Family History of Stroke Does Not Predict Risk of Stroke After Transient Ischemic Attack

Enrico Floßmann, MRCP; Peter M. Rothwell, MD, PhD, FRCP

Background and Purpose—Animal models suggest a genetic contribution to cerebral susceptibility to ischemia. Family history of stroke (FHxstroke) is a risk factor for ischemic stroke, but there is significant confounding by heritability of hypertension and other intermediate phenotypes, and it is uncertain whether genetic factors have a direct independent influence on cerebral susceptibility to ischemia in man.

Methods—We related detailed FHxstroke to baseline characteristics and subsequent risk of stroke in 2 population-based incidence studies and a consecutive hospital-referred series of patients with recent transient ischemic attack (TIA).

Results—In none of the cohorts or the pooled data (757 patients; 5515 patient years follow-up; 200 ischemic strokes; 126 myocardial infarctions [MIs]) did FHxstroke predict ischemic stroke (odds ratio [OR], 0.87; 95% CI, 0.57 to 1.32). No associations were revealed by analyses stratified by age or hypertension in the proband, FHxstroke in parents versus siblings, number of affected relatives, or their age at stroke. FHxstroke was unrelated to presence of ischemic lesions on baseline computed tomography (OR, 0.96; 0.52 to 1.76) or risk of MI during follow-up. There was no bias attributable to any relationship between FHxstroke and risk factor control or medication.

Conclusions—Family history of stroke does not predict risk of ischemic stroke after TIA. (Stroke. 2006;37:544-546.)

Key Words: heredity ■ prognosis ■ stroke, ischemic ■ transient ischemic attack

Animal models and twin studies suggest that genes influence susceptibility to ischemic stroke, and there are some rare Mendelian stroke syndromes, as well as evidence of heritability of sporadic ischemic stroke in man.1,2 Genetic factors could influence susceptibility to stroke through intermediate phenotypes, such as hypertension and atherosclerosis,3 but might also influence cerebral susceptibility to ischemia (ie, for a given ischemic insult, the extent of brain injury could vary). Animal models show evidence of genetic variation in cerebral susceptibility to ischemia,4,5 but there is as yet little evidence in man.

Follow-up of transient ischemic attack (TIA) patients might provide insight into cerebral susceptibility to ischemia in man. First, the risk of stroke is high,6 allowing detailed clinical studies with sufficient statistical power. Second, the prospective design avoids the recall bias inherent in case-control studies. Third, biases attributable to missing data in patients with severe stroke are avoided, and potential confounding factors (eg, blood pressure, glucose) are measured more reliably. Fourth, because most TIA patients have vascular pathology, confounding by intermediate phenotypes should be reduced, allowing more reliable determination of factors that directly influence cerebral susceptibility. Yet, there has been only 1 study of the predictive value of family history of stroke (FHxstroke) in TIA patients.7 We therefore studied detailed FHxstroke in 2 population-based TIA cohorts8,9 and a consecutive hospital-referred series.10

Methods

The methods of all 3 cohorts have been published previously.6,8–11 Briefly, the Oxfordshire Community Stroke Project (OCSP) studied the incidence, risk factors, and outcome of incident TIA during 1981 to 1986.6 The ongoing Oxford Vascular Study (OXVASC) uses identical methods of ascertainment to the OCSP.5,9 For this report, we included patients with any TIA without previous stroke during 2002 to 2004.8 The Oxford hospital-referred TIA series was a consecutive prospective cohort of patients with incident TIA assembled during 1976 to 1986.10

We calculated odds ratios (ORs) within individual studies and combined them by fixed-effects Mantel–Haenszel meta-analysis. Heterogeneity between studies was calculated with the χ² method. Where appropriate, data were pooled. To study differences in baseline characteristics, we used the χ² test for categorical variables and ANOVA for continuous variables. For any factor that showed an association with FHxstroke, we performed a logistic regression analysis, adjusting for age, sex, and study. ORs conferred by FHxstroke were calculated by multivariate binary regression analysis adjusting for study, age, sex, treated hypertension, cerebral versus ocular TIA, diabetes, atrial fibrillation, smoking, and baseline systolic and diastolic blood pressure. We reassessed antithrombotic drug use, blood pressure, and blood lipids at follow-up to test for possible bias attributable to differential treatment or control of risk factors in relation to FHxstroke.
Results

Of 209 TIA patients in OCSP and 175 in OXVASC, FHx_stroke was available in 202 (96.7%) and 164 (93.7%), respectively. Of 469 patients from the hospital-referred series, FHx_stroke was available in 202 (96.7%) and 164 (93.7%), respectively. FHx_stroke was most common in women (P = 0.013), in patients with treated hypertension (P = 0.003), and with cerebral TIA (P = 0.06). Subsequent analyses are thus adjusted for these differences or stratified appropriately. The proportions of patients with any ischemic lesion on computed tomography (CT) and the proportion with a lesion compatible with the presenting symptoms were unrelated to FHx_stroke.

Discussion

In patients with a recent TIA, FHx_stroke correlated with treated hypertension but did not predict appropriately located ischemic lesions on cerebral CT or the risk of subsequent stroke. These results will be useful in counseling TIA patients and
show that risk of ischemic stroke after TIA is not highly heritable.

A study of heritability of stroke after TIA has the advantages outlined in the introduction, but our study does have some potential shortcomings. First, patient-reported FHxstroke is sometimes inaccurate. Nevertheless, it has good discriminatory power. Second, in common with previous studies, we had no information on the stroke subtype in the FDRs. Studies of affected sib-pairs enable detailed examination of relatives, but it would be difficult to assemble a large enough cohort of sib-pairs with TIA to study cerebral susceptibility. We were also unable to stratify results by underlying etiological subtype in the proband. However, our observations suggest that any effects in specific subtypes are unlikely to be large. Third, it is possible that the presence of FHxstroke increased the likelihood of diagnosis of TIA. However, diagnoses were made by vascular neurologists according to strict criteria, and the proportion of patients with appropriately located lesions on CT was unrelated to FHxstroke. Fourth, factors determining susceptibility to TIA might be similar to those for susceptibility to stroke, and we have not studied the hypothetical group of individuals who do not have a TIA despite having microemboli. Fifth, the included studies varied in the available length of follow-up. Also, whereas the population-based studies included the high-risk period of stroke immediately after a TIA, this period was not covered by the hospital-based cohort, explaining the different rates of strokes between the studies. However, our results were highly consistent in all 3 studies, and there was also no significant difference between early and late strokes.

Acknowledgments

E.F. and P.M.R. are funded by the United Kingdom Medical Research Council. We thank Professor Charles Warlow and the Oxford Community Stroke Project collaborators for allowing us access to their data. We are very grateful to our OXVASC collaborators for their help with this study.

References

Family History of Stroke Does Not Predict Risk of Stroke After Transient Ischemic Attack
Enrico Floßmann and Peter M. Rothwell

*Stroke*. 2006;37:544-546; originally published online December 29, 2005;
doi: 10.1161/01.STR.0000198879.11072.f2

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/37/2/544

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/