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ORIGINAL RESEARCH

Is thrombophilia a major risk factor for deep vein thrombosis of the lower extremities among Lebanese patients?

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Aim: Factor V Leiden (R506Q) mutation is the most commonly observed inherited genetic abnormality related to vein thrombosis. Lebanon has one of the highest frequencies of this mutation in the world with a prevalence of 14.4% in the general population. The aim of this study is to define risk factors including inherited genetic abnormalities among Lebanese patients with lower extremity deep vein thrombosis. We report the clinical outcome of patients with thrombophilia.

Methods: From January 1998 to January 2008, 162 patients (61 males and 101 females) were diagnosed with lower extremity deep vein thrombosis. Mean age was 61 years (range: 21 to 95 years).

Results: The most frequent risk factors for vein thrombosis were surgery, advanced age, obesity, and cancer. Twenty-five patients had thrombophilia, 16 patients had factor V Leiden (R506Q) mutation, and seven patients had MTHFR C677T mutation. Ninety-two percent of patients screened for thrombophilia were positive. Screening was requested in young patients (16), patients with recurrent (11), spontaneous (8), and extensive (5) venous thrombosis, familial history (5), pregnancy (4), estroprogestative treatment (3), and air travel (1). Nine patients had one, 11 patients had two, and five had three of these conditions. Follow-up (6 to 120 months) of these 25 patients treated with antivitamin K did not reveal recurrences or complications related to venous thromboembolism.

Conclusion: Factor V Leiden mutation followed by MTHFR mutation are the most commonly observed genetic abnormalities in these series. Defining risk factors and screening for thrombophilia when indicated reduce recurrence rate and complications. Recommendations for thrombophilia screening will be proposed.

Keywords: venous thrombosis, risk factors, genetics, factor V Leiden, prothrombin G20210A, MTHFR C677T

Introduction

Lower extremity deep venous thrombosis (DVT) remains a common and serious medical condition manifesting in patients with recognized or unrecognized risk factors and complicates the outcome of critically ill patients and the postoperative recovery of surgical patients. More than one million cases of DVT are diagnosed in the United States annually, resulting in approximately 50 to 20,000 deaths due to pulmonary embolism (PE).[1,2] The pathogenesis of DVT is multifactorial and involves environmental, acquired, and genetic factors. In recent years, many authors have confirmed that thrombophilia, either acquired or genetic and defined as a predisposition to increased risk of venous and occasionally arterial

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thromboembolism due to hematological abnormalities, was often responsible for the occurrence of lower extremity DVT.[3–8] They recommended the detection of inherited genetic predisposing factors to thrombophilia in patients with spontaneous, unprovoked vein thrombosis and in patients with venous thrombosis associated with a family history of venous thromboembolism (VTE). Factor V Leiden (R506Q) mutation is the most commonly observed inherited genetic abnormality leading to thrombophilia and vein thrombosis. Lebanon has one of the highest frequencies of this mutation in the world with a prevalence of 14.4% of the general population.[9]

The aim of this study is to define risk factors, including genetic abnormalities, in a series of Lebanese patients with lower extremity DVT, to assess the contribution of thrombophilia to the constitution of venous thrombosis, to report clinical outcome of the patients with DVT associated with thrombophilia, and to propose recommendations for thrombophilia screening in patients with DVT.

Materials and methods

From January 1998 to January 2008, 162 patients (61 males, 101 females) were diagnosed at Saint George Hospital, University Medical Center for lower extremity DVT by duplex scan examination. The mean age was 61 years (range: 21 to 95 years). One hundred nineteen (73%) were outpatients and 43 (27%) were hospitalized patients. Venous thrombosis was localized on the left side in 94 patients (58%), on the right side in 57 patients (35%), and on both sides in 11 patients (7%). Venous thrombosis was observed at the iliofemoral level in 49 patients (30%), at the femoropopliteal level in 47 patients (29%), and at the calf level in 66 patients (41%). Nine patients had PE. Eight patients presented with DVT and PE and one patient had a delayed PE.

One hundred fifty-eight patients were treated with low molecular weight heparin and then antivitamin K. Four patients required inferior vena cava filter insertion for resistance to anticoagulation (one case of osteosarcoma) and for contraindication to anticoagulation (three cases of recent craniotomy, recent spine surgery, and recent major abdominal surgery).

