Family History in Young Patients With Stroke

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Background and Purpose—Family history of stroke is an established risk factor for stroke. We evaluated whether family history of stroke predisposed to certain stroke subtypes and whether it differed by sex in young patients with stroke.

Methods—We used data from the Stroke in Fabry Patients study, a large prospective, hospital-based, screening study for Fabry disease in young patients (aged <55 years) with stroke in whom cardiovascular risk factors and family history of stroke were obtained and detailed stroke subtyping was performed.

Results—A family history of stroke was present in 1578 of 4232 transient ischemic attack and ischemic stroke patients (37.3%). Female patients more often had a history of stroke in the maternal lineage (P=0.027) than in the paternal lineage. There was no association with stroke subtype according to Trial of Org 10172 in Acute Stroke Treatment nor with the presence of white matter disease on brain imaging. Patients with dissection less frequently reported a family history of stroke (30.4% versus 36.3%; P=0.018). Patients with a parental history of stroke more commonly had siblings with stroke (3.6% versus 2.6%; P=0.047).

Conclusions—Although present in about a third of patients, a family history of stroke is not specifically related to stroke pathogenic subtypes in patients with young stroke. Young women with stroke more often report stroke in the maternal lineage.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00414583.

A family history of stroke (FHS) predicts a higher incidence of subsequent stroke in family members.1 FHS may vary by stroke pathogenic subtype.2 Women more likely report a maternal history of stroke.3

We set out to study FHS in a large cohort of young patients with stroke enrolled in a prospective, multicenter European screening program for Fabry disease.4 We tested whether FHS was more frequent in patients with different pathogenic subtypes and with the presence of a patent foramen ovale, cervical artery dissection, or white matter disease. We also tested whether stroke in parental lineages (SIP) was associated with a higher probability of stroke in siblings or children.
Methods

The details and methods of the Stroke in Fabry Patients (SIFAP; NCT004414583) study have been described previously (Methods in the online-only Data Supplement). FHS is defined here as stroke occurring in parental or maternal lineages or stroke occurring in sibs or children of the probands. SIP is defined as stroke occurring in the paternal or maternal lineages.

Stroke Subtyping, Quality Assurance, and White Matter Hyperintensities

Investigators at each site classified the pathogenesis of stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.

White matter disease was rated without the knowledge of clinical characteristics of study participants by 1 of 3 experienced raters. The inter-rater reliability was tested on a random sample of 99 scans. The intra-rater reliability for white matter hypersensitivity scores was determined by computing a 2-way, mixed-model, intraclass correlation coefficient with measures of consistency. The intraclass correlation coefficient was >0.67 for white matter hypersensitivity scores.

Statistical Analysis

Statistical models were built using multiple random effects logistic regression analysis with the factors that were significant in bivariate analysis as fixed factors and center as a random effect to account for center heterogeneity. The following variables were tested in bivariate analysis: age, sex, hypertension, diabetes mellitus, hyperlipidemia, current smoking, history of stroke or transient ischemic attack, history of myocardial infarction and coronary artery disease, atrial fibrillation, peripheral artery occlusive disease, body height, weight, and lifetime history of migraine or migraine in the past 12 months.

In the final model (model 2) only significant covariates from the first model were included and the analysis was adjusted for age and sex. Two tailed *P* values of <0.05 were considered significant. All statistical tests were performed with IBM SPSS version 22 and STATA/IC 12.1.

Results

FHS and Relationship With Sex

FHS was reported in 37.3% (95% confidence interval [CI], 35.8%-38.8%) of patients (1578/4232). SIP was reported by 35.5% (95% CI, 34.0%-37.0%) of patients (1501/4232).5

Of those with FHS, 697 (50.3%) reported a history of stroke in the maternal lineage and 688 (49.7%) in the paternal lineage (*P*=0.830). Female probands with FHS more often had a FHS in the maternal lineage (54.6%; 95% CI, 50.5%-58.7%) than in the paternal lineage (45.4%; 95% CI, 41.3%-49.5%; *P*=0.027). By contrast, male probands with FHS had a nonsignificantly higher rate of stroke in the paternal lineage (52.9%) than in the maternal lineage (47.1%; *P*=0.109).

Risk Factors for SIP

Table I in the online-only Data Supplement (Results in the online-only Data Supplement) details the characteristics of patients reporting SIP. Factors that were significant in bivariate analyses were included in multiple analysis. Age, female sex, hyperlipidemia, and migraine were independently associated with SIP (Table).

Association of SIP With White Matter Disease, Patent Foramen Ovale, Dissection and TOAST

There was no significant association between parental or sibling history of stroke and the presence of higher degrees of white matter disease and with the presence of a patent foramen ovale (Results in the online-only Data Supplement).

