Genetic and Environmental Risk Factors for Intracerebral Hemorrhage
Preliminary Results of a Population-Based Study

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Background and Purpose—Intracerebral hemorrhage (ICH) has a 30-day mortality rate of 40% to 50% and lacks a proven treatment. We report a preplanned, midpoint analysis of the first population-based, case-control study that examines both genetic and environmental risk factors of ICH.

Methods—We prospectively identified cases of hemorrhagic stroke at all 16 hospitals in the Greater Cincinnati/Northern Kentucky region. All cases underwent medical record and neuroimaging review. Cases enrolled in the direct interview and genetic sampling arm of the study were matched to population-based control subjects by age, race, and sex. Multivariable logistic regression was performed to identify significant independent risk factors.

Results—We enrolled 188 cases of ICH (67 lobar, 121 nonlobar) and 366 control subjects in the direct interview arm of the study. Significant independent risk factors for lobar ICH included the presence of an apolipoprotein E2 or E4 allele, frequent alcohol use, prior stroke, and first-degree relative with ICH. Significant independent risk factors for nonlobar ICH were hypertension, prior stroke, and first-degree relative with ICH. An increasing level of education was associated with a decreased risk of nonlobar ICH. The attributable risk of apolipoprotein E2 or E4 for lobar ICH was 29%, and the attributable risk of hypertension for nonlobar ICH was 54%.

Conclusions—There is significant epidemiological evidence that the pathophysiology of ICH varies by location. We estimate that a third of all cases of lobar ICH are attributable to possession of an apolipoprotein E4 or E2 allele and that half of all cases of nonlobar ICH are attributable to hypertension. (Stroke. 2002;33:1190-1196.)

Key Words: apolipoproteins ■ hemorrhage ■ risk factors ■ stroke

S ponstantaneous intracerebral hemorrhage (ICH) occurs with an annual incidence rate of 15 to 19 per 100,000,1 and the 30-day case mortality rate is 40% to 50%.2 Although genetic and environmental risk factors likely play a role in the occurrence of ICH, previous studies have focused on either environmental or genetic risk factors alone.3–11 Several groups of investigators have reported an association between possession of an apolipoprotein E type e2 (apoE2) and/or e4 (apoE4) allele and lobar ICH,12–15 but the importance of apoE genotype in the incidence of lobar ICH in the general population is unknown.

In 1997, we began a prospective, population-based, case-control study of spontaneous hemorrhagic stroke in the Greater Cincinnati region that included collection of genetic material and a direct interview regarding environmental risk factors. We report here the results of a preplanned, midpoint analysis.
The definition for ICH is adapted from the Classification of Cerebrovascular Disease III (1989) and is identical to that used for previous epidemiological stroke studies by our investigative group. ICH is defined as nontraumatic abrupt onset of severe headache, altered level of consciousness, and/or focal neurological deficit that is associated with a focal collection of blood within the brain parenchyma as observed on CT or at autopsy and is not due to hemorrhagic conversion of a cerebral infarction. Study neurologists review clinical and neuroimaging information for each patient and make the final decision about case eligibility and assignment of location of ICH. We categorized each hemorrhage as lobar (involving predominantly the cortex and underlying white matter), deep (involving predominately the basal ganglia, periventricular white matter, or internal capsule), cerebellum, or brainstem. When categorization of the location of ICH or cases’ eligibility was not clear, the film was reviewed by a group of study neurologists for consensus.

To determine the ability to be interviewed, every case must pass a screening test consisting of 7 questions regarding orientation, ability to follow commands, and attention. Approximately 24% of the cases did not pass the test and required proxy interview. The first choice for proxy is the spouse, live-in companion, or designated power of attorney, followed by a child, parent, sibling, or close friend of the person (with preference in this order).

For those patients who are eligible but not interviewed, medical record and neuroimaging reviews are performed. These patients counted as cases for epidemiological purposes, but the data used in the univariate and multivariable analyses below include only those cases who participated in the direct interview and for whom a genetic specimen was collected.

