Thrombosis Research 132 (2013) 47–50

Contents lists available at SciVerse ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Factors associated with the development of superficial vein thrombosis in patients with varicose veins

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ARTICLE INFO

Article history:
Received 7 February 2013
Received in revised form 29 April 2013
Accepted 21 May 2013
Available online 12 June 2013

Keywords:
Superficial vein thrombosis
Varicose veins
Thrombophilia
Hypercoagulable states
Protein S deficiency
Obesity

ABSTRACT

Introduction: Superficial vein thrombosis (SVT) is a common and controversial clinical entity. Recent studies have demonstrated that SVT should be seen as a venous thromboembolism (VTE). The objective of this study was to investigate the prevalence of thrombophilia defects and to estimate the role of age, sex and body mass index (BMI) in patients with varicose veins (VVs) and SVT.
Materials and Methods: A total of 230 patients with VVs, 128 with, and 102 without SVT underwent thrombophilia testing included factor V Leiden, prothrombin G20210A, methylenetetrahydrofolate reductase and plasminogen activator inhibitor- 1 mutations, protein C, protein S (PS), anti-thrombin III and plasminogen deficiencies and levels of A_2 antiplasmin, activate protein C resistance and lupus anticoagulant. According to Clinical- Etiology- Anatomy- Pathophysiology (CEAP) classification patients were categorized in two subgroups: moderate disease ($C_{2,3}$) and severe disease ($C_{4,5,6}$). Age and body mass index were also assessed.
Results: The prevalence of thrombophilia defects was significantly higher in patients with moderate disease and SVT ($p = 0.002$). In the $C_{2,3}$ group, SVT was associated with PS deficiency ($p = 0.018$), obesity ($p < 0.001$), male gender ($p = 0.047$) and age ($p < 0.001$). There were no significant differences in patients with severe disease.
Conclusions: Age, male sex, obesity and PS deficiency are factors associated with SVT development among patients with VVs having moderate disease ($C_{2,3}$).

Introduction

Superficial vein thrombosis (SVT) of the lower limb is a common disease and in the past it has been consider as a benign condition with low clinical importance [1,2]. Recent findings have demonstrated SVT to be a potential dangerous entity causing deep vein thrombosis (DVT) and/or pulmonary embolism (PE), with reported incidence ranges of 6% to 53%, and 0% to 10%, respectively [1–4].

This association of SVT with venous thromboembolism (VTE) indicates a common pathogenic mechanism. Furthermore, a number of shared risk factors such as malignancy, estrogen exposure, recent surgery and auto-immune diseases support this concept [5]. Hypercoagulable states are associated with an increased risk of VTE, but whether they are also risk factors for SVT is uncertain and routine screening is not recommended [6,7]. Although previous studies demonstrated a high incidence of hypercoagulable states in patients with saphenous vein thrombosis, there are no large studies evaluating the prevalence of these disorders in different cohorts of patients with SVT [8–11].

The aim of this study was to determine the prevalence of thrombophilic defects and to estimate the role of age,sex and body mass index (BMI) in patients with varicose veins (VVs) and SVT.

Materials and Methods

Patients

From February 2009 to June 2012 all patients with SVT were examined prospectively at the Department of Vascular Surgery, Larissa, Greece. Patients with predisposing conditions such as malignancy, sepsis, recent surgery or trauma, prolonged immobilization, autoimmune disorders, pregnancy, hormone therapy, hepatic or renal insufficiency and patients with a history of DVT or PE were excluded. Also patients referred to our department during the same period with VVs without a history of a previous thrombosis were included as control group.

Abbreviations: CEAP, Clinical- Etiology- Anatomy-Pathophysiology; PS, protein S; SVT, superficial vein thrombosis; VTE, venous thromboembolism; VVs, varicose veins.

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http://dx.doi.org/10.1016/j.thromres.2013.05.017

In all patients bilateral venous duplex ultrasound (DUS) was performed. SVT was diagnosed when superficial veins were not compressible under the probe. Furthermore DUS was used to estimate the extent of thrombus, to exclude the presence of DVT, to define superficial and/or deep venous incompetence and for follow up. The vena cava inferior, iliac veins, sapheno-femoral junction, common femoral, deep femoral, femoral, popliteal and tibial veins were examined. In case of extension of the thrombotic process to deep veins the patient was excluded from the study. A second DUS was performed at the end of the treatment to exclude residual SVT.

According to the Clinical- Etiology- Anatomy- Pathophysiology (CEAP) classification for chronic venous disorders [12] and DUS patients were categorized based on their clinical presentation in four groups: SVT and VVs with moderate disease ($C_{2,3}$); SVT with VVs with severe disease ($C_{4,5,6}$); VVs with moderate disease and without SVT and VVs with severe disease and without SVT. Furthermore, age and BMI were also assessed.

Thrombophilia testing

In all patients blood samples were taken at least three months after the onset of SVT to ensure that the results were not affected by the thrombotic episode or anticoagulation therapy.