There was no significant difference in the frequency of SIP according to TOAST categories (Figure; *P*=0.188 overall; *P*=0.431 for transient ischemic attack; *P*=0.369 for ischemic stroke). Dissection patients (n=442) less often reported SIP (30.4%; 95% CI, 26.0%-34.8%) versus 36.3%; 95% CI, 31.7%-40.9%; *P*=0.018).

SIP and Risk of Stroke in Siblings and Children

In patients with SIP, the risk of having a sib with stroke was 56 of 1482 (3.8%) versus 71 of 2701 (2.6%, *P*=0.047). In patients with SIP, the risk of having a child with stroke was 4 of 1482 (0.3%), compared with 6 of 2701 (0.2%; *P*=0.750).

Discussion

FHS and SIP were surprisingly common, especially in women, as found in earlier studies, and the frequency of SIP did not differ by stroke subtype.8 Previous studies have investigated FHS in subtypes and found associations with small vessel disease and large vessel disease, but have not investigated young patients with magnetic resonance imaging.7 Magnetic resonance imaging may permit more accurate stroke subtyping than computed tomography and leads to a decreased diagnosis of small vessel disease. This together with the age difference may explain why we did not find a difference in TOAST stroke subtypes. In young patients with stroke, additional pathogeneses are also responsible beyond the ones of the older population. We cannot exclude that family history plays a role in the TOAST category of other determined strokes as we had insufficient power to detect a familial contribution of the different individual diseases collapsed in this category.

Cervical artery dissection patients were the only group with a lower frequency of FHS. A low rate of FHS and familial dissection has been observed previously.8,9 A traumatic cause, possibly together with a predisposing anatomy or connective tissue disease may be relatively more important in provoking...
dissection than genetic background, despite the recent finding of a polymorphism that is associated with dissection.\textsuperscript{11}

We confirm a maternal excess of stroke in female probands and extend this finding to a young stroke population.\textsuperscript{2,6} Our data may underestimate the true effect of female-to-female transmission. The female: male ratio of affected relatives is lower in a study of young probands. Many parents of these patients are still alive and have not had their stroke yet. This effect is more pronounced in women, as in the general population, women tend to have their stroke on average a few years later.

We found familial aggregation of stroke with a slightly higher than expected prevalence of stroke in siblings of patients who had SIP, after exclusion of Mendelian disorders.\textsuperscript{6} In the Oxford Vascular Study, familial clustering of stroke was not present, but the average age of the included patients was 70 years.

The strengths of this prospective multicenter study include the large sample size, the systematic and uniform collection of data, and the focus on a young stroke cohort.

Our study has several limitations. We did not investigate family members directly and did not record important variables such as age of family members, their vascular risk factors, or the family size. We only have information about whether the stroke occurred in the paternal or maternal line but not whether the strokes occurred in the first-degree paternal line or maternal line. In addition, we were not able to differentiate between migraine types. Also, we do not have a control group of healthy nonstroke patients. A case–case approach however reduces recall bias. Previous studies on FHS that combined population-based data and hospital-based studies did not show heterogeneity however.\textsuperscript{1}

In conclusion, although about one third of patients report FHS, the presence of FHS is not related to a particular stroke subtype in young patients with stroke. Young women with stroke more commonly have FHS, occurring with preference in their mothers.

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**Disclosures**

Dr Thijs serves on scientific advisory boards for Bayer, Boehringer Ingelheim, and Pfizer; serves on the editorial boards of *Stroke, European Journal of Emergency Medicine* and *Acta Neurologica Belgica*; and has received speaker honoraria and support from Bayer, Boehringer Ingelheim, Pfizer, Sygnis, and Daichi Sankyo. All fees and honoraria were paid to his employer. Dr Enzinger has received travel grants and speaker honoraria from Biogen-Idec, Teva-Aventis, Merck-Serono, Novartis, Bayer-Schering, and Genzyme—a sanofi company; has served as consultant for Biogen-Idec, Bayer-Schering, Genzyme—a sanofi company, and Novartis; and has received unrestricted research grants from Teva-Aventis, Biogen-Idec, and Merck-Serono. Dr Fazekas serves on scientific advisory boards for Biogen-Idec, Bayer-Schering, Merck Serono, Pfizer, Novartis, Perceptive Informatics, and Teva Pharmaceutical Industries Ltd; serves on the editorial boards of *Cerebrovascular Diseases, Multiple Sclerosis, the Polish Journal of Neurology and Neurosurgery, Stroke,* and the *Swiss Archives of Neurology and Psychiatry,* and has received speaker honoraria and support from Biogen Idec, Bayer.
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References
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Supplemental Methods

