Genetic Predisposition to Stroke in Relatives of Hypertensives

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Background and Purpose—The genetic basis of stroke is poorly understood. We evaluated patterns of familial aggregation of hypertension and stroke to test the hypothesis that inherited susceptibility to these disorders may be determined by a common set of factors.

Methods—Genealogical and medical history information was obtained for a cohort of 354 hypertensive probands ascertained in a clinic-based setting, their 1427 first-degree relatives, and 239 of their spouses. Risks of stroke and hypertension in biological and nonbiological relatives were compared with the logistic model of the generalized estimating equations adjusted for age and sex.

Results—The risk of hypertension was higher for the parents and siblings of the probands than for spouses (odds ratio [OR] = 2.4; 95% CI, 1.8 to 3.4; OR = 2.2; 95% CI, 1.6 to 3.0, respectively). When the spouses were used as a reference group, the risk of stroke for parents of the hypertensive probands was 7.3 times higher (OR = 7.3; 95% CI, 3.6 to 14.8), while a nonsignificant but slightly increased risk for siblings (OR = 1.6; 95% CI, 0.8 to 3.3) was observed. Controlling for hypertension, obesity, smoking, coronary heart disease, diabetes, and cholesterol resulted in decreased estimates of the risk of stroke for parents and siblings (ORparents = 5.4; 95% CI, 2.6 to 11.2; ORsiblings = 1.2; 95% CI, 0.6 to 2.5). The risk of stroke was significantly higher for hypertensive parents and siblings than for nonhypertensive parents (OR = 5.2; 95% CI, 2.8 to 9.7) and siblings (OR = 5.8; 95% CI, 2.1 to 15.9). A history of hypertension was not associated with an increased risk for stroke in spouses (OR = 0.7; 95% CI, 0.2 to 3.1). The risk of stroke in hypertensive relatives of probands with stroke was higher than that of the normotensive relatives (OR = 13.4). A less elevated risk ratio was observed in the relatives of probands who did not have a stroke (OR = 4.0).

Conclusions—Our data showing a higher occurrence of hypertension and stroke in parents of hypertensive probands compared with spouses suggest that some of the genetic factors predisposing to these conditions may be the same. The slightly increased risk to siblings compared with spouses was not significant, suggesting that elucidation of these factors through family studies of stroke may be difficult because of secular trends toward improved treatment for hypertension. Although a history of hypertension increases the risk of stroke among parents and siblings, multivariate analyses revealed a familial component to stroke independent of hypertension. (Stroke. 2000;31:487-492.)

Key Words: genetics ■ hypertension ■ stroke outcome

Despite the recent decline in the stroke mortality rates, stroke is still the most common life-threatening neurological disease and the third leading cause of death in the United States after heart disease and cancer.1,2 A large portion of the population is disabled as a consequence of stroke. Recent advances in the treatment of stroke and the underlying causes plus the control of certain risk factors such as blood pressure, salt intake, cigarette smoking, and weight can account for the trends in mortality. Although the available treatments for stroke have been helpful, the most effective way to decrease the mortality and morbidity of stroke is prevention, especially early in life.

Hypertension is the most influential known risk factor for stroke, conferring an increased odds of 1.5 to 3.0 depending on age, sex, and the severity of hypertension.4 Stroke incidence is directly proportional to age, with much higher rates and poorer survival in people older than 65 years.2,3 Previous studies have shown a higher risk for men than for women up to age 65, while this sex-related difference was reversed for those older than 65 years.1 Alter et al5 observed an association between history of hypertension and recurrence of stroke. It is well recognized that hypertension aggregates in families, suggesting a genetic basis. In fact, genes have been identified for several rare syndromic forms of hypertension.5,6 Family
history of stroke is perceived to be an important risk factor for stroke, but the importance of this risk factor has not been confirmed conclusively by epidemiological studies.\textsuperscript{7–17} To further understand the genetic relationship between stroke and hypertension, we evaluated the aggregation of stroke in families prone to hypertension.

