Different risk of deep vein thrombosis and pulmonary embolism in carriers with factor V Leiden compared with non-carriers, but not in other thrombophilic defects. Results from a large retrospective family cohort study


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Different risk of deep vein thrombosis and pulmonary embolism in carriers with factor V Leiden compared with non-carriers, but not in other thrombophilic defects. Results from a large retrospective family cohort study


1Division of Hemostasis and Thrombosis, Department of Hematology, University Medical Center Groningen, Groningen; 2Department of Vascular Medicine, Academic Medical Center, Amsterdam; 3Department of Clinical Epidemiology and Department of General Internal Medicine, Leiden University Medical Center; 4Department of Hematology, Maastricht University Medical Center, Maastricht; 5Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, The Netherlands

ABSTRACT

The term factor V Leiden (FVL) paradox is used to describe the different risk of deep vein thrombosis and pulmonary embolism that has been found in carriers of FVL. In a thrombophilic family-cohort, we estimated differences in absolute risks of deep vein thrombosis and pulmonary embolism for various thrombophilic defects. Of 2,054 relatives, 1,131 were female, 41 had pulmonary embolism and 126 deep vein thrombosis. Annual incidence for deep vein thrombosis in non-carriers of FVL was 0.19% (95% CI, 0.16-0.23), and 0.41% (95% CI, 0.28-0.58) in carriers; relative risk (RR) 2.1 (95% CI, 1.4-3.2). For pulmonary embolism these incidences were similar in carriers and non-carriers 0.07%, respectively; RR 1.0 (95% CI, 0.4-2.5). When co-inheritance of other thrombophilic defects was excluded the RR for deep vein thrombosis in FVL carriers was 7.0 (95% CI, 2.3-21.7) compared to non-carriers and 2.8 (95% CI, 0.5-14.4) for pulmonary embolism. For other thrombophilic defects no such effect was observed. Thus the FVL paradox was confirmed in our study. However, a similar paradox in carriers of other thrombophilic defects was not observed.

Key words: factor V Leiden, carriers, deep vein thrombosis, pulmonary embolism, paradox.

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Introduction

The annual incidence of venous thrombosis is 0.1-0.3% per year. Symptomatic pulmonary embolism is present in about a third of patients with venous thrombosis. Deep vein thrombosis and pulmonary embolism are generally considered to be two entities of the same disease. However, several studies have shown that the prevalence of some risk factors differs in patients with deep vein thrombosis compared with those with pulmonary embolism. In 1996, it was first described that the factor V Leiden mutation seems to be a stronger risk factor for deep vein thrombosis than for pulmonary embolism. This differential effect is known as the “factor V Leiden paradox” and has been reported repeatedly. A pathophysiological mechanism that can explain the factor V Leiden paradox is not at hand. The hypothesis that presence of factor V Leiden would often lead to fatal pulmonary embolism, resulting in a lower number of factor V Leiden carriers among those surviving pulmonary embolism and thereby explaining this paradox, has been rejected as autopsy studies have shown that among patients with fatal pulmonary embolism, the proportion of subjects with factor V Leiden did not differ from that in pulmonary embolism survivors or from the general population. Another explanation could be that clots in the venous system of the leg in factor V Leiden carriers are more resistant to embolization due to a different structure, but then one might expect similar observations in other thrombophilic defects as well. Whether the factor V Leiden paradox also exists in other thrombophilic defects is largely unknown, although one study has shown that it does not exist in carriers of prothrombin G20210A. Therefore, we assessed whether the risk of deep vein thrombosis and pulmonary embolism was different in relatives with various thrombophilic defects in a cohort study of families with thrombophilia.

Design and Methods

We pooled data of individual subjects from five large retrospective family cohort studies with various thrombophilic index defects who have been described previously. Between May 1998 and July 2004, first-degree relatives aged 15
years or older of consecutive patients (probands) with document-
ed venous thrombosis (i.e. deep vein thrombosis or pulmonary embolism) or any documented arterial thrombosis before the age of 50 years, were enrolled after obtaining informed consent. Detailed information about previous episodes of venous thrombo-
sis, exposure to exogenous risk factors for thrombosis and antico-
gulant treatment was collected by physicians at the outpatient clinics using a validated questionnaire\(^\text{18}\) and reviewing medical records. Clinical data was collected prior to laboratory testing. Relatives were tested for factor V Leiden, prothrombin G20210A, and hereditary deficiencies of antithrombin, protein C and protein S by methods described previously.\(^\text{15-17}\) To avoid bias, probands were excluded from the analyses. The study was approved by the institutional review boards of the participating hospitals.

