Feasibility of an Affected Sibling Pair Study in Ischemic Stroke

Results of a 2-Center Family History Registry

James F. Meschia, MD; Robert D. Brown, Jr, MD; Thomas G. Brott, MD; John Hardy, PhD; Elizabeth J. Atkinson, MS; Peter C. O’Brien, PhD

Background and Purpose—We sought to determine pedigree availability for a concordant sibling pair study of genetic risk factors in ischemic stroke.

Methods—Probands with confirmed ischemic stroke were prospectively enrolled. Family histories were obtained by systematic interview. A study neurologist prospectively assigned stroke subtype.

Results—Of 310 probands (median age, 75 years; range, 26 to 97 years; 48% women), 75% had at least 1 living sibling; 10%, at least 1 concordant living sibling; 2%, at least 1 concordant sibling living in the same city; and 7%, at least 1 concordant living and 1 discordant living sibling. Likelihood of having a concordant sibling increased significantly with proband age, even after adjustment for sibship size (P = 0.002). Positive family history of stroke was not related to either proband stroke subtype or risk factor profile.

Conclusions—Approximately 10 probands were screened to find 1 potentially concordant living sibling. A concordant sibling pair study should be multicentered and enable enrollment of siblings from diverse geographic areas. (Stroke. 2001;32:2939-2941.)

Key Words: cerebral infarction ■ feasibility studies ■ pedigree research ■ risk factors, genetic ■ stroke classification ■ stroke, ischemic

While studies of genes related to atherosclerosis and thrombosis may help to unravel the genetics of stroke risk, linkage studies in siblings might discover chromosomal regions of interest in genes that are not obvious candidates. The sibling pair approach appears promising, but because ischemic stroke typically affects the elderly and is often fatal, this method presents logistic challenges. To test the feasibility of a sibling pair study, we established a prospective registry of patients with recent ischemic stroke.

Subjects and Methods
Patients with recent ischemic stroke treated in 2 tertiary referral institutions were eligible if they presented within 180 days after onset of symptoms. Stroke was defined by World Health Organization criteria, and ischemic stroke was confirmed with CT or MRI of the head done within 7 days after onset of symptoms.

Patients with the following conditions were excluded: iatrogenic stroke (onset within 48 hours after an invasive cerebrovascular or cardiovascular procedure), stroke due to vasospasm (onset within 60 days after nontraumatic subarachnoid hemorrhage), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, Fabry disease, homocystinuria, mitochondrial encephalopathy with lactic acidosis and strokelike episodes, sickle cell anemia, mechanical heart valve, and biopsy-proven central nervous system vasculitis. We excluded probands when genetic causes were detected because their enrollment might confound future genome scans for novel risk factors. For each proband, a study neurologist confirmed the diagnosis of ischemic stroke and assigned a Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype using available clinical, cardiac, laboratory, and radiographic data.

Proband medical histories were obtained by systematic interview and record review. Family and spouse histories were obtained by systematic interview of the proband or surrogate. Parental histories were taken only for biological parents; sibling histories were taken only for full siblings (half siblings would not be enrolled in a genome screen). Because intracerebral hemorrhage and cerebral infarction are difficult to differentiate by history alone, both were included. Probands had opportunity to contact relatives or review personal records. Siblings were defined as concordant if a history of stroke was known and discordant if no history of stroke was known.

The relationship of family history characteristics to ischemic stroke subtype was tested with χ² and pairwise comparisons. Logistic regression with and without adjustment for sibship size was used to test the relationship of proband characteristics to family history. Exact 95% CIs were calculated for frequency data.

Mayo Foundation Institutional Review Board approved the study.

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From the Department of Neurology (J.F.M., T.G.B.) and Section of Pharmacology (J.H.), Mayo Clinic, Jacksonville, Fla, and the Department of Neurology (R.D.B.) and Section of Biostatistics (E.J.A., P.C.O’B.), Mayo Clinic, Rochester, Minn.

Reprint requests to James F. Meschia, MD, Department of Neurology, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224.

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Between January 1999 and August 2000, 310 probands were enrolled (162 men, 148 women; 306 white, 4 nonwhite). Median age was 75 years (mean, 72±12 years; range, 26 to 97 years). Every effort was made to screen every stroke patient seen in the study time interval. Two patients declined to answer our survey. Table 1 shows baseline characteristics. The 310 probands had a total of 954 siblings: 195 siblings were aged within 10 years of their respective proband; 68 (62%) were aged within 5 years of their respective proband; 15 (14%) had at least 1 concordant sibling; 11 (10%) had at least 1 living concordant sibling. Of 205 probands aged >70 years, 42 (20%) had at least 1 concordant sibling; 19 (9%) had at least 1 living concordant sibling. The likelihood of having a concordant sibling increased significantly with proband age (P=0.0015), even after adjustment for sibship size (P=0.002), but there was no relationship between proband age and likelihood of having a living concordant sibling or a discordant sibling. The likelihood of having a living discordant sibling decreased significantly with proband age (P<0.001), even after adjustment for sibship size (P<0.001). Men and women were equally likely to have a concordant sibling and were equally likely to have a living discordant sibling. Proband status for diabetes, hypertension, and smoking did not influence the likelihood of having a discordant sibling or the proband's stroke subtype. The percentage of probands who had at least 1 sibling with stroke was 16% (95% CI, 8% to 26%) for probands with large-artery, 25% (95% CI, 15% to 39%) for cardioembolic, 18% (95% CI, 10% to 29%) for small-vessel, 13% (95% CI, 0.3% to 53%) for other, and 17% (95% CI, 11% to 26%) for unknown subtype (P=0.647). The percentage of probands who had a sibling or parent with stroke was 42% (95% CI, 30% to 53%) for probands with large-artery, 45% (95% CI, 32% to 59%) for cardioembolic, 48% (95% CI, 35% to 60%) for small-vessel, 38% (95% CI, 8% to 76%) for other, and 51% (95% CI, 41% to 61%) for unknown subtype.

**Discussion**

Approximately 10 probands must be screened to find 1 potentially concordant sibling pair. Screening of an even larger number would be required to enroll a verified concordant sibling pair. Not every sibling with a history of stroke would have a well-documented ischemic stroke, and some would refuse participation. Because most siblings did not live in the proband’s city, a sibling pair study in stroke should be designed so that sibling phenotype can be verified and DNA collected even if the sibling does not live near a center enrolling probands. A multicenter sibling pair collection strategy would be feasible and efficient for this purpose. A pilot test of a multicenter strategy for recruiting pedigrees with a centralized phenotype verification process was recently completed.4 Larger studies should test whether positive family history for stroke relates to proband TOAST subtype. Our study suggests that the magnitude of inherited risk might not vary by ischemic stroke subtype. However, it may be relevant to
recognize heterogeneity of phenotype because the molecular basis for inherited risk may vary. Genetic risk may act through common intermediate phenotypes such as diabetes and hypertension, but we found no relationship of risk factors to familial clustering of stroke.

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