The Importance of Family History in Cerebrovascular Disease

Carmelo Graffagnino, MD, FRCPC; Andrew P. Gasecki, MD; Gordon S. Doig, MD; Vladimir C. Hachinski, MD, FRCPC, MSc, DSc(Med)

Background and Purpose The role of genetics in cerebrovascular disease remains controversial. The purpose of this study was to assess the influence of family history on atherothrombotic infarction or transient ischemic attack.

Methods Ninety patients with stroke or transient ischemic attack and 90 age- and sex-matched community control subjects were studied prospectively. Medical and family histories were obtained from all subjects, and a complete physical examination was performed.

Results Eighty-five patients and 86 control subjects knew their family history for ischemic heart disease and stroke. A positive history for ischemic heart disease was present in 62 (73%) of the patients and 46 (53%) of the control subjects (P = .019), and a positive family history for stroke was present in 38 (47%) of the patients and 21 (24%) of the control subjects (P = .014).

Conclusions Although a positive vascular family history was not an independent risk factor in a multivariate analysis, it was an excellent marker of the presence of other established vascular risk factors. Personal histories of ischemic heart disease, hypertension, and hyperlipidemia were found to be significant independent risk factors for stroke. (Stroke. 1994;25:1599-1604.)

Key Words • cerebral infarction • cerebral ischemia, transient • epidemiology • hereditary disease

Although a number of studies have addressed the role of genetics in stroke,1-15 controversies remain regarding this issue. Design weaknesses in these studies have led to variable conclusions regarding the influence of heredity in stroke. Most of the studies did not separate strokes into clinical or pathological subtypes, grouping both hemorrhagic and ischemic strokes into the same category. Cardioembolic strokes were often grouped together with thrombotic strokes, assuming that the same genetic factors would influence both subtypes.

The ascertainment of a complete and accurate family history is critical to a study of the role of heredity in stroke. However, many of the studies cited have depended on retrospective chart reviews or mailed questionnaires, often resulting in less than complete documentation.

The purpose of this study was to assess prospectively the prevalence of a positive family history for stroke or ischemic heart disease (IHD) in a population of patients with well-documented atherothrombotic stroke or transient ischemic attack (TIA) and to determine whether such a finding constituted an independent risk factor for stroke. The relative influence of a positive vascular family history (IHD or stroke) was compared with that of other well-established risk factors.

Received February 1, 1994; final revision received May 2, 1994; accepted May 16, 1994.

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for clinical research to the physician population of University Hospital. Approximately 65% of those contacted volunteered to enter the study. Inclusion and exclusion criteria similar to those used for the patients were applied to the control subjects. However, potential control subjects were excluded if a diagnosis of stroke or TIA had previously been made by a physician. Relatives of the stroke patients were ineligible to serve as control subjects.

All patients were reviewed at the time of hospital admission or clinic attendance and again 3 months after their stroke or TIA, at which time they underwent a second history review and physical examination. Control subjects were seen immediately after entry into the study.

A detailed family history was obtained from all patients and control subjects. The family history was taken from close relatives in patients whose stroke resulted in impaired cognition or impaired communication. As part of the family history review, everyone was asked whether they had a relative with a history of stroke or IHD. Whenever possible we attempted to determine from the respondent whether the stroke was due to a cerebral hemorrhage or an infarction. A history of TIA was determined to be unreliable and not used in determining family history. A history of physician-diagnosed myocardial infarction or angina pectoris was considered indicative of IHD.

A history of sudden death was not considered evidence of either IHD or stroke unless an autopsy had confirmed the diagnosis. Emphasis was placed on whether the affected relative was a first-degree relative (parent, sibling, or offspring) or a second-degree relative (grandparent, uncle, or aunt only).

The presence of vascular risk factors in the patients was based on their medical history before the stroke and a chart review. Patients were considered to be hypertensive if a physician had previously made such a diagnosis or if they had left ventricular hypertrophy on electrocardiography or echocardiography. The presence of IHD was based on either a previously diagnosed myocardial infarction or a medical history judged to be consistent with angina pectoris by a qualified cardiologist. Subjects with a history of dyslipidemia requiring either dietary or pharmacological intervention were grouped together in the "hyperlipidemia" category regardless of the specific type of lipid disorder. An active smoker was someone currently smoking or who had quit smoking within the previous 6 months.

