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

Anja B.U. Mäkelburg,[1] Nic J.G.M. Veeger,[1] Saskia Middeldorp,[3] Karly Hamulyák,[4] Martin H. Prins,[5] Harry R. Büller,[2] and Willem M. Lijfering[1]

[1]Division of Hemostasis and Thrombosis, Department of Hematology, University Medical Center Groningen, Groningen; [2]Department of Vascular Medicine, Academic Medical Center, Amsterdam; [3]Department of Clinical Epidemiology and Department of General Internal Medicine, Leiden University Medical Center; [4]Department of Hematology, Maastricht University Medical Center, Maastricht; [5]Department 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.[1,2] Symptomatic pulmonary embolism is present in about a third of patients with venous thrombosis.[3] 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.[4] This differential effect is known as the "factor V Leiden paradox"[5] and has been reported repeatedly.[6-10] 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.[11,12] 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,[10] 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.[10]

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.[13-17]

Between May 1998 and July 2004, first-degree relatives aged 15

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Correspondence: Anja B.U. Mäkelburg; Division of Hemostasis and Thrombosis, Department of Hematology, University Medical Centre Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands. E-mail: a.b.u.makelburg@int.umcg.nl

years or older of consecutive patients (probands) with documented 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 thrombosis, exposure to exogenous risk factors for thrombosis and anticoagulant treatment was collected by physicians at the outpatient clinics using a validated questionnaire[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.[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 venography, and pulmonary embolism by ventilation/perfusion lung scanning, spiral computed tomography or pulmonary angiography, or when the patient had received full-dose heparin and a vitamin K antagonist for at least three months without objective testing 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, pregnancy, 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 pulmonary 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 collected at the outpatient clinics. Hence, treatment and clinical outcome 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 pulmonary 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 pulmonary 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; categorical 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 analyses 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.

	Total (n=2054)	First venous thrombosis = proximal DVT (n=134)	First venous thrombosis = PE (n=41)
Women	1131 (55)	83 (62)	22 (54)
Age at enrollment	46 (15-92)	57 (28-89)	49 (16-87)
Age at onset first venous thrombosis	35 (15-84)	34 (16-73)	36 (15-84)
Idiopathic	69 (3)	52 (39)	17 (41)
Provoked by			
Oral contraceptives	28 (1)	20 (15)	8(20)
Pregnancy/puerperium	28 (1)	24 (18)	4 (10)
Surgery, trauma, immobilization	49 (2)	37 (28)	12 (29)
Malignancy	1 (0)	1 (1)	0 (0)
Prevalence thrombophilic defects *			
Antithrombin deficiency	59 (3)	18 (13)	7 (17)
Protein C deficiency	81 (4)	22 (16)	5 (12)
Protein S deficiency	83 (4)	20 (15)	7 (17)
Factor V Leiden	254 (12)	29 (22)	5 (12)
Prothrombin G20210A	255 (12)	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.*

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

		Observation years*	Relatives with event	Annual incidence, % (95% CI)	Relative risk (95% CI)	Relative risk (95% CI)†
Deep vein thrombosis						
No factor V Leiden	(n=1800)	53829	103	0.19 (0.16-0.23)	Reference	Reference
Factor V Leiden	(n=254)	7651	31	0.41 (0.28-0.58)	2.1 (1.4-3.2)	2.1 (1.4-3.2)
No AT deficiency	(n=1991)	59959	108	0.18 (0.15-0.22)	Reference	Reference
AT deficiency	(n=59)	1386	18	1.30 (0.77-2.05)	7.2 (4.4-11.9)	6.2 (3.8-10.2)
No Prot. C deficiency	(n=1916)	57180	95	0.17 (0.14-0.20)	Reference	Reference
Prot. C deficiency	(n=81)	2062	22	1.07 (0.67-1.62)	6.4 (4.0-10.2)	5.7 (3.6-9.1)
No Prot. S deficiency	(n=1920)	57777	97	0.17 (0.14-0.20)	Reference	Reference
Prot. S deficiency	(n=83)	1623	20	1.23 (0.75-1.90)	7.3 (4.5-11.9)	6.5 (4.0-10.6)
No G20210A-mutation	(n=1792)	53798	107	0.20 (0.16-0.24)	Reference	Reference
G20210A-mutation	(n=260)	7642	19	0.25 (0.15-0.39)	1.3 (0.8-2.0)	1.3 (0.8-2.1)
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)	9.2 (4.0-21.2)	9.7 (4.2-22.8)
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 with arterial thrombosis. AT denotes antithrombin, Prot. C denotes protein C and Prot. S denotes protein S.*

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

Annual incidence 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, 0.8-2.0), respectively, compared to their reference groups. Relatives 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[4-10] 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.

