Factor V Leiden Mutation Is a Risk Factor for Cerebral Venous Thrombosis
A Case-Control Study of 55 Patients

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Background and Purpose—Different coagulation disorders have been associated with cerebral venous thrombosis (CVT). Until now, fewer than 50 patients have been reported with CVT and the factor V Leiden (FVL) mutation. Although the prevalence of FVL-positive patients with CVT ranged from 10% to 25%, it was as low as 0.5% to 3% in the control groups. Most other studies had not systematically searched for concomitant risk factors or previous thromboembolic events. To better define the relevance of the FVL mutation in conjunction with additional risk factors in CVT, we conducted the present case-control study.

Methods—Fifty-five patients with CVT were compared with 272 healthy controls. A standardized interview regarding established risk factors for venous thrombosis and the patients’ and their families’ histories for thromboembolic events was performed. The presence of the FVL mutation was determined by polymerase chain reaction on DNA obtained from peripheral blood leukocytes.

Results—Of 55 patients, 8 (14.5%) were heterozygous for the FVL mutation compared with 17 of 272 controls (6.25%). The relative risk for the presence of FVL was 2.55 (95% confidence interval, 1.04 to 6.26; \( P = 0.04 \)). Additional risk factors for CVT were frequently found in both the presence and absence of FVL. Recurrence of venous thromboembolic events was more frequent in patients with the FVL mutation (5 of 8 patients, 62.5%) than in those without this anomaly (8 of 47 patients, 17%; \( P < 0.005 \)).

Conclusions—Our study confirms the FVL mutation as the most relevant hereditary risk factor for CVT. Coexisting risk factors are usually involved in the initiation of CVT. Patients with the FVL mutation are at an increased risk for recurrent venous thrombosis. (Stroke. 1998;29:2507-2510.)

Key Words: factor V ■ protein C ■ sinus thrombosis

A ctivated protein C (APC) is the antithrombotic protein that normally cleaves and inactivates coagulation factors Va and VIIIa.\(^1\) Functional resistance of coagulation factor Va against the anticoagulant activity of APC was first described by Dahlbäck et al in 1993.\(^2\) Bertina et al\(^3\) identified a point mutation (Arg506\(\rightarrow\)Gln) in the gene mapping for coagulation factor V and called this the factor V Leiden (FVL) mutation. This mutation is present in >95% of cases with resistance to APC.\(^3\) Within European populations, the prevalence of the FVL mutation ranges from 0% to 7%.\(^4\) Meanwhile, FVL has been identified as the most common autosomal dominantly inherited factor predisposing to deep venous thrombosis (DVT) and pulmonary embolism.\(^5,6\)

There are 22 case reports of cerebral venous thrombosis (CVT) associated with the FVL mutation. The first 2 descriptions were published in 1994\(^6\) and 1995.\(^7\) In 1996, 9 additional case histories were reported.\(^8-13\) Another 6 case reports followed in 1997,\(^14-18\) and 1 was published in 1998.\(^19\) Also in 1997, another 4 patients with sinus thrombosis after dural puncture were described with either the FVL mutation or APC resistance.\(^20\) Furthermore, 6 studies based on 12 to 40 patients with CVT found prevalences of FVL ranging from 10% to 25%.\(^21-26\) (Table 1). All patients with CVT described in these reports were heterozygous for the FVL mutation. Frequently, additional risk factors for CVT were found, mainly intake of oral contraceptives, pregnancy, or puerperium. In a patient prone to venous thrombosis caused by the genetic anomaly, an otherwise irrelevant, additional thrombophilic event may trigger a thrombosis.

For CVT without a detectable cause, called idiopathic CVT, no predisposition was found until recently in ~25% of patients.\(^27\) The prevalence of the FVL mutation in the general
population has been found to be up to 7%. The present case-control study was conducted to evaluate the association of CVT with FVL. Furthermore, we investigated the role of coexisting thrombogenic risk factors at the onset of the disease and related our laboratory findings to the previous personal and family histories of thromboembolic events.

Subjects and Methods

Patients

Fifty-five survivors (40 women, 15 men; age, 11 to 83 years; mean age, 40 years) of CVT were recruited from 2 university hospitals at Aachen and Münster in the state of Nordrhein-Westfalen, Germany. All had been hospitalized between 1992 and 1997. CVT had been documented by digital subtraction angiography, magnetic resonance imaging, or both. Two hundred seventy-two healthy subjects (age, 18 to 55 years) from the same region served as controls.

The patients’ hospital records were reviewed by 2 experienced neurologists. A questionnaire was given to each patient about his or her medical history, vascular risk factors, any thromboembolic event before or after CVT, and any thrombotic or embolic event in first-degree relatives (Table 2). Original laboratory investigations to detect thrombophilic coagulopathies included antithrombin III, protein C, and protein S. To find or exclude infections, C-reactive protein, erythrocyte sedimentation rate, and white blood cell count were performed.

Factor V Genotyping

Blood samples were collected by venipuncture in EDTA-coated plastic tubes. DNA analysis was performed by amplification of the DNA from peripheral leukocytes by polymerase chain reaction and Mnl I restriction as previously described.

Statistics

Proportional differences were evaluated by use of Yates’ corrected $\chi^2$ test. Additionally, the odds ratios and 95% confidence intervals were calculated. Statistical significance was declared at $P < 0.05$.

Results

Of the 55 patients, 8 with CVT (14.5%) and 17 of the 272 controls (6.25%) were heterozygous for the FVL mutation. The odds ratio for the presence of FVL in patients with CVT was 2.55 (95% confidence interval, 1.04 to 6.26; $P = 0.04$). Homozygotes were not found among the patients or controls. Other hereditary thrombophilic coagulopathies were found in only 2 FVL-negative patients (protein C deficiency in a 63-year-old man and protein S deficiency in a 39-year-old woman). An acquired thrombophilia, anticardiolipin antibodies, was discovered in an FVL-positive 35-year-old man (patient 1 in Table 2).

