Prevalence of intracranial aneurysms in first-degree relatives of patients with aneurysms

MARJORIE C. WANG, M.D., DAVID RUBINSTEIN, M.D., GLENN W. KINDT, M.D.,
AND ROBERT E. BREEZE, M.D.

Departments of Neurosurgery and Radiology, University of Colorado Health Sciences Center, Denver, Colorado

Object. A familial predisposition toward cerebral aneurysms has been previously described in patients with two or more affected family members. In the present study the familial incidence of unruptured intracranial aneurysms was studied in 96 patients with at least one first-degree relative (parent, sibling, or child) in whom a cerebral aneurysm was diagnosed.

Methods. All patients were between 20 and 70 years of age and underwent three-dimensional fast-spin echo magnetic resonance imaging. Sixty-one patients (63.5%) were women. The majority of patients (84%) were caucasian and the remainder were Hispanic (13%) or African-American (3%). No patient suffered a medical condition (excluding hypertension and smoking) known to be associated with cerebral aneurysm formation.

In four patients at least one aneurysm was found (two harbored multiple aneurysms). Three of the four patients were women. Two of the patients were siblings. The estimated prevalence in first-degree relatives was 4.2% (95% confidence interval 1.2–10.1). Of note, the mean age in the current study population was 39 years. The authors of recent metaanalyses have suggested that the prevalence of nonfamilial aneurysms is approximately 2%, despite earlier reports in which higher figures were cited.

Conclusions. The authors conclude that first-degree relatives of patients with aneurysms are at higher risk for harboring an intracranial aneurysm.

KEY WORDS • intracranial aneurysm • unruptured aneurysm • family • screening

A genetic predisposition for harboring saccular intracranial aneurysms has been described in the literature.^{1,4,5,11,13,21,23,25,47} In most studies investigators have targeted families with at least two index cases of cerebral aneurysms. The reported prevalence of cerebral aneurysms in these targeted families varies from 2.4¹⁸ to 29.4%.¹⁹ This prevalence has surpassed the nonfamilial incidence of cerebral aneurysms reported in most studies.

Given the extremely high rates of morbidity and mortality associated with aneurysm rupture, the goal of these studies has been to isolate high-risk populations to initiate treatment and avoid the severe sequelae of aneurysm hemorrhage. The benefits of operative intervention may outweigh the surgery-related morbidity and mortality, thus increasing life expectancy.^{19,26,28,43,47}

We studied the prevalence of intracranial aneurysms in first-degree relatives of patients with aneurysms. In contrast to most familial aneurysm studies, we required only one index family member to harbor a documented cerebral aneurysm. Our goal was to determine prospectively the risk of a first-degree relative harboring an asymptomatic cerebral aneurysm.

CLINICAL MATERIAL AND METHODS

This study was approved by our local institutional review board. Asymptomatic individuals between the age of 20 and 70 years, were recruited. In each case it was clearly established that one first-degree relative of the study individual harbored a true saccular cerebral aneurysm. In the index case the patient was not required to be symptomatic, although most were. Individuals with polycystic kidney disease,^{38,50} aortic coarctation, and other diseases believed to be associated with aneurysm formation were excluded. Patients with other risk factors such as hypertension^{3,37,46} or cigarette smoking,⁴⁹ however, were not excluded. Three-dimensional time-of-flight MR angiography and three-dimensional fast-spin echo T₂-weighted MR imaging were performed in each study individual.⁵¹ All images were reviewed by a staff neuroradiologist. Reformatted images were viewed in multiple planes on the monitor to provide maximum detail.

RESULTS

Data in 96 patients were studied. The majority (84%) of individuals were caucasian. Hispanic patients comprised 13% of the population, and African-American patients 3%. Sixty-four percent of the individuals were woman. Age ranged from 20 to 67 years. The mean age was 39

Abbreviations used in this paper: DS = digital-subtraction; MCA = middle cerebral artery; MR = magnetic resonance; SAH = subarachnoid hemorrhage.

years (median 37.5 years). Seventy-three percent of the patients were between 30 and 49 years of age.

