Family History in Patients With Transient Ischemic Attacks

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To determine the influence of family history on vascular disease, we surveyed hospital patients discharged with a diagnosis of transient ischemic attack. Of 117 respondents, 81 knew their family history for myocardial infarction and 81 knew their family history for stroke. Of 83 responding, 43 reported a personal history of myocardial infarction, and of 85 responding, 66 reported a personal history of stroke. As expected, there was an association between positive family and personal histories of myocardial infarction in younger (aged <70 years) patients (Fisher's two-tailed exact test, p = 0.014). This association was reversed for stroke (Fisher's two-tailed exact test, p = 0.017). Older (aged ≥70 years) patients had a stronger association between positive family and personal histories of stroke; 14 (74%) of 19 older patients with a positive personal history of stroke had a positive family history of stroke. The reason for this reversal in the relation between family and personal histories of stroke compared with myocardial infarction may relate to the older age at onset of most strokes, differing stroke subtypes in older age groups, or lower rates of fatal myocardial infarction. This study suggests that familial factors may be important in some subtypes of cerebrovascular disease. Familial effects may be different in vascular diseases of the heart and brain. (Stroke 1991;22:837–841)

Assessment of risk factors in different races, sexes, and age groups can provide important clues to the pathogenesis of cerebrovascular disease and provide direction for the development of preventive strategies. Strong familial risk factors, both genetic and environmental, have been implicated in coronary artery disease (CAD), especially in younger patients. Although strokes, both ischemic and hemorrhagic, have been observed to cluster in families, few studies have examined familial risks. Given the possible implications for preventive therapies, we began preliminary investigations into the familial risk of stroke in a high-risk population.

Subjects and Methods
To select a group at high risk for stroke, we surveyed all patients with a discharge diagnosis of transient ischemic attack (TIA) from Yale–New Haven Hospital, New Haven, Conn., for a 4-year period (January 1985–January 1989). Using the hospital's Clinical Information System, patients were identified using the International Classification of Diseases coding for TIA as either a primary or secondary discharge diagnosis.

A questionnaire was developed as part of a Department of Epidemiology project on risk factor modification after TIA. The questionnaire included information on personal and family histories of both myocardial infarction (MI) and stroke, as well as on common vascular risk factors. A positive family history was defined as a "yes" response to the question, "Has anyone in your immediate family (blood relative) had an MI/stroke/hypertension/diabetes?" Specific information on which family members were affected was not required, but nearly all patients responding to a subsequent question indicated that the family member affected was a parent (approximately 75%), aunt or uncle (approximately 10%), grandparent (approximately 10%), or sibling (approximately 10%). After an initial mailing, nonrespondents were telephoned and a second questionnaire was sent. Only "yes" and "no" responses were used; blanks, "don't know," and "unsure" were excluded from the calculations.

Age 70 years was used as the division point between older and younger patients because it was near the median age of our population (yielding sufficient numbers in each age category to permit examination of the association between family history and personal history in both younger and older patients).
TABLE 1. Associations Between Personal and Family Histories of Myocardial Infarction and Stroke

<table>
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<th>MI</th>
<th></th>
<th></th>
<th>p</th>
<th>Stroke</th>
<th></th>
<th></th>
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<td>%</td>
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<td>%</td>
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</table>

MI, myocardial infarction.

This age was also clinically sensible because it is similar to the division points reported in previous studies of vascular disease.1,2,4–9

Statistical analysis of the association between suspected risk factors and a history of MI or stroke was performed using 2×2 contingency tables. Fisher's two-tailed exact test was used for all calculations. Calculations were performed using SAS Version 6 (SAS Institute Inc., Cary, N.C.).

Results

Review of the hospital's data bank identified 294 admissions; 200 (68%) had TIA as a primary diagnosis and the other 94 (32%) had TIA as a secondary diagnosis. Five patients had died during their hospital stay. For 28, the complete medical record could not be located. There were 13 duplicate names on the list. The initial cohort consisted of the remaining 248 patients. There were 127 women and 121 men. The median age was 69 (range 14–99) years.

Of the 248 questionnaires mailed, 82 (33%) of the patients had died since discharge, 17 (7%) were unable to complete the survey due to disability (e.g., severe aphasia, dementia), six (2%) had no forwarding address and could not be located, and 26 (10%) declined participation. Of the 116 patients alive at the time of the survey, 117 (70%) responded.

For personal history, 83 (71%) of the 117 patients answered the question on MI and 43 (52%) reported a positive personal history; 85 (73%) of the 117 patients answered the question on stroke and 66 (78%) reported a positive personal history. For hypertension, 59 of 93 responding (63%) reported a positive personal history; for diabetes, 15 of 82 responding (18%) reported a positive personal history.

