Family History and Risk of Subarachnoid Hemorrhage
A Case-Control Study in Nagoya, Japan

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Background and Purpose—We sought to examine the relation between a family history of subarachnoid hemorrhage (SAH) and the risk of SAH by using a case-control study.

Methods—Case subjects consisted of a consecutive series of 195 patients with spontaneous SAH, aged 30 to 79 years, with aneurysms confirmed by angiography and/or CT scan. Hospital and community control subjects were identified and matched to each case by sex and age (±2 years). Multiple conditional logistic regression was used to calculate the odds ratio (OR) and 95% interval (CI) adjusted for potential confounders.

Results—Having a family member with SAH was significantly associated with an increased risk of SAH (OR, 4.0, 95% CI, 2.0 to 8.0), after adjusting for potential confounders. The risk for a positive family history of SAH was similar for men and women and was inversely related to the SAH patient’s age. A maternal positive SAH history (OR, 5.4; 95% CI, 2.0 to 8.0), after adjusting for potential confounders. The risk for a positive family history of SAH was similar for men and women and was inversely related to the SAH patient’s age.

Conclusions—A positive family history of SAH was significantly and strongly associated with the risk of SAH. To prevent the onset of SAH at a younger age, much more attention should be given to individuals with any family member (first-degree relatives) suffering SAH episodes. (Stroke. 2003;34:422-426.)

Key Words: case-control studies • family history • subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH), unlike other types of stroke, is a serious disease that occurs more frequently among those <65 years.1 The incidence of SAH is higher in Japan than in Western countries,2 and it has increased ≈3-fold during the past 20 years in Japan.3 Thus, this disease is now regarded as an important nationwide public health issue in Japan. Several epidemiological studies have examined the risk factors of SAH, focusing mainly on hypertension,4,5,6,11 cigarette smoking,1,4,5,7–9 alcohol drinking,4–6,10 and oral contraceptive use.6,11–13

A number of case reports and case series have increasingly demonstrated a cluster of SAH among families with 2 or more patients having intracranial aneurysms (ruptured or unruptured)14–20 since Chambers et al21 documented many such families with intracranial aneurysms in 1954. A few case-control studies,22–24 however, have examined the relation between the risk of SAH and a family history of SAH, but their findings were inconsistent: a positive association in 2 studies22,23 and no association in 1.24 In addition, no study continuously recruited incident patients in their analysis,22–25 and some were based on only a small number of patients.22,23

We therefore conducted a case-control study to explore a possible association between a family history of SAH and the risk of SAH by using a relatively greater number of newly diagnosed patients.

Subjects and Methods
Our methods were previously described in detail.26 In brief, we recruited all consecutive and incident SAH patients admitted to 2 large medical hospitals in Nagoya, Aichi Prefecture, Japan (Nagoya Daini Red Cross Hospital and Nagoya City Higashi Municipal Hospital) from April 1992 to March 1997. SAH was diagnosed by an aneurysmal bleeding pattern by CT, under the additional condition that the presence of 1 or more aneurysms had to be confirmed by cerebral angiography.

Case subjects included were aged 30 to 79 years, including some who had experienced their first spontaneous episode of SAH. Patients with other causes of SAH were not eligible as case subjects and were excluded. We also excluded SAH patients aged >80 years because of the difficulty in obtaining matched control subjects for them and those <30 years old because of possibly different etiologies.18

We set up 2 control groups (hospital and community) of subjects with no past history of SAH, matching them to each patient for age (±2 years) and sex. Hospital controls were selected from patients with gastrointestinal diseases treated at the same hospital as the study patients. Community controls were randomly selected from the general population in the same district where the patient lived. For this random sampling, we used the basic register of residents, because they are frequently updated and include all residents by

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distinct in Japan. When a potential control subject did not respond after 1 request, another eligible candidate was selected.

Data Collection

Two investigators (K.O. and R.H.) directly interviewed SAH patients and their matched controls. We asked patients to recall their lifestyle during the 5 years before the onset of SAH and controls, during the 5 years before the interview, by using a structured questionnaire specifically designed for this case-control study. Direct interviews were conducted for SAH patients and hospital controls at each hospital and for community control subjects at their homes. SAH patients were interviewed within 1 month after their admission and the 2 controls within 2 weeks after completing the interview of a case subject.

The information obtained from each study subject included demographic characteristics (age, sex, height, weight, years of education, and occupation held the longest), past medical history (including history of hypertension), family medical history (including history of SAH in any first-degree relatives), smoking habits, alcohol consumption, subjective stress level, the kinds and frequency of physical activities, and dietary habits with the intake frequency of various foods.

The data regarding family history of SAH were collected based on self-report. A positive family history of SAH was defined as any subject with first-degree relatives who had suffered from SAH in the past. Hypertension was considered present when a subject was diagnosed as such at any time before the survey. Smoking status was categorized into current smokers (at least 1 cigarette per day), past, and nonsmokers.