Intracranial aneurysms were identified in four individuals (Table 1). Two individuals were brother and sister (age 30 and 33 years, respectively). The other two individuals harbored multiple aneurysms. Thus the total number of lesions was seven. The two individuals harboring multiple aneurysms were age 59 and 64 years and both were women. All patients underwent clip ligation without complication. Six of seven aneurysms were located along the MCA. The remaining lesion was a basilar artery apex aneurysm.

The probability of a first-degree relative harboring an aneurysm (uncorrected for age) was 4.2% (95% confidence interval 1.2–10.1%).

DISCUSSION

Intracranial aneurysms have long been thought to occur more frequently in genetically predisposed individuals. Because the combined morbidity and mortality rate associated with aneurysmal SAH is extremely high (upwards of 70% in most studies),^{36,52} attention has been directed toward isolating risk factors for cerebral aneurysms. Many investigators have attempted to determine the prevalence of familial aneurysms, defined as intracranial aneurysms found in two or more family members.⁴⁷ We prospectively determined the prevalence of aneurysms in approximately 100 first-degree relatives of patients in whom cerebral aneurysms were documented using three-dimensional fast-spin echo and time-of-flight MR imaging.

The prevalence of familial intracranial aneurysms has ranged widely in the literature from 2.4¹⁸ to 29.4%.¹⁹ In our study, the prevalence was 4.2% (95% confidence interval 1.2–10.1%). There may be several reasons why our results have fallen at the lower end of the reported range. In many studies, including those from Finland,^{31,32,35} Japan,^{16,24} and Minnesota,^{40,42} the authors have reported a prevalence of familial aneurysms at the higher end of the aforementioned range. The populations in these studies are limited with little genetic drift. Indeed, the incidence of SAH has been shown to be higher in certain areas such as East Finland. The higher prevalence of familial aneurysms and of SAH in this area might be secondary to a local genetic predisposition toward aneurysms.^{20,27,34} In contrast, our population base was widely diverse, encompassing individuals from many areas.

The mean age of patients in this study was 39 years

(median 37.5 years). This is a much younger group of individuals compared with those in most familial studies in which the mean age is typically 50 years. In several large studies the incidence of cerebral aneurysms has been shown to increase with advancing age.^{3,12,22,52} Most notably, the authors of a study of 3100 patients in Japan reported that elderly patients (> 70 years of age) were more likely to suffer from both an unruptured cerebral aneurysm and aneurysmal SAH.⁵² The slightly lower prevalence of aneurysms found in our younger population would be consistent with these findings.

Although most familial studies in the literature required two or more index cases, we found an increased occurrence of cerebral aneurysms in first-degree relatives with only one index family member. An even higher prevalence might be anticipated in patients with two or more affected relatives. Those patients with a family history of aneurysms and in whom additional risk factors such as hypertension or smoking are present may have an even higher chance of manifesting an intracranial aneurysm, as was suggested in a recent study of siblings.⁹

In some studies investigators have included infundibula in their calculations, possibly elevating their prevalence results. Infundibula, although suspicious in nature, are not definitive precursors to aneurysms. The presence of infundibula, however, indicates that these patients should be followed closely for progression or even development of de novo aneurysms.^{19,18,30,48}

In this study women were more likely to harbor cerebral aneurysms and multiple aneurysms. This finding is in agreement with most of the literature.^{17,21} The location of aneurysms was also heavily weighted toward the MCA distribution, again consistent with data reported in most studies.^{2,7,14,33}

All patients in whom lesions were positively documented underwent definitive prophylactic clip ligation of their aneurysm(s). There were no cases of complications or mortality associated with these procedures. Prophylactic treatment of aneurysms may be beneficial, especially in a younger age group, as in our study. In addition, some authors have reported increased rates of morbidity and mortality due to SAH secondary to familial aneurysm compared with nonfamilial SAH.^{6,41} This fact, coupled with the widespread availability of excellent noninvasive testing, makes screening in this population even more attractive.

