ARTICLE ORIGINAL / ORIGINAL ARTICLE

ACQUIRED AND GENETIC RISK FACTORS FOR DEEP VEIN THROMBOSIS OF LOWER EXTREMITIES AMONG LEBANESE PATIENTS

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ABSTRACT • AIM : Venous thrombosis results from the interaction of environmental and genetic risk factors. These factors vary according to the ethnic and geographic distribution of the populations. The aim of this study is to define the role of acquired and genetic risk factors for venous thrombosis of lower extremities among Lebanese patients assessed in a university hospital and to discuss them according to the international literature.

MATERIAL AND METHODS : From January 2005 to January 2010, 166 patients (72 males and 94 females) were diagnosed with lower extremity deep vein thrombosis. Mean age was 67 years (range: 25 to 96 years).

RESULTS : The most frequently reported acquired risk factors for venous thrombosis in this study were advanced age, obesity, history of venous thromboembolism, immobilization, surgery, varicose veins and malignancy. Screening for prothrombotic genetic abnormalities was requested in patients with conditions highly suggestive of hypercoagulation state such as young patients, patients with spontaneous, recurrent or extensive venous thrombosis, patients with family history, oral contraceptives, air travel and pregnancy. All the 45 patients (27.1%) tested for thrombophilia were positive and were carriers for factors V-Leiden (17.4 %), MTHFR C 677 T (16.8%), MTHFR A 1298 C (4.8%), II G 20210 A (1.8%) and V H 1299 R (1.2%) mutation. Twelve patients (7.2%) had increased homocysteine level.

CONCLUSION : Advanced age is the most common risk factor for venous thrombosis in these series. Thrombophilia is the second most frequently observed risk factor and is related to the high prevalence of factor V-Leiden and MTHFR C 677 T mutation among the Lebanese population.

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Kreidy R, Waked M, Stephan E, Irani J, Chemali R, Jureidini I, Irani-Hakime N. Facteurs de risque acquis et génétiques de la thrombose veineuse profonde des membres inférieurs chez les patients libanais. J Med Liban 2012 ; 60 (1) : 24-29.

RÉSUMÉ • BUT : La thrombose veineuse résulte de l'interaction entre les facteurs de risque génétiques et acquis. Ces facteurs varient selon la distribution géographique et ethnique des populations. Le but de cette étude est de définir le rôle des facteurs de risque acquis et génétiques dans le développement de la thrombose veineuse des membres inférieurs chez des patients libanais investigués dans un hôpital universitaire et d'analyser ces facteurs en se référant aux publications internationales.

MATÉRIELS ET MÉTHODES : Entre janvier 2005 et janvier 2010, 166 patients (72 hommes et 94 femmes) ont présenté une thrombose veineuse profonde des membres inférieurs. L'âge moyen est de 67 ans (variant de 25 à 96 ans).

RÉSULTATS : Les facteurs de risque acquis de la thrombose veineuse les plus fréquemment retrouvés ont été l'âge avancé, l'obésité, l'histoire de maladie thromboembolique, l'immobilisation, la chirurgie, les varices et le cancer. Le dépistage de la thrombophilie a été réalisé chez les patients ayant des conditions suggérant fortement un état d'hypercoagulation tels que les patients jeunes, les patients avec thrombose veineuse spontanée, récidivante ou étendue, les patients avec histoire familiale, voyages en avion et les patientes enceintes ou traitées par des contraceptifs oraux. Tous les 45 patients (27,1%) testés pour la thrombophilie étaient positifs et porteurs d'une mutation des facteurs V-Leiden (17,4%), MTHFR C 677 T (16,8%), MTHFR A 1298 C (4,8%), II G 20210 A (1,8%) et V H 1299 R (1,2%). Douze patients (7,2%) avaient une hyper homocystéinémie.

CONCLUSION : L'âge avancé est le facteur de risque le plus commun de la thrombose veineuse dans cette série. La thrombophilie est le deuxième facteur le plus fréquemment observé et il est lié à la haute prévalence de la mutation du facteur V-Leiden et du facteur MTHFR C 677 T dans la population libanaise.