Venous thrombosis was considered established if deep vein thrombosis was confirmed by compression ultrasound or veno-
graphy, and pulmonary embolism by ventilation/perfusion lung scanning, spiral computed tomography or pulmonary angiogra-
phy, or when the patient had received full-dose heparin and a vita-
min K antagonist for at least three months without objective test-
ing at a time when these techniques were not yet available. Venous thrombosis was defined as provoked if it occurred within
three months after exposure to exogenous risk factors including
surgery, trauma, immobilization for more than seven days, preg-
nancy, puerperium, use of oral contraceptives or hormonal
replacement therapy, or malignancy. In the absence of these risk
factors, venous thrombosis was classified as unprovoked. Subjects
with concomitant deep vein thrombosis and pulmonary embolism were classified as having embolism.

Observation time was defined as the period from the age of 15
years until the first thrombotic episode or the end of study. End of
study was the date when clinical data and blood samples were col-
lected at the outpatient clinics. Hence, treatment and clinical out-
come were not influenced by the results of thrombophilia testing.

There was no administrative censoring. Annual incidences were
calculated by dividing the number of events by observed years.
Incidences and 95% confidence intervals (95%CI) were calculated
under the Poisson distribution assumption. When calculating the
annual incidence of deep vein thrombosis, subjects with pul-
monary embolism were censored and vice versa. To reduce the
possible difference in the prevalence of factor V Leiden and the
other thrombophilias based on relatives with concomitant pul-
monary embolism and deep vein thrombosis, an extra sensitivity
analysis was performed by censoring those relatives. To regard
heterogeneity of effects due to inclusion of family members of
probands with arterial thrombosis, another sensitivity analysis
was performed by excluding relatives of probands with arterial
thrombosis from the cohort. Venous thrombosis free survival was
analyzed by the Kaplan-Meier method. Continuous variables
were expressed as mean values and standard deviations; categori-
cal data as counts and percentages. Differences between groups
were evaluated by Student’s t-test or Mann-Whitney U test,
depending on the normality of data for continuous variables and
by Fisher’s exact test for categorical variables. A two-tailed P value
of less than 0.05 indicated statistical significance. Statistical analy-
zes were performed using SPSS software, version 16.0 (SPSS Inc.,
Chicago ILL).

Results and Discussion

Our study cohort comprised 4,128 relatives aged 15 years or older of 606 probands. Of the relatives, 890 (22%) had died before the start of the study. Another 924 (22%) relatives did not participate because of various reasons including refusal, inability to give informed consent, or residence outside the Netherlands, and 260 (6%) relatives could not be evaluated due to missing laboratory data. Forty-five percent of the evaluated 2,054 relatives were male (Table 1); mean age at enrollment was 46 years. Of the relatives with venous thrombosis, 134 had deep vein thrombosis and 41 had pulmonary embolism, of whom 8 concomitant with deep vein thrombosis. Mean age at onset of first venous thrombosis was 35 years. Of relatives with deep vein thrombosis, 52 (39%) had an unprovoked event whereas 17 (41%) of the pulmonary embolisms were unprovoked.

Heterozygosity for factor V Leiden mutation was detected in 244 relatives, of whom 26 developed a deep vein thrombosis and 5 pulmonary embolism as first venous thrombosis. Of the 10 relatives who were

| Table 1. Clinical characteristics of 2,054 relatives of thrombophilic families. |
|------------------|-----------------|------------------|
|                  | First venous thrombosis | First venous thrombosis |
|                  | = proximal DVT (n=134) | = PE (n=41) |
| **Women**        |                  |                  |
| Age at enrollment| 83 (62)          | 22 (54)          |
| Age at onset first venous thrombosis | 57 (28-89) | 49 (16-87) |
| Idiopathic       | 34 (16-73)       | 36 (15-84)       |
| Provoked by      |                  |                  |
| Oral contraceptives | 20 (15)         | 8 (20)           |
| Pregnancy/puerperium | 24 (18)         | 4 (10)           |
| Surgery, trauma, immobilization | 37 (28) | 12 (29) |
| Malignancy       | 1 (0)            | 0 (0)            |
| **Prevalence thrombophilic defects** * |                  |
| Antithrombin deficiency | 18 (13)         | 7 (17)           |
| Protein C deficiency | 22 (16)         | 5 (12)           |
| Protein S deficiency | 20 (15)         | 7 (17)           |
| Factor V Leiden  | 29 (22)          | 5 (12)           |
| Prothrombin G20210A | 19 (14)         | 5 (12)           |

