Familial Risk of Ischemic and Hemorrhagic Stroke
A Large-Scale Study of the Swedish Population

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Background and Purpose—Previous studies of familial risks have often combined ischemic and hemorrhagic stroke even though it seems unlikely that these 2 very different pathological conditions are under the same genetic influence. This study is the first to investigate the concordant (same subtype) and discordant (different subtype) association between ischemic and hemorrhagic stroke.

Methods—Data of first hospitalization for stroke were obtained from the Hospital Discharge Register during the study period 1987 to 2001. All individuals born in Sweden from 1932 onwards were included and linked to their siblings. Risks were calculated as standardized incidence ratios and compared with individuals without affected siblings. Results were standardized for age, gender, geographical region and socioeconomic status.

Results—Ischemic stroke (n=25 630) was associated only with ischemic stroke (n=7961), which was also the case for hemorrhagic stroke. The statistically significant standardized incidence ratios were 2.14 (95% CI, 1.21 to 3.74) and 1.82 (95% CI, 1.21 to 2.75), respectively. For discordant subtypes of stroke no significant associations were found.

Conclusions—The results suggest that ischemic and hemorrhagic stroke are not under the same genetic influence. However, further studies of the human genome are needed in order to identify the specific genes that play roles in the pathogenesis of common subtypes of stroke. (Stroke. 2006;37:1668-1673.)

Key Words: cerebral ischemia ■ families ■ stroke ■ Sweden

The general aim of this study was to investigate the familial risk for the 2 most common subtypes of stroke, ie, ischemic and hemorrhagic stroke. Stroke is a major cause of death and disability in western countries, leading to considerable suffering for the afflicted individuals and their relatives. Moreover, the financial burden of stroke on society is high, including both direct and indirect costs for stroke care.1

Several studies suggest a familial aggregation of stroke2–7 although a few studies have not detected any familial risk of stroke.8,9 Familial aggregation of certain diseases can be caused by genetic factors, a shared environment or the complex interplay between genetic and environmental factors. Environmental factors include, for example, shared smoking habits among family members. Other risk factors for stroke are hypertension, hyperlipidemia and diabetes, which are caused by both genetic and environmental factors.

Previous studies of familial risks have often combined ischemic and hemorrhagic stroke2 or failed to ascertain the exact subtype of ischemic stroke.10 A recent genome scan with 476 stroke patients clustered into 179 families found a significant linkage to the region of 5q12, suggesting that there is a general stroke-susceptibility gene.11 However, no consistent candidate genes have been identified in the different subtypes of stroke. Further studies of the human genome are needed in order to identify the specific genes that play roles in the pathogenesis of the 2 most common subtypes of stroke. It seems unlikely that ischemic and hemorrhagic stroke, 2 very different pathological conditions, are under the same genetic influence. Ischemic stroke is caused by obstruction of extra- or intracranial blood vessels, whereas hemorrhagic stroke is caused by rupture of intracranial blood vessels. In order to properly target molecular genetic studies, it is important to start by investigating the genetic epidemiology of the most common subtypes of stroke.

The creation of large population-based patient registers has allowed rapid development of genetic epidemiology during the last decade.12,13 However, to our knowledge, no previous large-scale population-based study has investigated the concordant (same subtype) and discordant (different subtype) association between ischemic and hemorrhagic stroke. The present study included hospital data of all individuals in Sweden born from 1932 onwards linked to their siblings, ie, in total 6.9 million individuals. The use of hospital register data eliminated potential recall bias, which is a problem when conducting case-control studies of familial risk because...
patients with manifest stroke are prone to report a positive family history.14

The first aim of this study was to examine the possible association between the 2 subtypes of stroke in concordant and discordant pairs of siblings. The second aim was to examine whether this possible association remained after adjustment for the environmental factors geographical region and occupation. In addition, these associations were also examined among spouses.

Materials and Methods

The research database used for this study is a subset of the national MigMed database at Karolinska Institute, Center for Family and Community Medicine. The MigMed database was compiled using data from several national Swedish registers provided by Statistics Sweden, including the Multigeneration Register in which persons (second generation) born in Sweden in 1932 or thereafter are registered shortly after birth and are linked to their parents (first generation). Sibships in the second generation, which was the present study population, was determined by linkages to the biological parents. National Census Data (1960–1990) and the Swedish population register (1990–2001) were incorporated into the database to obtain information on individuals’ occupation. Only 0.2% of all individuals were excluded because of missing data on occupation.