The University of Cincinnati Institute for Policy Research uses random-digit-dialing telephone survey techniques to identify 2 control subjects of the same sex, race, and age (±5 years) for each case. After informed consent is obtained, each case, control subject, and/or proxy are interviewed face to face in a highly structured and identical manner (see the Appendix). Control subjects were asked to identify risk factors based on the date of the corresponding case’s stroke. Because blood pressure is often increased as a result of ICH, we use a history of hypertension or prior treatment of hypertension as the primary definition in our analysis for both cases and control subjects.

**ApoE Genotyping**

Four buccal brush samples are obtained from each case and control at the time of interview and stored at −20°C. After DNA is isolated, 2 µL is used to perform polymerase chain reaction of the apoE genotype. ApoE analysis is performed by polymerase chain reaction with established protocols. Our cases and control subjects were found to be in Hardy-Weinberg equilibrium.

**Statistical Analysis**

The primary hypotheses included the following candidate risk factors for ICH: hypertension, prior cerebral infarction, current smoking, anticoagulant use, heavy alcohol use (>2 drinks per day), diabetes, family history of ICH, and presence of apoE4 or E2. The data were managed and analyzed with SAS® (SAS Institute). Bivariate and multivariable analyses for the association of independent variables with stroke were achieved by use of a conditional logistic modeling approach (PROC PHREG). Results are reported as odds ratios (ORs) with their associated 95% confidence intervals (CIs). A backward elimination procedure was used for the multivariable analysis. Each of the subtypes was analyzed separately.

Attributable risk was calculated by use of the prevalence rate from the matched control subjects. Thus, the attributable risk can be generalized to a population that is similar in demographics to the cases.

**Results**

Between June 1997 and February 2000, 1658 potential cases of hemorrhagic stroke were abstracted (the Figure), but 711 were removed from analysis because they had at least 1 exclusion criterion: trauma (n = 370), no hemorrhage (n = 95), hemorrhagic conversion of ischemic stroke (n = 86), hemorrhage into tumor (n = 59), resident outside 50-mile radius (n = 87), hemorrhage occurring outside of the study time period (n = 13), and <18 years of age at time of stroke (n = 1). Of the remaining 947 cases, 652 were not enrolled in the interview arm of the study and had medical record abstraction only (noninterview arm). Of these, 329 died before study nurse contact; 224 were contacted after 90 days; 48 were unable to provide informed consent; and 51 declined enrollment in the interview arm of the study. The remaining 295 cases underwent direct medical interview, genetic sampling, and medical record abstraction. Of the cases in the interview arm of the study, 188 were classified as an ICH, and the remaining were classified as SAH. The present analysis is for ICH cases only.

The demographic distribution of cases of ICH is presented in Table 1. Of the 188 cases enrolled, 178 (95%) had two control subjects and 10 (5%) had 1 control subject matched by age, race, and sex at the time of analysis. Of the 188 cases of ICH, 67 (36%) were classified as lobar and 121 (64%) as nonlobar (deep, n = 90; cerebellar, n = 22; brainstem, n = 9).

Univariate ORs for all cases of ICH, lobar ICH, and nonlobar ICH are listed in Table 2. Significant independent risk factors for ICH found through conditional logistic mod-

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**TABLE 1. Demographic Distribution of Cases of ICH and Control Subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All ICH</th>
<th>All Control Subjects</th>
<th>Lobar ICH</th>
<th>Lobar ICH Control Subjects</th>
<th>Nonlobar ICH</th>
<th>Non-lobar ICH Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>188</td>
<td>366</td>
<td>67</td>
<td>131</td>
<td>121</td>
<td>235</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>95 (50)</td>
<td>181 (49)</td>
<td>32 (48)</td>
<td>62 (47)</td>
<td>63 (52)</td>
<td>119 (51)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>39 (21)</td>
<td>73 (20)</td>
<td>13 (19)</td>
<td>25 (19)</td>
<td>25 (21)</td>
<td>48 (20)</td>
</tr>
<tr>
<td>Age (average), y</td>
<td>64.8 ± 16.1</td>
<td>64.4 ± 16.1</td>
<td>64.8 ± 17.8</td>
<td>63.8 ± 17.1</td>
<td>64.8 ± 15.2</td>
<td>64.7 ± 14.6</td>
</tr>
</tbody>
</table>

