

## Family history of subarachnoid hemorrhage and the incidence of asymptomatic, unruptured cerebral aneurysms

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**Object.** Previously the authors reported a significant correlation between a family history of subarachnoid hemorrhage (SAH) and the discovery of an unruptured aneurysm in a group of healthy volunteers. This study corroborates and extends previous findings regarding the relationship between genetic and acquired factors in the formation of cerebral aneurysms.

**Methods.** The incidence of asymptomatic, unruptured cerebral aneurysms was studied among patients with a family history of SAH within the second degree of consanguinity. Forty-one unruptured cerebral aneurysms were found in 34 (13.9%) of 244 patients. This incidence was significantly higher than that found in a control group of healthy volunteers (6%). Furthermore, patients who had a family history of SAH combined with multiple systemic risk factors were found to have the highest incidence of unruptured aneurysms (32%; odds ratio 3.49, 95% confidence interval 1.37-8.9).

**Conclusions.** These findings suggest that patients with a family history of SAH with or without the presence of more than one systemic risk factor are at significantly higher risk of harboring cerebral aneurysms. This high-risk group should be periodically screened and treated with appropriate surgical or other forms of therapy when necessary.

**KEY WORDS** • cerebral aneurysm • subarachnoid hemorrhage • familial aneurysm • hereditary • systemic risk factor

**I**N 1988 we began a formalized screening system for asymptomatic brain disease in healthy volunteers, termed "Brain Dock" in Japan, with the purpose of preventing cerebrovascular disease, especially subarachnoid hemorrhage (SAH). The term "dock" refers to an area in a port in which ships are repaired. In our 1994 study we reported a high discovery rate (6%) of an unruptured aneurysm in 400 healthy volunteers.<sup>5</sup> It was found in that study that the most significant factor correlating to an incidence of unruptured aneurysm was a family history of SAH. Thus, we further extended the screening study for unruptured aneurysms to include patients with a family history of SAH within the second degree of consanguinity. The results were compared with updated data gathered from 1000 healthy volunteers.

### Clinical Material and Methods

#### Family Group

The family group was restricted to patients who had a family history of SAH within the second degree of consanguinity and who had no previous symptoms or presumed episode of SAH. In this group, defined as the "Family group," there were 244 patients: 73 men and 171

women, ranging in age from 20 to 72 years (mean 50.9 years) (Fig. 1). All patients received a set of screening examinations for unruptured cerebral aneurysms while at the outpatient and inpatient settings of our hospital between May 1991 and April 1997. The screening examinations consisted of one or more of the following three angiographic studies: 1) magnetic resonance (MR) angiography performed in 234 cases (95.9%); 2) three-dimensional computerized tomography (3D-CT) angiography performed in 16 cases (6.6%); and 3) intraarterial digital subtraction (IA-DS) angiography performed in 37 cases (15.2%). In cases in which unruptured aneurysms were found on MR angiography, either 3D-CT angiography or IA-DS angiography was performed to ensure a precise assessment.

#### Brain Dock Group

To make a comparison with the Family group, healthy volunteers who underwent medical evaluation at our Brain Dock unit between March 1988 and October 1997 were defined as the "Brain Dock group." They had no symptoms or history of presumed SAH. There were 1000 volunteers: 664 men and 336 women, ranging in age from 22 to 78 years (mean 54.6 years) (Fig. 1). Most volunteers

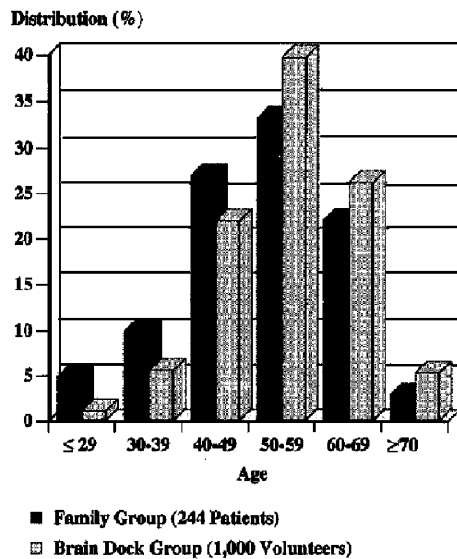


FIG. 1. Bar graph displaying the percentage age distribution in the groups studied. Both groups show uniform distribution of age.

