Family History of Stroke in Patients With Transient Ischemic Attack in Relation to Hypertension and Other Intermediate Phenotypes

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Background and Purpose—Family history of stroke (FHxstroke) is a risk factor for ischemic stroke, but there are insufficient data on the relationship with stroke subtypes and intermediate phenotypes (IPs), such as hypertension. Specifically, there are no reliable data on the associations of FHxstroke in patients with transient ischemic attack (TIA) in whom relationships with IPs are likely to be determined most reliably.

Methods—We studied FHxstroke and FHx of myocardial infarction (FHxMI) in TIA patients from 2 population-based incidence studies and 2 prospective consecutive hospital-referred series. We related the presence of FHx to baseline characteristics, clinical subtype, and IPs.

Results—Results were similar in the 4 cohorts, and so data on all 783 patients were pooled. FHxstroke was less common than FHxMI (189 versus 254; P=0.0003). FHxstroke and FHxMI were strongly related to history of hypertension in the proband (odds ratio [OR], 1.78; 95% CI, 1.28 to 2.48; P=0.0008; and OR, 2.10, 95% CI, 1.55 to 2.85; P<0.0001, respectively). Highest recorded premorbid systolic and diastolic blood pressures (mm Hg) were significantly higher in cases with FHxstroke than those without and increased with the number of affected first-degree relatives (0 181/100; 1 185/104; ≥2 198/109; P=0.03). There was no association between FHxstroke and age, diabetes, smoking, plasma glucose, cholesterol, or territory of TIA, but FHxstroke was less common in patients with ocular TIA than in cases with cerebral TIA (OR, 0.53; 95% CI, 0.34 to 0.82; P=0.004), although the association was no longer significant after adjustment for hypertension.

Conclusions—The strong association between hypertension and FHxstroke suggests that familial susceptibility to cerebral ischemia is attributable, at least partly, to familial predisposition to hypertension. This should be taken into account in studies of the genetics of ischemic stroke. (Stroke. 2005;36:830-835.)

Key Words: blood pressure ■ cerebral ischemia, transient ■ genetics ■ history

Animal models1 and twin studies2 suggest that genes influence susceptibility to ischemic stroke, and there are some rare Mendelian stroke syndromes in man.3,4 Polymorphisms in 2 genes have been associated recently with stroke in Iceland,5,6 but the observations have yet to be reproduced elsewhere and their mechanisms determined. Results of previous candidate gene studies have been inconsistent, and positive associations have not been reproduced.3,7,8 Interpretation of molecular genetic studies in ischemic stroke is also undermined by a lack of reliable data on the genetic epidemiology.2,3 For example, it is uncertain how heritability of stroke is associated with intermediate phenotypes (IPs), such as large artery atherosclerosis and hypertension, which both have substantial genetic components,9 and could be confounders in molecular genetic studies.

In the absence of detailed twin studies, family history (FHx) studies can provide useful data on the heritability of stroke.2,3 Several prospective cohort studies have been reported2,3 but have provided little detail on IPs. Case control studies are difficult to interpret because of recall bias, and few have taken account of the subtype of stroke, age of the proband or of the affected first-degree relative (FDR), the number of affected FDRs, and sibship size.2,3 An alternative approach is to do case-to-case studies (ie, to compare the characteristics of patients with versus without FHx). This methodology avoids recall bias inherent in case control comparisons because all patients have experienced a recent cerebrovascular event and can determine which characteristics of the proband (eg, age, subtype, IPs, etc) are associated with FHx. A study confined to transient ischemic attack (TIA) patients avoids other biases resulting from unavailability of data in stroke patients with dysphasia, intercurrent illness, or cognitive dysfunction, and is less liable to bias because of changes in measurements of IPs, such as blood pressure (BP), cholesterol, and glucose, caused by the acute event itself.

We investigated the relationships of FHx of stroke (FHxstroke) and FHx of myocardial infarction (FHxMI), including age of the proband, the FDRs affected, and the number of affected FDRs, with clinical characteristics and IPs in 2 population-
based incidence studies and 2 prospective consecutive hospital-referred series of patients with a recent TIA.

