Familial Aggregation of Ischemic Stroke in Young Women: The Stroke Prevention in Young Women Study

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Background and Purpose: Stroke occurs infrequently in young adults. While a familial basis for older onset stroke is well established, the extent of familial clustering in young-onset stroke is unknown. To address this issue, we compared the frequency of stroke in relatives of stroke cases to that in relatives of controls across different ages and by stroke subtype. **Methods:** Through a population-based case-control study of stroke, we identified 487 women aged 15–49 years with ischemic stroke and 615 women without stroke matched by age and geographic region. Family history of stroke was collected for 5,749 relatives (parents and siblings) of case and control probands by standardized interview. **Results:** Strokes were reported in 149 relatives of case patients and 119 relatives of controls. Siblings of stroke case patients had more than four times the risk of stroke compared to siblings of controls (OR, 4.17; 95% CI, 1.9–8.8) and mothers of stroke case patients had twice the risk of stroke compared to mothers of control subjects (OR, 2.02; 95% CI, 1.4–3.0). The association between stroke in probands and family history of stroke was strongest among women aged 15–24 years (OR, 2.5; 95% CI, 0.4–15.1), and diminished with increasing proband age (OR, 1.6; 95% CI, 0.8–3.3 among women 25–34 years and OR, 1.5; 95% CI, 1.1–1.9 among women 35–49 years; $P < 0.0001$ for trend). **Conclusions:** We conclude that young-onset stroke aggregates in families and that the magnitude of aggregation increases with decreasing proband age. *Genet. Epidemiol.* 30:602–608, 2006. Published 2006 Wiley-Liss, Inc.[†]

Key words: cerebral infarction; age of onset; genetics; risk factors

INTRODUCTION

Approximately 9% of adult strokes in the US occur in individuals younger than 45 years of age [Lethbridge-Çejku et al., 2004], leading to costly long-term disability or death. Family history of stroke is a risk factor for ischemic stroke [Casas et al., 2004; Flossmann et al., 2004] with strokes occurring in very old age tending to be less familial than those occurring at younger ages [Carrieri et al., 1994; Jerrard-Dunne et al., 2003; Kim et al., 2004; Liao et al., 1997; Schulz et al., 2004]. Some [Jerrard-Dunne et al., 2003; Schulz et al., 2004], but not all [Meschia et al., 2001], studies have also reported evidence that familial aggregation of stroke

may be stronger in some ischemic stroke subtypes than others.

Although strong evidence exists for familial aggregation of stroke, few studies have included substantial numbers of young-onset stroke cases (e.g., event age <50 years). Thus, while current studies have indicated a familial component to stroke in middle age and older, there are very few data addressing the familial component to stroke in young adults, including whether there is a gradient of increased familial aggregation with younger age even among young adults. Additionally, few studies have included cases from populations of non-European descent. Furthermore, prior reports that treated family history as an exposure or personal attribute of case patients may have biased risk estimates because factors such as family size and age structure were not considered in the analysis [Flossmann et al., 2004; Khoury and Flanders, 1995].

The goal of our study was to assess evidence for familial aggregation of stroke in a population-based sample of Caucasian and African-American women diagnosed with early onset stroke between the ages of 15 and 49. Our analyses addressed whether familial influences on stroke varied by age, ethnic background, or stroke subtype in this young population.

DESIGN AND METHODS

We studied case and control subjects enrolled in The Stroke Prevention in Young Women (SPYW) Study, a population-based study of ischemic stroke in young women. Case patients were recruited for SPYW-1 from 1992 to 1996 and for SPYW-2 from 2001 to 2003 from 55 acute care hospitals and four rehabilitation hospitals in the greater Baltimore-Washington area. Case patients were African-American and Caucasian women with clinical diagnosis of first non-traumatic ischemic stroke, identified by discharge surveillance and through direct referral by regional neurologists. Exclusion criteria were: (1) stroke occurring as an immediate consequence of trauma, (2) stroke within 48 h after a hospital procedure, (3) stroke within 60 days after onset of subarachnoid hemorrhage, and (4) cerebral venous thrombosis. Methods for discharge surveillance, chart abstraction, case adjudication, and assignment of probable and possible underlying causes have been described previously [Johnson et al., 1995; Kittner et al., 1996, 1998].