Patients with specific conditions suggestive of thrombophilia were screened for genetic mutation abnormalities. Patients with DVT associated with thrombophilia were treated with antivitamin K: 11 short-term, 14 long-term or lifelong (target international normalized ratio [INR]: 2.5; range 2 to 3). These 25 patients were followed for a long period (mean: 50 months; range: 6 to 120 months) to study the incidence of venous thrombosis recurrence and the incidence of events related to VTE.

Results

The most common acquired predisposing risk factors for DVT observed in these series were advanced age (20%) and surgery (19%). Orthopedic surgery had the higher incidence of DVT (11%), followed by general surgery (4%), cardiac surgery (3%), neurosurgery (3%), gynecology (1%), and vascular surgery (1%). Eighteen percent of the patients were obese. Sixteen percent of the patients had malignancy with metastasis (5%) and direct venous compression (2%). The most commonly observed malignant tumors associated with venous thrombosis were cancer of the colon, breast, and pancreas. The other acquired risk factors were history of VTE (9%), immobilization (9%), heart failure (8%), estroprogestative treatment (7%), chronic obstructive pulmonary disease (7%), varicose veins (6%), pregnancy and postpartum (4%), fracture (2%), Crohn's disease (2%), long-haul air travel (2%), paralysis (2%), family history of VTE (2%), trauma (2%), and cardiac catheterization (1%).

Twenty-five patients (15.4%) had thrombophilia (hypercoagulation). Twenty had one and five had two inherited genetic predisposing factors: antiphospholipid syndrome (1), heterozygote prothrombin G20210A mutation (1), heterozygote methylenetetrahydrofolate reductase (MTHFR) C677T mutation (7), factor V Leiden (R506Q) mutation (16; homozygote [1], heterozygote [15]) of whom five had associated protein C deficiency (1), protein S deficiency (1), MTHFR C677T heterozygote mutation (2), and prothrombin G20210A heterozygote mutation (1) (Table 1). Five patients had an increased

Table 1 Patients with deep vein thrombosis of lower extremities and thrombophilia

Thrombophilia	Number of patients
Heterozygote prothrombin G20210A mutation	1
Heterozygote MTHFR C677TC mutation	7
Antiphospholipid syndrome	1
Homozygote factor V Leiden mutation	1
Heterozygote factor V Leiden mutation	15
Protein C deficiency	1
Protein S deficiency	1
MTHFR mutation	2
Prothrombin mutation	1

homocystein plasmatic level which was isolated in two patients and associated with MTHFR mutation in three patients. Of the seven patients heterozygous for MTHFR C677 T mutation, two were heterozygous for factor V Leiden (R506Q) mutation and neither of these two patients showed an increased homocystein level.

Ninety-two percent of the patients tested for thrombophilia were positive. Screening was considered in young patients (16), recurrent thrombosis (11), spontaneous thrombosis (8), extensive thrombosis (5), family history of VTE (5), pregnancy (4), estroprogestative treatment (3), and long-haul air travel (1). Nine patients had one, 11 patients had two, and five patients had three of these conditions. Of the 25 patients screened for thrombophilia, 11 were treated with short-term antivitamin K and 14 were treated with long-term or lifelong antivitamin K. Follow-up of these patients during a mean period of 50 months (range: 6 to 120 months) did not reveal any case of recurrence or complications related to VTE.

Discussion

Acquired risk factors for venous thrombosis of the lower extremities are well documented in the literature.[8,10–15] The most frequently reported risk factors were surgery, cancer, trauma, and critical care conditions.[16–18]

The risk of venous thrombosis is high in cancer patients and in patients undergoing major surgery, essentially major orthopedic surgery. In major trauma, spinal cord trauma, and in critical care situations, this risk is extremely high and may reach 80%.[16] The frequency of thrombophilia outside the setting of surgery, trauma, or cancer is approximately 25%. Either alone, or associated with acquired risk factors, thrombophilia increases significantly the risk of venous thrombosis.

In the reported series, thrombophilia was detected in 15.4% of the patients with DVT and in 92% of the patients with DVT associated with high risk conditions for hypercoagulation. It is considered as the fifth most frequent cause of DVT occurring after major acquired risk factors such as advanced age, surgery, obesity, and cancer.