Methods
The population-based studies conformed to the standard quality criteria for stroke incidence studies.\textsuperscript{10,11} The methods and results of the Oxfordshire Community Stroke Project (OCSP)\textsuperscript{12} have been published previously.\textsuperscript{13,14} The ongoing Oxford Vascular Study (OXVASC) used identical methods of ascertainment to the OCSP.\textsuperscript{14,15} The methods of the Oxford hospital-referred TIA patient series have also been published previously.\textsuperscript{16} Briefly, a consecutive cohort of patients with cerebral or ocular TIA without previous stroke was assembled prospectively by a vascular neurologist between 1976 and 1986. We also collected data from all TIA patients seen at 3 dedicated TIA clinics in Oxford from 2002 to 2003. Researchers used a structured questionnaire to prospectively record clinical data. Studies were approved by the local ethics committee.

In all studies, a study neurologist assessed patients as soon as possible after notification and computed tomography brain imaging was obtained. A TIA was defined as an episode of sudden-onset focal neurological disturbance, presumed to be vascular in origin, with symptoms lasting <24 hours. Details of the presenting event, clinical characteristics, and medical history were recorded from the patient, relatives, family practitioner (FP), and hospital records.

Family History
FHx was collected using a semistructured (OCSP) or structured questionnaire (OXVASC and both hospital-based TIA series) separately for stroke and for myocardial infarction (MI) from the patients, their relatives, and their medical records. It was regarded as positive if ≥1 FDR was affected. All cohorts recorded whether father, mother, or siblings were affected. The number of affected FDRs and their relationship to the proband were recorded. Family trees and details of what age the relative was when affected and the overall number of siblings were collected in OXVASC and the second hospital-referred series.

The assessment of the history of stroke in an FDR was based on the patient’s or relative’s description. Histories of TIA, intracranial hemorrhage, or subarachnoid hemorrhage were excluded. The definition of MI in an FDR was also based on the clinical description and included sudden death. Previous work has shown that nonverified patient-reported FHx in FDRs is sometimes inaccurate but that the likelihood ratios for FHx\textsubscript{stroke} and FHx\textsubscript{MI} are 11.2 (95% CI, 9.2 to 13.6) and 8.6 (95% CI, 6.8 to 10.9), respectively, indicating good discriminatory power.\textsuperscript{17}

Baseline Data
Detailed baseline data were recorded, including age, sex, systolic BP (SBP), and diastolic BP (DBP; measured at the initial interview). The highest-ever premorbid SBP and DBP and the most recent BP predating the TIA were obtained from FP records in both population-based studies. Information on the following medical conditions before the TIA was obtained from patients or their medical records: previous ischemic heart disease (IHD; angina or MI), hypertension (on medication), cardiac failure (on medication), diabetes mellitus (DM; on medication), and peripheral vascular disease. Patients were classified as current smokers if they were smoking at the time of assessments or had given up smoking <1 year previously. The following information was recorded about the presenting event: carotid versus verteobasilar territory, cerebral versus ocular only (if carotid territory), and duration of longest event. Nonfasting blood was sampled for packed-cell volume, platelet count, erythrocyte sedimentation rate (ESR), and for random total cholesterol, triglyceride, and plasma glucose.

Statistical Analysis
Heterogeneity of associations between studies was calculated with the χ\textsuperscript{2} method. Where appropriate, data were pooled to increase statistical power. We allowed for possible differences between studies by adjusting or stratifying analyses by “study” where appropriate. We also calculated odds ratios (ORs) within individual studies and combined them by fixed-effects meta-analysis using the Mantel–Haenszel method. To study any differences in baseline characteristics between patients with and without FHx, we used the χ\textsuperscript{2} test for categorical variables. If a cell contained an expected number of ≤5, we used a 2-tailed Fisher exact test. We used ANOVA for comparison of continuous variables. For any factor that showed an association with FHx, we performed a logistic regression analysis, adjusting for age, sex, study, and the presence of other vascular risk factors. All analyses were performed with SPSS version 12.0.1 (SPSS).