This was a prospective European multicenter observational study of young adults (<55 years) with an acute stroke or TIA. The study was conducted in 47 centers across 15 European countries. All patients underwent a thorough evaluation with brain magnetic resonance imaging and vascular imaging, extensive laboratory testing according to the local laboratory routine, cardiac ultrasound examination, and ECG. Data on comorbidities and vascular risk factors were collected in a standardized prespecified case report form from medical records or where self-reported from the patient. In the case of missing or inconsistent information from the patients’ history for diabetes mellitus and arterial hypertension, the presence of a risk factor was based on the use of current medication. In SIFAP a family history of stroke and coronary artery disease was recorded in the paternal line, the maternal line and in siblings or children of included patients. If the patient could not provide the family history information, family members were contacted, and, if not available, the GP.

Ethics

All patients or their legal representatives provided written informed consent. All local ethical committees approved the study.

Classification of Qualifying Events

Transient ischemic attack (TIA) was defined as a cerebrovascular event with clinical symptoms lasting <24 hours; patients with stroke were classified as ischemic stroke or primary intracerebral hemorrhage based on imaging results.

Ancillary tests were performed, if deemed necessary by the individual study centers on a case-by-case basis. In order to perform quality assurance, the results of the TOAST classification were crosschecked against findings from patients’ history, ultrasound, and MRI. In the case of predefined inconsistencies that could not be clarified by queries, TOAST criteria were assigned missing values. The TOAST classification was also used for estimating underlying etiology in TIA patients; in these patients, the definition of the size of the lesion was not taken into account. The ASCO classification was performed post-hoc by an automated algorithm that took into account the different comorbidities and findings from ancillary tests. White matter hyperintensities (WMH) were defined as lesions with high signal intensity on T2-weighted brain images in the absence of evidence for complete tissue destruction and were rated as deep WMH (0 = absent; 1 = punctate; 2 = early confluent; 3 = confluent) and periventricular WMH (0 = absent; 1 = pencil-thin lining; 2 = halo of ≥5 mm thickness; 3 = irregular WMH extending into deep white matter).

Supplemental results

The patient provided information on family history in 96.2% (n=4298). The information on a family history was missing after interview of the patient, relatives or treating physician in 235 patients regarding stroke (5.3%) and in 247 patients regarding cardiovascular disease (5.5%). There was no higher frequency of family history in the very young (age<25, 38/118, family history in 32.2%) or the young (25-35, 133/413, family history in 32.2%).
There was also no relationship when this analysis was restricted to those with positive MRI findings (n=2660).

There was no significant association between parental history of stroke and the presence of higher degrees of white matter disease, as reflected by hyperintensities in the deep white matter (p=0.437), periventricular white matter (p=0.094) or in the pons (p=0.859). Compared to patients with no hyperintensities in deep white matter, the odds ratio for a mild degree of WMH was 0.97 (0.84-1.13), and moderate to severe degree of WMH was 1.15 (0.92-1.42).

There was no significant association between sib history of stroke and the presence of higher degrees of hyperintensity in the deep white matter (p=0.064), in periventricular regions (p=0.070) or in the pons (p=0.823). OR (95%CI). Compared to patients with no hyperintensities in deep white matter, the odds ratio for a mild degree of WMH was 1.48 (95% CI 0.98-2.24) and moderate to severe degree of WMH was 1.63 (95% CI, 0.93-2.86).

A PFO was looked for in 3479 patients and was found in 863 patients (24.7%). A PFO was not more commonly detected in patients with a parental history of stroke (23.7% versus 25.5%, OR 0.89 [95% CI 0.75-1.06], p=0.259) or a sib history of stroke (18.4% versus 25.0%, OR 0.67 [0.40-1.13], p=0.154).

According to the TOAST classification, the etiology of the index stroke or TIA was large-artery disease in 713 (16.4%), cardioembolism in 658 (13.7%), small-vessel disease in 594 (15.1%), other determined causes in 718 (16.5%), and undetermined cause in 1662 (38.3%) patients (122 patients had missing data).\textsuperscript{5} Using the A-S-C-O classification, atherosclerosis (A) was considered definitely the cause (grade 1) in 213 (4.8%), small vessel disease (S) in 280 (6.3%), cardioembolism (C) in 167 (3.7%) and other determined cause (O) in 735 (16.5%). Combining the grade 1 (definitely causal) and 2 (causality uncertain) categories the frequency was A in 433 (9.7%), S in 1304 (29.2%), C in 371 (8.3%) and O in 735 (16.5%).