**Subjects and Methods**

Subjects were ascertained between January 1996 and December 1998 at outpatient units and collaborating clinics of the Boston University Medical Center. The probands were chosen on the basis of a diagnosis of hypertension (consistent systolic blood pressure \(>140\) mm Hg or diastolic blood pressure \(>90\) mm Hg considered on consecutive measurements). Individuals taking long-term antihypertensive drugs were considered to be hypertensive even if their blood pressure was within normal limits. Patients signed an informed consent, which was approved by the Institutional Review Board at Boston University Medical Center. Family history and medical history information was collected with the use of standardized questionnaire instruments administered by direct interview or completed by the patient at home. Additional family informants were contacted to ensure accuracy and completeness of the responses. Families were ascertained consecutively to minimize the potential bias of selecting families with many individuals with hypertension. The family history focused on first-degree relatives (ie, parents, siblings, and children) and spouses. Children were excluded from this study since the occurrence of stroke would be rare in this age cohort. Occurrence, age of onset, and treatment of stroke were determined on the basis of medical records or information given by the proband or proxy informant. The diagnosis of stroke was based on standard clinical criteria,\textsuperscript{1} ie, history, neurological examination, plus, in recent years, brain imaging procedures. Data forms were reviewed by at least 2 project personnel and computerized with the use of an Oracle database.

**Statistical Analysis**

The logistic regression model of the generalized estimating equations (GEE)\textsuperscript{18,19} approach was used to assess the familial pattern of stroke and its relationship to hypertension. Hypertension and stroke were alternately considered as outcome and predictor variables. All regression models were adjusted for age and sex. Age was considered the age of onset for those who developed stroke or censoring age (ie, current age or age of death) for all other individuals. Risk ratios for disease and the corresponding 95% CIs were computed. A subset of analyses also adjusted for the presence or absence of obesity, coronary heart disease, diabetes, high cholesterol (>200 mg/dL), and history of smoking. Analyses included parents, siblings, and spouses of the probands (the spouses were considered the reference group). In studying the relationship of stroke and hypertension, the analyses were done separately for parents, siblings, and spouses. Additional analyses were performed in which families were stratified by stroke status of the proband. Furthermore, risk of stroke was assessed in the families of the 204 white and 91 black probands separately.

The risk of stroke for the first-degree relatives and spouses of the hypertensive probands was estimated with survival analysis techniques based on a maximum likelihood approach that accounts for missing censoring information.\textsuperscript{20} The risk of stroke was estimated for hypertensives and normotensives. The log-rank test was used to test the difference in risk among hypertensives and normotensives.

**Results**

The study sample was composed of 354 hypertensive probands and their 630 parents, 797 siblings, and 239 spouses (Table 1). Mean age was higher in female parents \((P<0.0007)\) and siblings \((P=0.01)\), while in spouses men had a higher mean age \((P=0.0004)\). The frequencies of stroke were the same in men and women in all groups of relatives.

| TABLE 1. General Information of All Subjects Included in the Study |
|-----------------|-----------------|-----------------|
|                 | Male            | Female          |
| **Proband**     |                 |                 |
| Total n         | 164             | 190             | 354             |
| Hypertension (%)| 164 (100)       | 190 (100)       | 354 (100)       |
| Stroke (%)      | 10 (6.1)        | 16 (8.4)        | 26 (7.3)        |
| Age, mean±SD, y | 60.5±12.8       | 63.2±12.8       | 61.9±12.8       |
| **Parents**     |                 |                 |
| Total n         | 311             | 319             | 630             |
| Hypertension (%)| 119 (38.3)      | 196 (61.4)      | 315 (50)        |
| Stroke (%)      | 49 (15.8)       | 68 (21.3)       | 117 (18.6)      |
| Age, mean±SD, y | 69.0±14.1       | 73.6±14.7       | 71.4±14.6       |
| **Siblings**    |                 |                 |
| Total n         | 378             | 419             | 797             |
| Hypertension (%)| 174 (46)        | 205 (48.9)      | 379 (47.6)      |
| Stroke (%)      | 21 (5.6)        | 27 (6.4)        | 48 (6)          |
| Age, mean±SD, y | 57.1±15.1       | 60.1±15.2       | 58.7±15.2       |
| **Spouses**     |                 |                 |
| Total n         | 119             | 120             | 239             |
| Hypertension (%)| 39 (32.8)       | 39 (32.5)       | 78 (32.6)       |
| Stroke (%)      | 5 (4.2)         | 4 (3.3)         | 9 (3.8)         |
| Age, mean±SD, y | 64.9±11.7       | 58.8±13.1       | 61.7±12.8       |

The prevalence of stroke was at least 3 times greater among parents than in probands \((P<0.0001)\), siblings \((P<0.001)\), or spouses \((P<0.001)\). Approximately one half of the parents and siblings had hypertension, but fewer than one third of the spouses were hypertensive.