Results
Of 184 patients with a TIA in OCSP, FHx was available in 178 (96.7%). Of the first 130 patients with a TIA in OXVASC, FHx was available in 124 (95.4%). Of 469 patients from the first Oxford hospital-referred series, FHx was available in 391 patients after exclusion of patients who were also enrolled in the OCSP. The second Oxford hospital-referred series recruited 95 consecutive patients; FHx was
TABLE 2. Baseline Clinical Characteristics According to the Presence or Absence of FHx\textsubscript{stroke} or FHx\textsubscript{MI}

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FHx\textsubscript{stroke}</th>
<th></th>
<th>FHx\textsubscript{MI}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=189)</td>
<td>No (n=594)</td>
<td>P</td>
</tr>
<tr>
<td>Male sex</td>
<td>100 (52.9%)</td>
<td>365 (61.4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>67.2 (11.0)</td>
<td>66.3 (12.1)</td>
<td>0.32</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>105 (55.6%)</td>
<td>245 (41.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Treated diabetes</td>
<td>16 (8.5%)</td>
<td>36 (6.1%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>28 (14.8%)</td>
<td>121 (20.4%)</td>
<td>0.09</td>
</tr>
<tr>
<td>IHD</td>
<td>38 (20.1%)</td>
<td>122 (20.5%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>11 (5.8%)</td>
<td>38 (6.4%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>26 (13.8%)</td>
<td>54 (9.1%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Current smoker</td>
<td>58 (30.7%)</td>
<td>219 (36.9%)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

| Presenting event(s)                   |         |         |                     |
|                                       |         |         |                     |
| Carotid TIA                           |         |         |                     |
| Of which ocular only                  | 155 (82.0%) | 466 (78.3%) | 0.29               |
| Median (range) maximum duration (min) | 20 (1–2300) | 30 (1–2400) | 0.62               |

| Measured mean BP (mm Hg)              |         |         |                     |
|                                       |         |         |                     |
| Mean BP (SE) at assessment (n=776)    | 160.4 (29.2) | 157.8 (31.7) | 0.32               |
| Mean DBP (SE) at assessment (n=773)   | 87.4 (12.6) | 86.0 (14.0)  | 0.22               |
| Most recent premorbid SBP (SE)* (n=288)| 151.8 (28.5) | 151.3 (25.0) | 0.87               |
| Most recent premorbid DBP (SE)* (n=287)| 83.7 (13.6) | 83.5 (11.7)  | 0.89               |
| Maximum premorbid SBP (SE)* (n=288)  | 187.9 (30.2) | 181.2 (30.6) | 0.10               |
| Maximum premorbid DBP (SE)* (n=288)  | 104.7 (19.8) | 100.3 (15.4) | 0.05               |

| Blood tests                           |         |         |                     |
|                                       |         |         |                     |
| Mean (SD) blood glucose (mmol/L; n=726) | 5.51 (1.98) | 5.39 (1.61)  | 0.43               |
| Mean (SD) total cholesterol (mmol/L; n=725) | 6.35 (1.56) | 6.48 (1.51)  | 0.32               |
| Mean (SD) triglyceride level (mmol/L; n=594) | 1.90 (1.02) | 1.76 (0.93)  | 0.12               |
| Mean (SD) packed red cell volume (n=728) | 0.44 (0.047) | 0.44 (0.048) | 0.95               |
| Mean (SD) platelet count (x10\textsuperscript{12}/L; n=722) | 260 (63) | 259 (73) | 0.91               |
| Median (range) ESR (mm/hour; n=681)   | 10 (1–112) | 9 (1–130)  | 0.77               |

*Data available only for OCSP and OXVASC.

available for 90 (94.7%). Of the resulting cohort of 783 patients with FHx available, 465 (59.4%) were male and the mean age was 66.5 years (SD 11.8).

