Parental History of Stroke Predicts Subclinical But Not Clinical Stroke

The Atherosclerosis Risk in Communities Study

Alanna C. Morrison, BS; Myriam Fornage, PhD; Duanping Liao, MD, PhD; Eric Boerwinkle, PhD

Background and Purpose—An individual with a positive family history of a disease may be at increased risk for the disease. We sought to examine whether parental history of stroke is associated with subclinical or clinical stroke in the Atherosclerosis Risk in Communities (ARIC) Study, and whether any observed association is independent of established stroke risk factors.

Methods—Parental history of stroke was determined by home interview at the baseline examination. Cerebral MRI was performed on individuals from 2 ARIC field centers. Subclinical cerebral infarct cases (n=202) were defined by the presence of cerebral infarcts >3 mm. The comparison group for the subclinical cases included all individuals participating in the MRI examination who were not identified as a subclinical case (n=1533). Incidence of clinical ischemic stroke was determined by following the ARIC cohort for potential cerebrovascular events. Two hundred sixty-one validated ischemic strokes were identified; 13 775 individuals from the ARIC cohort did not experience an ischemic event.

Results—Parental history of stroke was significantly associated with subclinical stroke after adjusting for age, gender, and race (OR 1.67, 95% CI1.23 to 2.26) and after further adjustment for multiple stroke risk factors (OR1.64, 95% CI1.20 to 2.24). Parental history of stroke was not a significant predictor of clinical stroke in either adjustment model.

Conclusions—The observed increased risk of subclinical stroke among individuals with a parental history of stroke is consistent with the expression of genetic susceptibility, a shared environment, or both in the etiology of stroke. This effect did not appear to be mediated by established stroke risk factors. Parental history of stroke does not confer an increased risk of clinical stroke in this sample of middle-aged Americans. (Stroke. 2000;31:2098-2102.)

Key Words: cerebral infarction ▪ genetics ▪ risk factors ▪ stroke, ischemic

Stroke is the leading cause of disability and the third leading cause of death in the United States.1 Stroke is a complex and heterogeneous disease with multiple risk factors, such as age, gender, race, hypertension, diabetes, heart disease, cigarette smoking, and previous personal and family history.1

Some studies have indicated that environmental factors are the primary contributors to stroke and other forms of cerebrovascular disease (CVD). For example, the Honolulu Heart Study2 evaluated the occurrence of stroke in men who migrated from Japan to Hawaii and concluded that environmental factors primarily contributed to stroke incidence. However, twin and family studies provide evidence that genetic factors play a significant role in the etiology of stroke. Although family history of stroke is often regarded as a predictor of stroke, studies investigating this association have yielded inconsistent results. For example, a number of studies have demonstrated that a positive family history of stroke is associated with the occurrence of stroke in offspring.3–10 Other studies, however, have not observed an association between family history of stroke and stroke risk.11–14 These conflicting results may be due to differences in study design, methods used to identify stroke events in family members, small sample size, or choice of study population.8 To our knowledge, no study has jointly investigated the association between family history of stroke and subclinically and clinically defined stroke. Similarly, no study has investigated the role of family history in predicting the onset of stroke in blacks.

The hypothesized importance of familial factors in predisposing certain individuals to increased stroke risk prompted us to evaluate the role of parental history in predicting the onset of stroke in the large prospective Atherosclerosis Risk in Communities (ARIC) study. Our objective was to consider both subclinical and clinical disease, and to gain insight into whether any observed association was independent of established stroke risk factors.
Subjects and Methods

Population

Study participants were selected from the Atherosclerosis Risk in Communities (ARIC) study, a prospective investigation of atherosclerosis and its clinical sequelae. The ARIC population-based cohort includes 15,792 subjects, who were 45 to 64 years old at recruitment (1988 to 1989). Subjects were selected by probability sampling from 4 communities: Forsyth County, North Carolina; Jackson, Mississippi (blacks only); northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland. The baseline examination included a home interview to ascertain cardiovascular risk factors, socioeconomic factors and family medical history, clinical examination, and blood drawing for laboratory determinations. Medical events were identified by an annual questionnaire, 3-year cycles of exams, and hospital surveillance. A detailed description of the ARIC study design and methods is published elsewhere.15

During the third examination visit in 1993 and 1994, all cohort members aged ≥55 years from 2 of the 4 ARIC field centers (Jackson, Miss, and Forsyth County, North Carolina) were screened for eligibility to participate in a cerebral MRI examination. For participant safety, specific criteria were used to exclude individuals as ineligible for the MRI examination,16 which resulted in a final sample size of 1931 individuals. MRI scanning and image interpretation was based on previously published protocols.17,18 Participants were excluded from this analysis (n=196) if they had a positive or unknown history of prevalent stroke or coronary heart disease at baseline, history of transient ischemic attack (TIA)/stroke symptoms at baseline, missing parental history of stroke information, or ethnic background other than white or black. Subclinical cerebral infarct cases (n=202) were defined by the presence of cerebral infarcts ≥3 mm. The comparison group for the subclinical cerebral infarct cases included all individuals participating in the MRI examination who were not identified as a cerebral infarct case (n=1533).

