Reduced incidence of ischemic stroke in patients with severe factor XI deficiency

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Inherited disorders of hemostasis are natural models for investigating mechanisms of thrombosis and development of antithrombotic therapy. Because mice with total factor XI deficiency are protected against ischemic stroke and do not manifest excessive bleeding, we investigated the incidence of ischemic stroke in patients with severe inherited factor XI deficiency. Incidence of ischemic stroke in 115 patients aged 45 years or more with severe factor XI deficiency (activity less than 15 U/dL) was compared with incidence in the Israeli population as estimated from a stroke survey of 1528 patients. Adjustment for major risk factors of stroke (hypertension, diabetes mellitus, hypercholesterolemia, current smoking) was based on comparison of their prevalence in the stroke survey to an Israeli health survey of 9509 subjects. Incidence of myocardial infarction in the factor XI cohort was also recorded. After adjustment for the 4 major risk factors of ischemic stroke, the expected incidence of ischemic stroke was 8.56 compared with one observed (P = .003). The reduced 1:115 incidence of ischemic stroke contrasted with a 19:115 incidence of myocardial infarction, similar to the expected incidence. Thus, severe factor XI deficiency probably is protective against ischemic stroke but not against acute myocardial infarction. (Blood. 2008;111:4113-4117)

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Introduction

Severe inherited disorders of hemostasis in humans or animals serve as models for investigating the mechanisms of thrombosis and atherosclerosis or as paradigms for development of new antithrombotic drugs. Recent studies in patients with severe hemophilia A or B, type 3 von Willebrand disease, and Glanzmann thrombasthenia have demonstrated that these profound hemostatic defects confer no or minimal protection against atherosclerosis.1-3 Nevertheless, longitudinal studies have shown that severe hemophilia A or B are associated with decreased incidence of myocardial infarction, suggesting that low coagulability protects afflicted patients against arterial thrombotic occlusions.4,5

Severe factor XI (FXI) deficiency is another potential protector against thrombosis because it is associated with reduced thrombin generation and augmented fibrinolysis related to decreased activation of thrombin activatable fibrinolysis inhibitor (TAFI).6 Indeed, FXI deficiency induced in animals by specific antibodies or gene targeting exerts an antithrombotic effect in arterial or venous models of thrombosis without compromising hemostasis; the tail bleeding time in mice lacking FXI is normal.7-14 Contrasting these models, patients with severe FXI deficiency present with acute myocardial infarction at an incidence similar to that expected in the general population.15 Whether or not patients with severe FXI deficiency are protected against venous thrombosis or ischemic stroke is unknown. The rather low incidence of unprovoked venous thromboembolism in different age groups of the general population (1:300-1:1000) and the relatively small number of patients with severe FXI deficiency make it hard to assess whether FXI deficiency is protective or not. Regarding stroke, mice with total FXI deficiency are protected against brain injury in an experimental stroke model.14 This finding prompted us to investigate the incidence of ischemic stroke in patients with severe FXI deficiency in comparison to the incidence in the general population.

Methods

We compared stroke incidence in 2 populations: a relatively small clinical cohort of patients with severe FXI deficiency and the entire population of Israel.

Patients with FXI deficiency

The FXI-deficient group consisted of unrelated patients whose plasma FXI activity was less than 15 U/dL and who were consecutively referred to our center during the last 8 years because of a prolonged activated partial thromboplastin time (aPTT) or a bleeding tendency that led to the diagnosis. We limit attention here to the 115 patients who were aged 45 years or older. Patients were interviewed regarding their clinical history, cerebrovascular or cardiovascular events, and major atherosclerotic risk factors (ie, hypertension, diabetes mellitus, hypercholesterolemia, current smoking, and medications). Medical records of the patients were also reviewed. Follow-up for each patient with FXI deficiency is from birth to the end of 2006, when data on all patients were updated for cerebrovascular events. Criteria for acute myocardial infarction (AMI) were adapted from the Cardiovascular Health Study16 and were defined by chest pain, increased biochemical markers, and typical electrocardiographic changes. The Institutional Review Board of Sheba Medical Center approved the study, and informed consent was obtained from each patient in accordance with the Declaration of Helsinki.


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For estimation of the expected number of strokes in the Israeli population, the data from the National Acute Stroke Israeli Survey (NASIS) were analyzed. This prospective survey included all consecutive patients with an acute cerebrovascular event admitted to all 28 Israeli Medical Centers in February and March 2004. Comprehensive information on demographic features, risk factors, clinical manifestations, diagnosis, and management were obtained. Of 2127 patients enrolled, 1528 had ischemic stroke, and their data were used for analyses performed in this study. Patients with transient ischemic attack (N = 372), intracerebral hemorrhage (N = 156), or patients who did not undergo imaging (N = 71) were excluded.