INTRODUCTION

Venous thromboembolism (VTE) is actually the third most common cardiovascular disorder in western populations following myocardial infarction and stroke [1]. American Heart Association statistics document two million cases of deep vein thrombosis (DVT) each year with

the incidence of DVT increasing as the population ages [2]. Pulmonary embolus (PE) accounts for 200 000 deaths each year and the annual cost of the treatment is measured in billions of dollars [3].

The appropriate management of venous thrombosis requires a thorough knowledge of diagnostic and treatment modalities. However, an understanding of the underlying epidemiology and associated risk factors is equally essential. The pathophysiology of venous thrombosis is multifactorial and involves environmental, acquired and genetic factors. These factors vary according to ethnic and geographic distribution of the populations [4]. The aim of this study is to define risk factors including prothrombotic inherited genetic abnormalities for venous thrombosis of lower extremities in out- and inpatients, to analyze these factors and to discuss them according to epidemiologic and pathophysiologic publications in the international literature.

MATERIAL AND METHODS

From January 2005 to January 2010, 166 patients (72 males and 94 females) were diagnosed at Saint George Hospital University Medical Center, with lower extremity DVT by color flow duplex scan examination. Indications for duplex scan was clinical suspicion of VTE. The mean age was 67 years (range 25 to 96 years). Seventy-three (44%) were outpatients and 93 (56%) were hospitalized patients. Venous thrombosis was localized on the right side in 59 patients (35.6%), on the left side in 83 patients (50%) and on both sides in 24 patients (14.4%). Venous thrombosis was observed at the calf level in 78 patients (47%), at the femoro-popliteal level in 49 patients (29.5%) and at the ilio-femoral level in 39 patients (23.5%). Ten patients developed PE and four patients required inferior vena cava filter insertion for resistance to adequate anticoagulation.

Acquired risk factors for DVT were documented. Thrombophilia was screened in patients with specific conditions highly suggestive of hypercoagulation states according to the guidelines proposed by the European Genetics Foundation, the Cardiovascular Educational and Research Trust, the International Union of Angiology and the Mediterranean League on Thromboembolism [5]. These conditions include young age, spontaneous, extended and recurrent DVT, family history, oral contraceptives and estroprogestative drugs, long-haul air travel, pregnancy, inferior vena cava congenital abnormalities and resistance to anticoagulation.

For genetic predisposition, peripheral blood was collected on EDTA. DNA extraction, polymerase chain reaction (PCR) and hybridization of the amplified product to the test strips were conducted according to the protocol supplied by the manufacturer (CVD Strip Assays R, ViennaLab, Austria).

Quantitative determination of total L-homocysteine in serum was performed by Chemiluminescent microparticle immunoassay on the ARCHITECT System according to the recommendation of the manufacturer (ARCHITECT Homocysteine, Abott, Germany).

Determination of the functional activity of protein C and protein S was done by measuring the coagulation time of the plasma using deficient plasmas in protein C and protein S respectively (Siemens Protein C Ac and Siemens Protein S Ac, Siemens Healthcare Diagnostics, Germany).

RESULTS

The most common acquired risk factor for DVT reported in these series was advanced age (≥ 70 years). More than 44% of the patients were 70 years of age and above. The other frequently detected risk factors were obesity (22.9%), recent surgery (19.2%), history of VTE (18%), immobilization (16.2%), varicose veins (12%), malignancy (10.8%), heart failure (6.9%), family history of VTE (6.3%), pregnancy and post-partum (4.4%), long-haul air travel (4.4%), fractures (4.4%), oral contraceptives and estroprogestative treatment (4.4%), trauma (3.1%) and inferior vena cava congenital abnormalities (1.3%) (Table I). Sixty-one patients (36.7%) had one acquired factor, 57 (34.3%) had two, 29 (17.4%) had three, 11 (6.6%) had four and 1 (0.6%) had five acquired factors. We couldn't identify any acquired risk factor among 10 patients (6%). All these 10 patients were genetically tested for thrombophilia and were positive.

