The association of factor V Leiden with various clinical patterns of venous thromboembolism—the factor V Leiden paradox

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Summary

Background: Factor V Leiden (FVL) supposedly carries relatively higher risk of deep vein thrombosis (DVT), compared to the risk of pulmonary embolism (PE).

Aim: To prove this paradox in a group of patients with various clinical presentation of venous thromboembolism (VTE).

Materials and methods: We retrospectively evaluated clinical pattern of VTE in patients who had been referred to vascular clinic shortly after an acute VTE event. In FVL positive and FVL negative groups we compared the prevalence of isolated symptomatic DVT (proximal or distal) and symptomatic PE with/without DVT, and, moreover, asymptomatic DVT or PE.

Results: Of 575 patients (mean age 57 years, 50.1% women), 120 were FVL positive and those had significantly higher prevalence of isolated symptomatic DVT, compared to symptomatic PE with/without DVT. Proximal DVT location was significantly more frequent in FVL carriers. The prevalence of asymptomatic PE did not differ between the two groups. The rate of asymptomatic DVT tended to be higher in FVL negative group. In a multivariate analysis, we confirmed FVL to be positively associated with isolated DVT presentation (odds ratio OR 1.757; 95% confidence interval (CI) 1.148–2.690). On the contrary, increasing age and unprovoked nature of VTE event carried a higher risk of symptomatic PE.

Conclusions: We confirmed FVL to be significantly associated with isolated symptomatic DVT despite higher prevalence of proximal DVT in FVL carriers. The fact of relatively lower risk of PE in FVL positive patients might have clinical implication. However, mechanisms of FVL paradox remain to be elucidated.

Introduction

Venous thromboembolism (VTE) is traditionally considered as a single disease entity, encompassing two main clinical forms—deep vein thrombosis (DVT) and pulmonary embolism (PE).¹ However, several studies indicate that risk factors for DVT and PE may not be identical.²

The most common hereditary disposition to venous thrombosis is congenital activated protein C resistance (APC-R), caused by factor V Leiden (FVL) mutation, discovered in 1993–94.³⁶ Surprisingly, higher prevalence of FVL in DVT patients, compared to PE patients has been reported repeatedly and quite consistently since 1996.⁷–¹⁰

Several possible mechanisms of this phenomenon, named FVL paradox have been proposed, e.g., a different quality of clots in the presence of FVL. The thrombus is supposedly more stable and more adherent to a vessel wall, perhaps because this
factor enhances local thrombin generation. Some authors found out that FVL carriers developed thrombi of smaller size and more often located distally and therefore less prone to embolize. However, neither differences in clot structure nor in the extent and location of thrombosis in FVL patients have been convincingly demonstrated. The last hypothesis assumed that the presence of FVL would be associated with higher frequency of fatal PE and consequently with a lower prevalence of FVL in PE survivors. However, autopsy studies have found no differences in FVL prevalence in patients with fatal PE, compared to VTE survivors or to general population.

So, satisfactory explanation has not been found so far and some still doubt whether the FVL paradox really exists.

The aim of our study was to compare VTE clinical pattern in FVL positive (FVL+) and FVL negative (FVL–) group.

Materials and Methods

Patients

The study had been performed since September 2003 to December 2011 in the setting of a tertiary university hospital. We included 575 consecutive VTE patients, aged over 18 years, referred to vascular clinic shortly after VTE—1–3 weeks after the event, respectively. The initial treatment of the event had been started either on inpatient basis, in the Department of Internal Medicine, or on outpatient basis in the general clinic for internal medicine. The patients had been referred to the specialized vascular clinic for further management and follow-up. All the patients provided a written informed consent.

We carefully reviewed medical reports and performed a structured interview with the patients in order to evaluate the symptoms and signs of VTE event at the time of diagnosis, to check the results of the applied imaging methods and to obtain detailed patients’ history focusing especially on previous VTE events, potential provoking factors of VTE, smoking status, concomitant diseases and medication. We measured patients’ anthropometric characteristics and calculated body mass index (BMI) as weight divided by the square of height, in kilograms per square meter (kg/m²).

VTE diagnosis and classification of clinical manifestation

The diagnosis had been objectively confirmed with complete compression ultrasound of both legs in the cases of DVT and high probability perfusion/ventilation lung scan or/helical CT pulmonary angiography in the cases of PE.