### INHIS-1

The Israel National Health Interview Survey (INHIS-1) was conducted as part of the European Health Interview Survey (EUROHIS) performed in 33 countries whose objective was to develop a standard tool for international comparison of health measurements based on standardized methods. In Israel, the survey was conducted by Israel’s Center for Disease Control between April 2003 and October 2004 and consisted of interviews using the EUROHIS questionnaire as a template. Of 16,346 households with individuals older than 21 years, 9509 (4028 men, 5481 women; 58.2%) agreed to participate. The questionnaire included demographic characteristics, health-related behavior, health status, use of health services, and medications. Participants reported on current smoking and on family physician diagnoses of hypertension, hypercholesterolemia, and diabetes mellitus. The variables were presented in the final INHIS-1 report by age and sex.

### Laboratory tests

FXI activity was determined by an aPTT-based assay. The common mutations causing FXI deficiency in Israel were determined by polymerase chain reaction (PCR) and restriction enzyme analysis.

### Statistical analyses

The statistical analysis used the standardized incidence ratio (SIR) to compare the incidence of ischemic strokes in the FXI-deficient cohort to the expected incidence. The expected number of ischemic strokes was computed from sex-specific incidence in 5-year age groups, as computed by dividing the annualized NASIS counts by population totals from the Israel Central Bureau of Statistics. Patients with FXI contribute person-years of exposure until the age of ischemic stroke incidence or the end of follow-up if they were stroke-free. A further analysis controlled for major risk factors for ischemic stroke in computing the expected number of strokes.

### Results

#### The incidence of ischemic stroke and AMI in the FXI-deficient cohort

The FXI-deficient cohort consisted of 53 men (mean age, 68.4 years) and 62 women (mean age, 62.8 years). Only one case of ischemic stroke was recorded in a woman who is currently 80 years old. At the age of 61 years she experienced an AMI and was found to have hypertension and hypercholesterolemia. In the subsequent years she had several episodes of atrial fibrillation, with one occurring at the time of presentation of ischemic stroke at the age of 63 years.

In a previous study of 96 FXI-deficient patients we recorded 16 patients who had AMI. An update of the incidence of AMI revealed a proportion of 19:115 among the currently studied patients. The prevalence of AMI was slightly higher than the expected, based on population incidence, in striking contrast with the low incidence of ischemic stroke (Table 1).

### Table 1. Clinical and genotypic data on unrelated patients with severe FXI deficiency

<table>
<thead>
<tr>
<th>FXI genotype</th>
<th>II/II</th>
<th>III/III</th>
<th>III/II</th>
<th>Other</th>
<th>Not tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 to 54 y</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>55 to 64 y</td>
<td>18</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>65 to 74 y</td>
<td>13</td>
<td>0</td>
<td>4</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Over 75 y</td>
<td>17</td>
<td>0</td>
<td>6</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>0</td>
<td>14</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45 to 54 y</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>55 to 64 y</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>15</td>
</tr>
<tr>
<td>65 to 74 y</td>
<td>15</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Over 75 y</td>
<td>15</td>
<td>1</td>
<td>5</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>1</td>
<td>5</td>
<td>15</td>
<td>30</td>
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<td>Grand total</td>
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<td>1</td>
<td>19</td>
<td>40</td>
<td>51</td>
</tr>
</tbody>
</table>

*Type I homozygote, FXI level less than 1 U/dL of normal.
†Type II/Tyr427Cys compound heterozygote, FXI level less than 1 U/dL.
‡Gly555Glu homozygote, FXI level less than 1 U/dL.

#### Risk factor adjustment

The prevalence of major ischemic stroke risk factors in the FXI-deficient cohort and the patients with first ischemic stroke (from NASIS) was compared with the prevalence in the Israeli population at large (from INHIS) by age groups and sex. The NASIS-to-INHIS comparison was used to estimate odds ratios for ischemic stroke incidence. Logistic regression models with main effects for the 4 risk factors were fitted to the data for each sex and age group combination. Additional models were run to check for the possibility of interactions between pairs of risk factors. Results from the main effects models were used to compute sex- and age group–specific estimates of the odds ratio for first ischemic stroke incidence for each of the 16 (2^4) possible combinations of risk factors. The odds ratios were then used to estimate, for each sex, adjusted annual incidence for each combination of risk factors.

