Major Risk Factors for Aneurysmal Subarachnoid Hemorrhage in the Young Are Modifiable

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Background and Purpose—To identify risk factors for subarachnoid hemorrhage (SAH) and intracerebral hemorrhage, we designed a case-control study of men and women 18 to 49 years of age (the Hemorrhagic Stroke Project [HSP]). This report focuses on SAH.

Methods—Patients were recruited from 44 hospitals in the United States. Cases with SAH must have had a ruptured aneurysm documented by angiography or surgery. Two controls, identified by random digit dialing and matched to each patient for age, sex, race, and telephone exchange, were sought for each case subject.

Results—Between 1994 and 1999, 425 patients with SAH were enrolled in HSP, and 312 cases met the criteria for aneurysmal SAH. The present analyses also included 618 matched controls. Of the 312 cases, 66% were current cigarette smokers compared with 30% of controls (adjusted odds ratio [OR], 3.73; 95% CI, 2.67 to 5.21). Cocaine use within the previous 3-day period was reported by 3% of cases and no controls (bivariate exact OR, 24.97; 95% exact CI, 3.95 to ∞; adjusted estimate not calculable). Other independent risk factors in the multivariable model included hypertension (adjusted OR, 2.21; 95% CI, 1.48 to 3.29), low body mass index (OR, 1.59; 95% CI, 1.08 to 2.35), primary family history of hemorrhagic stroke (OR, 3.83; 95% CI, 1.73 to 8.46), caffeine in pharmaceutical products (OR, 2.48; 95% CI, 1.19 to 5.20), lower educational achievement (OR, 2.36; 95% CI, 1.44 to 3.87), and nicotine in pharmaceutical products (adjusted estimate not calculable).

Conclusions—Aneurysmal SAH may be largely a preventable disease among the young and middle-aged because several prevalent risk factors can be modified by medication (eg, hypertension) or behavioral change (eg, cigarette smoking, cocaine use). The association of caffeine and nicotine in pharmaceutical products and aneurysmal SAH warrants further study.

Key Words: case-control studies • cerebrovascular disorders • cigarette smoking • cocaine • risk factors • subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) affect ≈55 000 to 60 000 patients in the United States every year.1 The mortality rate of hemorrhagic stroke is 39% to 50%, with half of the deaths occurring in the first 2 days.1–4 Therefore, primary prevention remains the most important means of reducing the morbidity and mortality associated with hemorrhagic stroke. Effective prevention depends on understanding the mechanisms and factors underlying the occurrence of SAH and ICH and knowing the populations that are at greatest risk.

Most SAHs are due to rupture of an intracranial aneurysm of a major artery at the base of the brain.2 A few SAHs occur secondary to rupture of an arteriovenous malformation. Only 10% to 20% of patients with SAH have no clear structural source of bleeding by brain imaging or cerebral angiography.2,5 However, identification of the factors leading to the formation and rupture of intracranial aneurysms remains an area of intense study because it provides the best way to develop effective prevention strategies.

The Hemorrhagic Stroke Project (HSP) is a collaboration between investigators of 4 clinical stroke centers and their surrounding hospitals, the Food and Drug Administration, and manufacturers of phenylpropanolamine.6 Its main purpose was to examine the relationship of phenylpropanolamine...
and the risk of hemorrhagic stroke in persons 18 to 49 years of age. Primary results of the HSP have been reported elsewhere. The goal of the present analysis was to determine the environmental risk factors for aneurysmal SAH.

Methods

Recruitment and Classification of Patients With Hemorrhagic Stroke

Between December 1994 and July 1999, we identified patients with symptomatic SAH or ICH from 44 hospitals in Connecticut, Massachusetts, Ohio, Kentucky, Rhode Island, and Texas (see the Appendix, which is available online at http://stroke.ahajournals.org). A SAH was diagnosed from clinical symptoms plus either CT evidence of subarachnoid bleeding or lumbar puncture showing xanthochromia. Eligibility criteria for cases included the following: age of 18 to 49 years, ability to communicate and complete the interview within 30 days of the stroke event, no previously diagnosed brain lesion predisposing to hemorrhage (ie, arteriovenous malformation, tumor, aneurysm), and no prior stroke. Cases were recruited in person or by telephone as soon as they were identified, provided that their personal physician approved. For the present analysis, we focused only on case subjects with aneurysmal SAH that was defined as SAH due to a documented intracranial aneurysm by cerebral angiography, surgery, or autopsy.

