Brief report

Increased risk of venous thrombosis in persons with clinically diagnosed superficial vein thrombosis: results from the MEGA study

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Superficial vein thrombosis (SVT) is regarded a self-limiting disorder, although the authors of recent studies showed that ultrasonographically diagnosed SVT is a precursor for venous thrombosis. We aimed to determine whether the same holds true for clinically diagnosed SVT and to what extent it is associated with thrombophilia in a population-based case-control study (ie, Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis). We found that a history of clinical SVT was associated with a 6.3-fold (95% confidence interval [CI] 5.0-8.0) increased risk of deep-vein thrombosis and a 3.9-fold (95% CI 3.0-5.1) increased risk of pulmonary embolism. Blood group non-O and factor V Leiden showed a small increase in SVT risk in controls, with odds ratios of 1.3 (95% CI 0.9-2.0) and 1.5 (95% CI 0.7-3.3), respectively. In conclusion, clinically diagnosed SVT was a risk factor for venous thrombosis. Given that thrombophilia was only weakly associated with SVT, it is likely that other factors (varicosis, obesity, stasis) also play a role in its etiology. (*Blood*. 2011; 118(15):4239-4241)

Introduction

Superficial vein thrombosis (SVT) is a controversial disease entity.[1] Previously called thrombophlebitis, the name suggests that both thrombosis and inflammation play a role in the disease mechanism. The authors of recent studies provide evidence that SVT should be seen as a form of venous thrombosis (VT), together with pulmonary embolism and deep-vein thrombosis.[1-6] In a recent clinical trial (Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo; CALISTO) investigators showed a symptomatic VT rate of 1.5% within 77 days after the diagnosis of SVT in placebo users.[2] This VT rate was probably positively influenced by the definition of SVT that CALISTO investigators used. Although most physicians learn that SVT is identifiable by a red, painful, palpable cord in the course of a superficial vein,[1,7] in CALISTO, SVT was only regarded as definitely diagnosed when in addition to these clinical signs an ultrasonography of the superficial vein showed a clot of at least 5 cm in length. The authors of current literature agree that such SVTs should be regarded as "real" SVT,[2,8] but this does not follow clinical practice, nor does it imply that there is no clot present in less-definite presentations. It is therefore uncertain whether patients with clinically diagnosed, but not necessarily ultrasonographically confirmed, SVT are at risk of VT and whether this risk can be explained by underlying thrombogenic causes.

For these reasons we sought to determine whether a history of clinically diagnosed SVT is associated with an increased risk of subsequent VT in a large population-based case-control study (ie, Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis [MEGA] study). We also analyzed whether common thrombophilic genetic risk factors for VT increase the risk of SVT, as well as whether the presence of such thrombophilia could explain the link between the 2 conditions.

Study design

The MEGA study is a population-based case-control study that has been described in detail elsewhere.[9] Approval for this study was obtained from the Medical Ethics Committee of the Leiden University Medical Center, and all participants provided written informed consent according to the Declaration of Helsinki. Participants were 18-70 years of age, and 4956 consecutive patients with deep-vein thrombosis or pulmonary embolism were enrolled, together with 6297 age- and sex-matched controls. A questionnaire was filled in to assess VT risk factors; one of the topics was the presence of SVT at any time before VT event onset or enrollment. In addition, participants provided a blood or buccal swab sample for DNA.

Common genetic risk factors were assessed, that is, the factor V Leiden mutation, prothrombin G20210A, and ABO blood group, which were determined by PCR with use of the TaqMan assay. Technicians were blinded to whether the samples came from patients or controls. For the present analysis, questionnaire data on SVT were available from 4290 patients and 5754 controls. No acquired risk factors for SVT (such as varicosis or cancer)[3,10,11] were analyzed to avoid temporality issues, that is, the questionnaire did not provide data on the time relation between these acquired risk factors in relation to date of SVT and enrollment in the study. Besides, previous studies have already shown that acquired risk factors such as varicosis, malignancy, and obesity are associated with SVT.[3,8,10,12]

Odds ratios (ORs) with 95% confidence intervals (CIs) for the risk of SVT on VT were calculated by the use of logistic regression models. ORs for genetic risk factors were calculated for SVT as a binary outcome. This was performed in the case group and in the

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Table 1. Superficial vein thrombosis as a risk factor for various types of venous thrombosis

	Patients, n (%)					Adjusted odds ratio (95% CI)*			
	All	DVT only	PE and DVT	PE only	Controls, n (%)	Overall	DVT only	PE and DVT	PE only
No SVT	3876 (90)	2211 (89)	359 (89)	1306 (93)	5644 (98)	Reference	Reference	Reference	Reference
SVT	414 (10)	265 (11)	45 (11)	104 (7)	110 (2)	5.4 (4.4-6.8)	6.3 (5.0-8.0)	6.5 (4.5-9.4)	3.9 (3.0-5.1)
Adjusted for FVL						4.6 (3.7-5.8)	5.3 (4.1-6.8)	5.6 (3.8-8.3)	3.5 (2.6-4.7)
Adjusted for FVL, FII, ABO						4.4 (3.5-5.5)	5.0 (3.9-6.4)	5.5 (3.7-8.3)	3.4 (2.5-4.5)

ABO indicates ABO blood group; CI, confidence interval; DVT, deep-vein thrombosis; FII, prothrombin G20210A; FVL, factor V Leiden; PE, pulmonary embolism; and SVT, superficial vein thrombosis.

*Adjusted for age and sex.

control group separately. Because the relation between SVT and VT could be explained by the presence of thrombophilia, we adjusted the association between SVT and VT for factor V Leiden, prothrombin G20210A, and the ABO blood group. All analyses were adjusted for age and sex to take the matching into account.