were motivated to participate in the study because of a family history of cerebrovascular disease including SAH and some other risk factors, whereas others wished to undergo medical evaluation because of vague uneasiness (Table 1). The IA-DS angiography was performed in 370 (37%) of 1000 cases from March 1988 to June 1992; after July 1992 MR angiography was performed in all the remaining 630 cases as the primary screening examination and either 3D-CT angiography or IA-DS angiography was performed as an additional screening examination in patients suspected of harboring cerebral aneurysms.

*Outline of Comparison Between Family Group and Brain Dock Group*

The incidence, location, size, and other characteristics of unruptured aneurysms were compared between both groups. History of cerebral infarction, hypertension, diabetes mellitus, presence of hyperlipidemia, and habitual smoking were considered risk factors.

Statistical analyses included formulating the odds ratio with a 95% confidence interval (CI), a chi-square test, and a test for differences of proportion. Comorbidity and presence of aneurysms were calculated by using commercial-

TABLE 1  
Motive for Brain Dock entry in 1000 cases\*

| Motive                | Percentage of Volunteers |
|-----------------------|--------------------------|
| family history of CVD | 48.1                     |
| family history of SAH | 9.9                      |
| hypertension          | 40.8                     |
| hyperlipidemia        | 34.9                     |
| headache              | 20.0                     |
| vague uneasiness      | 6.2                      |
| others                | 13.0                     |

\* Some patients stated multiple motives. Abbreviation: CVD = cerebrovascular disease including SAH.

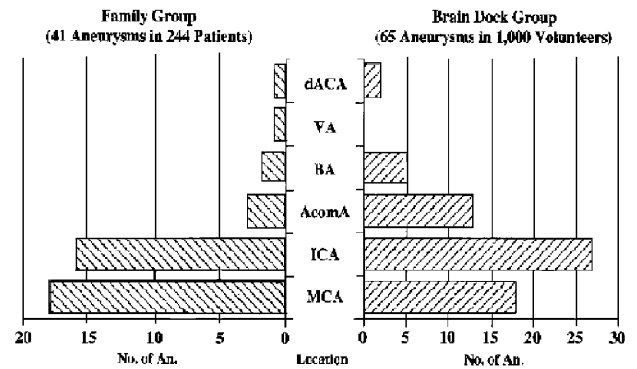


FIG. 2. Bar graphs depicting the locations of the discovered aneurysms in both groups. The Family group shows a predominance of aneurysms on the middle cerebral artery. AcomA = anterior communicating artery; BA = basilar artery; dACA = distal anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery; VA = vertebral artery.

ly available software (Statview; Abacus Concepts, Inc., Berkeley, CA).

**Results**

*Summary of Family Group*

Forty-one asymptomatic, unruptured cerebral aneurysms were found in 34 (13.9%) of the 244 patients in the Family group. In six (17.6%) of these patients there were multiple aneurysms. The incidence of aneurysms was eight (11%) of 73 men and 26 (15.2%) of 171 women.

Eighteen (43.9%) of aneurysms were located on the middle cerebral artery; 16 (39%) on the internal carotid artery; three (7.3%) on the anterior communicating artery; two on the basilar artery; and one each on the vertebral artery and the distal anterior cerebral artery (Fig. 2 left). The diameter of the aneurysm was 4 mm or less in 21 (51.2%) of 41 cases and 5 to 10 mm in 19 cases (46.3%) (Fig. 3 left).