There were no significant differences between population-based and hospital-referred cohorts in the frequency of FHx or in which FDRs were affected (Table 1), nor in age, sex, or other risk factors. Furthermore, the age at which relatives were affected, as well as the total number of siblings, was similarly distributed in both cohorts (OXVASC; and second hospital-referred series) that collected these data. For the following analyses, we therefore report results from the pooled data of all 4 cohorts where appropriate. An FHx\textsubscript{stroke} was less common (189 patients; 24.1%) than an FHx\textsubscript{MI} (254 patients; 32.4%; P=0.0003). FHx of both MI and stroke was present in 67 (8.6%), whereas 376 (48.0%) had FHx of either stroke or MI. Thirty-five (4.5%) had >1 affected FDR with stroke, and 73 (9.5%) had multiple affected FDRs with MI.

Age did not differ significantly between patients with and without FHx\textsubscript{stroke} or FHx\textsubscript{MI}.

A total of 185 patients had an ocular TIA only, with no history of recent cerebral ischemia, and 437 patients had a recent cerebral carotid territory TIA. FHx\textsubscript{stroke} was less common in cases with an ocular TIA only than in cases with cerebral events (20.6% versus 32.8%; OR, 0.53; 95% CI, 0.34 to 0.82; P=0.004). However, this association was no longer significant after adjustment for history of hypertension and source study (OR, 0.66; 95% CI, 0.41 to 1.05; P=0.08), but was changed little by further adjustment for age, sex, DM, IHD, and smoking (OR, 0.67; 95% CI, 0.42 to 1.08; P=0.10). FHx\textsubscript{stroke} did not differ between patients with carotid or vertebrobasilar TIA or in relation to TIA duration. FHx\textsubscript{MI} showed no significant association with TIA territory (Table 2).

Patients with FHx\textsubscript{stroke} were more likely to have a history of hypertension than those without (56.1% versus 41.2%; OR, 1.78; 95% CI, 1.28 to 2.48; P=0.0008; Table 3) with no significant heterogeneity between the cohorts (P=0.66; Figure). The association remained highly significant after multivariate adjustment for study, age, sex, DM, and smoking (OR, 1.66; 95% CI, 1.18 to 2.33; P=0.003). There was also a trend for higher mean SBP and DBP in patients with FHx\textsubscript{stroke} (Table 3), particularly in the 2 older studies, which were performed when antihypertensive treatment was less...
TABLE 3. Relationship Between No. of Affected FDRs With FHx_{stroke} or FHx_{MI} and History of Hypertension in the Proband and Measurements of BP in the Proband

<table>
<thead>
<tr>
<th>No. of Affected FDRs</th>
<th>History of Hypertension (n=783)</th>
<th>OR Against no FHx (95%CI)</th>
<th>At Assessment (n=776)</th>
<th>Highest Recorded Premorbid BP* (n=288)</th>
<th>Most Recent Recorded Premorbid BP* (n=288)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>245/594 (41.2%)</td>
<td>OR, 1.0</td>
<td>157.8 (31.7)</td>
<td>181.2 (30.6)</td>
<td>151.3 (25.0)</td>
</tr>
<tr>
<td>1</td>
<td>84/152 (55.3%)</td>
<td>OR, 1.76 (1.23–2.52)</td>
<td>158.8 (28.8)</td>
<td>184.9 (28.9)</td>
<td>151.4 (26.9)</td>
</tr>
<tr>
<td>≥2</td>
<td>21/37 (56.8%)</td>
<td>OR, 1.87 (0.96–3.66)</td>
<td>166.8 (30.7)</td>
<td>198.4 (33.3)</td>
<td>153.5 (34.1)</td>
</tr>
</tbody>
</table>

χ²_H \(P=0.003\)
χ²_T \(P=0.001\)

ANOVA
\(P=0.01\)
\(P=0.29\)
\(P=0.035\)
\(P=0.027\)
\(P=0.80\)
\(P=0.89\)