#### Comparison of groups

A 2-sided Poisson test was used to compare the FXI prevalence to the expected prevalence. The test is based on the fact that, under the hypothesis of equal incidence, the observed number of incident ischemic stroke cases in the FXI-deficient cohort will have a Poisson distribution whose mean is the expected incidence. Results were considered statistically significant if P values were less than .05. The Poisson distribution was used to compute 95% confidence intervals for the SIR.
The 2 common mutations causing FXI deficiency in Ashkenazi Jews are the Glu117stop null mutation and the Phe283Leu missense mutation. The genotypes in 111 of the 115 patients comprised 40 homozygotes for Glu117stop, 20 homozygotes for Phe283Leu, and 51 compound heterozygotes for Glu117stop and Phe283Leu (Table 1). As expected, mean plus or minus standard deviation FXI levels differed significantly among patients harboring these genotypes. In homozygotes for Glu117stop, the FXI level was 0.69 plus or minus 0.57 U/dL; in homozygotes for Phe283Leu, the FXI level was 8.0 plus or minus 3.04 U/dL; and in compound heterozygotes for Glu117stop and Phe283Leu, the FXI level was 3.29 plus or minus 1.77 U/dL. In the remaining 4 patients, FXI levels were less than 1 U/dL; the genotypes in 3 of the 4 patients are depicted in Table 1.

Expected and observed incidence of ischemic stroke

The expected number of individuals with an ischemic stroke in the FXI-deficient cohort (regardless of stroke risk factors) was 5.52 in men, 2.55 in women, and 8.07 in the entire cohort. The observed count of one ischemic stroke is significantly lower (P = .003). The standardized incidence ratio is 0.124 (95% confidence interval, 0.030-0.690).

The prevalence of ischemic stroke risk factors in the FXI-deficient cohort, the general population, and ischemic stroke patients

Table 2 compares the prevalence of current smoking, diabetes mellitus, hypertension, and hypercholesterolemia in men and women of the FXI-deficient cohort, INHIS, and NASIS. As expected, the prevalence of these risk factors was remarkably higher in patients with ischemic stroke (NASIS) than in the general population (INHIS). In FXI-deficient men, the prevalence of hypertension in the older age groups was higher than in the population (INHIS), the prevalence of diabetes mellitus was lower, and the prevalence of smoking and hypercholesterolemia similar. In FXI-deficient women, the prevalence of smoking, hypertension, and hypercholesterolemia were comparable with those of INHIS. However, only one FXI-deficient woman had diabetes mellitus, while its rate in the population was about 10%. When the incidence of ischemic stroke was adjusted for the 16 combinations of risk factors, the expected number of strokes was 6.68 among men and 1.88 among women, for an overall expected number of 8.56 ischemic strokes among patients with severe FXI deficiency. The observed count of only one patient with ischemic stroke is significantly lower (P = .003). The risk factor-adjusted standardized incidence ratio is 0.117 (95% confidence interval, 0.028-0.651).

Discussion

The major finding of this study was a remarkably reduced incidence of ischemic stroke in patients with severe FXI deficiency compared with the expected number based on incidence in the general Israeli population. The apparent protection against ischemic stroke that was conferred by severe FXI deficiency included patients with plasma FXI levels ranging from less than 1 U/dL to 14 U/dL, which corresponded with their genotypes (Table 1).

To understand the reduced incidence of ischemic stroke in the FXI-deficient cohort, we evaluated whether the frequency distribution of risk factors for ischemic stroke was for some reason diminished in the FXI-deficient cohort. A total of 2 large reference groups were available for comparison of the frequency of risk factors, 9509 representatives of the Israeli population (the INHIS study), and 1528 patients with ischemic stroke (the NASIS study). The comparison indicated that by and large, the frequency of the 4 major risk factors of ischemic stroke (current smoking, hypertension, diabetes mellitus, and hypercholesterolemia) in the FXI-deficient cohort was similar to the frequency in the general population except for a lower frequency of diabetes mellitus in women and a higher frequency of hypertension in men older than 65 years (Table 2). A more detailed analysis of stroke incidence for the 16 possible combinations of the 4 risk factors showed that the overall expected number of patients with ischemic stroke in the FXI-deficient cohort was 8.56, whereas only one case was observed (P = .003).

There are 2 limitations to our findings to consider. First, one could argue that our FXI-deficient cohort may have missed some individuals who had a fatal stroke. However, more than 30 years of follow-up of numerous FXI-deficient patients who were diagnosed at a young age by one of the authors (U.S.) has not revealed any case of ischemic stroke. Second, because 112 of the 115 patients with severe FXI deficiency are Ashkenazi Jewish, one could argue that perhaps Ashkenazi Jews in general have a reduced incidence of ischemic stroke compared with other ethnic groups in Israel. No data are available on such a potential difference, yet even if there would be an ethnic variability in the incidence of ischemic stroke, this is likely to be small and cannot account for the strikingly low incidence of ischemic stroke in the FXI-deficient cohort.

