26%) had a ratio ≤1.2, 38 (57%) had a ratio >1.2, and 12 (17%) had a ratio ≥3. We found no difference between the proportion of families (n=31; 49%) who both had IA at time of rupture <7 mm (n=20; 31%) or both ≥7 mm (n=11; 18%) and the proportion of those families with one patient with an IA <7 mm and another with an IA ≥7 mm (n=33; 51%; *P*=0.86). Overall, the repeatability in aneurysm size at rupture within familial IAs was 0.10 (95% CI, 0–0.35).

Conclusions—There is no good concordance in aneurysm size at rupture within familial IAs. These data suggest that size of a ruptured IA in a family member should not significantly impact on the management of a familial unruptured IA in a relative. **(*Stroke*. 2019;50:504-506. DOI: 10.1161/STROKEAHA.118.021911.)**

Key Words: human ■ intracranial aneurysm ■ risk ■ rupture ■ subarachnoid hemorrhage

Familial intracranial aneurysm (IA) is defined by the presence of at least 2 affected first-degree relatives with aneurysmal subarachnoid hemorrhage (ASAH) or unruptured IAs[1,2] A positive familial history for IAs is found in ≈10% of ASAH patients, and first-degree relatives of ASAH patients have a 2.5× to 7× greater risk of ASAH than the general population.[3] Preventive screening can be performed in this high-risk group aimed at detecting and treating IAs before they rupture.[4]

Affected relatives are more likely than affected individuals from unrelated families to have IAs in the same arterial location.[5] As IA size is also an important risk factor for ASAH,[6,7] and size at rupture differs between familial and nonfamilial ASAH patients,[8] we hypothesized that also a concordance of aneurysm size at time of rupture exists within families. Such a concordance could be considered when counseling relatives with familial unruptured IAs. It may justify more preventive treatment of a small IA, if the size at rupture of the index patient was small, or postponing treatment of an IA if the size at rupture of the index patient was large.

Therefore, we aimed to assess the concordance of aneurysm size at time of rupture within multicenter cohorts of Dutch, Finnish, and French families with a family history of IAs.

Methods

Anonymized data from the article are available upon request to the corresponding author.

Study Populations

For the Dutch families all available information from 1993 to 2015 was used from the prospectively collected database of a consecutive

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series of families with familial IA at the University Medical Center Utrecht, the Netherlands. For the Finnish families the saccular IA database of Neurosurgery of Kuopio University Hospital was used which includes all sporadic and familial IA patients admitted between 1980 and 2017. Last, we used the French families' data of the Understanding the Pathophysiology of Intracranial Aneurysm (ICAN) project, which is a noninterventional nationwide and multicentre research program, including large pedigrees with familial forms of IAs.[9] These families were recruited between 2015 and 2017. Ethics approval was obtained from the local institutional review board and informed consent was obtained from patients.

ASAH was defined as the presence of subarachnoid blood on head computed tomography compatible with a ruptured aneurysm and an IA on imaging, operative report, or an autopsy. Patients with fusiform IAs, with IAs that are part of an arteriovenous malformation or with medical conditions known to predispose to IAs (polycystic kidney disease, Moya Moya disease, or sickle cell disease) were excluded.

We only included families with 2 or more relatives related in the first degree with an ASAH. The index was defined as the affected family member who was first brought under medical attention.

Data Collection

The largest diameter of the IA at time of rupture in millimeter (mm) of the affected relatives was measured on imaging as part of clinical routine by (neuro)radiologists who were unaware of the sizes of the IA at time at rupture of other relatives within in the same family. The location of all IAs was recorded and classified into major arterial territories: the internal carotid artery, middle cerebral artery, anterior cerebral artery, and vertebrobasilar.

Statistical analysis is described in Methods I in the online-only Data Supplement.

Results

We included 130 patients with ruptured IAs from 64 families; (the baseline characteristics of the included patients are summarized in Table I in the online-only Data Supplement). We 64 families for the analysis of IAs smaller and ≥7 mm, 68 pairs for the ratio, and 130 patients for the repeatability analyses.

Figure 1 represents the IA sizes of the relatives versus those of the index patients. Figure 2 shows the ratio between the size of IA at time of rupture of the largest IA and the smallest IA of each pairs. Of the 68 affected pairs 18 (26%) had a ratio ≤1.2, 38 (57%) had a ratio >1.2, and 12 (17%) had a ratio ≥3.