Control subjects were seen within 7 days of recruitment and underwent the same history and physical examination as the patients. All control subjects provided their own medical and family histories.

As part of an ongoing study of the role of lipids and cerebrovascular disease, all patients and control subjects had blood taken for lipid levels after an overnight fast (results of that study to be reported separately).

Statistical Analysis

Before analysis, the comparability of the patients and control subjects regarding history of high blood pressure, cardiac disease, smoking, and history of hyperlipidemia was assessed. To take advantage of the matched case-control nature of the study, conditional logistic regression was used to generate estimates of risk. All risk factors were initially analyzed independently. A multivariate model was then constructed using a backward stepwise technique. All variables with univariate \( P < .25 \) were offered to the backward selection technique. Variables were removed from the model at multivariate \( P > .10 \). For the sake of parsimony, statistical interactions were not introduced into the model. As is the case in all case-control studies, a host of other variables, known and unknown, exist that cannot be controlled. We therefore assumed that they were distributed similarly in case and control subjects. Statistical analysis was performed on a UNIX-based computer using the statistical package SAS (version 6.07, SAS Institute Inc).

Results

Demographics

Ninety patients (61 men and 29 women) were recruited to participate in the study. Sixty patients were diagnosed with stroke and 27 with TIA. The mean ages of the patients and control subjects were 64.6 years (8.7, SD) and 64.5 years (8.45, SD), respectively. All patients were white.

Vascular Risk Factors

Histories of hypertension, IHD, hyperlipidemia, and smoking were present significantly more often in patients than in control subjects (Table 1). A personal history of IHD was the most powerful risk factor (risk ratio \( [RR] \) of 10.33) in the univariate analysis, followed by current smoking, history of hyperlipidemia, hypertension, and history of smoking.

Histories of hypertension, IHD, and hyperlipidemia were significant independent risk factors when analyzed in a multivariate model. IHD remained the most highly significant risk factor \( (P = .004, RR = 8.16) \), followed by hypertension \( (P = .033, RR = 3.02) \) and hyperlipidemia \( (P = .069, RR = 3.06) \). Smoking was not an independent risk factor in the multivariate analysis. Age-matched pairs were used in this study because age is a significant risk factor for stroke; however, to ensure that there were no residual confounding effects by age, all the regressions used included age. This did not affect the results.

Family History

Family histories of stroke and IHD in both groups were also analyzed. Eighty-five patients and 86 control subjects knew their family histories for stroke and IHD. Although it was common for both groups to have first-degree relatives (parents, siblings, or children) with IHD or stroke, there was a significant difference between the groups (Table 2). The two groups did not differ significantly with respect to the number of second-degree relatives having vascular disease.

<table>
<thead>
<tr>
<th>Table 1. Vascular Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
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<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>IHD</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Active smoker</td>
</tr>
<tr>
<td>Prior smoker</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; and IHD, ischemic heart disease.

*Univariate analysis.
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TABLE 2. Family History of Vascular Disease

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=85)</th>
<th>Control Subjects (n=86)</th>
<th>P*</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD in first-degree relative</td>
<td>35 (41%)</td>
<td>19 (22%)</td>
<td>.014</td>
<td>2.33 (1.19-4.59)</td>
</tr>
<tr>
<td>CVD in second-degree relative</td>
<td>6 (7%)</td>
<td>3 (4%)</td>
<td>.142</td>
<td>5.00 (0.58-42.799)</td>
</tr>
<tr>
<td>IHD in first-degree relative</td>
<td>59 (69%)</td>
<td>43 (50%)</td>
<td>.019</td>
<td>2.14 (1.14-4.04)</td>
</tr>
<tr>
<td>IHD in second-degree relative</td>
<td>9 (11%)</td>
<td>4 (5%)</td>
<td>.147</td>
<td>2.67 (0.71-10.05)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; CVD, cerebrovascular disease; and IHD, ischemic heart disease.
*Univariate analysis.