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Potential Hemorrhagic Stroke by ICD-9 Codes
n=1658

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Exclusions
n=711

Hemorrhagic Stroke
n=947

Medical Record Only
n=652

Genetic Testing & Interview n=295

1. Trauma = 370
2. No Hemorrhage = 95
3. Hemorrhagic Conversion of Ischemic Stroke = 86
4. Hemorrhage into Tumor = 59
5. Resident outside study region = 87
6. Resident outside study time period = 13
7. Resident <15 years at age = 7

Patient enrollment.
The risk factors for ICH and their attributable risks are shown in Table 3. Independent risk factors for ICH overall included a first-degree relative with ICH, previous stroke, frequent alcohol use, and hypertension. An increasing level of education was associated with lower risk. Of the control population, 17% were found to have undiagnosed hypertension. Significant independent risk factors for lobar ICH included a first-degree relative with ICH, previous stroke, frequent alcohol use, and the presence of an apoE2 or apoE4 allele. Significant independent risk factors for nonlobar ICH included a first-degree relative with ICH, previous stroke, and hypertension. An increasing level of education was associated with lower risk.

Table 4 presents attributable risks for significant independent risk factors. Hypertension was found to have the highest attributable risk for nonlobar ICH, and the presence of apoE4 and/or apoE2 allele was found to have the highest attributable risk for lobar ICH.

Additional analyses were performed to demonstrate the validity of our data. Agreement on interview items between cases and their proxies (n=145) was good to excellent.