Forty-five patients (27.1%) with conditions predisposing to hypercoagulation state were screened for thrombophilia and were all carriers of at least one prothrombotic genetic defect. Screening was required in young patients

TABLE I
ACQUIRED RISK FACTORS FOR DEEP VEIN THROMBOSIS

Acquired risk factor	% of patients
Advanced age (≥ 70 years)	44.6
Obesity	22.9
Recent surgery	19.2
History of VTE	18.0
Immobility	16.2
Varicose veins	12.0
Malignancy	10.8
Heart failure	6.9
Family history of VTE	6.3
Pregnancy and post-partum	4.4
Long-haul air travel	4.4
Fractures	4.4
Oral contraceptives & estro-progestative treatment	4.4
Trauma	3.1
Paralysis	3.1
Chronic renal failure	2.5
Chronic obstructive pulmonary disease	1.9
Inflammatory bowel disease	1.3
Hematological disorders	1.3
Inferior vena cava congenital abnormalities	1.3
Heart catheterization	0.6

VTE: venous thromboembolism

TABLE II
GENETIC MUTATIONS AMONG PATIENTS WITH DVT AND PATIENTS WITH DVT ASSOCIATED WITH CONDITIONS HIGHLY SUGGESTIVE OF THROMBOPHILIA

Thrombophilia	Patients	
	Total	Screened
FACTOR V-LEIDEN MUTATION	17.4 %	64.4 %
HOMOZYGOTE	2.4 %	8.8 %
HETEROZYGOTE	15.0 %	55.5 %
MTHFR C 677 T MUTATION	16.8 %	62.2 %
Homozygote	3.0 %	11.1 %
Heterozygote	13.8 %	51.1 %
MTHFR A 1298 C MUTATION		
Heterozygote	4.8 %	17.7 %
FACTOR II G 20210 A MUTATION		
Heterozygote	1.8 %	6.6 %
FACTOR V H 1299 R MUTATION	1.2 %	4.4 %
Homozygote	0.6 %	2.2 %
Heterozygote	0.6 %	2.2 %
PROTEIN C DEFICIENCY	0.6 %	2.2 %
PROTEIN S DEFICIENCY	0.6 %	2.2 %

DVT: deep vein thrombosis

(20), patients with spontaneous (16), recurrent (13) and extensive (8) venous thrombosis, patients with family history of VTE (11), oral contraceptives (7), long-haul air travel (5), pregnancy (4), inferior vena cava congenital abnormalities (2) and resistance to anticoagulation (2). Fifteen patients had one, 17 had two, 10 had three, 2 had four and 1 had five of these predisposing factors.

All the 45 patients (27.1%) screened for thrombophilia were positive and were carriers for factors V R 506 Q - Leiden (FVL) mutation (17.4% of all patients and 64% of screened patients), methylenetetrahydrofolate reductase (MTHFR) C 677 T mutation (16.8% of all patients and 62% of screened patients), MTHFR A 1298 C mutation (4.8%), II G 20210 A mutation (1.8%) and V H 1299 R mutation (1.2%) (Table II). Twelve patients (7.2%) presented an increased plasmatic homocysteine level (Table III). One patient presented a deficiency of protein C and another a deficiency of protein S. Twenty-nine patients (64.4%) were carriers for one, 8 patients (17.7%) for two, 6 patients (13.3%) for three and 1 patient (2.2%) for four genetic polymorphisms.

DISCUSSION

The development of clinically manifest venous thrombosis most often occurs with the convergence of multiple genetic and acquired risk factors. The simultaneous presence of multiple risk factors is a prerequisite for thrombosis, with synergistic gene-gene and gene-environment interactions often increasing the risk above the sum of individual risk factors [6].

Acquired risk factors for venous thrombosis of lower extremities are well documented in the literature [4, 7]. Venous thromboembolism is predominantly a disease of **older age** [4, 8]. The incidence of DVT rises nearly 90-fold between 15 and 80 years of age with a relative risk of 1.9 for each 10-year increase in age [4]. Forty-eight percent of the patients reported in our series were 70 years of age and older.

The second most frequently reported acquired risk factors in these series was **obesity**. Overweight has been associated with an increased thrombotic risk [9], particularly in hospitalized patients for acute medical illness [10], trauma [11], or surgery [12]. Fifty-three percent of the reported obese patients presented with one of these three aggravating conditions.