Eighty-one percent (69/85) of the patients had either a family history of stroke or IHD (ie, a positive vascular family history) compared with 60% (52/86) of the control subjects (P=.003). A positive vascular family history among the patients was very common, exceeding hypertension (56/90 [62%]), the next most significant risk factor, by 19% (P=.006). Family history of vascular disease, however, was not an independent risk factor in the multivariate analysis.

Hypertension, IHD, and dyslipidemia are risk factors with significant familial components. It has previously been shown that these factors tend to aggregate within families of patients with cerebrovascular disease, perhaps accounting for the role of family history in stroke. We found that individuals with cerebrovascular disease were more likely to have one or more risk factors compared with control subjects. There were only 17 patients (19% of total) free of risk factors (hypertension, IHD, hyperlipidemia) compared with 32 control subjects (36% of total) (P=.013).

Family history seemed to correlate with the presence or absence of risk factors. Among those patients who knew their vascular family histories (n=85), 58 of 69 (84%) with a positive vascular family history had one or more risk factors, whereas 10 of 16 (63%) with a negative family history had multiple risk factors (P=.05) (Table 3). A positive vascular family history therefore had a positive predictive value of 0.84, while the negative predictive value of a negative family history was only 0.38.

A family history of cerebrovascular disease or IHD was associated with the presence of a history of hyperlipidemia (Table 4).

Although it has been suggested that maternal family history of stroke is significant, we could not demonstrate any significant difference in the effect of having a paternal over a maternal family history of stroke. Among the subjects 14 patients had paternally affected relatives and 17 had maternally affected relatives (5 unknown, 8 siblings). In the control group the corresponding numbers were 12 and 7 (1 unknown, 3 siblings).

Discussion

Although previous studies have failed to show a genetic contribution to stroke, 2,4,8,15 we found that a positive family history of stroke and IHD was significantly more common in patients with stroke than in the general population. It has been shown that family information bias may exist in case-control studies. Patients with a specific illness are more likely to recall whether they had a relative with such a problem compared with healthy control subjects or nonaffected siblings. Most of the family history data in this study came directly from the patients and the control subjects. A more comprehensive family history may have been obtained had several members of the family been interviewed, but we were not able to do this.

Another source of potential bias in this study was the fact that only patients who survived until 3 months after the index event (stroke or TIA) were entered into the study. It is possible that factors that increased the risk for a bad outcome from the stroke (large strokes or other concurrent disease) would be missed in such a study. If family history were such a factor, our study design would miss this, and this must be taken into

Table 3. Relation of Family Vascular History to Presence of Risk Factors

<table>
<thead>
<tr>
<th>Patients</th>
<th>≥1 Risk Factors (n=88)</th>
<th>No Risk Factors (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive family history (n=58)</td>
<td>58</td>
<td>11</td>
</tr>
<tr>
<td>Negative family history (n=30)</td>
<td>10</td>
<td>6</td>
</tr>
</tbody>
</table>

Control Subjects

<table>
<thead>
<tr>
<th>Control Subjects</th>
<th>≥1 Risk Factors (n=32)</th>
<th>No Risk Factors (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive family history (n=23)</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>Negative family history (n=30)</td>
<td>21</td>
<td>13</td>
</tr>
</tbody>
</table>
A positive vascular family history was only found to be significant in the univariate analysis, suggesting as expected that vascular family history was not an independent risk factor but rather a marker of the presence of other risk factors. Dyslipidemia, hypertension, and diabetes are vascular risk factors with familial patterns of inheritance. IHD commonly clusters within families. Determining whether genetics is an independent risk factor for IHD is controversial because multiple vascular risk factors aggregate within families of people with IHD, causing some to suggest that this aggregation may reflect conjoined environmental and genetic effects. Gertler et al. have shown that even healthy volunteers with a family history of IHD had higher cholesterol and glucose levels than a comparable group without such a family history. These risk factors have genetic components in excess of common environmental factors. Despite the apparent inheritance of common vascular risk factors in patients with IHD, a positive family history of such disease, especially in a first-degree relative, has been shown to be a significant independent risk factor for IHD.