Recruitment of Controls

We attempted to identify 2 matched controls for each case using random digit dialing. Matching criteria included telephone exchange, sex, ethnic group (black versus nonblack), and age (within 3 years for case subjects <30 years of age and within 5 years for cases ≥30 years of age). When a perfectly matched control could not be located, we enrolled an imperfectly matched control rather than exclude the case. All control interviews had to be completed within 30 days of the case’s stroke event to minimize seasonal differences in exposures.

Ascertainment of Exposure Data and Other Subject Information

Trained researchers used a structured questionnaire to obtain demographic, risk factor, behavioral, and pharmaceutical information from all subjects. Interviews were conducted in person unless the subject refused or a meeting could not be arranged within 30 days of the case’s focal time.

The patient interviews included questions about medical history, including hypertension, diabetes, polycystic kidney disease, thyroid disease, menopausal status, and prior family history of hemorrhagic stroke. Social and behavioral histories included questions on cigarette smoking, alcohol consumption, illicit drug use, caffeine consumption, and education level. Because the primary focus of the HSP was the use of phenylpropanolamine and the risk of hemorrhagic stroke, subjects were also asked to recall cold symptoms, medications used to treat them, and any other medications taken during the 2 weeks before focal time. After all volunteered medications were recorded, subjects were asked if they had taken several specific medications or classes of medications (eg, aspirin, anticoagulants, diet pills).

To verify exposures, participants were asked to pick out reported brand-name cough-cold or appetite-suppressant medications from a book containing package photographs. They were then asked to produce each medication so that the exact name and manufacturer’s lot numbers could be recorded. If the container was not available, a brand-name medication was considered verified if the subject had identified it in the book. Only verified medication exposures were counted in the analysis.

To determine the active ingredients in each medication, we relied on published sources. For national brands and prescription drugs that had possible formulation changes during the study period and for generic or store-brand medications, we verified active ingredients directly with the manufacturer.

To ensure confidentiality, patients were assigned a unique number to identify them in computerized files. Paper research records were maintained in locked offices accessible only to the investigators and research staff. A certificate of confidentiality was obtained from the US Department of Health and Human Services to enable the investigators to withhold names and identifying characteristics of research subjects from persons not connected with the research.

Statistical Analysis

In the first phase of analysis, we estimated the odds ratio (OR) and associated probability value for the association between aneurysmal SAH and a subject characteristic or exposure using exact conditional logistic modeling for matched sets. To identify independent risk factors, dichotomous features with \( P<0.10 \) for the bivariate association with SAH were considered for inclusion in a multivariate logistic model using a forward selection algorithm (with criterion for entry set at \( P=0.05 \)). Multivariate modeling was performed with asymptotic methods. Exact logistic models were estimated by the LogXact Program, version 2.1 (Cytel Software Corporation). Adjusted models were estimated with SAS, version 8.0 (SAS Corp).

Results

The final case group for the HSP comprised 702 subjects, including 425 (60%) with an SAH and 277 (40%) with an ICH. Of the 425 cases of SAH, 312 cases met the criteria for aneurysmal SAH and represent the basis for the present analyses (Table 1).

Two controls were enrolled for 306 cases (98%) and 1 control for 6 cases. All 618 controls were matched to their cases on sex and telephone exchange. Age matching was successful for 617 controls, and ethnicity matching was achieved for 601 controls (97%). Compared with controls, cases with aneurysmal SAH were significantly more likely to report lower educational achievement in bivariate analysis (Table 2). With regard to medical history, cases were more likely to report a diagnosis of hypertension

