A Study of Twins and Stroke

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Background and Purpose: Although there are strong genetic contributions to coronary artery disease, only a few studies have considered heritable influences on stroke.

Methods: We investigated the role of genetic factors in stroke using the Twin Registry maintained by the National Academy of Sciences-National Research Council. The registry includes 15,948 male twin pairs born between 1917 and 1927. In 1985, 9,475 twins responded to a mailed questionnaire, which covered vascular risk factors, cardiac events, and stroke.

Results: Analysis of twin pairs in which both responded to the questionnaire, and a question on stroke, indicated proband concordance rates of 17.7% for monozygotic pairs and 3.6% for dizygotic pairs (relative risk = 4.3; \(\chi^2 = 4.94, df = 1; p < 0.05\)).

Conclusions: This nearly fivefold increase in the prevalence of stroke among the monozygotic compared with the dizygotic twin pairs suggests that genetic factors are involved in the etiology of stroke. The twin study paradigm holds considerable promise for identifying both genetic and environmental influences on stroke. (Stroke 1992;23:221-223)

Genetic factors play a significant role in myocardial infarction and vascular risk factors. Aside from reported associations in small numbers of cases with Mendelian diseases, few studies have investigated the role of genetics in stroke. Most have been circumstantial, and the results conflicting.

Twin studies, comparing concordance rates between monozygotic and dizygotic twins, have long been used to estimate the heritability of a trait or disorder. These studies have been useful in understanding the heritability of complex traits such as cardiovascular risk factors, diabetes, hypertension, lipid (cholesterol and lipoprotein) disorders, obesity, personality traits, cognitive functions, and cardiac mortality. Results from these studies have paved the way for the current investigations into the molecular biology of cardiovascular disease. Twin registries continue to provide important information on the role of genetics in cardiovascular disease. As part of a preliminary investigation, we applied this technique to the study of cerebrovascular disease.

Subjects and Methods

The sample for this study was the National Academy of Science-National Research Council Twin Registry, a unique national resource. The details of the construction of this twin panel have been described. In brief, birth certificates from the years 1917-1927, for multiple white male births occurring in the continental United States, were reviewed. Approximately 108,000 birth certificates were identified. It is estimated that this represents about 93% of all such births occurring during these years. These records were crossed with the master index file of the Veterans Affairs (VA). This yielded 15,948 pairs of twins who both had served in the military, most during World War II and a minority during the Korean conflict. These 31,896 individuals constitute the initial cohort. The methods of zygosity determination have been previously described and are estimated to be correct in approximately 95% of twin pairs.

The methods of ascertainment and follow-up for the twin registry have also been described. Periodic mortality reviews are performed through the computer-based Beneficiary Identification and Records Locator Subsystem of the VA. Veterans are eligible for a burial allowance and the VA is notified of about 98% of deaths among World War II veterans by relatives or morticians claiming this allowance. Survival for veterans is slightly better compared with the US population of the same sex and age. Additional

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information on nonresponding living or deceased siblings of affected individuals can be obtained by cross-reference with the VA patient treatment file.

In the classic twin model, the difference between the within-pair variances of dizygotic and monozygotic twins is a maximum likelihood estimate of the genetic variation within dizygotic twins. There are many available formulas for estimating concordance and heritability in twin studies. Because members of the pairs were identified independently, concordance was estimated by calculating the probandwise concordance rate. In this method, the number of affected individuals is divided by the number of index cases. The significance was measured by $\chi^2$ analysis.

### Results

Approximately 8,000 of the initial cohort are dead. Of the 24,000 individuals still alive, there are approximately 9,500 twin pairs with both members alive. There were 9,475 individuals who responded to the 1985 survey (4,292 monozygotic twins, 4,664 dizygotic twins, and 519 twins of unknown zygosity). Of the complete 2,722 twin pairs, there were 1,382 monozygotic twin pairs, 1,221 dizygotic twin pairs, and 119 twin pairs of unknown zygosity. Of the 24,000 individuals still alive, there are approximately 9,500 twin pairs with both members alive. There were 9,475 individuals who responded to the 1985 survey (4,292 monozygotic twins, 4,664 dizygotic twins, and 519 twins of unknown zygosity). Of the complete 2,722 twin pairs, there were 1,382 monozygotic twin pairs, 1,221 dizygotic twin pairs, and 119 twin pairs of unknown zygosity. To the question, “Have you ever been told by a doctor that you had a stroke?” members of the twin panel responded as follows: 292 reported having been told of a stroke; 3.1% (292 of 9,315). It was the same for monozygotic twins 0.177 (14/14+65) and for dizygotic twins 0.036 (2/2+53). By $\chi^2$ analysis (comparing the number of individuals in concordant pairs to the total number of pairs), $\chi^2=4.94$ (df=1). This corresponds to a relative risk of 4.3 ($p<0.05$).

### Discussion

In the classic twin study, a comparison is made between monozygotic and dizygotic twins. If genes influence the prevalence of stroke, there should be a greater concordance rate for stroke among monozygotic twin pairs than dizygotic pairs. Several assumptions are made in applying the twin method, including the degree of environmental similarity and similarities between types of twins (dizygotic twins tend to be more frequently associated with older mothers, previous siblings, and fertility drugs; this is not true for monozygotic twinning). These issues have not had a significant impact on previous studies of cardiac risk and, similarly, are not expected to significantly influence our conclusions.

Published work with twins and cerebrovascular disease is limited to two reports. One study demonstrated a genetic influence of smoking on carotid atherosclerosis. Another study was unable to document a genetic effect on “cerebrovascular deaths,” but suffered from small numbers and poor documentation of the cause of death.

The difference between the concordance rates of stroke of monozygotic and dizygotic twins in our study suggests that there is a genetic contribution to stroke prevalence in this cohort. There were too few twin pairs with stroke to make a reliable estimation of the magnitude of heritability.

Although this study concentrated on possible genetic influences of stroke prevalence, this is only part of the possible genetic contributions to cerebrovascular disease. Animal studies suggest that genetic factors may play a role in the susceptibility to infarction during cerebral ischemia. It also seems likely that there are genetic influences on recovery after a stroke.

Heritable risk does not imply unmodifiable risk. The risk of cardiovascular disease associated with an apparently inherited predisposition appears to be profoundly affected by modifiable behavior. For example, in one study, over two thirds of the familial risk of cardiovascular mortality was due solely to the interaction of family history with smoking habit (i.e., susceptibility to cigarette smoking) and was therefore potentially avoidable.

Although biases may exist between respondents and nonrespondents in any large survey, this has been studied in a subgroup of our cohort. Minor differences did exist: respondents were slightly more obese and smoked less. The analyses used in this study should be relatively unaffected by this selection. Other major potential biases of this study design include the following: It is a survival cohort, stroke is self-reported, and information on stroke subtypes is not available. In spite of these limitations,
this preliminary investigation should be encouraging to those searching for a heritable role in stroke risk.

If a genetic risk is confirmed for stroke, early preventive measures can begin in high-risk groups as early as childhood, an approach already being applied to cardiovascular disease.31,32 Demonstration of a significant heritable risk for stroke should also prompt, and help direct, further investigation into the molecular mechanisms of the genetic influences on stroke and may identify new approaches for stroke prevention and treatment, as it has for cardiovascular research.33

As the members of this registry continue to age, their stroke risk increases dramatically. We plan to use our data to prepare for a larger, prospective investigation, before deaths in this aging population make it impossible. Our next study should provide estimates of heritability, including the heritable contribution to individual stroke risk factors and the impact of the genetic determination of vascular risk factors on the genetic determination of stroke.

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