Control subjects were identified by random digit dialing and matched to case subjects by age group and geographic region. SPYW-1 included cases aged 15–44 years recruited within 1 year of stroke and was designed with a 1:2 case-to-control ratio. SPYW-2 included cases aged 15–49 recruited within 3 years of stroke and was designed with a 1:1 case-to-control ratio. For both study periods, additional cases were recruited after completion of control recruitment. In SPYW-1, of 450 eligible controls, 392 agreed to participate, thus the response rate based on numbers successfully screened was 87.1%. In SPYW-2, of 337 eligible controls, 225 agreed to participate, thus the response rate based on numbers successfully screened was 66.8%.

We identified 490 women with young-onset stroke. Study neurologists carefully reviewed clinical criteria of all cases and classified ischemic stroke subtype into one of the following categories: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of other undetermined etiology [Johnson et al., 1995; Kittner et al., 1998]. This classification can be applied retrospectively and is reproducible with fair to good reliability [Johnson et al., 1995]. Of 490 adjudicated cases and 617 controls, three case subjects and two control subjects with known monogenetic disorders (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) or sickle cell anemia) were excluded from the current analyses.

The overall goal of our analyses was to compare the frequency of stroke between relatives of case and control subjects. Family history of stroke was collected from case and control probands on first-degree relatives. During a standardized interview, case and control subjects were asked, "For your blood relatives, what is the present age of your mother, father, brother, or sister? If they have died, what was their age at death?" and "Of your blood relatives, did your mother, father, brother, or sister have a stroke?" Potential confounders and effect modifiers of the association between family history of stroke and ischemic stroke were also collected by proband self-report. They included proband age, ethnicity, and history of hypertension, diabetes, myocardial infarction, and current smoking status. Relative age and relation to proband (father, mother, or sibling) were also noted and analyzed.

We compared characteristics of study variables between case and control subjects to verify the

comparability of the two groups using *t*-tests for continuous variables and χ^2 tests for categorical variables. We then compared the proportion of affected relatives (parents and siblings) between case and control subjects. Reported half-siblings were excluded from these analyses. Because multiple relatives could be included from the same family, we used generalized estimating equations (GEE) [Liang and Beaty, 2000] (SAS version 8.2) [SAS Institute Inc., 1999–2001] to account for the correlations among related individuals. From the GEE models, we computed odds ratios as an estimate of the association between proband affection status (case or control) and reported presence of stroke in family members, while controlling for potential confounders (e.g., age and ethnicity). The Breslow Day test for homogeneity was used to test for ethnic group interaction, and the Cochran-Armitage test for trend was used to test for trend across age strata.

The study was approved by Institutional Review Boards at the University of Maryland, the Centers for Disease Control and Prevention, and at all participating hospitals. Each patient gave written informed consent prior to enrollment. Funding agencies had no role in the study design, data collection, data analysis, data interpretation, or writing of this report.

RESULTS

Risk factor profiles of case and control subjects are shown in Table I. Family history data were analyzed for 487 case probands and 615 control probands. Cases were significantly older on average compared to controls and were more likely to be of African-American ethnicity. Cases were also more likely than controls to report a history of hypertension, diabetes, and myocardial infarction and were more likely to be current smokers.

Large-vessel atherosclerotic strokes and small-vessel lacunar strokes made up approximately 12% of case patients each, 9% of case patients were cardioembolic strokes, and approximately 57% were of an undetermined etiology. The remaining 10% of case patients were classified with stroke of other determined etiology (including dissection, vasculitis, and a variety of hematologic causes) and were not included in stroke subtype analyses.

Stroke history was evaluated among 2,581 relatives of case probands and 3,168 relatives of control probands. Relatives of case probands were slightly older than relatives of control probands. Specifically, mothers and siblings of case probands were older than mothers and siblings of control probands, (61.9 years $\pm$11.3 compared to 60.2 years $\pm$11.2, $P = 0.0003$; and 39.3 years $\pm$11.2 compared to 36.9 years $\pm$10.4, $P < 0.0001$, respectively). There was no statistical difference in average age of fathers of case probands (60.8 years $\pm$13.4) compared to fathers of control probands (61.4 years $\pm$11.5) ($P = 0.5$).