There was no age difference between FVL-positive and FVL-negative patients. Additional risk factors that may have contributed to the development of CVT—ie, the use of oral contraceptive drugs, pregnancy, puerperium, infection, operation or trauma, and obesity—were found in 6 of 8 FVL-positive patients and in 35 of the 47 FVL-negative ones ($P = \text{NS}$). The

<p>| TABLE 2. Additional Risk Factors and History of Thromboembolic Events in CVT Patients With FVL Mutation |
|---------------------------------------------|-------------------------------------------------|---------------------------------|---------------------------------|--------------------------------|</p>
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at CVT</th>
<th>Sex</th>
<th>Additional Risk Factor/Additional Thrombophilia</th>
<th>Personal History of Thromboembolism</th>
<th>Family History of Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>M</td>
<td>Anticardiolipin antibodies positive at time of CVT</td>
<td>DVT 15 and 2 y before CVT; CVT under prophylaxis with 50 mg aspirin</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>F</td>
<td>None</td>
<td>DVT 2 years later, no oral contraceptives, no prolonged anticoagulation</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>F</td>
<td>Oral contraceptives, obesity</td>
<td>DVT, pulmonary embolism during pregnancy 3 y later, no prolonged anticoagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>M</td>
<td>Immobilization</td>
<td>DVT, pulmonary embolism during pregnancy 3 y later, no prolonged anticoagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>F</td>
<td>Oral contraceptives</td>
<td>DVT 5 y earlier, no prolonged anticoagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>F</td>
<td>Immobilization for pneumonia, CVT after discontinuation of heparin</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>44</td>
<td>F</td>
<td>Oral contraceptives</td>
<td>DVT, pulmonary embolism 2 y earlier, no prolonged anticoagulation</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>67</td>
<td>F</td>
<td>Immobilization, postoperative, CVT after discontinuation of heparin</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
frequency of extracranial, recurrent venous thromboembolic events, however, was significantly higher in FVL-positive patients (5 of 8 patients, 62.5%) than in FVL-negative ones (8 of 47 patients, 17%; P<0.005). Of the FVL-positive patients, 2 had a single DVT with pulmonary embolism, another 2 patients had a single DVT without pulmonary embolism, and 1 patient had 2 episodes of DVT. No patient had recurrent CVT. Family history was positive in 4 of 8 FVL-positive patients (50%) and in 22 of 47 FVL-negative patients (46.8%) (P=NS).

**Discussion**

We found the heterozygous FVL mutation in 14.5% of this cohort of patients with CVT but in only 6.25% of controls. This leads to a relative risk for FVL of 2.55. Our results are in the range of previously published, smaller series (ie, 10% to 25%).21-26 and confirm FVL as a risk factor for CVT.

As in the previously published data on individuals with CVT and FVL, we found heterozygosity and no homozygosity in all 8 patients. Presumably, the absence of homozygotes can be explained by the lower frequency of homozygotes in the population.

Of the patients discussed in the literature, only 3 had been completely free of additional risk factors for CVT.12,15,23 Absence of additional risk factors was also found in 1 of our FVL patients (12.5%). The almost invariable presence of acquired risk factors, superimposed on the underlying prothrombotic state caused by FVL, results in recurrent venous thromboses. This is especially important for the prevention of further thromboembolism.

In a recently published follow-up study of 251 patients with a first episode of peripheral venous thromboembolism, the prevalence of the FVL mutation was 16.3%.28 Thus, the prevalences of the FVL mutation in venous thrombosis at either a cerebral or a peripheral location are almost identical. Recurrent peripheral venous thromboembolism was found in 39.7% of patients having the FVL mutation. Compared with FVL-negative patients, the hazard ratio was 2.4.28 In only 3 of the previously discussed patients with CVT and FVL, a history of previous venous thrombosis had been reported.12,21 Quite contrary, in our cohort, patients with the FVL mutation had antecedent DVT significantly more frequently (62.5%) than FVL-negative patients (P<0.005).

The appropriate antithrombotic prophylaxis in FVL heterozygotes is still unclear. In other hereditary thrombophilias, the annual incidence of recurrent venous thromboembolism seems to decline after the first years.29 Surprisingly, Eichinger et al20 found no increased risk of recurrent venous thromboembolic events in patients with the FVL mutation during the first 2 years after discontinuation of oral anticoagulants. In a recent study of the effect of prophylactic oral anticoagulation after a second peripheral venous thromboembolism, indefinite continuation of the therapy was superior to a 6-month treatment with respect to recurrence (2.6% versus 20.7%).31 In hereditary thrombophilia, including the FVL mutation and the recently discovered prothrombin mutation G20210A26 after CVT, anticoagulant treatment should be continued for >6 months32 and probably should be extended as long as an additional risk factor is still operative. If permanent anticoagulation is not feasible, FVL-positive patients can be advised to perform short-term anticoagulation with subcutaneous heparin in situations of an elevated risk of venous thrombosis, such as hospitalization, long-distance flights, vital infections, or pregnancies.

We conclude that the autosomal dominantly inherited FVL mutation is an important risk factor for CVT. Patients with this mutation are at an increased risk of further venous thromboembolic events, mainly extracranial. Therefore, knowledge of this defect is vital to properly prevent the recurrence of venous thrombosis, particularly if additional prothrombotic risk factors are operative.

**References**


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Stroke. 1998;29:2507-2510
doi: 10.1161/01.STR.29.12.2507
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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