<table>
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<tr>
<th>TABLE 1. Assembly of Cohort</th>
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<tr>
<td>SAH identified (December 1994–August 1999)</td>
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<tr>
<td>Ineligible subjects</td>
</tr>
<tr>
<td>Died within 30 d of stroke</td>
</tr>
<tr>
<td>Not able to communicate within 30 d of stroke</td>
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<tr>
<td>Prior history of stroke</td>
</tr>
<tr>
<td>Prior history of brain tumor or AVM</td>
</tr>
<tr>
<td>In hospital &gt;72 h before stroke</td>
</tr>
<tr>
<td>Eligible subjects—HSP</td>
</tr>
<tr>
<td>Not enrolled</td>
</tr>
<tr>
<td>Not contacted within 30 d</td>
</tr>
<tr>
<td>Refused participation</td>
</tr>
<tr>
<td>No physician approval to contact</td>
</tr>
<tr>
<td>Enrolled</td>
</tr>
<tr>
<td>Aneurysmal SAH subjects for present analyses</td>
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AVM indicates arteriovenous malformation.

*For nonenrolled subjects, stroke events were confirmed to be eligible, but ability to communicate within 30 days of event was not assessed.
†Three subjects were removed from analysis: 1 had uncertain index date; 1 completed the interview >30 d after event; 1 had 1 matching control identified.
(before the index stroke), to report a history of brain hemorrhage in a primary family member, and to have low body mass index (BMI; $<23$ kg/m$^2$). Controls were more likely to report a history of elevated cholesterol. With regard to health behaviors and use of medicine, cases were more likely to be current cigarette smokers, to be heavy alcohol (2 drinks daily) and caffeine (5 drinks daily) users, and to report exposure to cocaine, marijuana, caffeine (in pharmaceuticals), and nicotine (in pharmaceuticals) in the 3 days before the index date.

In the multivariable model, the OR for the association with risk for aneurysmal SAH was highest for family history of hemorrhagic stroke (OR, 3.83) and current cigarette smoking (OR, 3.73) (Table 3). Other significant independent risk factors included hypertension, lean body mass, caffeine in pharmaceutical products, and less than a high school educat-
significant association between cocaine use and the risk of
aneurysmal SAH. Use of cocaine and other illicit drugs has
been reported in cases series of hemorrhagic stroke.9–18
However, because only 3% to 4% of cases of aneurysmal
SAH report exposure to cocaine, the statistical significance of
such a relationship is difficult to demonstrate without a large
number of cases, as in our present study.

Several biological explanations for the relationship be-
tween cocaine use and rupture of intracranial aneurysm have
been hypothesized. One possibility is that the acute elevations
in blood pressure associated with cocaine use cause already
present unruptured aneurysms to rupture.12,14 Another possi-

bility is that cocaine causes the intracranial aneurysm to
develop and rupture acutely because of markedly elevated
blood pressure or an intracranial arteriopathy.17

Our study also confirms that cigarette smoking is the most
important modifiable risk factor for SAH.19–26 The OR or
relative risk of SAH associated with current smoking in other
case-control or cohort studies ranges from 3 to 4 with a clear
dose response, as was also seen in the present study.19–25 In
population-based or cohort studies, 70% to 75% of persons
with SAH have a prior history of smoking, and 50% to 60%
are current smokers. Our study has the highest reported
percentage of current smokers among cases (66%) because
our population of cases of SAH includes only those 18 to 49
years of age, the segment of the population with the highest
rates of smoking. Because 30% of the control subjects also
smoke, we estimate that 45% of the cases of aneurysmal SAH
in this age group may be attributed to current smoking of
cigarettes. In addition, the risk of aneurysmal SAH was less
for former smokers than current smokers. Thus, smoking is
by far the most important preventable cause of aneurysmal
SAH.

Our findings include an association between use of nico-
tine and caffeine in pharmaceutical products and risk for
aneurysmal SAH. Pharmaceutical products containing nico-
tine are not known to increase risk for stroke, although a few
case reports exist.27,28 Pharmaceutical doses of caffeine in
combination with phenylpropanolamine have been associated
with risk for stroke in case reports.29,30 but caffeine in coffee
beverages is not associated with an increased risk for stroke.31
None of our caffeine users were also using phenylpropan-
amine. Our results must be regarded as only suggestive.