Dates of hospitalization for stroke were obtained during the study period from the Swedish Hospital Discharge Register. Since 1986, complete data on all discharges, with dates of hospitalization and diagnoses, have been recorded in this register. All patients registered for hospitalization stayed at least 1 night in the hospital, usually in wards with specialist consultation or neurology departments; the Register does not include outpatients in hospitals or healthcare centers. Diagnoses were reported according to the 9th (1987–1996) and 10th (1997–2001) version of the International Classification of Diseases (ICD). All linkages were performed using the national 10-digit civic identification number that is assigned to each person in Sweden for his or her lifetime. This number was replaced by a serial number for each person in order to provide anonymity and to check that each individual was only entered once, for his or her first hospitalization for stroke. Over 6.9 million individuals were included in the second generation of the research database.

Individual Variables

Gender: men and women. Age at diagnosis was categorized as follows: <50, 50 to 59, 60 to 69 years. Socioeconomic status for the men and women was divided into 6 groups according to occupation: (1) farmers, (2) unskilled/skilled workers, (3) white-collar workers, (4) professionals, (5) self-employed and (6) all others. Region was divided into 3 groups: (1) large cities, (2) southern Sweden and (3) northern Sweden.

Outcome Variable

The 2 subtypes of stroke were based on the 9th and 10th versions of the ICD (ICD-9 and ICD-10): (1) hemorrhagic stroke (ICD 9: 431, 432 and ICD 10: I61, I62) and (2) ischemic stroke (ICD 9: 433, 434, 435, 437.0 437.1 and ICD 10: I63, I65, I66, I67.2, I67.8). Only the first hospitalization for both fatal and nonfatal stroke was included during the study period.

Statistical Analysis

Person-years were calculated from start of follow-up on January 1, 1987 until hospitalization for the first stroke event, death, emigration, or closing date, December 31, 2001. Age-specific incidence rates were calculated for the whole follow-up period, divided into eight 5-year periods. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected number of cases. The expected number of cases was based on the observed number of cases in the reference category. The expected number of cases was calculated for age (5-year groups), sex, period (5-year groups), region and occupation-specific standard incidence rates. Sibling risks were calculated for individuals with siblings affected with hemorrhagic or ischemic stroke compared with individuals whose siblings were not affected by these conditions, using the cohort methods as described.13 For each subcategory, the reference group consisted of the corresponding subcategory whose siblings were not affected by hemorrhagic and ischemic stroke. In rare families where >2 siblings were affected, each was counted as an individual patient. Confidence intervals (95% CI) were calculated assuming a Poisson distribution, and they were adjusted for dependence between the sibling pairs.13

Ethics

This study was approved by the Ethics Committee at Karolinska Institute, Stockholm.

Results

Table 1 shows number of cases and hospitalization rates for stroke in the study population, by sex. There were 21 814 cases among the men and 11 777 cases among the women. Hemorrhagic stroke constituted 23.7% of all cases and ischemic stroke constituted 76.3% of all cases (data not shown). The mean age at diagnosis did not differ between the sexes. The hospitalization rates for stroke appeared to be considerably higher among those with a sibling history than in the general population.

Figure 1 shows age-specific rates of stroke, by subtype and sex. Among both men and women the rates increased with age for both ischemic and hemorrhagic stroke. Figure 2 shows age-specific rates of stroke, by subtype, sex, and sibling history. Among those with a sibling history of ischemic or hemorrhagic stroke the rates (by subtype of stroke) seemed to be higher than among those without a sibling history of ischemic or hemorrhagic stroke.

Table 2 shows SIRs for familial risk for the 2 subtypes of stroke, adjusted for geographic region and occupation. The overall risk for all types was 1.67 (95% CI, 1.12 to 2.49). For concordant, ie, the same subtype of stroke, there was a significant positive association between siblings. Hemorrhagic stroke only associated with hemorrhagic stroke, which

| TABLE 1. No. of Cases and Incidence Rates of Stroke in the 0–69 Years Population |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | Hemorrhagic Stroke | Ischemic Stroke |
| Characteristics                | Men              | Women           | Men              | Women           |
| No. of cases                   | 5186             | 2775            | 16 628           | 9002            |
| Mean age, y                    | 49.75±13.27      | 48.56±14.22     | 53.91±9.59       | 52.61±11.02     |
| Median age, y                  | 53               | 52              | 55               | 55              |
| Incidence rate per 100 000 person-years, total | 18.71            | 9.72            | 69.28            | 37.11           |
| Incidence rate per 100 000 person-years with sibling history | 26.47            | 15.54           | 105.74           | 64.39           |
also was the case for ischemic stroke. For example, if 1 sibling was affected by hemorrhagic stroke, the SIR of hemorrhagic stroke for the other sibling was 2.14 (95% CI, 1.21 to 3.74). The corresponding SIR for ischemic stroke was 1.82 (95% CI, 1.21 to 2.75). For discordant subtypes of stroke no significant associations were found.