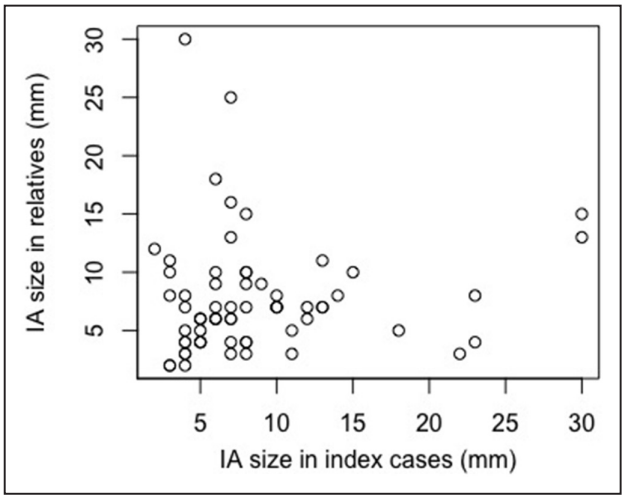

Figure 1. Scatter plot representing the sizes of the intracranial aneurysm (IA) at time of rupture of all index cases vs the sizes of the IA at time of rupture of all relatives.

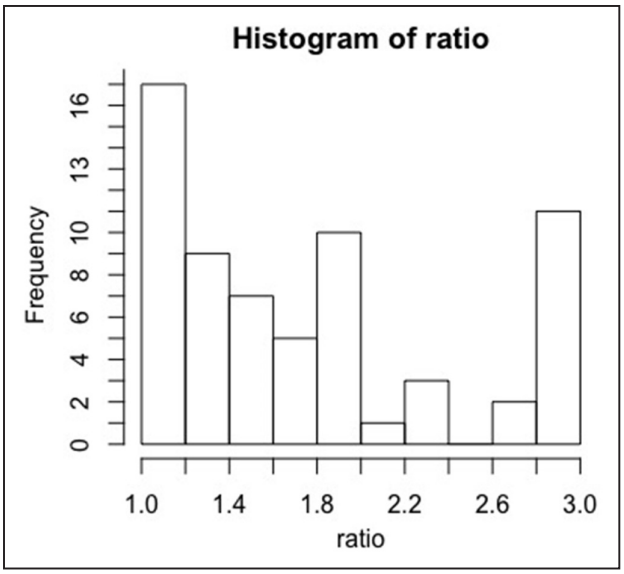

Figure 2. Ratio between the size of intracranial aneurysm at time of rupture of the largest intracranial aneurysm (IA) and the smallest IA of each pair of patients. The *y*-axis represents the number of pairs and the *x*-axis the ratio between the size of the larger IA of the pairs and the smallest. For this purpose, we divided the largest IA size in millimeter by the smallest IA size of each pairs.

We found no difference between the proportion of families (n=31; 49%) who both had IAs at time of rupture <7 mm (n=20, 31%) or both ≥7 mm (n=11; 18%) and the proportion of those families who had one patient with an IA smaller and another patient with an IA ≥7 mm (n=33; 51%) *P*=0.86.

Results of the repeatability analysis are summarized in the Table. Overall, we found a poor agreement with repeatability of 0.10 (95% CI, 0–0.35). The subgroup analyses showed comparable results, with only slightly higher, but still poor agreement for the subgroup of women (repeatability of 0.27, 95% CI, 0.11–0.70). We only found 4 pairs with ruptured middle cerebral artery IA.

Discussion

The concordance of the size at rupture within families with ASAH is poor. In the vast majority of patients' pairs, the ratio of the IA at time of rupture is >1.2. Furthermore, no difference was found between the proportion of affected families who had IAs at time of rupture both smaller or both ≥7 mm and

Table. Repeatability for Aneurysm Size at Time of Rupture Within Families Adjusted for Location of IA as Fixed and Families as Random Effect

Groups	R	95% CI
Overall (n=130)	0.10	0–0.35
Women (n=40)	0.27	0.11–0.70
Men (n=30)	0.12	0.09–0.70
Finnish subjects (n=87)	0.08	0–0.43
Non-Finnish subjects (n=43)	0.01	0–0.53

IA indicates intracranial aneurysm; n, no. of subjects included in the calculation; and R, repeatability.

the proportion of those families who had one patient with an IA smaller and another patient with an IA ≥7 mm. Last, we found a poor repeatability in IA size at time of rupture within these families.

Our study is the first that approached the clinically relevant question on the concordance of aneurysm size at time of rupture within a large international cohort of well-phenotyped families with a history of IAs. In addition, we performed 3 distinct analyses (ie, ratio analysis, analysis of families with IA smaller, and ≥7 mm and repeatability analysis). Figure 1 underpins the lack of concordance graphically.

Our study also has limitations. First, we included a large number of Finnish families while for the Finnish population a higher incidence of ASAH and different aneurysm and patient characteristics have been reported.[10,11] However, we do not think that inclusion of these families has influenced our findings, since our subgroup analysis in Finnish and non-Finnish families both revealed poor repeatability in IA size at time of rupture. Moreover, the number of subjects with middle cerebral artery aneurysms was too small to allow subgroup analysis according to this characteristic.

Since we found no good concordance in size at rupture within familial IA, these data suggest that size of a ruptured IA in a family member should not significantly impact on the management of a familial unruptured IA in a relative.

Disclosures

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