Figure 1 shows the prevalence of stroke in relatives of case and control subjects according to relative type. History of stroke was more common among mothers of case patients compared to mothers of control subjects ($P = 0.0003$), and among siblings of case patients compared to siblings of control subjects ($P < 0.0001$). There was no significant difference between case and control subjects with regard to number ($\chi^2 = 0.77$, $P = 0.68$) or gender of siblings ($\chi^2 = 8.98$, $P = 0.25$ for male siblings and $\chi^2 = 4.04$, $P = 0.78$ for female siblings). No difference in history of stroke was observed between fathers of case probands compared with fathers of control probands ($P = 0.82$). Results were unchanged when we adjusted for age and gender of relatives.

Unadjusted and adjusted odds ratios for family history of stroke and family history of stroke stratified by proband age, relative relation to proband, and stroke subtypes are shown in Table II. A history of stroke was reported for 149 case relatives (5.7%) and 119 control relatives (3.7%) (OR, 1.56; 95% CI, 1.22–2.00). A significant trend showing a stronger familial aggregation with younger stroke onset was observed across 10-year age bands ($P < 0.0001$ for Cochran-Armitage test for trend). This trend toward stronger familial aggregation of stroke among women with younger stroke onset remained after controlling for other risk factors. When stratified by relative type, familial aggregation of stroke was strongest among mothers and siblings of cases
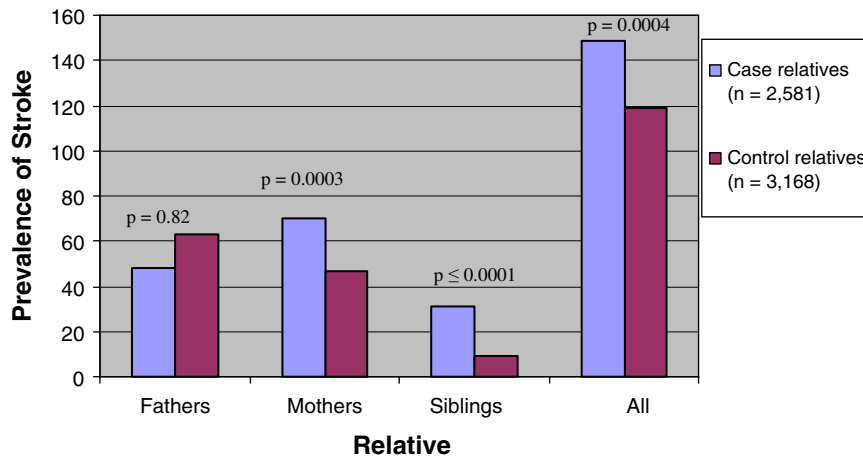
TABLE I. Prevalence of risk factors in case and control probands

	Cases ($n = 487$)	Controls ($n = 615$)	*P* value
Age	39.1+7.6	36.8+7.9	<0.0001
African-American	225 (46%)	231 (38%)	0.002
Hypertension	173 (36%)	84 (14%)	<0.0001
Diabetes	72 (15%)	23 (4%)	<0.0001
Myocardial infarction	23 (5%)	1 (0.01%)	<0.0001
Smoking	332 (68%)	292 (48%)	<0.0001

Fig. 1. Stroke history among proband relatives.

TABLE II. Effect of a family history of stroke stratified by case and control proband risk factors (odds ratio and 95% confidence interval)