The relationship between the incidence of aneurysms and the density of family history of SAH was as follows: aneurysms were found in 17 (14%) of 121 patients with a history of aneurysms in parents alone, 15 (14.9%) of 101 patients with a history in siblings alone, and two (14.3%) of 14 patients with a history of more than one family member (Fig. 4). Aneurysms were not found in patients with a history of SAH in grandparents.

In this group (Fig. 5 left), hypertension was found in 74 (30.3%) of 244 cases, habitual smoking in 62 (25.4%), hyperlipidemia in 20 (8.2%), and diabetes mellitus in eight cases (3.3%). Eight patients suffered cerebral infarction (3.3%). Twenty-five (10.2%) of 244 patients had more than one risk factor, whereas 108 patients (44.3%) had no such risk factors (Fig. 5 left).

Regarding the relationship between the incidence of aneurysms and risk factors, aneurysms were found in 15 (20.3%) of 74 patients with hypertension, two (25%) of eight with diabetes mellitus, five (25%) of 20 with hyperlipidemia, and 11 (17.7%) of 62 who were habitual smokers. In patients in whom there was more than one risk factor, aneurysms were found in eight (32%) of 25 cases

## Risk factors for cerebral aneurysm

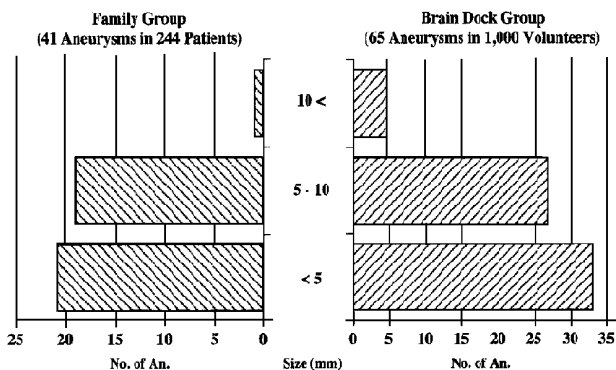


FIG. 3. Bar graphs showing size distribution of aneurysms in both groups. Most aneurysms were smaller than 10 mm in both groups. An = aneurysms.

(odds ratio 3.49, 95% CI 1.37–8.9). This correlation was statistically significant (Table 2).

### Summary of Brain Dock Group

In the Brain Dock group, 65 asymptomatic, unruptured cerebral aneurysms were found in 60 (6%) of 1000 patients. When analyzed according to gender, the incidence was 34 (5.1%) of 664 men and 26 (7.7%) of 336 women.

The aneurysms were found in the following locations: 18 (27.7%) on the middle cerebral artery; 27 (41.5%) on the internal carotid artery; 13 (20%) on the anterior communicating artery, and five (7.7%) on the basilar artery (Fig. 2 right). The diameter of the aneurysms was 4 mm or less in 33 (50.8%) of 65 cases and 5 to 10 mm in 27 cases (41.5%) (Fig. 3 right).

In this group of 1000 volunteers, there was associated hypertension in 408 cases (40.8%), hyperlipidemia in 349 cases (34.9%), habitual smoking in 310 cases (31%), and diabetes mellitus in 82 cases (8.2%) (Fig. 5 right).

Regarding the incidence among volunteers with risk factors, aneurysms were found in 31 (7.6%) of 408 cases with hypertension; 33 (6.8%) of 487 cases with a family history of cerebrovascular disease (including cerebral infarction, cerebral hemorrhage, and SAH); 21 (6.8%) of 310 cases associated with habitual smoking; and 18 (5.2%) of 349 cases with hyperlipidemia (Fig. 5 right). In those volunteers having a family history of SAH, aneurysms were found in 12 of 99 patients. This incidence was statistically significant at 12.1% (odds ratio 2.74, 95% CI 1.4–5.35) (Table 2).

### Summary of Group Comparison

The Family group had a much higher incidence of unruptured cerebral aneurysms (13.9%) than the Brain Dock group (6%) ( $Z_0 = 4.204$ ,  $p < 0.001$ ). Aneurysms were found in 34 of 244 patients in the Family group and in 60 of 1000 volunteers in the Brain Dock group.