Similar issues have been raised with respect to the genetic influence of vascular family history on cerebrovascular disease. Several studies have shown that, as in IHD, multiple vascular risk factors may accumulate within families of patients with cerebrovascular disease, raising the possibility that this accounts for the familial nature of cerebrovascular disease. Although we did not find a positive vascular family history to be an independent risk factor for stroke, other studies have found family history of stroke to be a significant and independent risk factor, particularly with a maternal history of stroke. Recent studies in twins with strokes have also shown a significant genetic effect, as the concordance rate for stroke was higher for monozygotic twins (17.7%) than for dizygotic twins (3.6%). The number of subjects in our study was relatively small, and therefore it is possible that we missed a true positive effect of family history as a result of a β-type error. However, we did find, as have others, that a positive vascular family history was a good marker for the presence of other risk factors (positive predictive value of 0.84).

We also found that subjects with cerebrovascular disease were more likely to have multiple risk factors compared with control subjects. This is significant because it is known that the risk of stroke increases with the number of risk factors present. In our study hypertension, IHD, smoking, hyperlipidemia, and a positive vascular family history were all more prevalent in the stroke and TIA group. However, only IHD, hypertension, and hyperlipidemia were significant independent risk factors in the multivariate model. Hypertension has been the most studied risk factor for stroke and indisputably shown to be a significant and modifiable risk factor. IHD likewise is an established risk factor for stroke. Smoking, on the other hand, has been controversial as a stroke risk factor. It has been shown by some to be a significant risk factor for stroke that is reduced by cessation of smoking. We did not find smoking to be an independent risk factor in our multivariate analysis, however.

The role of hyperlipidemia as a risk factor for stroke has been controversial. Earlier studies have not shown a positive correlation between elevated serum lipids and stroke. These studies were often inconclusive as a result of poor definition of study groups, small numbers, and other methodological weaknesses. More recent studies have shown an association between dyslipidemic states and cerebrovascular disease. We found that a history of previously diagnosed dyslipidemia was significantly more prevalent among the stroke population than the control subjects and was an independent risk factor in the multivariate analysis. A detailed report of the lipid profiles of the patients and control subjects is being prepared. A family history of vascular disease in a first-degree relative (IHD or cerebrovascular disease) served as a good marker for the presence of hyperlipidemia in that it was significantly more prevalent among those with hyperlipidemia than those without a history of hyperlipidemia (Table 4).

Recent approaches to the study of the molecular genetics of atherosclerotic vascular disease have used the candidate gene approach. For the most part they have focused on studying genes involved in lipoprotein
metabolism. Polymorphisms of these genes distributed throughout populations may be associated with variable risks of developing disease and may therefore be used to study familial influences on disease. This approach has already been applied to HHD and in a limited sense to cerebrovascular disease. Ideally the knowledge of the high-risk genetic profile could be used to screen high-risk individuals, particularly in childhood, so that intervention could be started earlier. In cardiovascular disease early preventive measures have already been shown to be possible in high-risk groups as early as childhood. Further studies of the genetics of cerebrovascular disease will undoubtedly contribute to our understanding and ultimate prevention of this disease and should therefore be regarded as significant as the early epidemiological stroke studies to our current understanding of stroke.

Acknowledgments

Dr Graffagnino is a Canadian Heart and Stroke Foundation Research Fellow, and Dr Hachinski is a career investigator with the Heart and Stroke Foundation of Ontario. We wish to thank Gordon Dog, MSC, Sharish Hastak, MD, and Jonathan Streiff, MD, for their assistance in this study.

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The importance of family history in cerebrovascular disease.
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Stroke. 1994;25:1599-1604
doi: 10.1161/01.STR.25.8.1599

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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World Wide Web at:
http://stroke.ahajournals.org/content/25/8/1599

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