The onset of stroke in parents (67.6 years) occurred earlier than in siblings (73.5 years; \(P=0.006\)) and spouses (73.3 years; \(P=0.20\)). Hypertensive individuals had a 3-year earlier onset age of stroke than nonhypertensive individuals, but this difference was not significant.

The logistic regression model of the GEE was used to compare the age- and sex-adjusted odds of hypertension or stroke in the parents and siblings with the corresponding odds in spouses. Table 2 shows that parents and siblings had an approximately 2.5 times higher risk of being hypertensive compared with spouses \((P=0.0001)\). Adjustment for other factors did not change the estimates. Parents had a much higher risk of stroke than spouses, whereas the slightly increased risk of stroke among siblings compared with spouses was not significant. Because these families were ascertained through hypertensive probands, the possibility of increased familial incidence of stroke due to factors underlying hypertension was explored by adjustment for hypertension in the regression model that considered stroke as the outcome. Adjustment for hypertension as well as for several other covariates decreased (but not significantly) the risk of stroke in parents compared with spouses.

To explore the possibility that the higher risk seen in parents but not in siblings was due to an age cohort effect since parents are on average 10 years older than the siblings...
and spouses (reflecting the fact that most parents have been followed until death), analyses were repeated on samples stratified on the basis of an age cutoff of 65 years. For the group aged <65 years, the parents (odds ratio [OR]=13.2; 95% CI, 4.6 to 38.5) but not the siblings (OR=1.9; 95% CI, 0.7 to 5.7) had a significantly higher risk than spouses. When we adjusted for all covariates including hypertension, these effects were decreased to 8.2 (95% CI, 2.7 to 25.2) and 1.3 (95% CI, 0.4 to 4.0) for the parents and siblings, respectively. A similar trend was observed for the group aged ≥65 years, in which the parents showed an increased risk of stroke (OR=4.6; 95% CI, 1.8 to 12.0) compared with the spouses, while the siblings showed a nonsignificant but increased odds (OR=1.4; 95% CI, 0.5 to 3.8). These results were nominally changed with the adjustment of all the covariates (OR=4.0; 95% CI, 1.5 to 10.7 for the parents and OR=1.2; 95% CI, 0.4 to 3.3 for the siblings).

To study the familial aggregation of hypertension and stroke, risk of stroke was estimated for groups of parents, siblings, and spouses stratified by hypertension status. The pattern of risk for stroke differed between biological relatives and spouses. The risk of stroke among hypertensive parents and siblings was increased 5 times compared with normotensive spouses (log-rank test, P=0.0001). The risk of stroke at the maximum onset age common to both groups (80 years) was significantly higher in the hypertensives (25%) than in the normotensives (7%). There was no difference in the lifetime risk of stroke among hypertensive and normotensive spouses (log-rank test, P=0.48).

The relationship of stroke and hypertension was also studied by estimating the cumulative risk of stroke for the biological relatives and spouses of the probands stratified by hypertension status (Figure ). The cumulative risk of stroke for hypertensive first-degree relatives was consistently higher than that for nonhypertensive first degree relatives after 50 years of age, and this difference was statistically significant (log-rank test, P=0.0001). The risk of stroke at the maximum onset age common to both groups (80 years) was significantly higher in the hypertensives (25%) than in the normotensives (7%). There was no difference in the lifetime risk of stroke among hypertensive and normotensive spouses (log-rank test, P=0.48).

The prevalence of hypertension is known to differ by race. In our sample we studied the familial aggregation of stroke and its relation to hypertension separately for whites and blacks. The white subgroup was composed of 204 probands and their 366 parents, 476 siblings, and 140 spouses, while the black subgroup was composed of 91 probands and their 157 parents, 228 siblings, and 49 spouses. The risk of stroke for hypertensive relatives versus that for normotensive relatives was higher among blacks (ORwhite = 9.9; 95% CI, 1.2 to 79.1; ORblack = 15.23; 95% CI, 2.1 to 109.3) than among whites (ORwhite = 5.3; 95% CI, 2.5 to 11.1; ORblack = 3.9; 95% CI, 1.3 to 11.7). Parents of white hypertensive probands had a higher odds of stroke (but not significantly) than parents of black hypertensive probands (ORwhite = 8.3; 95% CI 3.3 to 21.0; ORblack = 4.7; 95% CI, 1.1 to 21.2), while the ORs for the siblings were similar in the 2 ethnic groups.