In our population, hypertension is a clear risk factor for
aneurysmal SAH confirming other population-based stud-
ies.19–21 Because 21% of the control population in this age
group have a history of hypertension, hypertension is the
most important preventable risk factor after current smoking.

Discussion

Ours is the first large case-control study to demonstrate a
significant association between cocaine use and the risk of

<table>
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<tr>
<th>TABLE 3. Adjusted ORs for Risk of Aneurysmal SAH*</th>
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<tr>
<td>Adjusted Matched OR 95% CI</td>
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<tr>
<td>Education &lt;12th grade 2.37 1.45–3.87</td>
</tr>
<tr>
<td>Medical history</td>
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<tr>
<td>Primary family history 3.32 1.54–7.12</td>
</tr>
<tr>
<td>Hypertension 2.22 1.51–3.28</td>
</tr>
<tr>
<td>Body mass index &lt;23 kg/m² 1.77 1.22–2.58</td>
</tr>
<tr>
<td>Health behaviors</td>
</tr>
<tr>
<td>Current cigarette smoking 3.66 2.64–5.07</td>
</tr>
<tr>
<td>Cocaine use</td>
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<td>††</td>
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*311 case subjects and 614 controls subjects were included in the analysis (no missing data).
††Cocaine use was included in model, but estimates were not calculable with asymptotic methods.

We further investigated the relationship between cigarette
smoking, lean body mass, and risk of SAH. As shown in
Table 2, there was a significant dose response between
number of cigarettes smoked on average in the prior 6 months
and risk for aneurymal SAH. The relationship between lean
body mass and stroke was strongest among current smokers
(smokers in our data.) In this analysis, the association of lean
body mass and smoking in control

subjects (32% of current and 35% of former compared with 22%
smokers, smokers were more likely to be lean than nonsmok-
ers). However, in our data, there was no
relationship between lean body mass and smoking in control
subjects (≈20% had BMI <23 kg/m² in all smoking groups).
Accordingly, the risk for SAH associated with lean body
mass was observed among current and former smokers but
not among subjects classified as never smokers (Table 4).
When we examined the risk of lean body mass according to
strata defined by average daily cigarette use in the prior 6
months, however, we found an elevated OR in all groups,
including subjects who reported no daily use in the prior 6
months (Table 5). (This latter finding was due to the strong
relationship of low BMI and stroke status among former
smokers in our data.) In this analysis, the association of lean
body mass and stroke was strongest among current smokers
who smoked at least 1 pack daily (OR, 3.35; P=0.05).

<table>
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<th>TABLE 4. Relationship of Lean Body Mass (BMI&lt;23 kg/m²) to Risk of SAH</th>
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<tr>
<td>Overall and by Smoking Strata</td>
</tr>
<tr>
<td>Cases</td>
</tr>
<tr>
<td>n Lean, n Lean, %</td>
</tr>
<tr>
<td>All subjects 312 96 31 618 132 21</td>
</tr>
<tr>
<td>Current smokers* 203 66 32</td>
</tr>
<tr>
<td>Ex-smokers 49 17 35</td>
</tr>
<tr>
<td>Never smokers* 59 13 22</td>
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</tbody>
</table>

*Among current smokers, 1 case and 1 control were missing body mass data; among never
smokers, 3 control subjects were missing body mass data.
Other independent risk factors in our study included a low BMI, family history of hemorrhagic stroke, and low educational achievement. The association of low BMI with SAH has been previously reported,21,22,26 but the biological mechanism underlying this association is unclear. When this relationship was examined according to average daily cigarette use, we found an association in all groups, including subjects who reported no daily use in the prior 6 months. Of particular interest in this analysis is the observation that the association of lean body mass and stroke was strongest among current smokers who smoked at least 1 pack daily.