FHx_{MI}

<table>
<thead>
<tr>
<th>No. of Affected FDRs</th>
<th>History of Hypertension (n=288)</th>
<th>OR Against no FHx (95%CI)</th>
<th>Highest Recorded Premorbid BP* (n=288)</th>
<th>Most Recent Recorded Premorbid BP* (n=288)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>205/529 (38.9%)</td>
<td>OR, 1.0</td>
<td>159.7 (32.3)</td>
<td>151.8 (26.2)</td>
</tr>
<tr>
<td>1</td>
<td>101/180 (56.1%)</td>
<td>OR, 2.02 (1.43–2.85)</td>
<td>156.1 (28.7)</td>
<td>152.7 (25.1)</td>
</tr>
<tr>
<td>≥2</td>
<td>44/74 (59.5%)</td>
<td>OR, 2.32 (1.41–3.81)</td>
<td>154.9 (28.1)</td>
<td>147.0 (25.9)</td>
</tr>
</tbody>
</table>

χ²_H \(P<0.0001\)
χ²_T \(P<0.0001\)

ANOVA
\(P=0.10\)
\(P=0.09\)
\(P=0.23\)
\(P=0.06\)
\(P=0.47\)
\(P=0.31\)

*Highest recorded premorbid BP and most recent recorded premorbid BP available for population-based studies only.

χ²_H indicates chi square of heterogeneity for odds of personal history of hypertension for patients stratified by No. of FDRs with FHx; χ²_T, chi square for trend of association of history of hypertension with No. of FDRs with FHx.

prevalent (mean SBP 167 versus 160; \(P=0.028\); and mean DBP 90 versus 87; \(P=0.073\)) in patients with versus without FHx_{stroke}. The most recent BP measurements predating the TIA and maximum-ever premorbid BPs were available in the 2 population-based cohorts (Table 3). Again, patients with FHx_{stroke} had higher SBP and DBP, particularly for the highest-ever premorbid SBP (\(P=0.10\) and DBP (\(P=0.05\)). The strength of the relationship between FHx_{stroke} and highest-ever premorbid BP was related to the number of affected FDRs (mean BP: 0.181/100; 1 185/104; ≥2 198/109; Table 3; \(P=0.035\) for SBP and \(P=0.027\) for DBP). These trends remained significant (\(P=0.05\)) after adjusting for study, age, sex, DM, and smoking. FHx_{MI} showed a similar association with history of hypertension (OR, 2.10; 95% CI, 1.55 to 2.85; \(P<0.0001\)), but the association with measured BP was not as strong (Table 3).

FHx_{MI} was strongly associated with a history of IHD in the proband (OR, 1.98; 95% CI, 1.39 to 2.83; \(P=0.0002\)). In contrast, there was no association with FHx_{stroke} and IHD (OR, 0.97; 95% CI, 0.65 to 1.46; \(P=0.90\)). Neither FHx was associated with a history of peripheral vascular disease, cardiac failure, DM, atrial fibrillation, or current smoking after adjusting for source study (Table 2).

There was no association between FHx_{stroke} or FHx_{MI} and total cholesterol, mean glucose, packed-cell volume, platelets, or ESR. However, FHx_{MI} was associated with higher mean triglyceride levels (1.90 versus 1.74 mmol/L; \(P=0.05\)). However, this association was no longer significant after multivariate adjustment for study, age, sex, DM, hypertension, and smoking. FHx_{stroke} showed no association with triglyceride levels (Table 2).

Discussion

This study is the largest published report examining FHx in patients with TIA. Our combined cohort is nearly 10× larger than the only previous published study.\[^{18}\] Our results were generally consistent across the 2 population-based studies and 2 hospital-referred series. We found associations between FHx_{stroke} and personal history of hypertension and actual measurements of BP, particularly in the population-based studies, in which data on premorbid BP were available. We also found some interesting differences between patients with FHx_{stroke} versus FHx_{MI} in the presence of other vascular risk factors. Because we confined our comparisons to TIA patients rather than patients versus controls, our findings are unlikely to be undermined by recall bias. We also reported data on the frequency of multiple affected FDRs, which are useful in the planning of linkage-based genetic studies, such as affected sibling pair studies.