We classified VTE events as unprovoked or provoked—triggered by following factors: injury, plaster cast, surgery within 2 months prior to VTE; active malignancy; acute infection; immobility for at least three consecutive days; pregnancy, delivery, puerperium; oestrogen therapy; long distance travel within a month prior to VTE.

We classified the patients into two groups: symptomatic DVT only (without any symptoms of PE); symptomatic PE with or without symptomatic DVT. Screening for a silent PE had not been performed systematically but had been at the treating physician’s discretion. Nevertheless, a majority of patients with isolated DVT symptoms had undergone testing for PE (68.9%). Moreover, venous ultrasound searching for an asymptomatic DVT had been performed in almost all the patients with isolated PE symptoms (95.9%).

As to DVT location, we considered calf vein thrombosis as distal and thrombosis in popliteal vein or above as proximal DVT.

Blood collection, laboratory tests

Factor V Leiden 1691G>A and factor II gene 20210G>A genotypes were determined using PCR-based DNA test as described in the literature.

Statistical analysis

For database management and statistical analysis, we used SAS software version 9.2 (SAS Institute, Cary, USA). We compared means and proportions using Student t-test and Fisher exact test, respectively. We used multivariable logistic regression to explore the effect of FVL on clinical manifestation of VTE. As covariates, we considered those variables whose distributions were at least borderline different in FVL+ and FVL– groups.

Results

Demographic, clinical and laboratory characteristics of patients

We enrolled 575 patients (288 women; 50.1%), aged 18–90 years (mean 57, median 59 years). Nearly half of VTE events (49.0%, respectively) were evaluated as unprovoked.

Relatively high proportion of the patients (20.9%) had recurrent VTE—they had a history of previous VTE episodes prior to the index event, respectively. Symptoms of DVT were present in 379 patients,
those of PE in 282 ones, with simultaneous occurrence of both clinical manifestations in 86 cases.

Of the whole group, FVL was found in 120 cases (20.9%). Prothrombin gene mutation G20210A was revealed in 26 cases (4.5%).

The comparison of FVL positive and FVL negative patients

The characteristics as well as various VTE clinical forms in FVL+ and FVL− subjects are presented in Table 1. FVL+ patients were significantly younger and the percentage of current smokers was significantly higher in this group. Further on, VTE events were more frequently unprovoked in FVL+ individuals but this difference did not reach statistical significance.

As to the differences in clinical manifestation, isolated symptomatic DVT was significantly more frequent and isolated symptomatic PE significantly less frequent in FVL+ group. However, no difference in the prevalence of silent PE between FVL+ and FVL− patients was found (the percentage of tested patients in both groups was comparable). Asymptomatic DVT tended to be more frequent in FVL− subjects. Moreover, proximal DVT was significantly more common in FVL+ patients.

A significant association of FVL and VTE clinical pattern was further confirmed by a multivariable logistic regression. The results are presented in Table 2. The presence of FVL was confirmed to be significantly associated with isolated DVT presentation (odds ratio OR 1.757; 95% confidence interval (CI) 1.148–2.690), as compared to symptomatic PE (with or without symptomatic DVT). On the contrary, increasing age and unprovoked nature of the event were independently associated with symptomatic PE.

Discussion

In our study of VTE patients, FVL+ subjects had PE presentation significantly less often, compared to FVL− group.

Similar results came from RIETE, a large VTE international registry. In a group of 22 428 patients, PE was significantly less present in FVL carriers vs. non-carriers (31% vs. 45%, P<0.001).

On the contrary, Danish authors did not confirm FVL paradox. However, the design of their study was different. They performed a cohort study of 9253 randomly selected individuals with 23 years of follow-up and evaluated the rate of hospitalization and death from VTE. They assessed OR for DVT as 2.4 in FVL heterozygotes and 22 in homozygotes while the respective OR for PE was 3.0 and 11.0, as compared to non-carriers. Thus, they did not find

Table 1  FVL positive and FVL negative patients—characteristics, VTE clinical presentation