Supplemental tables
Supplemental Table I. Characteristics of TIA/ischemic stroke patients reporting a parental history of stroke

<table>
<thead>
<tr>
<th>Characteristic (number reporting feature)</th>
<th>Parental history present</th>
<th>Parental history absent</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>p-value</th>
<th>Age-adjusted Odds Ratio (95% CI)</th>
<th>p, age adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years (median, IQR)</strong></td>
<td>n=1501</td>
<td>n=2731</td>
<td>47 (41-51)</td>
<td>46 (40-51)</td>
<td>1.12 (1.03-1.21)</td>
<td>0.007</td>
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<tr>
<td></td>
<td></td>
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<td>(for age in decades)</td>
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<tr>
<td><strong>Female sex, n (%)</strong></td>
<td>650 (43.3%)</td>
<td>1073 (39.3%)</td>
<td>1.19 (1.04-1.35)</td>
<td>0.010</td>
<td>1.22 (1.07-1.39)</td>
<td>0.003</td>
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<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>745 (49.9%)</td>
<td>1206 (44.4%)</td>
<td>1.27 (1.11-1.44)</td>
<td>&lt;0.001</td>
<td>1.22 (1.06-1.40)</td>
<td>0.004</td>
</tr>
<tr>
<td>n=4209</td>
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<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>159 (10.7%)</td>
<td>264 (9.7%)</td>
<td>1.13 (0.92-1.39)</td>
<td>0.253</td>
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<tr>
<td>n=4214</td>
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<tr>
<td><strong>Hyperlipidemia, n (%)</strong></td>
<td>572 (39.8%)</td>
<td>847 (32.1%)</td>
<td>1.43 (1.25-1.65)</td>
<td>&lt;0.001</td>
<td>1.40 (1.21-1.61)</td>
<td>&lt;0.001</td>
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<tr>
<td>n=4078</td>
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<tr>
<td><strong>Previous stroke or TIA, n (%)</strong></td>
<td>306 (20.5%)</td>
<td>483 (17.8%)</td>
<td>1.18 (1.00-1.38)</td>
<td>0.048</td>
<td>1.60 (0.99-1.36)</td>
<td>0.073</td>
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<tr>
<td>n=4206</td>
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<tr>
<td><strong>Atrial fibrillation, n (%)</strong></td>
<td>35 (2.3%)</td>
<td>65 (2.4%)</td>
<td>1.02 (0.67-1.55)</td>
<td>0.941</td>
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<td>n=4206</td>
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<tr>
<td><strong>Current smoking, n (%)</strong></td>
<td>643 (42.8%)</td>
<td>1136 (41.6%)</td>
<td>1.03 (0.91-1.18)</td>
<td>0.626</td>
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<td>n=4232</td>
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<tr>
<td><strong>History of MI or CAD, n (%)</strong></td>
<td>82 (5.5%)</td>
<td>122 (4.5%)</td>
<td>1.21 (0.90-1.61)</td>
<td>0.205</td>
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<tr>
<td>n=4228</td>
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<tr>
<td><strong>Peripheral artery occlusive disease, n (%)</strong></td>
<td>30 (2.0%)</td>
<td>59 (2.2%)</td>
<td>0.89 (0.57-1.39)</td>
<td>0.603</td>
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<tr>
<td>n=4198</td>
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<tr>
<td><strong>Migraine in past 12 months, n (%)</strong></td>
<td>340 (23.0%)</td>
<td>538 (20.1%)</td>
<td>1.19 (1.02-1.39)</td>
<td>0.029</td>
<td>1.13 (1.04-1.22)</td>
<td>0.004</td>
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<tr>
<td>n=4151</td>
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<tr>
<td><strong>Migraine in lifetime, n (%)</strong></td>
<td>439 (29.7%)</td>
<td>676 (25.3%)</td>
<td>1.25 (1.08-1.45)</td>
<td>0.002</td>
<td>1.27 (1.10-1.47)</td>
<td>0.001</td>
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<tr>
<td>n=4152</td>
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<tr>
<td><strong>Body height, cm (SD)</strong></td>
<td>172.7 (9.4)</td>
<td>173.6 (9.4)</td>
<td>0.89 (0.83-0.96)</td>
<td>0.001</td>
<td>0.89 (0.84-0.96)</td>
<td>0.001</td>
</tr>
<tr>
<td>n=4229</td>
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<tr>
<td><strong>Weight, kg (SD)</strong></td>
<td>80.9 (17.3)</td>
<td>80.7 (17.2)</td>
<td>1.00 (0.99-1.00)</td>
<td>0.718</td>
<td></td>
<td>---</td>
</tr>
</tbody>
</table>
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