There was no statistical difference in aneurysm distribution between the two groups ( $p = 0.25$ ). Both groups showed a predominance of aneurysms on middle cerebral and internal carotid arteries, and there were fewer aneurysms on the anterior communicating artery in comparison with ruptured cases (Fig. 2).

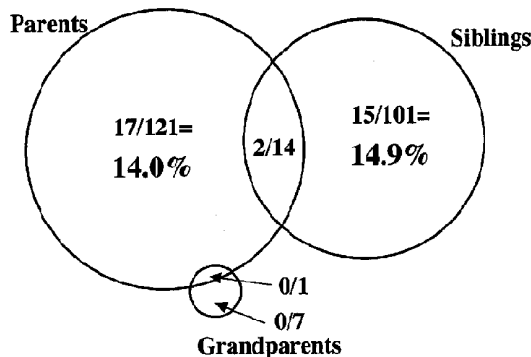


FIG. 4. Venn diagram showing the correlation of aneurysms and family history of SAH. Among the second degree of consanguinity, family history of grandparents did not show any incidence of SAH, whereas other histories such as those including parents or siblings showed a uniform degree of correlation.

There was no statistical difference in the size distribution of aneurysms between the two groups ( $p = 0.47$ ). In both groups, 90% of aneurysms were 10 mm or smaller and approximately 50% were smaller than 5 mm (Fig. 3).

The relationship between the incidence of aneurysms and risk factors was statistically analyzed by formulating the odds ratio with the 95% CI for both groups (Table 2). The incidence of aneurysms tended to be lower for men in both groups, and there was a significantly high incidence of aneurysms in the Family group members with more than one risk factor (odds ratio 3.49, 95% CI 1.37–8.9), indicating a strong correlation between a family history of SAH and multiple risk factors. On the other hand, the Brain Dock group members who had multiple risk factors did not have a high incidence of aneurysms, although a high incidence was observed in members of this group who had a family history of SAH (12.1%; odds ratio 2.74, 95% CI 1.4–5.35).

## Discussion

The incidence of unruptured aneurysms in healthy volunteers in our Brain Dock group was higher than dis-

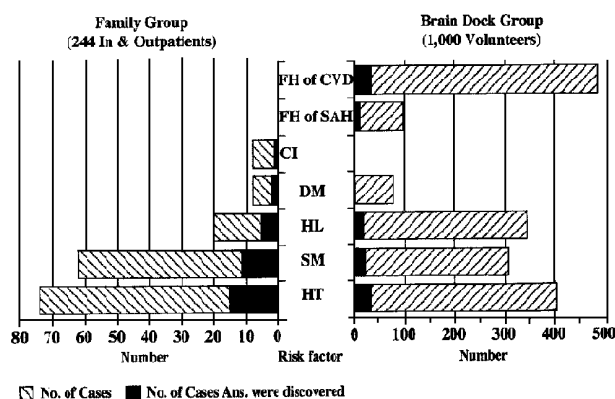


FIG. 5. Bar graphs depicting incidences of comorbidity in both Family and Brain Dock groups. CI = cerebral infarction; DM = diabetes mellitus; FH = family history; HL = hyperlipidemia; HT = hypertension; SM = smoking.