It has been suggested in one study that there is a lack of efficacy for screening procedures in families with intracranial aneurysms.¹⁰ The authors estimated the cost of such screening starting when a patient was 30 years of age; evaluation would entail using both MR angiography and DS angiography; and the estimated morbidity rate would be 8%. The authors were unable to show any benefit to screening.¹⁰ Morbidity rates, however, are difficult to generalize; some centers report rates as low as 1.9%.⁴⁴ In addition, some surgeons perform surgery based on MR angiography or computerized tomography angiography, thereby excluding the risk associated with digital subtraction angiography. Finally, statistical analysis must take into account the differences between treatments even within a disease process. Giant posterior fossa aneurysms, for example, are associated with a much higher morbidity

TABLE 1
Summary of data in first-degree relatives in whom aneurysms were found*

Case No.	Age (yrs)	Race	Index Case	No. of Aneurysms	Location (no.)
1	30	Hispanic	brother	1	rt MCA
2	33	Hispanic	brother	1	lt MCA
3	59	caucasian	sister	3	BA apex (1), rt MCA (2)
4	64	caucasian	son	2	lt MCA

* BA = basilar artery.

Aneurysm prevalence in first-degree relatives

and mortality rate than anterior circulation aneurysms.¹⁵ Familial aneurysm may have a size and location profile that is different from the general population.

Brown and Soldevilla⁸ also studied treatment costs, comparing MR angiography and surgical treatment of a ruptured aneurysm with screening mammography. When MR angiography studies documented a positive finding, DS angiography was then conducted. They found the annual cost of MR angiography screening for familial aneurysms to be one half the cost of treating a single patient with a ruptured aneurysm, and 2.9% of the annual cost for mammography performed for screening purposes.

Assessing the relative risk of harboring an aneurysm for any specified population necessarily requires knowing the "background" prevalence in the general population. The prevalence of aneurysms in the general population has been variously estimated to be between 0.5 and 9%.^{39,45} In a recent metaanalysis the authors estimated this figure to be 2.3%; they reviewed 56,304 patients in 23 studies published between 1955 and 1996.²⁹ Using a background prevalence rate of 2.3%, we obtain a relative risk of 1.8 for our study population.

CONCLUSIONS

We conclude that first-degree relatives of an individual with a proven cerebral aneurysm are at higher risk for an aneurysm than the general population. The prevalence of 4.2% in this series is likely an underestimation. Patients at risk for familial aneurysms, especially those with additional risk factors, may benefit from undergoing timely screening and operative intervention to prevent the severe morbidity and mortality associated with aneurysmal rupture.