Table 3 shows SIRs for the 2 subtypes of stroke among spouses. There were some small and significant associations for stroke between spouses; the significant SIRs varied between 1.03 and 1.07.

**Discussion**

The main findings of this study were that for concordant stroke, ie, the same subtype of stroke, there was a significant positive association between siblings. Hemorrhagic stroke was associated only with hemorrhagic stroke, which was also the case for ischemic stroke. The relative risks were 2.14 and 1.82, respectively. For discordant subtypes of stroke no significant associations were found. For spouses the association between the 2 subtypes of stroke was weak, ranging between 1.03 and 1.07.

The strong association of stroke between siblings compared with the rather weak association of stroke between spouses suggests that genetic factors might be stronger predictors of stroke than environmental factors. A recent systematic review of the genetic epidemiology of stroke found a small genetic contribution to stroke in twin studies. However, the authors concluded that “reliable interpretation of published family history studies is undermined by major heterogeneity, insufficient detail and potential publication and reporting bias”. Reporting bias or recall bias is often present in case-control studies, which constituted 62% of the studies in the systematic review. In addition, many previous studies did not differentiate between ischemic and hemorrhagic stroke. To our knowledge, this is the first large-scale study that has investigated the concordant and discordant
association of the 2 most common subtypes of stroke, ie, ischemic and hemorrhagic stroke.

The results of our study suggest that ischemic and hemorrhagic stroke do not share the same genetic influence, which contradicts findings from a recent genome-scan from Iceland that suggested that there is a general stroke-susceptibility gene.11 Several rare conditions inherited in a Mendelian pattern are known to be associated with stroke.17 A few specific genes responsible for some of these rare conditions have been identified. For example, a mutation in the \textit{NOTCH3} gene causes cerebral autosomal dominant arteriopathy, which leads to lacunar infarction and vascular dementia.18

However, these conditions only account for a very small proportion of all stroke cases in the population. Ischemic and hemorrhagic stroke are the subtypes of stroke that cause the vast majority of all stroke cases. In addition, a recent study found an increasing stroke incidence between 1989 and 2000 among persons aged 30 to 65 years.19 This calls for further investigations of the etiology and pathogenesis of this common and disabling disease.

**Limitations and Strengths**

There are several limitations with the present study. The Swedish Hospital Discharge Register has complete data only since 1987. Thus, the present study covered a time period of no longer than 15 years, which implied that pedigrees would not be very informative. Another limitation is that the diagnostic accuracy could have varied between geographic regions. It is also possible that selective hospitalization bias exists between regions. However, we adjusted the analyses for geographic region in order to minimize this possible bias. Cardiovascular risk factors may also cause familial aggregation of a stroke. Unfortunately, our data did not include risk factors. As a compromise, we adjusted for socioeconomic status (occupation) in the models. Occupation and other measures of socioeconomic status have been shown to be strong predictors of many cardiovascular risk factors.20 How-
ever, this parameter does not take into account the possible genetic role of pathological conditions such as hypertension and diabetes. Another potential limitation is that only data on hospital admissions were included in the analysis; data on outpatients were not available. This should not constitute a severe bias because in Sweden most patients with acute stroke are treated at hospitals. Finally, we did not divide stroke any further than into the 2 largest groups, ischemic and hemorrhagic stroke. However, attempts to focus on subtypes of ischemic stroke are not without limitations. Existing classification systems need extensive work, and as many as 47% of subjects cannot be classified.17

The limitations of this study are balanced by its strengths. An important strength of this nationwide, register-based study is that the results are not affected by recall bias because both the probands and cases are medically diagnosed. For example, systematic differences between case-control and register-based studies have been repeatedly observed in studies of familial cancer: case-control studies tend to exaggerate risks.21 Similar exaggeration of risks in case-control studies has been reported for stroke.14 The unique Swedish population registers are highly complete with very few missing data. For example, data about occupational status were 99.2% complete. In 2001, the main diagnosis was missing in 0.9% and the national civic registration number in 0.4% of hospitalizations.22 Finally, even though the design of this study does not allow a disentanglement of causal mechanisms behind the familial aggregation of stroke, the findings of a positive association between concordant subtypes of stroke, but not discordant, is of interest for future studies in molecular biology and genetic epidemiology.

**Summary**

The findings that ischemic stroke was associated only with ischemic stroke, which also was the case for hemorrhagic stroke, suggest that these 2 very different pathological conditions are not under the same genetic influence. In addition, the strong association of stroke between siblings compared with the rather weak association of stroke between spouses suggests that genetic factors might be stronger predictors of stroke than environmental factors. However, further studies of the human genome are needed in order to identify the specific genes that play roles in the pathogenesis of the most common subtypes of stroke affecting a large number of people in the ageing western populations.

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Disclosures

None.

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