Surgery was the third most common acquired risk factor in this study. The risk of postoperative venous thromboembolism increases with advanced age [13], general anesthesia and major orthopedic procedures [14-15]. Fifty percent of the reported patients having DVT after recent surgery underwent orthopedic procedures for either hip fracture, hip or knee arthroplasty. The mean age of these patients was 76 years (range 60 to 96 years).

Eighteen percent of the patients reported in these series had a **history of VTE**. The incidence of recurrent DVT is higher among patients less than 65 years of age, patients with idiopathic DVT, irreversible thrombotic risk, primary hyper-coagulopathy essentially FVL mutation and hyper-homocysteinemia [16-17]. We have detected FVL mutation in 25.7% of patients with recurrent DVT and in 66.6% of patients with recurrent DVT younger than 60 years.

Venous thrombosis following **bed rest** is frequently bilateral and its incidence increases with the duration of confinement. Forty-six percent of the patients reported in these series with bilateral DVT were bedridden or had very restricted physical activity and 42% of patients confined to bed suffered from bilateral DVT.

Oger *et al*. suggested that **varicose veins** are an independent risk factor for DVT only among women and those greater than 65 years of age [18]. We did not observe significant difference in the incidence of DVT associated to varicose veins with gender. However, 77% of the patients reported with varicose veins were above 65 years of age.

Twenty percent of thromboembolic events in the community are related to **malignancy** [19]. Gastrointestinal

TABLE III
PATIENTS WITH INCREASED HOMOCYSTEINE LEVEL AND GENETIC MUTATION

Increased homocysteine level and genetic mutation	Patients N
No mutation found	1
MTHFR C 677 T mutation	5
Heterozygote	3
Homozygote	2
Heterozygote MTHFR A 1298 C mutation	2
Heterozygote MTHFR C677T & MTHFR A 1298 C mutation	4

malignancy is the most commonly observed cancer in our study (47%), followed by cancer of the breast (11.1%), pancreas (11.1%), uterus (11.1%) and bladder (11.1%).

All the 11 patients with a family history of VTE tested for thrombophilia in our study were positive. This suggests to screen for thrombophilia all patients with a strong family history of VTE essentially when the thrombosis is spontaneous or occurs at a young age.

VTE is second only to abortion as a cause of **pregnancy**-associated death. One of our pregnant patients had twins and another had triplets. VTE rate seems increased in this high risk group. However, no studies have been published supporting this observation. Pregnant women carriers for inherited thrombophilia have a very high risk for VTE [20]. All the pregnant women observed in these series were carriers for prothrombotic genetic polymorphism.

The evidence of association between **long-haul air travel** and VTE is more and more recognized. The risk increases significantly in the presence of advanced age, thrombophilic disorders, history of VTE, obesity and oral contraceptive treatment [21]. All the patients reported in this study with VTE after air travel had at least one of these associated risk factors.

Approximately one-quarter of thromboembolic events among women of childbearing age have been attributed to **oral contraceptives** [22]. All the reported patients treated with oral contraceptives and tested for thrombophilia were positive.

DVT of lower extremities is uncommon in young adults and occurs usually secondary to prothrombotic genetic polymorphism [23]. **Congenital inferior vena cava abnormalities** are often associated with inherited thrombophilia in the young patient leading to seven-fold increased risk for venous thrombosis [24]. We have observed in our series two young patients with congenital inferior vena cava abnormalities (one agenesia and one left-sided) associated with inherited thrombophilia.

A fine balance exists between anticoagulant, procoagulant and fibrinolytic factors. A hypercoagulation state or thrombophilia is common and is observed in approximately 50% to 70% of patients with unexplained VTE [25], in 39.5% to 53.5% of pregnant women [26-27] and in 72% of individuals with travel-related VTE [28]. In the reported study, thrombophilia was detected in 27.1% of the patients with DVT and in all the patients with DVT associated with high risk conditions for hypercoagulation and consequently requiring thrombophilia screening. Thrombophilia was the second most frequent cause of VTE in these series, occurring before major acquired risk factors.