When the patients were unable to provide any information on their lifestyle and exposure because of early death or impairment, proxies (mainly spouses) were interviewed. Whenever possible, a standardized in-person interview was conducted with the patients and their 2 matched controls. Only when this was not possible was a proxy interview performed. To minimize information bias, when the proxy to a SAH patient was interviewed, the proxy to the control was also interviewed even if the control was competent to be interviewed.

Institutional Ethics Committees at each of the 2 hospitals approved the study protocol before the study was launched. Informed consent was obtained from each study subject by an interviewer after verbal explanation of the study’s purpose and methods.

Statistical Analysis

The differences in mean values or frequencies between SAH patients and controls were statistically examined by an unpaired t test, \( \chi^2 \) test, or Mantel extension test. The odds ratio (OR) and its 95% confidence interval (CI) were estimated by using multiple conditional logistic-regression models in which matched variables (sex and age at diagnosis) and potential confounders (past episode of hypertension, smoking) were controlled. Unconditional logistic models including sex and other confounding factors (hypertension and smoking status), however, were also used when analyzing data by age at diagnosis and by age at diagnosis and type of family history. Smoking status was classified into current smokers or nonsmokers (including exsmokers) in the analysis.

### Results

A total of 204 consecutive patients aged 30 to 79 with a first spontaneous SAH were identified in the study period. Among them, 3 patients were excluded because of other causes of SAH (arteriovenous malformation and traumatic SAH); 6 patients were also excluded because of incomplete information regarding their family history of SAH. This left 195 SAH patients for the present analysis. The distribution of gastrointestinal problems was as follows: gastric or duodenal ulcer (52.6%), hepatitis (11.2%), cirrhosis (10.2%), gastritis (6.3%), acute enteritis (5.2%), and others (14.5%). Table 1 presents selected background characteristics of patients and controls.

Because there was no difference between hospital and community controls, the 2 groups were combined for all analyses. The mean overall age was \( \approx 59.0 \) years in both cases (59.2 ± 10.3 years) and controls (59.1 ± 10.4 years), accounting for \( \approx 60\% \) in women in both patients and controls. Proxy interviews accounted for 31.7% in all groups. The average interview time was not significantly different between patients (19.9 ± 5.6 minutes) and controls (20.1 ± 5.4 minutes).

SAH patients included significantly more hypertensive-subjects \( (P=0.0000) \) and more current smokers \( (P=0.05) \). Among SAH patients, the mean age of subjects with a positive family history of SAH (54.9 ± 10.6 years) was younger than those without (60.0 ± 10.1 years). Table 2 summarizes the crude and adjusted ORs of SAH risk for a
positive family history of SAH. A positive family history of SAH was significantly associated with an increased risk of SAH with an OR of 4.0 (95% CI, 2.0 to 8.0), adjusting for hypertension and smoking status. Risks for a positive family history of SAH were similar for men (OR, 3.9; 95% CI, 1.1 to 16.0) and women (OR, 3.8; 95% CI, 1.5 to 9.7).

Table 3 shows SAH risk adjusted for 2 confounders by type of first-degree relatives. The highest SAH risk was found for those with a positive maternal history of SAH (OR, 5.4; 95% CI, 1.8 to 16.0), although a positive paternal history was also had a significantly high risk, with an OR of 3.8 (95% CI, 1.1 to 13.4). A family history of SAH in sibling(s) was not significantly related to SAH risk, even though their OR was 3.2.

Table 4 shows the relation between family history of SAH and SAH risk stratified by age at diagnosis. We observed that a positive family history of SAH was significantly associated with an increased risk of SAH in all age groups. That association was strongest among subjects <50 years old (OR, 4.4; 95% CI, 1.2 to 14.0) and weakest among subjects ≥60 years (OR, 2.8; 95% CI, 1.0 to 8.5).

**Discussion**

This study demonstrated 3 major findings of statistical significance: SAH risk was elevated when (1) any first-degree relative had a positive episode of SAH, (2) a mother or father had a relative with a positive episode of SAH (an effect much greater in magnitude in a positive maternal rather than paternal history, (3) any first-degree relative <50 had had an SAH.

Several investigators have repeatedly reported familial aggregations of SAH in case studies, including Kojima et al, who found that asymptomatic aneurysms were more likely to rupture among family members with aneurysmal SAH than among those without. A few case-control studies have demonstrated that a positive family history of SAH was associated with an increased risk of SAH. We confirmed this association as involving an approximate 4-fold increased risk; likewise, previous studies analyzed aneurysmal SAH. In this study, we also found that the magnitude of SAH risk for those with a positive family history of SAH was about equal to that for hypertension, which is commonly accepted as an independent risk factor for SAH. These findings suggest that a positive family history of SAH may be an independent risk factor for SAH and may have a much larger effect on an increased risk of SAH.

Some investigators have reported a higher prevalence of familial cerebral aneurysms in women than in men (2 times more often in women), but few studies have examined the sex differences in SAH risk according to family SAH history. In this study, we found that the risk for a positive family history was similar for men and women, suggesting that there may be no marked sex difference in the risk for a positive family history.