Incidence of clinical ischemic stroke was determined by review of hospital records, contacting participants annually, identifying hospitalizations during the previous year, and surveying discharge lists from local hospitals and death certificates from state vital statistics offices for potential cerebrovascular events.15,19,20 Details on quality assurance for ascertainment and classification of ischemic stroke events are published elsewhere.21 Participants were excluded for this analysis (n=1756) if they had a positive or unknown history of prevalent stroke or coronary heart disease at baseline, history of TIA/stroke symptoms at baseline, missing parental history of stroke information, or ethnic background other than white or black. A total of 261 incident clinical ischemic stroke cases were identified. Incident clinical ischemic stroke cases include validated definite or probable hospitalized embolic or thrombotic strokes. Individuals from the ARIC cohort who did not experience an ischemic stroke (n=13,775) are referred to as “noncases.”

Examination and laboratory procedures performed at the baseline examination have been reported for measurement of fibrinogen.22 Blood pressure was measured 3 times with a random-zero sphygmomanometer, and the last 2 measurements were averaged. Hypertension was defined as a diastolic blood pressure (DBP) ≥90 mm Hg, systolic blood pressure (SBP) ≥140 mm Hg, or self-reported use of antihypertensive medication. Body mass index (BMI, kg/m²) was calculated from height and weight measurements. The ratio of waist to hip circumference was calculated as a measure of fat distribution. Diabetes was defined by a fasting glucose level ≥126 mg/dL, a nonfasting glucose level ≥200 mg/dL, and/or a history of or treatment for diabetes. Maternal and paternal history of stroke was determined at the baseline home interview from responses to the questions “Did your natural mother have a stroke?” and “Did your natural father have a stroke?” Positive history of stroke was defined as an answer of “Yes” to these questions, and negative history of stroke was defined as an answer of “No.” “Unknown” responses were considered missing information. Positive parental history was defined as reporting a positive history for either or both parents. Negative parental history included negative history for both parents, or negative history for one parent when information about the other parent was missing.

Statistical Methods

The proportions, means, and standard deviations of established stroke risk factors were determined for the subclinical cerebral infarct cases, MRI examination control group, incident clinical ischemic stroke cases, and the noncases. Multivariable logistic regression models were used to assess the relationship between subclinical cerebral infarct case status and positive parental history of stroke. Cox proportional hazards models were used to estimate the ratios of hazard rates of incident clinical ischemic stroke between those who have or without a positive parental history of stroke. For incident clinical ischemic stroke cases, the follow-up time interval was defined as the time between the baseline clinical visit and the date of the first ischemic stroke. For the noncases, follow-up continued until December 31, 1997, the date of death, or the date of last contact if lost to follow-up, whichever came first. Each logistic regression and Cox proportional hazards model included age, gender, and race as covariates. The established stroke risk factors evaluated as potential confounders in the logistic regression and Cox proportional hazards models included hypertension, diabetes and smoking status, systolic and diastolic blood pressures, fibrinogen levels, body mass index (BMI), and waist-to-hip ratio. Covariates were assessed for statistical significance in the models by the Wald $\chi^2$ statistic.

Results

Group-specific means and standard deviations for each risk factor variable are presented in Table 1. Univariate comparison of the subclinical cerebral infarct cases with the MRI examination control group indicated significant differences ($P<0.05$) between the mean values for age, BMI, waist-to-hip ratio, fibrinogen level, and systolic and diastolic blood pressures. The subclinical cerebral infarct cases had a significantly greater frequency ($P=0.01$) of blacks, hypertensives, diabetics, and smokers than the control group. The subclinical cerebral infarct cases also had a significantly greater frequency of positive parental history of stroke than the control group ($P<0.01$). Mean size and frequency of cerebral infarct location among individuals with a positive parental history of stroke was not significantly different from the size and location of cerebral infarcts among individuals with a negative parental history of stroke (data not shown). Univariate comparison of the incident clinical ischemic stroke cases with the noncases indicated that the incident ischemic stroke cases had significantly greater ($P<0.01$) mean values for all variables than the noncases. The frequency of males, blacks, hypertensives, diabetics, and smokers was significantly greater ($P<0.01$) among incident clinical ischemic stroke cases than the noncases. The frequency of individuals with positive parental history of stroke was not significantly different between incident clinical ischemic stroke cases and noncases.