For family history, 81 (69%) of the 117 patients answered the question on MI and 57 (70%) were positive; 81 (69%) of the 117 patients answered the question on stroke and 37 (46%) were positive. Of those responding, 55 of 78 (71%) had a positive family history of hypertension and 25 of 71 (35%) had a positive family history of diabetes.

Sixty-six people answered both the personal and family history questions for MI with a definite yes or no; 67 answered both questions for stroke.

When a family history of MI was tested with a personal history of MI for all ages, there was no significant association (Table 1). Of the 66 people who responded to both MI questions, 38 were younger than age 70 years. In these younger patients, there was a significant association between family history and personal history of MI: 16 (100%) of 16 patients with a positive personal history of MI had a positive family history of MI compared with seven of 22 (32%) with neither (p=0.014). For older patients there was no significant association.

The influence of a family history of MI on a personal history of stroke (Table 1) was also examined (66 people answered both questions). There was a significant association found across the entire co-
hort, regardless of age; 38 (79%) of 48 patients with a positive personal history of stroke had a positive family history of MI compared with nine of 18 (50%) with neither (p=0.032).

When we examined the association of a family history of stroke with a personal history of stroke (Table 1), there was no significant association for the entire cohort. However, when the relation between family history and personal history of stroke was examined within different age categories, a significant association was found. In contrast to MI, the positive association was found in older patients. For the 28 older patients answering both stroke questions, 14 of 19 (74%) with a positive personal history of stroke had a positive family history of stroke compared with seven of nine (78%) with neither (p=0.017). For the 39 younger patients, 11 of 32 (34%) with a positive personal history of stroke also had a positive family history of stroke compared with three of seven (43%) with neither (p=0.40).

A family history of stroke was not associated with a personal history of MI in the younger patients, the older patients, or the entire cohort (Table 1).

**Discussion**

To define a cohort at high risk for stroke, we studied patients admitted to the hospital after a TIA. Risk in this group represents a diagnostic, prognostic, and therapeutic challenge and influenced our selection of the study design and patient cohort. A control group of patients without symptomatic cerebrovascular disease may be useful for subsequent studies. Such a control group may have helped clarify the results in this study.

Although we had a high response rate of eligible patients, the persons who did not respond to the survey or those not certain about their family history could have influenced our results. Other potential biases should also be noted. There may be considerable variability in reporting a diagnosis, especially in a family member. Also, our cohort consisted of patients with physician-diagnosed TIA, but there may be significant disagreement in this diagnosis, even among neurologists. It is possible that our cohort included patients with deficits that cleared after 24 hours, but this may be of little consequence because TIA and minor stroke appear to have similar recurrence rates, mortality, and risk factors.

The prevalence of comorbid diseases in our cohort was much higher than in population-based studies. The majority of patients reported a stroke, raising concern about whether our cohort should be viewed as a TIA cohort. The mortality rate was also significantly higher in our cohort than in others. Patients with TIs admitted to the hospital (i.e., included in our study) may represent a sicker group. This effect may be even greater in New Haven, which has traditionally been very conservative about cerebrovascular disease. Many neurologists in this community do not admit patients with "uncomplicated" TIs.

Lastly, our responding patients survived 1–4 years after their TIA. Our results may therefore represent a familial influence on survival after a stroke. Survival varies with stroke subtype; a similar effect is likely to occur after TIA. It is possible that stroke survival cohorts, like ours, have a higher percentage of patients with small-vessel disease because of the higher mortality associated with large-vessel disease. We may be noting a familial influence on a particular stroke subtype.

Subgroup analyses to look for possible explanations for the above associations were attempted (e.g., familial associations of vascular risk factors), but cell sizes were too small for meaningful calculations. Small cell sizes also limit statistical power. The lack of demonstration of a difference in this setting is not equivalent to the absence of an effect.

Twin and family history studies have provided strong evidence that familial and genetic factors are important, especially in early-onset CAD. Estimating the contribution of established risk factors, familial environmental factors, or genetic attributes has been controversial. However, it does appear as if, after correcting for traditional risk factors, having a first-degree relative with premature CAD is, by itself, a significant risk factor. These studies support the association with family history seen in our younger patients with MI.

A positive family history of MI was also associated with stroke in both age categories in our study. Although the numbers were small, the association was significant. A similar association has been described in women. In our cohort, a positive family history of stroke did not predict MI, an association described by others.

Few studies have investigated the genetic and familial contributions to cerebrovascular disease. Most studies have been very limited in their classification of stroke and have relied on a patient's recollection or death certificates for family history. The results have been mixed.

Gifford found excessive death from cerebrovascular disease among parents and relatives of stroke patients. The diagnosis of stroke included thrombosis, embolism, and hemorrhage. Alter found higher disease rates in siblings (12-fold) and parents (three-fold) of stroke patients than in controls. Our study also included a variety of stroke subtypes.