### Table 2. Distribution of Candidate Risk Factors for ICH: Univariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>All ICH (n=188)</th>
<th>All Control Subjects (n=366)</th>
<th>OR (95% CI)</th>
<th>Lobar ICH (n=67)</th>
<th>Lobar ICH Control Subjects (n=131)</th>
<th>OR (95% CI)</th>
<th>Nonlobar ICH (n=121)</th>
<th>Nonlobar ICH Control Subjects (n=235)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td>119 (63)</td>
<td>160 (44)</td>
<td>2.5 (1.7–3.7)</td>
<td>30 (45)</td>
<td>62 (47)</td>
<td>0.9 (0.5–1.7)</td>
<td>89 (74)</td>
<td>98 (42)</td>
<td>5.0 (2.9–8.8)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>37 (20)</td>
<td>60 (16)</td>
<td>1.3 (0.8–2.1)</td>
<td>7 (10)</td>
<td>20 (15)</td>
<td>0.6 (0.2–1.6)</td>
<td>30 (25)</td>
<td>40 (17)</td>
<td>1.7 (1.0–2.9)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>43 (23)</td>
<td>70 (19)</td>
<td>1.3 (0.8–2.0)</td>
<td>19 (28)</td>
<td>21 (16)</td>
<td>2.4 (1.1–5.2)</td>
<td>24 (20)</td>
<td>49 (21)</td>
<td>0.9 (0.5–1.6)</td>
</tr>
<tr>
<td>Former</td>
<td>66 (35)</td>
<td>150 (41)</td>
<td></td>
<td>22 (33)</td>
<td>53 (40)</td>
<td></td>
<td>44 (36)</td>
<td>97 (41)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>79 (42)</td>
<td>146 (40)</td>
<td></td>
<td>26 (39)</td>
<td>57 (44)</td>
<td></td>
<td>53 (44)</td>
<td>89 (38)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent</td>
<td>20 (11)</td>
<td>20 (5)</td>
<td>2.1 (1.0–4.1)</td>
<td>8 (12)</td>
<td>5 (4)</td>
<td>3.7 (1.1–12)</td>
<td>12 (10)</td>
<td>15 (6)</td>
<td>1.5 (0.6–3.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>41 (22)</td>
<td>119 (32)</td>
<td></td>
<td>12 (18)</td>
<td>48 (37)</td>
<td></td>
<td>29 (24)</td>
<td>71 (30)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>127 (68)</td>
<td>227 (62)</td>
<td></td>
<td>47 (70)</td>
<td>78 (60)</td>
<td></td>
<td>80 (66)</td>
<td>149 (63)</td>
<td></td>
</tr>
<tr>
<td><strong>Medication use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>22 (12)</td>
<td>15 (4)</td>
<td>3.1 (1.6–6.2)</td>
<td>5 (7)</td>
<td>7 (5)</td>
<td>1.5 (0.4–5.0)</td>
<td>17 (14)</td>
<td>87 (3)</td>
<td>4.5 (1.9–11)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>51 (27)</td>
<td>126 (34)</td>
<td>0.7 (0.5–1.1)</td>
<td>18 (27)</td>
<td>45 (34)</td>
<td>0.6 (0.3–1.3)</td>
<td>33 (27)</td>
<td>81 (35)</td>
<td>0.7 (0.4–1.2)</td>
</tr>
<tr>
<td>Marijuana use</td>
<td>6 (3)</td>
<td>9 (2)</td>
<td>1.4 (0.5–4.0)</td>
<td>3 (4)</td>
<td>4 (3)</td>
<td></td>
<td>3 (2)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Cocaine use</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td></td>
<td>2 (3)</td>
<td>0 (0)</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>History of heart disease</strong></td>
<td>45 (24)</td>
<td>69 (19)</td>
<td>1.4 (0.9–2.2)</td>
<td>12 (18)</td>
<td>30 (23)</td>
<td>0.7 (0.3–1.6)</td>
<td>33 (27)</td>
<td>39 (17)</td>
<td>1.9 (1.1–3.4)</td>
</tr>
<tr>
<td><strong>History of previous ischemic stroke</strong></td>
<td>28 (15)</td>
<td>10 (3)</td>
<td>8.3 (3.4–20)</td>
<td>9 (13)</td>
<td>5 (4)</td>
<td>4.0 (1.2–13)</td>
<td>19 (16)</td>
<td>5 (2)</td>
<td>17 (4.0–74)</td>
</tr>
<tr>
<td><strong>Education, y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>53 (28)</td>
<td>49 (13)</td>
<td>0.57 (0.44–0.73)</td>
<td>17 (25)</td>
<td>21 (16)</td>
<td>0.7 (0.5–1.1)</td>
<td>36 (30)</td>
<td>28 (12)</td>
<td>0.5 (0.3–0.6)</td>
</tr>
<tr>
<td>12</td>
<td>66 (35)</td>
<td>124 (34)</td>
<td></td>
<td>24 (36)</td>
<td>49 (37)</td>
<td></td>
<td>42 (35)</td>
<td>75 (32)</td>
<td></td>
</tr>
<tr>
<td>&gt;12</td>
<td>69 (37)</td>
<td>193 (53)</td>
<td></td>
<td>26 (39)</td>
<td>61 (46)</td>
<td></td>
<td>43 (36)</td>
<td>132 (56)</td>
<td></td>
</tr>
<tr>
<td><strong>First-degree relative with ICH</strong></td>
<td>11 (6)</td>
<td>5 (1)</td>
<td>5.2 (1.6–16)</td>
<td>4 (6)</td>
<td>1 (1)</td>
<td>8.0 (0.9–72)</td>
<td>7 (6)</td>
<td>4 (2)</td>
<td>4.2 (1.1–16)</td>
</tr>
<tr>
<td><strong>Second-degree relative with ICH</strong></td>
<td>12 (6)</td>
<td>11 (3)</td>
<td>2.3 (0.88–5.3)</td>
<td>5 (7)</td>
<td>3 (2)</td>
<td>3.3 (0.8–14)</td>
<td>7 (6)</td>
<td>8 (3)</td>
<td>1.8 (0.6–5.3)</td>
</tr>
<tr>
<td>ApoE2</td>
<td>39 (21)</td>
<td>64 (17)</td>
<td>1.2 (0.8–1.9)</td>
<td>17 (25)</td>
<td>22 (17)</td>
<td>1.8 (0.8–3.7)</td>
<td>22 (18)</td>
<td>42 (16)</td>
<td>1.0 (0.6–1.7)</td>
</tr>
<tr>
<td>ApoE4</td>
<td>53 (28)</td>
<td>96 (26)</td>
<td>1.1 (0.8–1.6)</td>
<td>24 (36)</td>
<td>30 (23)</td>
<td>1.7 (0.9–3.2)</td>
<td>29 (24)</td>
<td>66 (28)</td>
<td>0.8 (0.5–1.4)</td>
</tr>
<tr>
<td>ApoE2 or E4</td>
<td>89 (47)</td>
<td>151 (41)</td>
<td>1.3 (0.9–1.8)</td>
<td>39 (58)</td>
<td>49 (37)</td>
<td>2.2 (1.2–4.0)</td>
<td>50 (41)</td>
<td>102 (43)</td>
<td>0.9 (0.6–1.4)</td>
</tr>
</tbody>
</table>