FXI displays both procoagulant and antifibrinolytic activities. Thrombin, initially formed by the tissue factor–FVIIa pathway, 

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Smoking, %</th>
<th>Diabetes, %</th>
<th>Hypertension, %</th>
<th>Hypercholesterolemia, %</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>FXI</td>
<td>INHIS</td>
<td>NASIS</td>
<td>FXI</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>45 to 54 y</td>
<td>20.0</td>
<td>34.2</td>
<td>55.1</td>
<td>0</td>
</tr>
<tr>
<td>55 to 64 y</td>
<td>27.8</td>
<td>25.3</td>
<td>41.6</td>
<td>16.7</td>
</tr>
<tr>
<td>65 to 74 y</td>
<td>25.0</td>
<td>18.0</td>
<td>26.7</td>
<td>8.3</td>
</tr>
<tr>
<td>Over 75 y</td>
<td>29.0</td>
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<td>13.1</td>
<td>0</td>
</tr>
<tr>
<td>Women</td>
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<td>41.2</td>
<td>23.5</td>
<td>38.6</td>
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<td>55 to 64 y</td>
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<td>16.9</td>
<td>19.3</td>
<td>0</td>
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<tr>
<td>Over 75 y</td>
<td>13.3</td>
<td>7.0</td>
<td>1.8</td>
<td>6.7</td>
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</table>
activates FXI leading through additional reactions to further thrombin generation, which is followed by fibrin clot formation. FXIa also promotes thrombin generation after a fibrin clot has formed, which gives rise to activation of TAFI. TAFIa then removes from fibrin lysine binding sites for plasminogen and tissue plasminogen activator, thereby stabilizing the fibrin clot by making it resistant to fibrinolysis. Consequently, when FXI is absent from plasma, there is diminished fibrin clot formation and augmented fibrinolysis demonstrable in vitro and in vivo. Interestingly, increased plasma levels of FXI or TAFI have recently been identified as risk factors of ischemic stroke. Together, these observations suggest that the apparent protection against ischemic stroke in patients with severe FXI deficiency is attributable to reduced thrombin generation and augmented lysis of blood clots formed or embolized into cerebral arteries.

If this is indeed the explanation for the beneficial effect of severe FXI deficiency in preventing ischemic stroke, why is there no protective effect against myocardial infarction (Table 1)? It has long been recognized that there are vascular bed specificities which can impart variable site-specific thrombotic events. These specificities stem from a substantial heterogeneity of structure and function of the respective endothelial cells and their interactions with cells and components of blood. One feature that characterizes the cerebral vasculature is the abundance of amyloid β protein precursor protein (AβPP), unlike the heart, in which it is probably absent. AβPP is a type I transmembrane protein that upon proteolytic processing by secretases yields amyloid β protein that promotes fibrinolytic activity, and is deposited in the brains of patients with Alzheimer disease. There are 3 alternatively spliced AβPPs, of which the larger 2 isoforms with 751 or 770 amino acids contain a 56-residue peptide functioning as a Kunitz protease inhibitor, which is analogous to protease nexin 2 present in platelet α granules. This inhibitor was shown to neutralize FXIa, FIXa, and FXa, and was therefore termed “the cerebral anticoagulant.” Notably, a 2-fold overexpression of AβPP in platelets of transgenic mice caused marked inhibition of carotid artery thrombosis, while in AβPP gene knock-out mice, thrombosis was more pronounced than in wild-type mice. Although the relevance of these in vitro and in vivo activities of AβPP and amyloid β protein to the brain circulation in health and disease is yet to be defined, it is tempting to speculate that the anticoagulant and prothrombinolytic effects of both AβPP and FXI deficiency are responsible for the specific protection against ischemic stroke in patients with severe FXI deficiency.

Among several inherited disorders prevalent in Ashkenazi Jews such as Gaucher, Tay Sachs, or Canavan diseases, FXI deficiency is the most common; 1 in 11 individuals are heterozygotes for Glu117stop or Phe283Leu. The remarkable frequency of all these rare inherited disorders in Ashkenazi Jews has been attributed to genetic drift, founder effects, and a phenomonal growth of this population from 1500 until 1940. Notably, for each one of these rare inherited disorders, more than one mutation was identified, raising the possibility of evolutionary advantages conferred by the mutant alleles. To date, however, no such advantages have been discerned. Whether the apparent protective effect against ischemic stroke in patients with severe FXI deficiency constitutes an advantage is difficult to accept at this time because the estimated frequency of severe FXI deficiency in Ashkenazi Jews is only 1 in 450. However, if heterozygotes for either of the 2 common FXI mutations in whom there is partial FXI deficiency will also display a low incidence of ischemic stroke, then it would be reasonable to regard FXI deficiency as advantageous.

Authorship

Contribution: O.S. designed and performed the research; D.M.S. developed the statistical analyses and wrote the paper; N.K. and D.T. analyzed the data of the NASIS and INHIS studies; and U.S. designed the study, analyzed the data, and wrote the paper.

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