The factor VII–activating protease (FSAP) variant Marburg I is known to attenuate the profibrinolytic system in vitro and was recently shown to be a significant predictor for the evolution and progression of carotid stenosis. The objective of this case-control study was to assess FSAP Marburg I’s role in the occurrence of venous thromboembolism (VTE). The frequency of FSAP Marburg I was significantly increased in patients with a history of VTE (17 of 213 patients, 8.0%, \textit{P} = .014) or idiopathic VTE (12 of 103 patients, 11.7%, \textit{P} = .002) compared to healthy controls (5 of 213 controls, 2.3%). Logistic regression analysis confirmed FSAP Marburg I to be an independent risk factor for VTE (odds ratio, 3.5; 95% confidence interval [CI], 1.2-10.0) and idiopathic VTE (odds ratio, 6.2; 95% CI, 2.0-18.9). (Blood. 2005;105:1549-1551)

Brief report

Marburg I polymorphism of factor VII–activating protease is associated with idiopathic venous thromboembolism

Berthold Hoppe, Farzaneh Tolou, Hartmut Radtke, Holger Kiesewetter, Thomas Dörner, and Abdulgabar Salama

Study design

During May 2003 and May 2004, a total of 239 patients with a history of VTE were admitted to our institution for thrombolysis work-up. Patients were referred from regional hospitals and primary care physicians from Berlin-Brandenburg (Germany). We excluded 21 patients with axillary, mesenteric, or cerebral vein thrombosis because natural history might be different to deep vein thrombosis (DVT). Five patients refused to participate in this study. The remaining 213 patients with objectively confirmed DVT and/or pulmonary embolism (PE) (DVT, n = 151; PE, n = 17; DVT + PE, n = 45) were enrolled. The median interval between VTE and presentation was 9.5 months (range, 0.4-83 months). The clinical characteristics of patients and controls are shown in Table 1. Secondary VTE due to acquired risk factors (immobilization, surgery, trauma, pregnancy, puerperium, malignancy) was present in 51.6% (n = 110) of cases. VTE was defined as idiopathic (n = 103, 48.4%) if it had not occurred during or fewer than 3 months after exposure to one or more acquired risk factors. During the initial examination the following parameters were determined: Factor V 1691G → A (factor V Leiden) and prothrombin (PT) 20210G → A; activity of antithrombin (n = 205), protein S (n = 129), and protein C (n = 128); anticardiolipin IgG/IgM (n = 211), and lupus anticoagulants (n = 206). FSAP Marburg I (1601G → A) was analyzed retrospectively using the same protocol and the following primer pairs: FSAP 1601G/wild-type: forward primer: 5’ tggggcctggagtgtga 3’; reverse primer: 5’ ggtgctcattgtggcc 3’; FSAP 1601A/Marburg I: forward primer: 5’ tggggcctggagtga 3’; reverse primer: 5’ ggtgctcattgtgga 3’. Blood donors (n = 213, controls) from the same geographical area as the patients were recruited by sex/age-stratified sampling (age strata [y]: < 20, 20-29, 30-39, 40-49, 50-59, and ≥60) according to the distribution of cases. Consecutive donors with no history of VTE were enrolled until the respective sex/age groups reached the number of cases. Controls were tested for factor V 1691G → A, PT 20210G → A, and FSAP 1601G → A. The study was approved by the local ethics committee. All participants gave informed consent.

Results and discussion

The laboratory characteristics of patients and controls are shown in Table 2. The overall frequencies of FSAP Marburg I in cases and controls were 8.0% (n = 17) and 2.3% (n = 5), respectively. FSAP Marburg I was independently associated with VTE (odds ratio, 3.5; 95% CI, 1.2-10.0). All carriers of FSAP Marburg I were heterozygous for this variant. Regarding patients with idiopathic VTE, the independent association with FSAP Marburg I was even stronger than that identified for all patients (odds ratio, 6.2; 95% CI, 2.0-18.9). After exclusion of patients who developed idiopathic...
Table 1. Clinical characteristics of patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Idiopathic</th>
<th>Secondary</th>
<th>Controls</th>
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<tbody>
<tr>
<td>No.</td>
<td>213</td>
<td>103</td>
<td>110</td>
<td>213</td>
</tr>
<tr>
<td>Female, %</td>
<td>71.8</td>
<td>72.8</td>
<td>70.9</td>
<td>71.8</td>
</tr>
<tr>
<td>Age, median, y (range)</td>
<td>35 (15-80)</td>
<td>37 (15-80)</td>
<td>34 (15-78)</td>
<td>35 (18-66)</td>
</tr>
</tbody>
</table>

No. clinical events

<table>
<thead>
<tr>
<th></th>
<th>DVT</th>
<th>DVT + PE</th>
<th>PE</th>
<th>No. with acquired risk factor*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>151</td>
<td>63</td>
<td>88</td>
<td>0</td>
</tr>
<tr>
<td>DVT + PE</td>
<td>45</td>
<td>27</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>PE</td>
<td>17</td>
<td>13</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

*Combinations of acquired risk factors were found in 6 cases.

DVT indicates deep vein thrombosis; PE, pulmonary embolism; NA, not applicable.

VTE under hormonal contraception (n = 18), FSAP Marburg I remained independently associated with VTE (odds ratio, 5.7; 95% CI, 1.7-19.6). In patients with secondary VTE (n = 5, 4.5%) due to acquired risk factors, no association with FSAP Marburg I could be demonstrated.

Significant hereditary thrombophilic risk factors other than FSAP Marburg I, for instance, factor V Leiden (n = 54), PT 20210G -> A (n = 13), factor V Leiden + PT 20210G -> A (n = 3), factor V Leiden + protein S deficiency (n = 2), protein S deficiency (n = 1), and antithrombin deficiency (n = 1) were found in 74 patients. A history of VTE in relatives of patients with FSAP Marburg I and no other significant hereditary thrombophilic risk factors was found in 4 of 10 cases. The frequencies of carriers of factor V Leiden and PT 20210G -> A in controls, patients with VTE, and idiopathic VTE (Table 2) are in agreement with previously published data, reflecting the comparable composition of our collectives.

Based on our data FSAP Marburg I appears to be a candidate for hereditary thrombophilia. However, some details of our study should be discussed. We analyzed prevalent and not incident cases. Thus, there might be a tendency for inadequate recall of past events. This will not influence the accuracy of the detection of FSAP Marburg I. Secondary VTE and who raised the question whether these 2 conditions might share common risk factors. Interestingly, FSAP Marburg I was initially described as a predictor for the evolution and progression of carotid stenosis, and in our study it could be demonstrated to be associated with idiopathic but not with secondary VTE (Table 2).

Larger studies are needed to conclusively determine the importance of FSAP Marburg I in VTE.

Acknowledgments

This work is dedicated to my father, Prof Dr Immo Hoppe.

We thank Gisela Diederich for excellent technical assistance.

References

7. Lindmark P, Schulman S, Sten-Linder M, Wiman B, Egberg N, Johnsson H. The risk of


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