### Table 3. Multivariable Independent OR for ICH, Lobar ICH, and Nonlobar ICH

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>All ICH (n=188)</th>
<th>Lobar ICH (n=67)</th>
<th>Nonlobar ICH (n=121)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-degree relative with ICH</td>
<td>6.3 (1.8–22)</td>
<td>12 (1.3–122)</td>
<td>6.3 (1.1–35)</td>
<td></td>
</tr>
<tr>
<td>Previous ischemic stroke</td>
<td>7.0 (2.7–186)</td>
<td>4.1 (1.1–15)</td>
<td>13 (2.7–61)</td>
<td></td>
</tr>
<tr>
<td>Frequent alcohol use</td>
<td>2.3 (1.1–5.0)</td>
<td>5.3 (1.4–20)</td>
<td>1.8 (0.65–5.1)*</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.2 (1.5–3.5)</td>
<td>0.98 (0.47–2.0)*</td>
<td>4.2 (2.3–7.8)</td>
<td></td>
</tr>
<tr>
<td>Education category</td>
<td>0.63 (0.47–0.83)</td>
<td>0.78 (0.51–1.2)*</td>
<td>0.5 (0.33–0.73)</td>
<td></td>
</tr>
<tr>
<td>ApoE2 or E4</td>
<td>1.4 (0.96–2.1)*</td>
<td>2.3 (1.2–4.4)</td>
<td>1.1 (0.66–1.9)*</td>
<td></td>
</tr>
</tbody>
</table>

*Not significant.
(κ=0.54 to 0.90). Similar results were obtained when control subjects (n=45) and proxies of control subjects (κ=0.35 to 1.0) were compared.

Interviewed cases had a much lower mortality rate than noninterviewed cases (4% versus 45%). To determine the representativeness of our interviewed cases, we compared the prevalence of risk factors through medical record review among interviewed and noninterviewed cases for the first year of the study. Because noninterviewed cases were, on average, older than interviewed cases (72 versus 61 years of age) and the prevalence of risk factors varies by age, the comparison was age adjusted. Very small differences existed in risk factor prevalence between interviewed and noninterviewed cases of ICH, and none were statistically significant other than older age and lower mortality. In addition, the proportion of lobar ICH was not different among noninterviewed cases than interviewed cases (36% versus 36%). This analysis demonstrates that the interviewed cases of ICH are representative of the noninterviewed cases of ICH with respect to clinical risk factors.