<table>
<thead>
<tr>
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<th>FVL+ n=120</th>
<th>FVL− n=455</th>
<th>P*</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>53.8 ± 17.8</td>
<td>57.4 ± 16.8</td>
<td>0.042</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>56 (46.7)</td>
<td>232 (51.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>29.2 ± 5.5</td>
<td>29.0 ± 5.6</td>
<td>0.78</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>31 (25.8)</td>
<td>79 (17.4)</td>
<td>0.036</td>
</tr>
<tr>
<td>Unprovoked VTE event, n (%)</td>
<td>60 (50.0)</td>
<td>189 (41.5)</td>
<td>0.096</td>
</tr>
<tr>
<td>Recurrent VTE event, n (%)b</td>
<td>27 (22.5)</td>
<td>93 (20.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>Prothrombin gene G20210A</td>
<td>5 (4.2)</td>
<td>21 (4.6)</td>
<td>0.83</td>
</tr>
<tr>
<td>Isolated symptomatic DVT, n (%)</td>
<td>74 (61.7)</td>
<td>219 (48.1)</td>
<td>0.0083</td>
</tr>
<tr>
<td>Symptomatic DVT with symptomatic PE, n (%)</td>
<td>18 (15.0)</td>
<td>68 (15.0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Isolated symptomatic PE, n (%)c</td>
<td>28 (23.3)</td>
<td>168 (36.9)</td>
<td>0.0052</td>
</tr>
<tr>
<td>Asymptomatic DVT, n (%)d</td>
<td>10 (37.0)</td>
<td>89 (55.3)</td>
<td>0.079</td>
</tr>
<tr>
<td>Asymptomatic PE, n (%)d</td>
<td>15 (30.0)</td>
<td>55 (36.2)</td>
<td>0.42</td>
</tr>
<tr>
<td>Proximal DVT, n (%)e</td>
<td>71 (69.6)</td>
<td>215 (57.2)</td>
<td>0.023</td>
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</table>

*a*-test used for age and BMI, X² for categorical variables.

bRefers to patients with positive personal history of VTE, prior to the index event.

cRefers to patients with isolated PE symptoms who were examined for DVT, i.e. 27 FVL+ and 161 FVL− patients.

dRefers to patients with isolated DVT symptoms who were examined for PE, i.e. 50 FVL+ and 152 FVL− patients.

eRefers to all patients with DVT, both symptomatic and asymptomatic, i.e. 478 patients, i.e. 102 FVL+ and 376 FVL− patients (eight asymptomatic patients of the whole group had not venous ultrasound performed).

Abbreviations: FVL, factor V Leiden; BMI, body mass index; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism
the association of FVL with DVT presentation. However, it is possible that counting the numbers of hospitalization and death from VTE, the authors might have missed the cases of DVT treated on outpatient basis.

One older pooled analysis including 8 case-control studies with 2,310 VTE cases calculated OR for PE in the presence of FVL as 0.69 (95% CI 0.51-0.92). The authors compared the rate of isolated DVT to the rate of PE with/without DVT and their finding is very much similar to our results. However, they did not distinguish proximal and distal DVT location.

The latest meta-analysis included 19 studies with 11,111 VTE patients. Unlike in the previous analysis, the authors evaluated the association of FVL with presentation as DVT with/without PE, compared to presentation as isolated PE. Therefore, their results are not fully comparable to ours. They calculated OR for DVT presentation in FVL+ patients as 2.39 (95% CI 2.08-2.75). Again, the authors did not comment on proximal or distal DVT location.

There was a remarkable heterogeneity among the studies, especially in the design and population. In some studies, the population was highly selected, e.g. relatively younger patients were included. Further on, potential misclassification of VTE events might have occurred. Namely, the terms symptomatic—asymptomatic—isolated DVT or PE might have been confused. In most studies all patients with PE symptoms were routinely tested for DVT. However, none of the studies systematically searched for silent PE in patients with DVT symptoms. Therefore, the term ‘DVT’ was used probably for both symptomatic and asymptomatic DVT while ‘PE’ meant symptomatic PE only.

In our study, we strictly distinguished symptomatic from asymptomatic DVT and/or PE. In our opinion, patients with isolated symptomatic PE and those with symptoms of both DVT and PE should be merged in a single symptomatic PE group. Symptomatic PE is generally considered as more severe VTE form, with potentially fatal or disabling consequences. Therefore, it might be useful to specify risk (or protective) factors for this more significant manifestation.

To our knowledge, no study has addressed the relationship between FVL and silent PE so far. In our study, symptomatic PE was less frequent in FVL+ while asymptomatic PE was found almost equally in FVL+ and FVL– group. In this context, data from RIETE registry indicate that PE event (if developed) in FVL+ patients is less often accompanied with hypoxemia. The authors hypothesize that this may mean less severe clinical course of PE in FVL+ patients.