TABLE 2  
Comorbidity and presence of aneurysms in both groups\*

| Risk Factor             | Family Group |                 |                     | Brain Dock Group |                 |                     |
|-------------------------|--------------|-----------------|---------------------|------------------|-----------------|---------------------|
|                         | No. of Cases | No. W/ Aneurysm | Odds Ratio (95% CI) | No. of Cases     | No. W/ Aneurysm | Odds Ratio (95% CI) |
| hypertension            | 74           | 15              | 2.02 (0.96–4.24)    | 408              | 31              | 1.60 (0.95–2.69)    |
| diabetes mellitus       | 8            | 2               | IDA                 | 82               | 1               | 0.18 (0.03–1.31)    |
| hyperlipidemia          | 20           | 5               | 2.24 (0.76–6.63)    | 349              | 18              | 0.79 (0.45–1.39)    |
| smoking                 | 62           | 11              | 1.49 (0.68–3.27)    | 310              | 21              | 1.21 (0.70–2.10)    |
| gender (male)           | 73           | 8               | 0.69 (0.30–1.60)    | 664              | 34              | 0.64 (0.38–1.09)    |
| stroke                  | 8            | 1               | 0.88 (0.11–7.38)    | 0                | 0               | IDA                 |
| family history of SAH   | 244          | 34              | —                   | 99               | 12              | 2.74 (1.40–5.35)    |
| more than 1 risk factor | 25           | 8               | 3.49 (1.37–8.90)    | 321              | 21              | 1.15 (0.66–1.99)    |

\* IDA = insufficient data available; — = not applicable, all patients in group.

covery rates previously reported in the literature. The presumed average incidence of cerebral aneurysms has varied in each reported study. This may be due to differences in the size of the series, the patient age distribution, the complication of disease, and whether the study focused on live patients or autopsy specimens. The average incidence of asymptomatic unruptured cerebral aneurysm has generally been considered to be from 1 to 3%.<sup>10</sup> To make a statistical comparison of the incidence rate, it is important that the age distribution of the patients and volunteers compared be within the same range and uniform. Concerning this point, the following two reports are comparable to ours. Inagawa and Hirano<sup>3</sup> reported that 84 incidental saccular aneurysms (0.83%) were found in 10,112 autopsy cases, excluding SAH and fusiform aneurysm cases. On the other hand, Atkinson, et al.,<sup>1</sup> reported in their angiographic reevaluation that three incidental aneurysms (1.1%) were found in 278 cases, excluding SAH cases. On the basis of these two reports, we presumed the incidence of unruptured aneurysms among adults to be approximately 1%. Recently, Rinkel, et al.,<sup>6</sup> reviewed studies published between 1955 and 1996 and concluded that the incidence of aneurysms for adults without risk factors for SAH was approximately 2%. Compared with the three preceding reports, our consecutive 1000 cases in the Brain Dock group revealed a much higher incidence of 6% and an even higher incidence of 12.1% was found in Brain Dock volunteers with a family history of SAH. Therefore, we have stressed the significance of screening people with a family history of SAH to help prevent its devastating impact.<sup>5</sup>

To confirm the correlation between a family history of SAH and the discovery of an unruptured aneurysm, we extended our study to include outpatients and inpatients with a family history of SAH. Our strategy was to recommend and perform MR angiography studies in patients who had a family history of cerebrovascular disease. Once a patient deemed positive or suspected of harboring a cerebral aneurysm was found, 3D-CT angiography and/or IA-DS angiography was performed for a precise assessment. The possibility of overlooking an aneurysm larger than 2 mm has proven to be very low in our clinical experience. In those patients in whom a screening examination provided negative findings, follow-up MR angiography

was still performed every 1 to 3 years. Fortunately, we have not seen any SAH in these patients.

Because our study participants were patients who visited our hospital with various complaints, our results might have some bias in elucidating the exact incidence of familial aneurysms among the general population. Nevertheless, the incidence of unruptured aneurysms in the Family group seemed remarkably higher than that in healthy volunteers in the Brain Dock group, and this figure was statistically significant, given the fact that the age distribution between the two groups was uniform (Fig. 1). Our results suggest that some cerebral aneurysms are hereditary and that people with a family history of SAH need further screening studies.<sup>7</sup>

Ronkainen and associates<sup>9</sup> also reported that screening for unruptured incidental intracranial aneurysms is worthwhile if more than one family member within the first degree of consanguinity is affected by one. They conducted a study to compare the prevalence and relative risk of unruptured incidental intracranial aneurysms between families of persons who harbored them and the general population in one geographically defined area in eastern Finland. The relative risk for intracranial aneurysms among first-degree relatives in families in which more than one person harbored such aneurysms was a 4.2 odds ratio, and among first-degree relatives in families with only one affected family member, the odds ratio was 1.8 compared with the general population. In our study there was no difference in the incidence of unruptured aneurysms between patients with more than one affected family member and those with only one affected family member, although only a few cases were available for comparison. However, it is our impression that the incidence of unruptured aneurysms would be higher for people with more than one affected family member as Ronkainen and associates<sup>9</sup> reported.