Heyden et al compared the mortality patterns in parents of patients with severe carotid occlusive disease undergoing internal carotid endarterectomy and the parents of controls with vascular and nonvascular disease. The parents of patients with carotid disease had higher rates of death from vascular disease (any cause) than did parents of either control group, but patients in the control groups had significantly lower rates of hypertension. Hypertension is known to have a strong familial component. It is possible that familial clustering of risk factors accounted for all or part of this association.
A recent investigation addresses this point. Welin et al29 found a threefold increase in the incidence of stroke among middle-aged men whose mothers had died of stroke. There was no difference with respect to vascular risk factors, including blood pressure, between this group and a group without maternal death from stroke. The etiologic fraction for maternal death from stroke was 0.19, nearly as strong a risk as systolic hypertension (0.23).

Howard and colleagues30 noted that the risk of death from stroke varies considerably among families of stroke patients. These workers examined the risk of death from stroke or CAD in children of stroke patients. Most families had low risk, but a few demonstrated a strong familial tendency, which was most strongly correlated with a parental history of diabetes and a young parental age at first stroke. Those results, although demonstrating an age association opposite to ours, may have measured a different aspect of vascular risk factors, predisposition to stroke, or survival after stroke.

Several studies have failed to demonstrate a genetic contribution to stroke.31-33 The overall conclusions are equivocal. The World Health Organization Task Force on Stroke and Other Cerebrovascular Disorders34 concluded that genetic or familial factors have not yet been demonstrated to be an important risk factor for stroke.

In our study, the effect of age and family history on cerebrovascular disease was opposite that for cardiac disease. The reason for this is not clear. It is possible that we were measuring a familial tendency for recurrent stroke, but most of the known risk factors associated with recurrent stroke appear to be the same as those for first stroke: age, cardiac comorbidity, diabetes, and hypertension.11,20,35-37

It is also possible that we are seeing an effect on survival after stroke, but long-term survival after infarction is also influenced by many of the factors associated with the occurrence of stroke. These factors include hypertension, advanced age, and cardiac comorbidity.36,38 It is possible that these risks interact with each other and with familial or genetic factors to account for our findings.

Age is important in interpreting the risk of a family history for vascular disease; which parent is affected, important in familial cardiac disease, may be important in cerebrovascular disease. Scholdkraut et al9 noted an association between coronary risk and parental history of death by CAD. The effect was strongest in young patients with CAD (both parents contributed to risk), but in those older than age 60 years only maternal death from CAD was a strong predictor.

The relative importance of vascular risk factors for stroke also appears to vary with age and sex.39 Hypertension, blood pressure, left ventricular hypertrophy, smoking, and hematocrit appear to have strong associations with stroke in younger patients (<65 years old). Diabetes appears to be a strong factor for stroke in women. Increased serum lipids have generally not been associated with an increased risk of stroke, except in men <60 years old.40 Serum cholesterol, a strong risk factor for ischemic cardiac disease, does not have a strong predictive value in the elderly, although the usual risk is still associated with low density lipoprotein and high density lipoprotein cholesterol.41 In addition, carotid stenosis appears to be correlated with hypercholesterolemia, but in the elderly this association may not be as strong.42 Alter et al43 demonstrated an age-dependence of vascular risk factors for recurrent stroke (MI, hypertension, diabetes), but in their cohort there was a stronger association in the older age groups.

Information from the Stroke Data Bank44 suggests that the prevalence of stroke—and most likely TIA subtype varies with age. Our results may represent a familial influence on a single stroke subtype.

In summary, our data suggest that age is an effect modifier45 in the relation between personal and family histories of both stroke and MI. Age is also generally acknowledged to act as a confounder in vascular disease,46 but with our limited sample sizes we were unable to assess this reliably.

The best and most cost-effective approach to cerebrovascular disease is prevention. The first lines of defense in stroke prevention are the detection and management of risk factors.39 There may be some debate whether familial risks can be modified. Studies on CAD suggest that they can. It may be that the effect of risk modification is greater in familial disease than in the general population. For example, Khaw and Barrett7 estimated that 68% of excess deaths in men with a family history of heart attack were attributable solely to the interaction of family history with smoking habits and are therefore potentially avoidable. Thus, the risk of vascular disease associated with an inherited predisposition may be profoundly affected by modifiable behavior. Further examination of the genetic and familial contributions to stroke risk may permit the development of interventions in lifestyle and diet at an early age, when preventive measures may have the greatest impact.47

This work raises important questions not only in the genetic contribution to stroke, but also in vascular risk factors in the elderly. Studies addressing risk factors for vascular disease in the elderly are difficult to find, even for cardiac disease. The few studies that exist suggest that there may be important differences.43,48

Although potential selection biases may exist, our study suggests that different familial risks play a role in at least some subgroups of stroke. Age, important in familial cardiac disease, may be important in cerebrovascular disease, but the associated risks may not be identical.

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References


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