Continuous variables denoted as median (range), categorical variables as number (%). *Numbers of relatives tested were for antithrombin 2,050, for protein C deficiency 1,997, for protein S deficiency 2,003 and for prothrombin G20210A-mutation 2,052, respectively.
of all relatives (n=334) of probands (n=106) with arterial thrombosis change outcomes.

When analyzing deep vein thrombosis free survival, relatives with pulmonary embolism were censored and vice versa. †Analysis after exclusion of relatives of probands who passed away in January 2009.

Table 2. Annual incidences of deep vein thrombosis and pulmonary embolism in relatives of probands with a thrombophilic defect.

<table>
<thead>
<tr>
<th>Observation years*</th>
<th>Relatives with event</th>
<th>Annual incidence, % (95% CI)</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deep vein thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No factor V Leiden (n=1800)</td>
<td>53829</td>
<td>103</td>
<td>0.19 (0.16-0.23)</td>
<td>Reference</td>
</tr>
<tr>
<td>Factor V Leiden (n=254)</td>
<td>7651</td>
<td>31</td>
<td>0.41 (0.28-0.58)</td>
<td>2.1 (1.4-3.2)</td>
</tr>
<tr>
<td>No AT deficiency (n=1991)</td>
<td>59959</td>
<td>108</td>
<td>0.18 (0.15-0.22)</td>
<td>Reference</td>
</tr>
<tr>
<td>AT deficiency (n=59)</td>
<td>1386</td>
<td>18</td>
<td>1.30 (0.77-2.05)</td>
<td>7.2 (4.4-11.9)</td>
</tr>
<tr>
<td>No Prot. C deficiency (n=1916)</td>
<td>57180</td>
<td>95</td>
<td>0.17 (0.14-0.20)</td>
<td>Reference</td>
</tr>
<tr>
<td>Prot. C deficiency (n=81)</td>
<td>2062</td>
<td>22</td>
<td>1.07 (0.67-1.62)</td>
<td>6.4 (4.0-10.2)</td>
</tr>
<tr>
<td>No Prot. S deficiency (n=1920)</td>
<td>57777</td>
<td>97</td>
<td>0.17 (0.14-0.20)</td>
<td>Reference</td>
</tr>
<tr>
<td>Prot. S deficiency (n=83)</td>
<td>1623</td>
<td>20</td>
<td>1.23 (0.75-1.90)</td>
<td>7.3 (4.5-11.9)</td>
</tr>
<tr>
<td>No G20210A-mutation (n=1792)</td>
<td>53798</td>
<td>107</td>
<td>0.20 (0.16-0.24)</td>
<td>Reference</td>
</tr>
<tr>
<td>G20210A-mutation (n=260)</td>
<td>7642</td>
<td>19</td>
<td>0.25 (0.15-0.39)</td>
<td>1.3 (0.8-2.0)</td>
</tr>
</tbody>
</table>

| **Pulmonary embolism** |
| No factor V Leiden (n=1800) | 53829 | 36 | 0.07 (0.05-0.09) | Reference | Reference |
| Factor V Leiden (n=254) | 7651 | 5 | 0.07 (0.02-0.15) | 1.0 (0.4-2.5) | 0.6 (0.2-2.0) |
| No AT deficiency (n=1991) | 59959 | 34 | 0.06 (0.04-0.08) | Reference | Reference |
| AT deficiency (n=59) | 1386 | 7 | 0.51 (0.20-1.04) | 8.9 (3.9-20.1) | 8.7 (3.8-20.0) |
| No Prot. C deficiency (n=1916) | 57180 | 29 | 0.05 (0.03-0.07) | Reference | Reference |
| Prot. C deficiency (n=81) | 2062 | 5 | 0.24 (0.08-0.57) | 4.8 (1.9-12.4) | 5.0 (1.9-13.0) |
| No Prot. S deficiency (n=1920) | 57777 | 27 | 0.05 (0.03-0.07) | Reference | Reference |
| Prot. S deficiency (n=83) | 1623 | 7 | 0.43 (0.17-0.89) | Reference | Reference |
| No G20210A-mutation (n=1792) | 53798 | 36 | 0.07 (0.05-0.09) | Reference | Reference |
| G20210A-mutation (n=260) | 7642 | 5 | 0.07 (0.02-0.15) | 1.0 (0.4-2.5) | 0.7 (0.2-2.1) |