	Number of case/ control relatives with stroke	Proportion of stroke in relatives of cases	Proportion of stroke in relatives of controls	OR (95% CI) unadjusted	OR (95% CI) adjusted[a]
All subjects	149/119	0.057	0.037	1.56 (1.22–2.00)	1.19 (0.88–1.61)
Age of proband					
Age 15–24	3/2	0.020	0.008	2.53 (0.43–14.9)	1.83 (0.18–18.5)[b]
Age 25–34	16/15	0.036	0.023	1.63 (0.83–3.23)	1.55 (0.73–3.30)
Age 35–49	130/102	0.065	0.045	1.47 (1.12–1.93)	1.13 (0.81–1.57)
Relation to proband					
Paternal	48/63	0.098	0.102	0.96 (0.64–1.42)	0.66 (0.39–1.12)
Maternal	70/47	0.143	0.076	2.02 (1.37–2.99)	1.67 (1.05–2.66)
Sibling	31/9	0.019	0.005	4.17 (1.97–8.80)	2.84 (1.20–6.68)
Stroke subtype					
LV	19/119	0.052	0.037	1.42 (0.79–2.57)	1.11 (0.56–2.19)
SV	22/119	0.070	0.037	1.95 (1.29–2.95)	0.83 (0.46–1.51)
CE	20/119	0.078	0.037	2.18 (1.34–3.55)	2.31 (1.29–1.53)
UN	79/119	0.059	0.037	1.50 (1.11–2.03)	1.04 (0.73–1.50)

[a]Adjusted for age, race, smoking, myocardial infarction, and relative age;
[b]Adjusted for age, race, and relative age.
LV, large-vessel; SV, small vessel; CE, cardioembolic; UN, undetermined etiology.

compared with mothers and siblings of controls. Cases were significantly more likely than controls to have a maternal history of stroke (adjusted OR = 2.02, 95% CI, 1.37–2.99), and a sibling history of stroke (adjusted OR = 4.17, 95% CI, 1.97–8.80). Although attenuated, these associations remained significant after controlling for other risk factors. There was no increased risk of stroke observed among fathers of case probands compared with fathers of control probands.

Univariate analyses showed increased risk for family history of stroke among relatives of probands with small-vessel disease (OR, 1.95; 95% CI, 1.29–2.95), cardioembolic stroke (OR, 2.18; 95% CI, 1.34–3.55), and stroke of undetermined etiology (OR, 1.50; 95% CI, 1.11–2.03), compared with relatives of control subjects. After adjustment for risk factors, the relation between cardioembolic stroke and family history of stroke increased slightly and remained significant, (OR, 2.31; 95% CI, 1.29–1.53), whereas the risks for family history of stroke associated with small-vessel disease and stroke of undetermined etiology were attenuated.

To evaluate differences in familial influence on stroke across ethnic groups, we compared the proportion of case relatives with a history of stroke to the proportion of control relatives with

a history of stroke, stratified by ethnicity. The risk of stroke observed in relatives of African-American case probands was 50% greater compared with relatives of African-American control probands (OR, 1.50; 95% CI, 1.05–2.15), and the risk of stroke in relatives of Caucasian case probands was 46% greater compared with relatives of Caucasian control probands (OR, 1.46; 95% CI, 1.00–2.14). There was no difference in stroke risk observed between relatives of African-American probands and relatives of Caucasian probands ($\chi^2 = 0.01$, $P = 0.9$), and race did not appear to confound the association between proband status and family history of stroke.

DISCUSSION

In this family history study of young African-American and Caucasian women, we detected significant evidence for familial aggregation of stroke. Subgroup analyses of age, relative type, and stroke subtype indicated that (1) the younger the onset of stroke, the stronger the familial aggregation was, (2) proband case status was a strong predictor of maternal and sibling stroke history; no association was observed between proband case status and paternal stroke history, (3) proband stroke subtypes including small-vessel stroke, cardioembolic, and undetermined etiologies were associated with familial aggregation of stroke, and (4) family history of stroke was stronger for cardioembolic stroke than for other stroke subtypes. No association between large-vessel stroke and familial history of stroke was observed. Race was not a significant confounder or effect modifier of the association between case proband status and family history of stroke in our study, suggesting that genetic and/or other familial influences have a homogenous effect in African-American and Caucasian women.

We found a significant trend between younger age and stronger familial aggregation of stroke among very young-onset stroke patients and control subjects (between 15 and 49 years of age). Given the young age range of our study population, it is unlikely that the observed trend was due to better recall in younger age groups compared with older age groups. This finding is consistent with that reported by Schulz et al. of a stronger familial aggregation of stroke associated with younger age groups across 10-year age bands. However, the youngest age group in that analysis included subjects aged 60 or younger

[Schulz et al., 2004]. To our knowledge, no prior study has examined the effect of age on familial aggregation of stroke risk within the young adult age range. Our data support the suggestion that future candidate gene studies of ischemic stroke may increase study efficiency by focusing on young-onset stroke patients, a group in which genetic susceptibility may present an increased risk relative to traditional environmental risk factors.