### Discussion

Our data support the hypothesis that the pathogenesis of lobar ICH may differ from nonlobar ICH. Lobar ICH accounts for 33% to 42% of all ICH. Although our study describes the most important risk factors by location of ICH, pathological confirmation of the mechanism of ICH was not performed and is unlikely to be performed given current autopsy rates and the low rates of surgery for spontaneous ICH. Nevertheless, future epidemiological studies that analyze risk factors for ICH should consider location of ICH in the analyses.

We also report that having a first-degree relative with ICH is an independent risk factor for both lobar and nonlobar ICH. This finding suggests that other genetic risk factors may be important in the incidence of ICH. This analysis is limited by the small number of cases with a family history of ICH and the potential recall bias of cases and proxies of cases for family history of ICH. The accuracy with which a subject can recall whether a relative’s stroke was ischemic, an ICH, or an SAH also requires further study.

Prior stroke was found to be a risk factor for both lobar and nonlobar ICH. Previous epidemiological studies have reported an increased risk of ICH with prior cerebral infarction, and these data suggest that this occurs independent of aspirin or anticoagulant use.

### Lobar ICH

Previous studies have demonstrated an association between the apoE4 genotype and pathologically proven or suspected cases of cerebral amyloid angiopathy, as well as an earlier onset of lobar hemorrhage. Nicoll et al reported that when one controlled for the presence of Alzheimer’s disease, apoE2 but not apoE4 was associated with lobar ICH. Yamada et al reported no association of apoE4 with cerebral amyloid angiopathy or severity of amyloid deposition compared with control subjects in an autopsy study of elderly Japanese patients, suggesting that racial heterogeneity may exist. Recurrent lobar ICH is a hallmark of cerebral amyloid angiopathy, and O’Donnell et al reported an association of recurrent lobar ICH with apoE2 or apoE4 genotypes.

A major limitation of these studies is that cases were ascertained from referral hospitals or by autopsy, which may lead to a selection and/or severity bias. In addition, control subjects for these studies were not from the same population as cases and were not matched by demographic variables, which may affect the distribution of allele frequencies. Minimal adjustment with multivariable analysis for the presence of other risk factors associated with ICH was performed in these studies. In our study, cases are matched by age, race, and sex to control subjects who are from the same defined population as the cases. Our population-based case ascertainment that includes referral and community hospitals allows us to estimate the importance of a risk factor to the overall incidence of ICH.

Our data confirm case-control studies that have reported an association between frequent alcohol use and ICH. One study reported that this association is more significant with lobar ICH. Many studies have reported a high rate of hypertension among cases of ICH, and several reported that the rate was not significantly different by location of ICH. Few studies have controlled for the presence of other risk factors and demographic variables that may affect the rate of hypertension. Thrift et al, in the Melbourne Stroke Risk Factor Study, compared cases of lobar ICH to control subjects matched by age and sex and found a higher rate of hypertension among cases with ICH compared with control subjects. We are unable to identify a similar association between hypertension and lobar ICH.

### Nonlobar ICH

History of hypertension was the most prevalent risk factor among cases of nonlobar ICH (75%), consistent with previ-
ous reports. Our study estimates that 40% to 65% of nonlobar ICH would be prevented if the effects of hypertension were eliminated.

ICH as a complication of anticoagulant therapy has been reported in numerous studies. In our univariate analysis, use of anticoagulants was strongly associated with nonlobar ICH, but after the presence of other risk factors such as prior stroke and hypertension was controlled for, anticoagulant use alone was not an independent risk factor. With recruitment of additional cases, the importance of anticoagulant use in ICH, as well as the relationship between anticoagulant use, age, and apoE alleles, will be explored.

Higher education has been associated with a lower incidence of cardiovascular risk factors. We found that higher education was associated with less risk of ICH even after adjusting for the presence of cardiovascular risk factors. We found that higher education was associated with a higher incidence of cardiovascular risk factors. We found that higher education was associated with less risk of ICH even after adjusting for the presence of cardiovascular risk factors. We found that higher education was associated with less risk of ICH even after adjusting for the presence of cardiovascular risk factors.