### Discussion

Evidence for a genetic basis of stroke is suggested by family and twin studies. In the Framingham Offspring Study, it was...
shown that a history of paternal (relative risk = 2.4) or maternal (relative risk = 1.4) transient ischemic attack or stroke was associated with the prevalence of transient ischemic attack and stroke in the offspring. This effect diminished after adjustment for age, sex, and other confounding risk factors. Graffagnino et al found that a larger percentage of patients with stroke had a family history of stroke than did age- and sex-matched control subjects. A recent Finnish study observed that a positive parental history of stroke was a predictor for the risk of stroke. Kubota et al, using a univariate analysis, showed that family history of subarachnoid hemorrhage and intracerebral hematoma was associated with an increased risk for each of these subtypes of stroke (OR = 11.24 and OR = 2.39, respectively), while family history of cerebral infarction was not a significant risk factor for developing stroke of this type. In a separate study, first-degree relatives were found to have a risk almost 7 times higher than second-degree relatives of developing subarachnoid hemorrhage. However, family history and stroke risk were unrelated in several other studies. Perhaps the most compelling evidence for a genetic risk of stroke comes from twin studies. Brass et al estimated a 17.7% concordance rate for stroke among monozygotic twins, whereas the concordance rate for dizygotic twins was only 3.6%. Although these relatively low concordance rates implicate a substantial environmental influence, the high rate in monozygotic twins relative to dizygotic twins supports the hypothesis for a major genetic contribution to the prevalence of stroke.

Our study demonstrated a higher risk of hypertension in biological relatives of hypertensive probands compared with spouses. Similarly, the higher risk of stroke in the parents and siblings (OR_{parents} = 7.3, OR_{siblings} = 1.6) compared with the spouses suggests that stroke also aggregates in these families. Coaggregation of hypertension with stroke could account for a large part for the increased familial risk of stroke. The risk of stroke in the first-degree relatives and spouses.
relatives was decreased (OR_{parents} = 5.2, OR_{siblings} = 1.2) once the effect of hypertension on stroke was accounted for, but the effect seen in the parents remained significantly higher than that seen in the spouses. Previous studies suggest that a variety of risk factors (obesity, smoking status, coronary heart disease, diabetes, and high cholesterol level) inflate the risk of stroke.\(^1\)\(^{22}\)\(^{25}\) However, adjustment for these risk factors resulted in only a small decrease in the odds of developing stroke for the first-degree relatives in our modeling studies. Thus, most of the unexplained variance in risk of stroke is likely due to unmeasured shared environmental or genetic factors.

We observed a significantly increased risk of stroke for parents but not for siblings. One explanation for this difference could be the variability in age distributions among parents, siblings, and spouses. This explanation is unlikely since the age-stratified analyses showed a similar effect within age groups. A more likely explanation is a secular trend resulting in better treatment or better prevention measures of the underlying causes of stroke for the generation encompassing most of the siblings and spouses. If we assume that susceptibility to stroke is governed by the interaction of genetic and environmental factors, removing some nongenetic risk factors would decrease the risk of stroke. Thus, the relatively recent introduction of better treatments and preventive measures for hypertension might give the appearance of a reduced risk to siblings when, in fact, parents and siblings have the same genetic predisposition to stroke.