The association between FHx_{stroke} and hypertension is important because BP is the single most powerful risk factor for stroke\[^{19,20}\] and has a strong heritable component itself.\[^{21}\] The corresponding associations between FHx_{stroke} and measured BP are likely to be underestimates of the true associations because of intraindividual variation in BP and consequent regression dilution of associations based on single measurements.\[^{22}\] The observed relationships will also have been weakened by treatment of hypertension, which would...
explain why the association between FHx\text{stroke} and BP was stronger for the highest-ever recorded premorbid measurement than for the most recent measurement. Hypertension was also associated with FHx\text{MI}, but measured levels of BP had a weaker correlation compared with FHx\text{stroke}. We have shown previously that FHx\text{stroke} but not FHx\text{MI} was linked with a history of hypertension in stroke patients\textsuperscript{23}. These associations between hypertension and FHx\text{stroke} could reflect familial clustering of hypertension attributable to either shared genetic or environmental factors\textsuperscript{24}.

Virtually all IHD and many ischemic strokes are manifestations of atherosclerotic vascular disease and share common risk factors. This close relationship is further highlighted by the fact that even in our patients with TIA, FHx\text{MI} was more prevalent than FHx\text{stroke}. We have shown previously that FHx\text{stroke} but not FHx\text{MI} was linked with a history of hypertension in stroke patients\textsuperscript{23}. These associations between hypertension and FHx\text{stroke} could reflect familial clustering of hypertension attributable to either shared genetic or environmental factors\textsuperscript{24}.

Comparison of the proportion of patients with versus without FHx\text{stroke} to have a previous diagnosis of hypertension (A), IHD (B), DM (C), or atrial fibrillation (D). E, Comparison of the proportion of patients with FHx\text{stroke} in ocular only versus cerebral TIA. F, Comparison of the proportion of patients with FHx\text{stroke} in carotid versus vertebrobasilar TIA. ORs are displayed together with 95% CIs for strength of association for patients with versus without FHx\text{stroke}.

Although patients with ocular TIA(s) only were just as likely as patients with cerebral TIA(s) to have FHx\text{MI}, indicating a possible heritability of large vessel atherosclerosis, they were less likely to have FHx\text{stroke}. This suggests perhaps that genetic factors are involved in cerebral susceptibility to ischemia, given the lower risk of stroke associated with ocular TIAs. However, the association was diminished and was no longer statistically significant after adjustment for hypertension.

Our study had some shortcomings. First, in common with most other published studies of the genetic epidemiology of stroke, details of the FHx were limited. Not all of our studies recorded the age at which stroke or MI occurred in the relative, and we had no information on the subtype of stroke in the FDR. In particular, we were not able to reliably higher mean triglyceride levels. Neither FHx correlated with a previous diagnosis of DM or serum glucose. This is consistent with previous studies in stroke patients\textsuperscript{2}.
distinguish between ischemic and hemorrhagic stroke in FDRs because many of their strokes predated routine brain imaging. Nevertheless, although this limited our analyses to some extent, it is unlikely to have led to any systematic bias because hypertension has a similarly strong association with ischemic and hemorrhagic stroke. Therefore, it is unlikely that the confounding of heritability by hypertension we found is accounted for by inclusion of some FDR with hemorrhagic stroke. Second, although we used FHx as a possible indicator for genetic influences, familial clustering of a disease can also be attributable to a shared environment. Third, it is possible that patients with FHx were more likely to have had health screening before their TIA than patients without FHx. However, this would be true for FHxstroke and FHxMP. Therefore, it is unlikely that the strong association of FHxstroke but not FHxMP with highest-ever BP is accounted for by this potential bias. Finally, the lack of significant heterogeneity between the studies could reflect the comparatively small size of each individual cohort.

In conclusion, we found a strong association between FHxstroke, history of hypertension, and maximum recorded premorbid BPs. In contrast to FHxMP, there was no association between FHxstroke and history of IHD or triglyceride level in the proband. Of the established IPs, our findings suggest that heritability of BP is the most important contributor to heritability of stroke. Candidate gene studies should adjust for differences in measured BP, history of hypertension, and treatment of hypertension between cases and controls.

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References
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