Results and discussion

Our study included 2887 patients with deep-vein thrombosis only, 447 patients with pulmonary embolism only, and 1622 with both deep-vein thrombosis and pulmonary embolism. Median age (interquartile range) was 50 years (39-59 years) for patients and 48 years (37-57 years) for controls. SVT prevalence was 10% (n = 414) in patients and 2% (n = 110) in controls (Table 1). Participants with previously diagnosed SVT were 6 times more likely to have a deep-vein thrombosis (OR 6.3; 95% CI 5.0-8.0) than controls and 4 times more likely to have a pulmonary embolism (OR 3.9; 95% CI 3.0-5.1) than controls. Genetic risk factors for SVT are shown in Table 2. In both patients and controls, blood group non-O had a 1.3-fold increased risk for SVT with blood group O as a reference group. For patients with factor V Leiden, this OR was 2.0 (95% CI 1.6-2.6), whereas for controls the OR was 1.5 (95% CI 0.7-3.3). Prothrombin G20210A was associated with a 1.3-fold (95% CI 0.9-2.0) increased risk of SVT in patients and 0.9-fold (95% CI 0.2-3.7) in controls. Subsequently, we adjusted the association between SVT and deep-vein thrombosis for factor V Leiden, prothrombin G20210A, and ABO blood group. This attenuated the effect estimates slightly, indicating that a small part of the association could be explained by these prothrombotic mutations.

Our results show that a history of clinically diagnosed SVT is a risk factor for future VT, wherein the risk for deep-vein thrombosis was 6-fold increased compared with persons without SVT and 4-fold increased for pulmonary embolism. These results are in line with recent studies in which authors regard SVT diagnosed by ultrasonography as a precursor of VT.[1,3,12] Furthermore, we found that clinically diagnosed SVT was weakly associated with thrombophilia, something that has been hypothesized[1] but has never been studied before in an unselected population. As far as we know, 3 studies have been performed in which the authors assessed the same genetic risk factors for SVT.[10,13,14] The first, in a case-control study, investigators found an OR for SVT of 6.1 (95% CI 2.6-14.2) for factor V Leiden carriers versus noncarriers.[13] In the second study, a case series, investigators found a factor V Leiden prevalence of 22%.[14] Both studies suggest that SVT is a thrombotic disease like deep-vein thrombosis because the prevalence of factor V Leiden in deep-vein thrombosis is very similar to that found for SVT.[12]

However, in both studies, authors only considered ultrasonographically confirmed SVT, and the patients had been referred to specialized clinics for thrombophilia testing. Therefore, selection must have contributed to the high prevalence of thrombophilia in these studies. The third study resembled our study the most, in that the investigators included SVTs that were not necessarily ultrasonographically confirmed, and compared these with healthy donors.[10] Here factor V Leiden increased the risk of SVT 2.1-fold (95% CI 0.8-5.3) compared with noncarriers. At any rate, the thrombotic component of SVT is probably much smaller compared with deep-vein thrombosis because the effect of the prothrombotic mutations is clearly less pronounced.

Our study has some methodologic issues that warrant comment. First, SVT has been collected as self-reported data in a questionnaire; therefore, no objective verification of diagnoses was possible. However, this fits with our aim to study the role of common clinical practice in the diagnosis of SVT.[6,12] It is possible that symptoms of another condition may have erroneously been reported as SVT, which would have led to misclassification of the exposure. Such misclassification would most likely have occurred in cases and controls to the same extent, and the relative risk we found would then be an underestimation of the true effect. Second, we had no data on the time duration between SVT and the subsequent VT event in our study, so we could not calculate specific risk estimates for different time frames. In line with the

Table 2. Genetic risk factors for SVT (thrombophlebitis) in patients and controls in the MEGA study

	Patients, thrombophlebitis				Controls, thrombophlebitis			
	Yes (n)	No (n)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*	Yes, n	No, n	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)*
Blood group O	96	1034	Reference	Reference	40	2109	Reference	Reference
Blood group non-O	286	2509	1.2 (1.0-1.6)	1.3 (1.0-1.6)	61	2457	1.3 (0.9-2.0)	1.3 (0.9-2.0)
No factor V Leiden	290	3020	Reference	Reference	94	4324	Reference	Reference
Factor V Leiden	97	532	1.9 (1.5-2.4)	2.0 (1.6-2.6)	7	244	1.3 (0.6-2.9)	1.5 (0.7-3.3)
No prothrombin G20210A	361	3373	Reference	Reference	99	4478	Reference	Reference
Prothrombin G20210A	26	182	1.3 (0.9-2.0)	1.3 (0.9-2.0)	2	91	1.0 (0.2-4.1)	0.9 (0.2-3.7)

CI indicates confidence interval; MEGA, Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis; and SVT, superficial vein thrombosis..

*Adjusted for age and sex.

previous comment, we presented the results unadjusted for possible acquired confounders because it was unknown whether these possible confounders came before or after SVT in time. Adjusting for confounders in an unknown time relation could introduce rather than remove bias. Therefore, our data continue to erode the notion that SVT is a separate and benign form of VT. We recommend clinicians to include a patient's history of clinically diagnosed SVT in their risk stratification analysis.

In summary, clinically diagnosed SVT was associated with a 4- to 6-fold increased risk of pulmonary embolism and deep-vein thrombosis, respectively. That genetic VT risk factors were only weakly associated with SVT suggests that other components (inflammation, obesity, stasis) also play a role in causing SVT.

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Authorship

Contribution: K.v.L. drafted the manuscript and performed statistical analyses; W.M.L. designed the analyses and revised the manuscript; F.R.R. was responsible for the MEGA study concept and design and revision of the manuscript; and S.C.C. revised the manuscript.

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