The concept that genetic factors influence the formation of familial aneurysms has been generally acknowledged. Our results have corroborated some previously known characteristics of familial aneurysms: they tended to be located on the middle cerebral artery, which is different from the distribution of aneurysms in SAH cases,<sup>2,8</sup> and most familial aneurysms were smaller than 10 mm, which is compatible with the concept that familial aneurysms are

## Risk factors for cerebral aneurysm

significantly smaller than those in individuals without a family history of SAH.<sup>4,8</sup>

Although our study was primarily focused on genetic factors, our risk factor analysis revealed other acquired factors related to the incidence of cerebral aneurysms. Each risk factor alone did not have any correlation with the existence of cerebral aneurysms, but more than one risk factor had a significant correlation with the presence of unruptured aneurysms. These findings have not previously been reported and cannot be overemphasized. Therefore, our data imply that some aneurysms are not only hereditary, but also acquired because of multiple systemic risk factors.

### Conclusions

The incidence of unruptured cerebral aneurysms was studied among outpatients and inpatients with a family history of SAH within the second degree of consanguinity. In this study, both genetic and acquired factors were observed to influence aneurysm incidence. Unruptured cerebral aneurysms were found in 34 (13.9%) of 244 patients with a family history of SAH and in eight (32.3%) of 25 patients (odds ratio 3.49, 95% CI 1.37–8.9) with a family history and multiple systemic risk factors. Family history of SAH, especially with the addition of more than one risk factor, should identify a high-risk group of patients with possible cerebral aneurysms. Aggressively screening these high-risk patients combined with optimum surgical treatment of unruptured aneurysms should decrease the incidence of SAH in the future.

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### References

1. Atkinson JLD, Sundt TM Jr, Houser OW, et al: Angiographic frequency of anterior circulation intracranial aneurysms. *J Neurosurg* **70**:551–555, 1989
2. Bromberg JEC, Rinkel GJE, Algra A, et al: Familial subarachnoid hemorrhage: distinctive features and patterns of inheritance. *Ann Neurol* **38**:929–934, 1995
3. Inagawa T, Hirano A: Autopsy study of unruptured incidental intracranial aneurysms. *Surg Neurol* **34**:361–365, 1990
4. Lozano AM, Leblanc R: Familial intracranial aneurysms. *J Neurosurg* **66**:522–528, 1987
5. Nakagawa T, Hashi K: The incidence and treatment of asymptomatic, unruptured cerebral aneurysms. *J Neurosurg* **80**:217–223, 1994
6. Rinkel GJE, Djibuti M, van Gijn J: Prevalence and risk of rupture of intracranial aneurysms: a systematic review. *Stroke* **29**:251–256, 1998
7. Ronkainen A, Hernesniemi J, Ryyänen M: Familial subarachnoid hemorrhage in east Finland, 1977–1990. *Neurosurgery* **33**:787–796, 1993
8. Ronkainen A, Hernesniemi J, Tromp G: Special features of familial intracranial aneurysms. (Report of 215 familial aneurysms.) *Neurosurgery* **37**:43–47, 1995
9. Ronkainen A, Miettinen H, Karkola K, et al: Risk of harboring an unruptured intracranial aneurysm. *Stroke* **29**:359–362, 1998
10. Sekhar LN, Heros RC: Origin, growth, and rupture of saccular aneurysms: a review. *Neurosurgery* **8**:248–260, 1981

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