Each risk factor variable was further evaluated, among case and comparison groups, conditional on the other variables within the table (Table 1). Subclinical and clinical stroke risk profiles differ with respect to waist-to-hip ratio, systolic blood pressure, diabetic status and positive parental history of stroke.

Results from the multivariable logistic regression and Cox proportional hazards models examining the ability of parental history of stroke to predict subclinical and clinical stroke are presented in Table 2. After adjusting for age, gender, and race (model 1), parental history of stroke (OR1.67, 95% CI 1.23 to
2.26, \(P<0.01\) was significantly associated with subclinical stroke. This association remained statistically significant (OR 1.64, 95% CI 1.20 to 2.24, \(P<0.01\)) after further adjustment for multiple stroke risk factors (model 2). After adjusting for age, race, and gender (model 1), parental history of stroke (hazard rate ratio [HRR] 1.11, 95% CI 0.85 to 1.43) was not a significant predictor of incident clinical ischemic stroke. Parental history of stroke did not significantly predict incident clinical ischemic stroke after further adjustment for multiple stroke risk factors (HRR 1.05, 95% CI 0.81 to 1.37; model 2).

Multivariable logistic regression and Cox proportional hazards analyses were repeated after stratification by ethnicity (Table 2). In whites, parental history of stroke significantly predicted subclinical stroke after adjustment for age, gender, and race (OR 2.12, 95% CI 1.32 to 3.41, \(P<0.01\)) as well as after adjustment for multiple stroke risk factors (OR 2.10, 95% CI 1.29 to 3.42, \(P<0.01\)). This association was not significant among blacks. Parental history of stroke was not significantly associated with incident clinical ischemic stroke in either blacks or whites.

**Discussion**

We have investigated the association between parental history of stroke and clinical and subclinical stroke in individ-

**TABLE 1. Characteristics of the Case and Comparison Groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cerebral Infarct Cases (n=202)</th>
<th>MRI Exam Controls (n=1533)</th>
<th>Comparison of Cerebral Infarct Cases and MRI Exam Controls</th>
<th>Incident Ischemic Stroke Cases (n=261)</th>
<th>Noncases (n=13775)</th>
<th>Comparison of Incident Ischemic Stroke Cases and Noncases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Age at visit 1, y</td>
<td>57.8</td>
<td>4.5</td>
<td>56.2</td>
<td>4.5</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.1</td>
<td>5.1</td>
<td>27.3</td>
<td>5.0</td>
<td>0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>Waist-to-hip ratio, cm/cm</td>
<td>0.93</td>
<td>0.08</td>
<td>0.92</td>
<td>0.07</td>
<td>0.01</td>
<td>0.22</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>314</td>
<td>76</td>
<td>302</td>
<td>65</td>
<td>0.03</td>
<td>0.44</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128.3</td>
<td>21.9</td>
<td>122.8</td>
<td>18.0</td>
<td>&lt;0.01</td>
<td>0.31</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.3</td>
<td>13.3</td>
<td>73.9</td>
<td>11.7</td>
<td>0.01</td>
<td>0.69</td>
</tr>
</tbody>
</table>

*Univariate comparison.
†Comparison conditional on the other variables in the table.

2.6, \(P<0.01\) was significantly associated with subclinical stroke. This association remained statistically significant (OR 1.64, 95% CI 1.20 to 2.24, \(P<0.01\)) after further adjustment for multiple stroke risk factors (model 2). After adjusting for age, race, and gender (model 1), parental history of stroke (hazard rate ratio [HRR] 1.11, 95% CI 0.85 to 1.43) was not a significant predictor of incident clinical ischemic stroke. Parental history of stroke did not significantly predict incident clinical ischemic stroke after further adjustment for multiple stroke risk factors (HRR 1.05, 95% CI 0.81 to 1.37; model 2).