References

1. Acosta-Rua GJ: Familial incidence of ruptured intracranial aneurysms. Report of 12 cases. **Arch Neurol** 35:675-677, 1978
2. Andrews RJ: Familial intracranial aneurysms. **Arch Neurol** 36:524, 1979
3. Andrews RJ, Spiegel PK: Intracranial aneurysms. Age, sex, blood pressure, and multiplicity in an unselected series of patients. **J Neurosurg** 51:27-32, 1979
4. Bannerman RM, Ingall GB, Graf CJ: The familial occurrence of intracranial aneurysms. **Neurology** 20:283-292, 1970
5. Brisman R, Abbassioun K: Familial intracranial aneurysms. **J Neurosurg** 34:678-682, 1971
6. Bromberg JE, Algra A, Rinkel GJ, et al: The prognosis of familial versus nonfamilial aneurysmal subarachnoid hemorrhage. **Stroke** 27: 340-341, 1996 (Letter)
7. Bromberg JE, Rinkel GJ, Algra A, et al: Familial subarachnoid hemorrhage: distinctive features and patterns of inheritance. **Ann Neurol** 38:929-934, 1995
8. Brown BM, Soldevilla F: MR angiography and surgery for unruptured familial intracranial aneurysms in persons with a family history of cerebral aneurysms. **AJR Am J Roentgenol** 173:133-138, 1999
9. Connolly ES Jr, Choudhri TF, Mack WJ, et al: Influence of smoking, hypertension, and sex on the phenotypic expression of familial intracranial aneurysms in siblings. **Neurosurgery** 48:64-68, 2001
10. Crawley F, Clifton A, Brown MM: Should we screen for familial intracranial aneurysm? **Stroke** 30:312-316, 1999
11. Hashimoto I: Familial intracranial aneurysms and cerebral vascular anomalies. **J Neurosurg** 46:419-427, 1977
12. Heiskanen O: Surgical management of unruptured cerebral aneurysms, in Schmidek HH, Sweet WH (eds): **Operative Neurosurgical Techniques: Indications, Methods, and Results**, ed 3. Philadelphia: WB Saunders, 1995, Vol 1, pp 1155-1162
13. Kak VK, Gleadhill CA, Bailey IC: The familial incidence of intracranial aneurysms. **J Neurol Neurosurg Psychiatry** 33:29-33, 1970
14. Kasuya H, Onda H, Takeshita M, et al: Clinical features of intracranial aneurysms in siblings. **Neurosurgery** 46:1301-1306, 2000
15. Kirkpatrick PJ, McConnell RS: Screening for familial intracranial aneurysms. **BMJ** 319:1512-1513, 1999
16. Kojima M, Nagasawa S, Lee Y, et al: Asymptomatic familial cerebral aneurysms. **Neurosurgery** 43:776-781, 1998
17. Leblanc R: Familial cerebral aneurysms. A bias for women. **Stroke** 27:1050-1054, 1996
18. Leblanc R, Melanson D, Tampieri D, et al: Familial cerebral aneurysms: a study of 13 families. **Neurosurgery** 37:633-639, 1995
19. Leblanc R, Worsley K, Melanson D, et al: Angiographic screening and elective surgery of familial cerebral aneurysms: a decision analysis. **Neurosurgery** 35:9-19, 1994
20. Linn FH, Bromberg JE, Rinkel GJ, et al: Familial intracranial aneurysms. **Lancet** 349:1477-1478, 1997
21. Lozano AM, Leblanc R: Familial intracranial aneurysms. **J Neurosurg** 66:522-528, 1987
22. Minyard AN, Parker JC: Intracranial saccular (berry) aneurysm: a brief overview. **South Med J** 90:672-677, 1997
23. Morooka Y, Waga S: Familial intracranial aneurysms: report of four families. **Surg Neurol** 19:260-262, 1983
24. Nakagawa T, Hashi K: The incidence and treatment of asymptomatic, unruptured cerebral aneurysms. **J Neurosurg** 80:217-223, 1994
25. Nakajima H, Kishi H, Yasui T, et al: Intracranial aneurysms in identical twins. **Surg Neurol** 49:306-308, 1998
26. Obuchowski NA, Modic MT, Magdinec M: Current implications for the efficacy of noninvasive screening for occult intracranial aneurysms in patients with a family history of aneurysms. **J Neurosurg** 83:42-49, 1995
27. Puchner MJ, Freckmann N, Herrmann HD: Familial subarachnoid hemorrhage in East Finland, 1977-1990. **Neurosurgery** 35:173-174, 1994
28. Raaymakers TW, Rinkel GJ, Ramos LM: Initial and follow-up screening for aneurysms in families with familial subarachnoid hemorrhage. **Neurology** 51:1125-1130, 1998
29. Rinkel G, Djibuti M, Algra A, et al: Prevalence and risk of rupture of intracranial aneurysms: a systematic review. **Stroke** 29:251-256, 1998
30. Rinne J, Hernesniemi J: De novo aneurysms: special multiple intracranial aneurysms. **Neurosurgery** 33:981-985, 1993
31. Ronkainen A, Hernesniemi J, Puranen M, et al: Familial intracranial aneurysms. **Lancet** 349:380-384, 1997
32. Ronkainen A, Hernesniemi J, Ryyanen M: Familial subarachnoid hemorrhage in East Finland, 1977-1990. **Neurosurgery** 33:787-797, 1993
33. Ronkainen A, Hernesniemi J, Tromp G: Special features of familial intracranial aneurysms: report of 215 familial aneurysms. **Neurosurgery** 37:43-47, 1995
34. Ronkainen A, Hernesniemi J, Vanninen R, et al: Familial intracranial aneurysms. **Lancet** 349:1477-1479, 1997 (Letter)
35. Ronkainen A, Miettinen H, Karkola K, et al: Risk of harboring an unruptured intracranial aneurysm. **Stroke** 29:359-362, 1998
36. Ronkainen A, Puranen M, Hernesniemi J, et al: Intracranial aneurysms: MR angiographic screening in 400 asymptomatic individuals with increased familial risk. **Radiology** 195:35-40, 1995