The genetic mutations examined included factor V Leiden G1691A (FV Leiden), prothrombin G20210A (FII), plasminogen activator inhibitor-1 factor 5G/4G (PAI-1) and methylenetetrahydrofolate reductase C677T and/or A1298C (MTHFR). All the gene mutations, as well as MTHFR polymorphisms, were determined by an enzymatic reaction of DNA amplification known as Polymerase Chain Reaction (PCR) and allele- specific hybridization. The remaining thrombophilia markers consisted of protein C (PC), protein S (PS), anti-thrombin III (AT III) and plasminogen (Plg) deficiencies and levels of A_2 antiplasmin (A_2 Apl), activate protein C resistance (APCR) and lupus anticoagulant (LA). Anticoagulant proteins (PS, PC, AT III, Plg), and A_2Apl were determined by a chromogenic method while APCR and LA were measured using an aPTT based clotting method. PS deficiency was diagnosed based on low levels of free PS antigen.

The study was approved by the ethical committee of our institution in accordance with the Helsinki Declaration. All patients were informed about the nature and aim of the research and provided their consent to participate.

Statistical methods

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) version 18.0. Chi square tests were applied to initially assess possible statistically significant risk factors at $p < 0.25$. These were then used in a logistic regression model with the forward likelihood ratio method. Interactions of all statistically significant factors at $p < 0.10$ were then examined. All factors entered in the final model had a *p* values equal to or less than 0.05.

Table 2
Comparison of the study population according to age, gender and smoking.

		SUPERFICIAL VEIN TROMBOSIS	CONTROL GROUP	p- value	OR	95%CI
Age	>45 y.o	97	59	0.004	2.28	1.29-4.01
	<45 y.o	31	43			
Gender	Male	43	27	0.243	1.41	0.79-2.49
	Female	85	75			
Smoking	Yes	40	26	0.337	1.33	0.74-2.38
	No	88	76			

Results

A total of 240 patients were included into the study. Ten patients had progression of SVT to deep vein system and were excluded. The SVT group consisted of 128 patients and the control group of 102 patients.

Table 1 shows the main characteristics of the study population. Patients in the SVT group were older than controls. In addition 41% of the patients in the SVT group were overweight ($25 < BMI < 29.9$ Kg/m^2) and 25% obese (BMI > 30 Kg/m^2), while in the control group overweight and obesity were in 34% and 12%, respectively. The location of thrombi in both SVT groups are presented in Table 1. Some patients had more than one thrombotic location and in 45% of the patients the thrombus was confined to varicose tributaries. Among the groups with severe disease, an active venous ulcer was present in 5/7 in patients with SVT and in 2/11 in controls.

Table 2 demonstrates a preliminary analysis of the study population. Person Chi-square test showed that patients older than 45 years had an increased risk of SVT by 2.2 fold compared to younger (OR 2.28, $p = 0.004$, 95%CI 1.29-4.01), while gender and smoking are not significant.

The results of thrombophilia testing in all groups are presented in Table 3. In patients with VVs and moderate disease a hypercoagulable defect was present in 74% in the SVT group and 55% in the control group, while in patients with VVs and severe disease this was found in 100% and 63%, respectively. The prevalence of multiple defects, in patients with C_2 and C_3 disease were, 36% in the SVT group and 17% in the control group, and in patients with C_4 to C_6 disease 43% in SVT group and 27% in controls, respectively. Thirty two patients in the SVT group with multiple defects had a past history of SVT. Among patients with active venous ulcer multiple thrombophilia defects had 3 out of 5 patients with SVT and 1 out of 2 patients without SVT.

Gene mutations were present in 64% of the SVT group with moderate disease, 57% of the SVT with severe disease and in 42% and 81% in the control groups with moderate and severe disease, respectively. Among patients in SVT groups with APCR, in 88% (8/9) this was FV Leiden dependent, while this was found in the only one patient with APCR in the control group. The prevalence of heterozygous MTHFR 677T, MTHFR 1298C polymorphisms, and PAI-1 5G mutations are presented in Table 4. The different distribution of these mutations

Table 1
Demographics and characteristics of the study population.

	SVT group n (%)		Control group n (%)	
	Moderate Disease	Severe Disease	Moderate Disease	Severe Disease
No	121	7	91	11
Female	80 (66%)	5 (71%)	69 (75%)	6 (54%)
Age (mean), (min-max)	56 (23–87)	55 (34–78)	48(20–80)	55(29–68)
Age > 70 y	24(20%)	1(14%)	7 (8%)	0
BMI (mean), (min-max)	27.2 (20.1- 46.9)	28.1 (23.2- 42.1)	25.3(18.8-36)	25.5(20–33.6)
BMI > 30 Kg/m^2	31 (25%)	1 (14%)	9 (10%)	3 (27%)
GSV involvement	59 (49%)	2 (24%)	-	-
SSV involvement	3 (2%)	0	-	-
Other major superficial vein involvement	5 (4%)	1 (14%)	-	-

BMI: body mass index; GSV: great saphenous vein; SSV: small saphenous vein.