We observed a strong association between case proband status and histories of maternal and sibling stroke that was not present between case proband status and history of paternal stroke. This result should be interpreted cautiously. Although it could reflect a parent-of-origin effect, it is also likely that it is an artifact of differential knowledge of parental stroke history, as has been suggested elsewhere [Mitchell et al., 1995]. Our results regarding differences in stroke risk associated with relative type contrast with those reported by Jerrard-Dunne et al., which indicated no difference in the risk of stroke conferred by maternal, paternal, or sibling history of stroke among those aged 65 years or younger. Differences in study populations including age, sex, and ethnic background may have contributed to our differing findings.

Family history of stroke was associated with all stroke subtypes except large-vessel stroke in unadjusted analyses. After controlling for potential confounders, risk for family history of stroke remained elevated among relatives of case probands with cardioembolic stroke compared with relatives of control probands. Our results differ from previous reports on the relation of family history of stroke and stroke subtype. Meschia et al. [2001] found no association and Jerrard-Dunne et al. [2003] reported significant associations between small- and large-vessel stroke and family history of stroke among those aged 65 and younger. Shulz et al. [2004] reported a trend towards higher frequency of family history of stroke in patients younger than 60 for large- and small-vessel, cardioembolic, and undetermined subtypes, while their meta-analysis concluded that family history of stroke was least frequent for cardioembolic subtypes and equally frequent for others. Reasons for the differing results from stroke subtype analyses may be the variation between studies in the age and sex of subjects. Second, our power to detect associations for particular stroke subtypes was limited due to small sample sizes.

Strengths of this study are threefold. Our study population included both Caucasian and African-American women. Few studies have examined familial aggregation of stroke risk among African-Americans. Our study population consisted of young adults. Prior work with mainly older populations suggested that family history of stroke is a stronger risk factor for younger-onset strokes [Carrieri et al., 1994; Jerrard-Dunne et al., 2003; Kim et al., 2004; Liao et al., 1997; Schulz et al., 2004] but had not examined the effect of age within the young adult age range. Finally, we used a family case-control design [Liang and Beaty, 2000] for our analyses rather than a traditional case-control design since family history is not a personal attribute of case and control subjects, but rather it involves many factors including family size and the age of relatives. We were able to control for these factors in our statistical models. These methods should have resulted in more control of unmeasured confounding and more precise effect estimates than in earlier studies of family history of stroke [Flossmann et al., 2004; Khoury and Flanders, 1995].

Limitations of our study include the potential for recall bias between case and control subjects. It is possible that case patients more accurately recalled history of stroke in their family than control subjects due to the experience of their own stroke event. It is also possible that we did not interview the best family informant, potentially resulting in imprecise information on age or stroke history of family members. We do note, however, that one validation study of family history of stroke in men and women between 45 and 64 years of age reported a strong correlation between proband-reported family history of stroke and self-reported personal history of stroke in the relatives. Overall kappa statistics for the agreement of proband-reported family history and the self-reported personal history of stroke in members of the proband's family were 0.77 for proband-reported father's history versus father's self-reported history of stroke; 0.76 for proband-reported mother's history versus mother's self-reported history, and 0.69 for proband-reported sibling's history versus sibling-reported history of stroke [Liao et al., 1997]. This study also reported no difference in patterns of associations when proband-reported family history was used versus self-reported family history. Therefore, we believe that the affect of bias due to misclassification of family history of stroke on our study results and conclusions may be minimal. A second limitation of our study is that we were not able to adjust for the risk-factor status of family members, although we did control for family size, age structure, and the risk-factor status of case and control subjects. Finally, our power was limited for age-stratified and stroke subtype analyses. This likely resulted in failure to detect significant associations, where present, and conservative risk estimates.

In summary, our data provide evidence of an increased risk of a family history of stroke among the relatives of case probands compared to control probands, particularly for young-onset strokes and for women with maternal or sibling stroke history. Our findings support previous recommendations that genetic studies investigating stroke risk may be most efficiently conducted among younger age groups.

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