Other case-control studies of SAH have found that cases of aneurysmal SAH are more likely to report a family history of SAH and intracranial aneurysm than matched controls.21,32,33 Our data also indicate that there may be a heritable component to the formation and rupture of intracranial aneurysm.21,32,34–37 In 2001, Onda and colleagues38 reported the results of a genome-wide linkage (104 affected sibpairs) and haplotype association study that mapped the occurrence of intracranial aneurysms to chromosome 7q11. The best evidence for linkage was detected at D7S2472, in the vicinity of the elastin gene (ELN), an excellent candidate gene for intracranial aneurysm given the importance of elastin in the structure and function of intracranial arteries. Fourteen distinct single-nucleotide polymorphisms were identified in ELN, and no obvious allelic association between intracranial aneurysms and each single-nucleotide polymorphism was observed. The haplotype between the intron-20–intron-23 polymorphisms of ELN was strongly associated with intracranial aneurysm (P=0.0000381), and homozygous patients were at high risk (P=0.002), with an OR of 4.39. These findings suggest that a genetic focus for intracranial aneurysms may lie within or close to the ELN locus on chromosome 7.

In another genome-wide linkage study of 48 affected sibpairs collected from 24 extended Finnish pedigrees, investigators found the strongest association between the presence of intracranial aneurysm and chromosome 19q13.2,39 The region on chromosome 19 contains several loci related to cerebrovascular or cardiovascular physiology, including apolipoprotein E, CII and CI, notch 3, cardiac troponin I, and genes associated with abnormalities in cardiac conduction. A large National Institute of Neurological Disorders and Stroke–funded study to identify genetic risk factors for intracranial aneurysms, called the Familial Intracranial Aneurysm Study, is also underway in North America, Australia, and New Zealand. Further familial linkage and association studies are needed to explore the genetic basis for intracranial aneurysm.

Low educational achievement has been associated with a increased risk of aneurysmal SAH in previous studies, but ours is the first to demonstrate a statistically significant association in a multivariable model.21,26 The finding of an association between SAH and socioeconomic status is consistent with a recent study on SAH from any cause40 and with findings on other adverse health events, including stroke mortality,41 ischemic stroke incidence,42 other cardiovascular disease, and all-cause mortality.43 Although these and other reports have firmly established the importance of socioeconomic status as a determinant of health, the mechanism for the association is not fully understood. Traditional vascular risk factors explain only part of the association.43,44 Other important factors may include health behavior, occupational stress, access to care, and nontraditional biological events such as insulin resistance and altered coagulation.45

Biases that might have affected this analysis of the HSP include selection and recall bias. We adopted several strategies to reduce the possibility of bias in selection of cases, including active case surveillance and objective eligibility determination. In the 2 centers with the largest number of enrolled subjects (Yale and University of Cincinnati), we ascertained cases from all regional hospitals. However, one limitation of this study is that a large majority of cases of SAH were excluded because of early mortality or because significant brain injury did not allow a reliable interview of the potential case. For example, of the 883 potential cases, only 428 were enrolled in the study. Most cases were excluded because of death or inability to complete the interview. It is possible that these very severe cases of SAH may have a different distribution of risk factors. Thus, it is more accurate to say that the risk factors that we have identified are for less severe cases of SAH in the young and middle-aged population.

A subsequent case-control study of ICH and SAH examining all ages is ongoing in Greater Cincinnati/Northern Kentucky, 1 of the 4 participating communities in the HSP.21,46 In this study, risk factor information from the medical records of all cases of SAH is abstracted, regardless
of whether the subjects undergo an in-person structured interview. The distribution of risk factors, as documented in the medical record, among cases of SAH who died is very similar to that among interviewed controls.21 This latter study suggests that the risk factor data from the HSP is generalizable to all cases of SAH in persons 18 to 49 years of age.

Recall bias refers to the tendency of case subjects, compared with control subjects, to have more or less accurate recall of exposures. Although recall bias is discussed in relation to case-control studies, efforts to demonstrate that it has an important effect on measured associations have commonly failed.47,48 In the HSP, we adopted several safeguards against recall bias, including a highly structured interview. In addition, to overcome greater stimulation for recall among cases, we used a shorter interval between the focal time and interview dates for controls.

In summary, aneurysmal SAH is largely a preventable disease among the young and middle-aged because current cigarette smoking, illicit drug use, and hypertension are 3 of the most important and common risk factors. Our study also confirms the importance of family history of hemorrhagic stroke, a lean body mass, and low educational achievement as risk factors for aneurysmal SAH.

Acknowledgments

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References


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