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**Discussion**

We have investigated the association between parental history of stroke and clinical and subclinical stroke in individ-

**TABLE 2. Relationship Between Parental History of Stroke and Case Status**

<table>
<thead>
<tr>
<th>Cerebral Infarct Case Status</th>
<th>Model 1*</th>
<th></th>
<th></th>
<th>Model 2†</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
<td>OR</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Positive parental history of stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>1.67</td>
<td>1.23–2.26</td>
<td>&lt;0.01</td>
<td>1.64</td>
<td>1.20–2.24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Whites</td>
<td>2.12</td>
<td>1.32–3.41</td>
<td>&lt;0.01</td>
<td>2.10</td>
<td>1.29–3.42</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Blacks</td>
<td>1.40</td>
<td>0.93–2.09</td>
<td>0.10</td>
<td>1.34</td>
<td>0.87–2.05</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender (and race in the total sample).
†Adjusted for hypertension, diabetes and smoking status, systolic and diastolic blood pressures, fibrinogen level, body mass index, waist-to-hip ratio, and the covariates in model 1.

**Incident Ischemic Stroke Case Status**

<table>
<thead>
<tr>
<th>Positive parental history of stroke</th>
<th>Model 1*</th>
<th></th>
<th></th>
<th>Model 2†</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample</td>
<td>1.11</td>
<td>0.85–1.43</td>
<td>0.45</td>
<td>1.05</td>
<td>0.81–1.37</td>
<td>0.71</td>
</tr>
<tr>
<td>Whites</td>
<td>0.97</td>
<td>0.68–1.38</td>
<td>0.85</td>
<td>0.95</td>
<td>0.66–1.35</td>
<td>0.76</td>
</tr>
<tr>
<td>Blacks</td>
<td>1.28</td>
<td>0.88–1.88</td>
<td>0.20</td>
<td>1.22</td>
<td>0.81–1.82</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Adjusted for age, gender (and race in the total sample).
†Adjusted for hypertension, diabetes and smoking status, systolic and diastolic blood pressures, fibrinogen level, body mass index, waist-to-hip ratio, and the covariates in model 1.
uals selected from the large prospective ARIC study. This investigation was motivated by the idea that family history of stroke may influence stroke risk by means of genetic susceptibility, a shared environment, or both. Parental history of stroke was significantly associated with subclinical disease in the total sample of individuals and in whites. The effect of parental history of stroke did not appear to be mediated by established stroke risk factors. A significant association between parental history of stroke and incident clinical ischemic stroke was not observed in the total sample or after stratification by ethnicity.

Previous reports suggest that MRI-detected abnormalities of the brain are markers of subclinical cerebrovascular disease, and share similar risk factors with clinically diagnosed stroke. However, our current study indicates that parental history of stroke is a differentiating risk factor for subclinical and clinical stroke. This discrepancy may result from other factors shared among family members but not accounted for in our analysis models.

Although our parental history of stroke information is not precise as to stroke type, it is likely that most parental cases were ischemic. Thus, the discrepant relationship observed between parental history of stroke and subclinical and clinical stroke is not likely explained by inclusion of parental history of hemorrhagic stroke, with differing etiology. The observed difference in association may best be explained under the assumption that parental history of stroke influences stroke risk primarily by means of genetic susceptibility. In this context, increased genetic susceptibility, represented by a positive parental history of stroke, may directly result in the development of subclinical disease. Manifestation of clinical disease, however, may simply follow a stochastic process, despite increased genetic susceptibility. In other words, the effect of parental history of stroke on increased clinical stroke risk may be diluted by the stochastic nature of the event.

Strengths of this study include its population-based design with blacks and whites and careful risk factor and stroke end point assessments. A limitation is that given the small sample sizes after stratification by ethnicity, lack of a significant association in blacks should be interpreted with caution. An additional limitation is that parental history of stroke information was obtained by home interview, which possibly resulted in some degree of misclassification. Kornegay et al have reported that there is reasonable agreement between proband-reported family history of stroke and self-reported personal history of stroke in members of the proband’s family. Additionally, it has been shown that the accuracy of reporting is high for other common diseases, such as myocardial infarction, coronary heart disease, diabetes, hypertension, and asthma.

In summary, parental history of stroke is significantly associated with increased risk of subclinical MRI-detected cerebral infarction, but not incident clinical ischemic stroke, in the ARIC Study. The effect of parental history of stroke on subclinical stroke did not appear to be mediated by established stroke risk factors. Further characterization of familial factors, specifically genetic factors, that contribute to increased stroke risk independent of established risk factors will be useful for the early identification of individuals at increased risk for stroke and for developing a better understanding of the etiology and pathophysiology of the disease. This study underscores the need for timely, well-designed, and comprehensive genomic studies of the occurrence of stroke in humans to identify and localize stroke susceptibility genes.

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