* When analyzing deep vein thrombosis free survival, relatives with pulmonary embolism were censored and vice versa. †Analysis after exclusion of relatives of probands who passed away in January 2009.

Some aspects of our study warrant comment. The strength of our study is the large number of subjects evaluated and the possibility of comparing a factor V Leiden paradox effect with the effect of other thrombophilic defects. A weakness of our study is its retrospective design and that despite this large cohort, especially the number of relatives with pulmonary embolism was quite low. A proper multivariate analysis taking confounders into account when calculating relative risk estimates was not feasible due to these small numbers. Another possibility that could explain the factor V Leiden paradox is if patients with deep vein thrombosis are underdiagnosed with pulmonary embolism. In fact, it is known that approximately 70% of subjects with acute deep vein thrombosis have perfusion lung scans with signs of pulmonary embolism. However, it is unlikely that this explains the factor V Leiden paradox in our cohort, as it was not found for one of the other thrombophilias.

We conclude that in our thrombophilic family-cohort, the factor V Leiden paradox is present in relatives carrying factor V Leiden without evidence for a similar paradox in carriers of other thrombophilic defects.

**Dedication**

This article is dedicated to Professor Jan van der Meer who was an inspiring head of our division for many years and who passed away in January 2009.

**Authorship and Disclosures**

All authors contributed to conception, design, analysis and interpretation of data, drafting and critically revising the article for important intellectual content, and final approval of the version to be published.

The authors reported no potential conflicts of interest.

homozgyous for this mutation, 3 developed deep vein thrombosis and none pulmonary embolism.

Annual events for deep vein thrombosis in non-carriers of factor V Leiden was 0.19% (95% CI, 0.19-0.23), and 0.41% (95% CI, 0.28-0.58) in carriers of the mutation; relative risk 2.1 (95% CI, 1.4-3.2) (Table 2). For pulmonary embolism, these incidences were 0.07% (95% CI, 0.05-0.09), and 0.07% (95% CI, 0.02-0.15), respectively; relative risk 1.0 (95% CI, 0.4-2.5). When co-inheritance of other thrombophilic defects was excluded, the RR for deep vein thrombosis in factor V Leiden carriers was 7.0 (95% CI, 2.3-21.7) compared to non-carriers and 2.8 (95% CI, 0.5-14.4) for pulmonary embolism. Relative risks for deep vein thrombosis in antithrombin, protein C or protein S deficient relatives and prothrombin G20210A carriers were 7.2 (95% CI, 4.4-11.9), 6.4 (95% CI, 4.0-10.2), 7.3 (95% CI, 4.5-11.9), and 1.3 (95% CI, 0.3-2.0), respectively, compared to their reference groups. Relative risks for pulmonary embolism and their 95% CIs in these relatives were similar to deep vein thrombosis relative risk estimates. Extra sensitivity analysis censoring relatives with concomitant pulmonary embolism and deep vein thrombosis did not change outcomes (data not shown). Neither did exclusion of all relatives (n=334) of probands (n=106) with arterial thrombosis change outcomes.

We observed the factor V Leiden paradox which has been described elsewhere in our population as well. As to the suggestion of different clot-structure in persons carrying factor V Leiden, which could be supposed to be due to activated protein C resistance, one would expect to also find it in other thrombophilic defects influencing activated protein C, like protein S deficiency for example. Still, with no other thrombophilic defect a paradox similar to that observed in relatives with factor V Leiden was seen. Therefore, we have found no leads in this study that could explain why the factor V Leiden paradox exists.
References