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.[19] 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.

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References

1. Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. J Intern Med. 1992;232(2):155-60.
2. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A. The prevalence of risk factors for venous thromboembolism among hospital patients. Arch Intern Med. 1992;152(8):1660-4.
3. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost. 2007;5(4):692-9.
4. Desmarais S, de Moerloose P, Reber G, Minazio P, Perrier A, Bounameaux H. Resistance to activated protein C in an unselected population of patients with pulmonary embolism. Lancet. 1996;347(9012): 1374-5.
5. Bounameaux H. Factor V Leiden paradox: risk of deep-vein thrombosis but not of pulmonary embolism. Lancet. 2000;356(9225): 182-3.
6. Martinelli I, Cattaneo M, Panzeri D, Mannucci PM. Low prevalence of factor V:Q506 in 41 patients with isolated pulmonary embolism. Thromb Haemost. 1997; 77(3): 440-3.
7. Turkstra F, Karemaker R, Kuijer PM, Prins MH, Büller HR. Is the prevalence of the factor V Leiden mutation in patients with pulmonary embolism and deep vein thrombosis really different? Thromb Haemost. 1999;81(3):345-8.
8. Meyer G, Emmerich J, Helley D, Arnaud E, Nicaud V, Alhenc-Gelas M, et al. Factors V leiden and II 20210A in patients with symptomatic pulmonary embolism and deep vein thrombosis. Am J Med. 2001; 110 (1):12-5.
9. Emmerich J, Rosendaal FR, Cattaneo M, Margaglione M, De Stefano V, Cumming T, et al. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism--pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Study Group for Pooled-Analysis in Venous Thromboembolism. Thromb Haemost. 2001;86(3): 809-16.
10. van Stralen KJ, Doggen CJ, Bezemer ID, Pomp ER, Lisman T, Rosendaal FR. Mechanisms of the factor V Leiden paradox. Arterioscler Thromb Vasc Biol. 2008; 28(10):1872-7.
11. Kuismanen K, Savontaus ML, Kozlov A, Vuorio AF, Sajantila A. Coagulation factor V Leiden mutation in sudden fatal pulmonary embolism and in a general northern European population sample. Forensic Sci Int. 1999;106(2):71-5.
12. Vandenbroucke JP, Bertina RM, Holmes ZR, Spaargaren C, van Krieken JH, Manten B, et al. Factor V Leiden and fatal pulmonary embolism. Thromb Haemost 1998; 79(3):511-6.
13. Bank I, Libourel EJ, Middeldorp S, van Pampus EC, Koopman MM, Hamulyak K, et al. Prothrombin 20210A mutation: a mild risk factor for venous thromboembolism but not for arterial thrombotic disease and pregnancy-related complications in a family study. Arch Intern Med. 2004;164(17): 1932-7.
14. Bank I, Libourel EJ, Middeldorp S, Hamulyak K, van Pampus EC, Koopman MM, et al. Elevated levels of FVIII:C within families are associated with an increased risk for venous and arterial thrombosis. J Thromb Haemost. 2005;3(1):79-84.
15. Brouwer JL, Veeger NJ, van der Schaaf W, Kluin-Nelemans JC, van der Meer J. Difference in absolute risk of venous and arterial thrombosis between familial protein S deficiency type I and type III. Results from a family cohort study to assess the clinical impact of a laboratory test-based classification. Br J Haematol. 2005;128(5): 703-10.
16. Brouwer JL, Veeger NJ, Kluin-Nelemans JC, van der Meer J. The pathogenesis of venous thromboembolism: evidence for multiple interrelated causes. Ann Intern Med. 2006;145(11):807-15.
17. Lijfering WM, Coppens M, van de Poel MH, Middeldorp S, Hamulyak K, Bank I, et al. The risk of venous and arterial thrombosis in hyperhomocysteinaemia is low and mainly depends on concomitant thrombophilic defects. Thromb Haemost. 2007; 98(2):457-63.
18. Frezzato M, Tosetto A, Rodeghiero F. Validated questionnaire for the identification of previous personal or familial venous thromboembolism. Am J Epidemiol. 1996; 143(12):1257-65.
19. Büller HR, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. J Thromb Haemost. 2008;6(8):1313-8.