37. Sacco RL, Wolf PA, Bharucha NE, et al: Subarachnoid and intracerebral hemorrhage: natural history, prognosis, and precursive factors in the Framingham Study. **Neurology** **34**:847–854, 1984
38. Schievink WI: Genetics of intracranial aneurysms. **Neurosurgery** **40**:651–663, 1997
39. Schievink WI: Familial intracranial aneurysms: an autopsy study. **Neurosurgery** **43**:1258–1259, 1998 (Letter)
40. Schievink WI, Parisi JE, Piepgras DG: Familial intracranial aneurysms: an autopsy study. **Neurosurgery** **41**:1247–1252, 1997
41. Schievink WI, Schaid DJ: The prognosis of familial versus non-familial aneurysmal subarachnoid hemorrhage. **Stroke** **27**:340–341, 1996
42. Schievink WI, Schaid DJ, Michels VV, et al: Familial aneurysmal subarachnoid hemorrhage: a community-based study. **J Neurosurg** **83**:426–429, 1995
43. Schievink WI, Schaid DJ, Rogers HM, et al: On the inheritance of intracranial aneurysms. **Stroke** **25**:2028–2037, 1994
44. Solomon RA: Should we screen for familial intracranial aneurysm? **Stroke** **30**:1291–1293, 1999
45. Stehbens WE: Familial intracranial aneurysms: an autopsy study. **Neurosurgery** **43**:1258–1259, 1998
46. Taylor CL, Yuan Z, Selman WR, et al: Cerebral arterial aneurysm formation and rupture in 20,767 elderly patients: hypertension and other risk factors. **J Neurosurg** **83**:812–819, 1995
47. ter Berg HE, Dippel DW, Limburg M, et al: Familial intracranial aneurysms. A review. **Stroke** **23**:1024–1030, 1992
48. Wakai S: Familial intracranial aneurysms. **Lancet** **349**:1477–1479, 1997 (Letter)
49. Wang PS, Longstreth WT, Koepsell TD: Subarachnoid hemorrhage and family history. A population-based case-control study. **Arch Neurol** **52**:202–204, 1995
50. Wiebers DO, Torres VE: Screening for unruptured intracranial aneurysms in autosomal dominant polycystic kidney disease. **N Engl J Med** **327**:953–955, 1992
51. Wilcock D, Jaspan T, Holland I, et al: Comparison of magnetic resonance angiography with conventional angiography in the detection of intracranial aneurysms in patients presenting with subarachnoid haemorrhage. **Clin Radiol** **51**:330–334, 1996
52. Yamashita K, Kashiwagi S, Kato S, et al: Cerebral aneurysms in the elderly in Yamaguchi, Japan. Analysis of the Yamaguchi Data Bank of Cerebral Aneurysm from 1985 to 1995. **Stroke** **28**:1926–1931, 1997

Manuscript received July 18, 2002.

Accepted in final form August 14, 2002.

Address reprint requests to: Robert E. Breeze, M.D., University of Colorado Health Sciences Center, Department of Neurosurgery, 4200 East 9th Avenue Box C307, Denver, Colorado 80262. email: Robert.Breeze@UCHSC.edu.