Among the inherited thrombophilias, factor V-Leiden gene mutation is the most common predisposing factor, accounting for 10% to 20% of VTE [29-30]. The prevalence rate of FVL in the general population varies by 0% to 15% according to ethnicity [4, 31-32]. Lebanon exhibits one of the highest frequencies of FVL mutation in the eastern Mediterranean and in the world with a prevalence of 14.4% in the general population [33]. Thrombotic risks increase significantly with oral contraceptive use, hormonal replacement therapy, pregnancy and with associated prothrombotic genetic abnormalities, essentially factor II G 20210A mutation [34]. At least one of these concurrent conditions was observed in 82.7% of the reported patients with FVL mutation.

Hyper-homocysteinemia is associated with both arterial and venous thrombosis. Inherited hyper-homocysteinemia results essentially from MTHFR C 677 T and MTHFR A 1298 C mutations. These mutations may or may not lead to hyper-homocysteinemia, depending on the homozygosity or heterozygosity of the mutations, co-inheritance with another mutation or the presence of concurrent B vitamin deficiency [30]. The association between MTHFR C 677 T genetic polymorphism and the increased risk of VTE is still controversial [35-37]. Ray *et al*. suggest that the risk of this mutation is weak, increasing in older patients and with co-inheritance with another mutations [38]. The prevalence of MTHFR C 677 T among Lebanese patients is high and varies between 35% and 50% according to the series [30-31, 39-40]. Almawi *et al*. suggested that FVL and factor II G 20210 A more than MTHFR C 677 T were important risk factors for VTE among Lebanese patients [41]. Our findings suggest that MTHFR C 677 T mutation either alone or associated with other prothrombotic genetic defects, essentially FVL, increases the risk of venous thrombosis. MTHFR A 1298 C mutation is less common than MTHFR C 677 T [29-30]. Lebanese population harbors a very high prevalence of MTHFR A 1298 C polymorphism with an overall carrier rate of 74.14% [39]. Some authors could not demonstrate a significant association of MTHFR A 1298 C mutation with venous thrombosis [37, 42]. Others confirmed that MTHFR A 1298 C is an independent risk factor for venous thrombosis and that MTHFR C 677 T and A 1298 C mutations are associated with 3-5-fold increased risk for thrombosis [35-36].

Factor V H 1299 R polymorphism has been reported to be a possible risk factor for the development of VTE with a high prevalence in Lebanon (10.4%) and in the world (9.5-15 %) [43]. A recent Lebanese study concluded that the factor V H 1299 R halotype significantly affects the risk of VTE and recommended to screen for this polymorphism in VTE patients with normal FVL [44]. We suggest to screen understudied polymorphism such as MTHFR A 1298 C and factor V H 1299 R in severe extended cases of VTE resistant to anticoagulation and not explained by the most usual mutations.

Factor II G 20210 A mutation is uncommon in the general population worldwide and in Lebanon (1-2 %) [45]. The relative risk of VTE increases considerably for a combination of prothrombin and FVL mutation. All the described patients carriers for prothrombin mutation had combined FVL mutation.

Protein C and protein S deficiency is rare but very thrombogenic. Reported cases of proteins C and S deficiency observed in our series were associated with FVL mutation.

CONCLUSION

Once that risk factors for venous thrombosis are recognized, appropriate observation, prophylaxis and treatment may ensue. The number of acquired factors predisposing to thrombosis usually outweighs the number of prothrombotic genetic factors. Advanced age, an underestimated acquired risk factor was the most commonly observed in this study (44.6%). Few thromboses are generally caused by inherited thrombophilia alone. Thrombophilia was the second most frequently reported cause of venous thrombosis in these series (27.1%) and was related to the high prevalence of factor V-Leiden and MTHFR C 677T among Lebanese population. The mutant allele was highly expressed in patients with DVT and high risk conditions for thrombophilia. The finding that patients with thrombophilia can harbor more than one prothrombotic state have further increased the relevance of the congenital thrombophilic states. We suggest screening for less frequently tested V H 1299 R and MTHFR A 1298 C factors in countries with very high prevalence of these factors and in patients with extended VTE resistant to anticoagulation and not justified by the most common mutations.

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