A limitation of our study is that a significant number of patients died before they could be enrolled. Although we found no significant differences in risk factor prevalence between interviewed and noninterviewed cases, it is possible, for example, that lobar, hypertensive ICH cases are more likely to die. This mortality bias would lead to an underestimation of the true impact of hypertension on lobar ICH. The very early mortality associated with ICH and the emotional devastation of relatives facing imminent death of their loved one limit enrollment of subjects in any study of ICH that involves a detailed interview and genetic testing.

Undiagnosed hypertension is likely to have occurred among our cases. Among our control subjects, the rate of undiagnosed hypertension was 17%, which is identical to the rate of undiagnosed hypertension in the Third National Health and Nutrition Examination Survey (NHANES). However, we are unable to determine the rate of undiagnosed hypertension among cases. Although it is possible that undiagnosed hypertension may explain why hypertension was not found to be a risk factor for lobar ICH, it is difficult to know how to estimate the rate among cases. In our study, 47% of control subjects had a history of hypertension, and 45% of lobar ICH cases had a history of hypertension. If we assume that the rate of undiagnosed hypertension among control subjects is 17%, then nearly 33% of all lobar ICH cases would need to have undiagnosed hypertension for it to be a significant risk factor ($P < 0.05$) for lobar ICH in univariate analysis.

In summary, our study is the first to report the population-based attributable risks of both genetic and environmental risk factors of ICH. These data are the first to demonstrate the significant impact of apoE genotypes on the incidence of lobar ICH and to confirm the prominent prevalence of potentially modifiable risk factors such as hypertension and frequent alcohol use. Future analyses with additional data will explore potential interactions between risk factors such as apoE genotype and anticoagulation and clarification of the role of risk factors by location and age stratification.

Appendix

Structured Interview

The structured interview contains questions regarding hypertension, prior stroke, diabetes, alcohol, tobacco and cocaine use, oral contraceptive use (both present and past), estrogen replacement therapy, menopause, current or recent use of over-the-counter medications, aspirin or anticoagulants, personal and family history of dementia, family history of stroke and type of stroke (patients were given a choice of ischemic stroke, transient ischemic attack, SAH, and ICH and asked to choose the subtype), personal history of coagulation disorders, migraine headaches, hypercholesterolemia, body weight and height (self-reported), employment and family status, type of medical insurance, educational level (<12th grade, 12th grade or >12th grade), and household income. Smoking data include amount used, duration of use, and length of time since the person last smoked. Alcohol use includes the type, amount, and frequency of alcohol use and time since the last drink. One drink is considered to be 0.5 oz of pure alcohol (the amount in 12 oz of beer, 4 oz of wine, or 1.0 oz of liquor). Patients who ingest an average of >2 drinks per day are classified as heavy or frequent drinkers. Estrogen deficiency is defined as no menstruation in the past 12 months without estrogen replacement therapy. Race was defined as self-reported.

Blood pressure is measured 3 times, with the readings taken 1 minute apart. A subject with an average systolic blood pressure of ≥140 mm Hg or diastolic blood pressure of ≥90 mm Hg on the 3 readings is considered hypertensive only for secondary analyses.

Acknowledgments

This study was funded by grants from the National Institute of Neurological Diseases and Stroke (01-NS 36695-03); the National Heart, Lung and Blood Institute (R-01-HL-61781); and the National Institute of Environmental Health (R-01-ES 06096-06).

References

Beyond Hypertension: Unraveling the Causes of Intracerebral Hemorrhage

Intracerebral hemorrhage (ICH) is more deadly than ischemic stroke but is also rarer and more difficult to study. Our understanding of its causes as well as its subtypes therefore remains limited. Chronic hypertension has been consistently identified as a strong risk factor for ICH in cohort and case-control studies, but the extent of its role within the population and its importance as a risk factor for all ICH subtypes is still being assessed. Other risk factors have been identified, including excessive alcohol consumption, low-serum cholesterol, anticoagulation, drug abuse, and cerebral amyloid angiopathy (CAA), but none has been established at the level of the population with the strength of hypertension.