In contradiction to some studies, we found the presence of FVL to be significantly associated with proximal thrombus location. This is in agreement with the results of recent meta-analysis of 12 studies, including 5733 patients. Thus, our results do not confirm the hypothesis that lower prevalence of proximal DVT in FVL+ patients might be the explanation of FVL paradox.

A recent epidemiologic research of Dutch investigators focused in detail on VTE risk factors and their differential effect on clinical manifestation. It is hardly possible to compare the findings of this large systematic review with the results of our single-centre retrospective study but in some aspects we revealed similar relations between respective risk factor and VTE clinical pattern. The authors not only confirmed FVL paradox but broadened it—they proved an effect comparable to FVL for other risk factors (many of them, in fact, represent acquired APC-R) and, moreover, they also found some conditions with an opposite effect (i.e. a higher risk of PE). Oral contraceptive use, pregnancy, puerperium, obesity and minor leg injuries were stronger risk factors for DVT than for PE in their review. In our study, BMI was not significantly related to VTE clinical presentation. We did not evaluate the other mentioned factors separately.

### Table 2
Factors associated with isolated symptomatic DVT compared to symptomatic PE with/without symptomatic DVT—results of multivariate logistic regression

<table>
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<th>Factor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
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<tr>
<td>Age</td>
<td>0.988</td>
<td>0.977–0.998</td>
<td>0.025</td>
</tr>
<tr>
<td>FVL</td>
<td>1.757</td>
<td>1.148–2.690</td>
<td>0.0095</td>
</tr>
<tr>
<td>Unprovoked VTE event</td>
<td>0.557</td>
<td>0.390–0.796</td>
<td>0.0013</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.281</td>
<td>0.816–2.011</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; FVL, factor V Leiden.
we took them into account in the classification of VTE cases to provoked and unprovoked (together with surgery, immobility, active malignancy and acute infection). We proved a negative association of an unprovoked nature of the event with isolated symptomatic DVT. Moreover, age was associated with a higher risk for PE in the systematic review and the same association was found in our study.

In accordance with the review, we did not prove any effect of sex and smoking on VTE manifestation. Unlike the authors of the review, we did not evaluate the influence of chronic obstructive pulmonary disease and sickle cell disease—these were associated with a higher risk of PE in the review but in our group the proportion of these conditions was quite low. We neither assessed the impact of prothrombin gene mutation because its prevalence in our group was quite low as well. We neither assessed the impact of prothrombin gene mutation because its prevalence in our group was quite low. We neither assessed the impact of prothrombin gene mutation because its prevalence in our group was quite low. We neither assessed the impact of prothrombin gene mutation because its prevalence in our group was quite low. We neither assessed the impact of prothrombin gene mutation because its prevalence in our group was quite low. We neither assessed the impact of prothrombin gene mutation because its prevalence in our group was quite low. We neither assessed the impact of prothrombin gene mutation because its prevalence in our group was quite low.

We are aware of potential limitations of our study. It was retrospective and the classification of VTE clinical forms (though evaluated thoroughly and based both on medical report and patient’s description) may be biased to some extent. We did not limit the inclusion to the subjects with the first VTE event. But the percentage of patients with a positive history of previous VTE did not differ in the compared groups. The other objection might be incomplete screening for asymptomatic events. However, venous ultrasound was performed in all but eight patients. Further on, the proportion of patients tested for silent PE did not differ between FVL+ and FVL− individuals.

However, our study seems to have also some strengths. We included consecutive unselected patients, treated both on inpatient and outpatient basis. Venous ultrasound was performed bilaterally and included calf veins systematically. Our classification of VTE events to symptomatic PE with/without symptomatic DVT and isolated symptomatic DVT seems to have clinical relevance. We also attempted to evaluate the association of FVL with asymptomatic events. Moreover, we took into consideration some other factors potentially relevant to VTE clinical presentation.

Our results may have some practical implications. In the patients with known FVL, presenting with DVT, the awareness of lower PE probability may support the decision about outpatient treatment. Further on, this knowledge may also influence the decision about the length of anticoagulation.

Our findings might also inspire further research, aiming at the elucidation of biological background of FVL paradox and, in a broader sense, focusing on the differences in natural history of VTE in patients with and without thrombophilia and the possible interaction of respective risk factors.

In conclusion, in the group of 575 patients, the presence of FVL was significantly associated with isolated DVT, compared to PE with or without DVT. This phenomenon, called FVL paradox, deserves further clinical as well as basic research.

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**References**