Few studies have evaluated SAH risk according to the type of first-degree relatives. Two case-control studies reported, as did ours, that SAH risk was higher among those with a positive sibling’s SAH history, though without statistical significance. In our study, SAH risk was significantly associated with both a positive paternal and maternal history of SAH, although a much larger effect was derived from a positive maternal history. It is, however, unclear why a positive maternal history was more strongly associated with SAH compared with other first-degree relatives. Previous studies have mentioned that intracranial aneurysms are inherited in an autosomal dominant fashion without significant differences in the fashion of inheritance between both sexes. According to Hannula et al, methylation changes occurred most commonly on paternal chromosome 7, which was reported to be a genetic locus for intracranial aneurysm(s), whereas alterations on maternal chromosome 7 were more infrequent and weaker. These findings might explain our finding of a marked difference in the magnitude of SAH risk between a positive maternal and paternal SAH history.

Consistent with previous studies, we found that the mean age of subjects with a positive family history of SAH (60.0±10.1 years) was younger than those without (54.9±10.6 years). However, whether or not the risks of a family history of SAH vary by age remain underdetermined. We observed a significant relation between a positive family history of SAH and SAH risk in all age groups, but the risk was 1.5 times as high in the youngest than in the oldest age group. According to Leblanc, cerebral aneurysms in patients with a positive family history might result from a mesenchymal defect affecting the cerebral vessel wall produced by a lesion of chromosome 16. According to Denarie et
al,\textsuperscript{24} intima-media thickness, lumen diameter, and cross-sectional area intima-media thickness increased with aging owing to exposure of the arterial wall over time to atherogenic effects. These findings suggest that younger individuals with a positive family history of SAH might be much more prone to rupture of cerebral aneurysms because of the their vessel fragility. In short, our findings may indicate an urgent need for early prevention of SAH by screening individuals with any positive family members (first-degree relatives) with an SAH episode.

There are some methodological limitations to this study. First, exposure suspicion bias due to the interviewers might have been involved while collecting the data. Interviews in this study were conducted by 2 permanent interviewers (K.O. and R.H.), and standardized interview procedures were determined in detail before the survey to minimize interviewer and inter-interviewer variations. The average interview duration did not differ among SAH patients and their matched controls, indicating that exposure suspicion bias and interviewer bias were successfully minimized. Second, we found a higher proportion of a positive family history of SAH in SAH patients than in the 2 controls, as also shown by previous studies.\textsuperscript{23,35,36} SAH patients were more likely to be familiar with a family history of SAH than controls and were therefore more likely to incorrectly retain details of a relative’s event SAH.\textsuperscript{23} Our information on family members who experienced SAH was only self- or proxy-reported, because we could not confirm a history of SAH of all family members. The Japanese Medical Practitioners Law obligates medical institutes to keep medical records for 5 years after a disease has been cured. However, because no subjects’ first-degree relatives in our study experienced SAH during the 5 years before the survey, their medical records had already been discarded. According to Bromberg et al.,\textsuperscript{22} “the positive predictive” value of detecting familial SAH was $\approx 70\%$, suggesting possible misclassifications in our study. The measured risk based on information obtained from patients with a positive family history may, in general, tend to be overestimated.\textsuperscript{37} This suggests that associations observed in our study were probably overestimated, although it was difficult to determine the extent of the recall bias involved. Third, we used information provided by proxy respondents for approximately one third of our study subjects. The effect of potential bias by proxy respondent has to be carefully considered. According to Nelson et al.,\textsuperscript{38} ORs based on proxy-derived data were similar in magnitude to those obtained from index subject data. Agreement between subjects’ and proxies’ reports has been shown to be very high for certain medical conditions.\textsuperscript{39} We have also previously reported that proxy responses were acceptable for such information as family history of SAH, hypertension, smoking, and drinking habits.\textsuperscript{40} In our study, associations between family SAH history and SAH occurrence still remained after excluding the data obtained from proxy respondents (data not shown). Finally, any case-control study is generally prone to be affected by selection bias. We recruited all consecutive SAH patients, and almost all patients with severe and acute medical conditions are usually admitted to Nagoya City Higashi Municipal Hospital, if they live in the eastern area, or to Nagoya Daini Red Cross Hospital, if they are from the southern area of the city. In addition, community controls were randomly selected from inhabitants in the same residential areas as case subjects. We have just finished reviewing all death certificates registered in Nagoya City from 1992 through 1997 to analyze the causes of death in patients who expired before reaching the hospital. These study designs suggest that our study may be considerably close to a population-based case-control study, although generalizability of our findings would be limited to those aged 30 to 79 years old. Two strengths of our study warrant mention.

First, all SAH patients were incident patients, and we included dead and alive subjects to avoid the distorting effect of survival bias. Second, bias due to misclassification is also unlikely, because all patients’ conditions as to the presence of aneurysm(s) were confirmed by cerebral angiography and CT or surgical inspection. In conclusion, a family history of SAH was found to be significantly linked to subsequent occurrences of SAH. Because a family history of SAH is not modifiable, it is vitally important to conduct early examinations of those with such a history so as to prevent the onset of SAH. Our findings will be useful in targeting individuals/population for primary and/or secondary prevention of SAH.

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