In defining the pathogenesis and risk factors for primary ICH, it is useful to distinguish between those hemorrhages occurring in lobar brain regions and those in nonlobar, typically deep hemispheric areas. Small studies have demonstrated that the risk of recurrence may be different, with that for lobar ICH being as much as 5 times higher.1,2
Further, most studies suggest that hypertension has a less important role in lobar than in deep ICH. Our limited knowledge of genetic risk factors also points to differences between these ICH subtypes. Apolipoprotein E genotype (APOE) in particular appears to have specific effects on risk of lobar ICH, with possession of the APOE ε2 or ε4 allele associated with increased risk of lobar ICH due to CAA.1,3

The present report from the greater Cincinnati/Northern Kentucky study of risk factors for ICH,4 though only a midpoint analysis, has several important methodological strengths that lend credence to its findings. The data represent a prospective, population-based, matched case-control analysis of ICH patients drawn from all 16 hospitals within a 50-mile radius of the University of Cincinnati. The study therefore captured information on every case of ICH severe enough to require hospitalization within a defined population, enabling estimation of attributable risk. The strengths of this approach are in part offset by several limitations. Only 31% of eligible cases were enrolled for interview and genetic testing, with the remainder assessed by retrospective chart review, a potentially less accurate technique. Because the authors restrict their analysis only to those cases they were able to interview, another potential issue is that the source population is likely biased toward ICH survivors rather than all patients with ICH. Indeed, 50% of the 652 eligible patients without interview and genetic testing died before being contacted by members of the study team. Thus, there is a possibility of confounding when analyzing risk factors such as hypertension and APOE that may be associated with both occurrence of ICH and outcome from ICH.

The results of the study clearly establish important differences between the risk factors for deep and lobar ICH. Not surprisingly, hypertension was the strongest risk factor for deep ICH. Its attributable risk of 54%, while high, suggests that there are other important risk factors in the community for deep ICH. Indeed, the multivariable analysis revealed significant associations with previous ischemic stroke, family history, and low education level. Analysis of lobar ICH produced strikingly different results. Notably, hypertension was not associated with lobar ICH in this cohort. The greatest attributable risk (29%) for lobar hemorrhage was instead associated with possession of either the APOE ε2 or ε4 allele. The elevation in the frequency of these specific APOE alleles likely reflects a high prevalence of CAA among lobar ICH patients in the general population and highlights the importance of this pathological process as a cause of stroke in the elderly.

Although these conclusions are tempered by the small numbers of patients and resultant large confidence intervals of the point estimates, Woo and colleagues have nonetheless opened up important new questions for exploration. The independent link between previous ischemic stroke and the development of both deep and lobar ICH, for example, raises the possibility that ischemic damage can lead to changes in the brain parenchyma or vasculature that increase susceptibility to developing hemorrhage. Another implication of these data is that there are almost certainly more genetic polymorphisms beyond APOE involved in the genesis of ICH.5 Such genetic risk factors may include genes involved in coagulation or blood vessel stability, to name just a few mechanistic pathways. Finally, the findings offer important support for possible trials of anti-amyloid therapies aimed at preventing the substantial proportion of ICH apparently caused by CAA.

The state of the art for the treatment of ICH is dismal. Careful population-based studies like that of Woo and colleagues are crucial for generating hypotheses that can lead to both improved identification of individuals at risk and new candidate therapeutic approaches to ICH prevention.

Jonathan Rosand, MD, Guest Editor
Steven M. Greenberg, MD, PhD, Guest Editor

References
Genetic and Environmental Risk Factors for Intracerebral Hemorrhage: Preliminary Results of a Population-Based Study

Stroke. 2002;33:1190-1196
doi: 10.1161/01.STR.0000014774.88027.22

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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