Coaggregation of stroke and hypertension in biological relatives of the probands was higher than expected given the frequencies of the individual conditions. Hypertensive relatives had a \(>5\)-fold increased risk of stroke compared to normotensive relatives. In contrast, the risk of stroke was the same in hypertensive and normotensive spouses. One possible explanation for this is that since the spouses are close to the probands who are hypertensive, they have better knowledge of the environmental risk factors for hypertension and stroke and are thus more likely to follow certain preventive measures (ie, better diet, exercise). Alternatively, individuals with genetic susceptibility to hypertension (siblings and parents) are more likely to develop stroke than hypertensive individuals without such susceptibility (ie, spouses). A higher risk of stroke was observed for the normotensive spouses than the hypertensive spouses after the age of 75 years, suggesting that factors other than hypertension may be involved in the development of stroke. The relationship of stroke and hypertension was also observed when the risk of stroke was examined in hypertensive and nonhypertensive relatives of probands with stroke compared with relatives of probands without stroke. The observation that hypertensive relatives of probands with stroke had a \(3\)-fold higher risk of stroke than hypertensive relatives of probands without stroke suggests that some of the genetic factors for stroke and hypertension may be the same. Moreover, the results showing that the odds of stroke among hypertensives versus normotensives in blacks are higher than the corresponding odds in whites suggest that the relationship between stroke and hypertension varies across these ethnic groups.

Our study has several strengths. This is 1 of the 2 largest family studies of stroke\(^7\) and, to our knowledge, the first study that evaluated familial coaggregation of stroke and hypertension. Second, our design exploits the fact that family members tend to share certain environmental and cultural factors, although the sharing among siblings occurs primarily in early life, whereas comparisons involving spouses adjust only for exposures in adulthood. Third, we used multiple and rigorous analytical methods to account for several known risk factors that obfuscate the effects of the genetic component to stroke.

There are caveats to the interpretation of our results associated with diagnostic uncertainty and study design. First, the relatives of the probands were not examined in a manner as rigorous as that for the probands, and thus there is the possibility of misclassification. However, family history information was collected with the use of standardized procedures, including multiple informants to reduce the possibility of misclassification due to recall bias, and this approach has been shown to be highly reliable.\(^{26}\)\(^{27}\) Misclassification may be more prominent in the prior generation (ie, parents), likely resulting in the underdiagnosis of hypertension. Thus, this bias would unlikely weaken the strong correlation between stroke and hypertension in parents, ie, 87% of the parents with stroke were known to be hypertensive. Second, our study does not allow for the possibility of varying genetic risk by stroke subtype. We did not stratify our subjects for several reasons. Although stroke is a result of 2 pathological processes, ischemia (80%) and hemorrhage (20%), a number of stroke types are included in each of these categories that would be too small (in sample size) to show an effect. The reliability of information regarding causes of stroke in relatives is compromised in the case of the parents who had stroke at an age when diagnostic procedures were limited. There is also no logical way to divide the subjects since there can be multiple distinct causes of stroke within a family. Finally, despite the fact that antihypertensive medications are associated with reduced occurrence of stroke,\(^{28}\)\(^{29}\) we did not account for treatment of subjects in this study. It is difficult to obtain accurate medication history information on relatives. Even when data are available, there are no standard methods to make a meaningful adjustment given the complexity of the multiple medications prescribed to an individual simultaneously or at different times. Although we did not adjust for treatment, there is no reason to expect differences in treatment between our comparison groups (eg, siblings of patients and spouses), except for differences due to age of the subjects, which were explored above.

Our results suggest that biological relatives of hypertensive probands have a greater risk of stroke than persons in the general population, adjusted for age, sex, and hypertension. This excess risk might be due to genetic factors, which enhance susceptibility to both disorders. A portion of the genetic component of stroke may be independent of hypertension, as suggested by a residual increased risk in parents after controlling for hypertension. Coaggregation of hypertension and stroke in these relatives also suggests that genes influencing susceptibility to hypertension may also be risk factors for stroke. One such candidate is the angiotensin
1–converting enzyme gene, in which an insertion-deletion polymorphism has been associated with hypertension\textsuperscript{30,31} and stroke,\textsuperscript{22,23} although the role of angiotensin 1–converting enzyme in hypertension is controversial.\textsuperscript{14,15} Alternatively, a common genetic basis for stroke and hypertension might be affected through genes underlying the risk factors for these traits (eg, obesity, atherosclerosis, diabetes). Advancements in prevention of stroke have made the task of finding genetic factors for stroke difficult because many genetically vulnerable individuals avoid detection. Our data suggest that greater emphasis should be placed on the evaluation of loci linked to hypertension for an association with stroke.

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References


4. Alter M, Friday G, Lai SM, O’Connel J, Sobel E. Hypertension and risk factors for stroke difficult because many genetically vulnerable individuals avoid detection. Our data suggest that greater emphasis should be placed on the evaluation of loci linked to hypertension for an association with stroke.


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