Resistance to activated protein C caused by a mutation in the factor V Leiden (R506Q) is the most prevalent inherited cause of venous thrombosis. The risk of venous thrombosis is increased by 3- to 8-fold in the heterozygote form of factor V Leiden mutation and 80-fold in the homozygote form of factor V Leiden mutation. The prevalence rate of factor V Leiden mutation in the general population varies by 0% to 15% according to ethnicity.[19] It is low in African (1%–3%), Asian (1%–3%), south European (2%), and United States populations (5%).[20] Mediterranean populations harbor a relatively high mutant allele with a prevalence of 13.6% in Syria, 12.3% in Jordan, and 13.4% in Greece.[9,16]

Lebanon has one of the highest frequencies of factor V Leiden (R506Q) mutation in the eastern Mediterranean region and in the world with a prevalence of 14.4% in the general population.[9] Mutation factor V Leiden was observed in 10% of the patients with venous thrombosis and in 64% of patients with DVT associated with conditions highly suggestive of hypercoagulation. It is considered as the most common cause of thrombophilia in these series.

In a recent publication, Sabbagh and colleagues[20] demonstrated that the prevalence of MTHFR C677T polymorphism among the Lebanese population is very high (34.6%). With the routine screening of MTHFR C677T mutation in Lebanese patients with venous thrombosis, a high rate of this mutation has been recorded. It is observed in 9.3% of reported patients with DVT and in 43.75% of reported patients with DVT and conditions predisposing to thrombophilia. It represents the second most frequent cause of thrombophilia in this study. MTHFR C677T mutation is an independent risk factor for DVT among Chinese and South Indian populations.[21,22] This mutation was not associated with DVT in Turkey and northwestern Greece.[23,24] Almawi and colleagues[25] suggested that factor V Leiden and prothrombin G20210A more than MTHFR C677T were important risk factors for DVT in the Lebanese population. Further studies are required to confirm the importance of MTHFR C677T mutation as an inherited risk factor for DVT of lower extremities in Lebanese patients.

Prothrombin mutation G20210A is uncommon and is found in about 1%–2% in the general population worldwide. A similar prevalence has been reported in the Lebanese population.[26] The relative risk for VTE increases 2–3-fold for prothrombin G20210A mutation alone and 20-fold for a combination of prothrombin mutation and factor V Leiden mutation.[27] We observed heterozygote prothrombin G20210A mutation in one of our patients and the combination in another patient. Prothrombin mutation was detected in 1.23% of the patients with DVT and in 8% of the patients with DVT and high risk conditions for thrombophilia. A recent study compared the contribution of factor V Leiden and prothrombin G20210A single nucleotide polymorphisms to the genetic susceptibility of DVT among Lebanese and Tunisian patients and concluded that factor V Leiden mutation is a common risk factor for both countries. However, prothrombin G20210A mutation

was significantly higher in Lebanese than Tunisians.[28] These findings illustrate the need to determine prothrombotic gene polymorphisms associated with DVT among Mediterranean basin communities.

Antiphospholipid antibody syndrome is uncommon. It is associated with arterial and venous thrombosis and increases 2.5-fold the risk of venous thrombosis.[29] Only one patient with DVT associated with this syndrome was reported in our series. Antiphospholipid antibody syndrome can be genetic or acquired. It can vary widely in its clinical penetrance depending on the presence of triggering factors for VTE such as cancer, the use of chemotherapy, or central venous lines which increase the thrombotic risk. It has the most adverse outcomes due to a high rate of recurrence and high mortality rate if anticoagulation is discontinued.

Antithrombin III deficiency, protein C and S deficiency are very rare and their prevalence in the general population does not exceed 0.4%. Reported cases of protein C and S deficiency observed in our series were associated with heterozygote factor V Leiden mutation.

When acquired risk factors are associated with inherited genetic factors, the risk of venous thrombosis is seriously increased. This risk becomes prohibitive when homozygote forms of mutation is observed or when an association of multiple allele mutation is demonstrated.

DVT of lower extremities is very rare before the age of 20 years and is uncommon in young adults.[30] When venous thrombosis occurs at a young age, it is often secondary to inherited genetic abnormalities. Six of nine patients younger than 30 years reported in our series had thrombophilia. Congenital inferior vena cava anomalies, either isolated or associated to thrombophilia, is a rare cause of DVT in young patients but should be always excluded.[31–33] In a recent study, these congenital anomalies were present in 16.2% of young patients with iliac vein thrombosis.[34] Although these anomalies are rare, however, they represent an important risk for venous thrombosis.[35,36] When they are associated with genetic polymorphism leading to thrombophilia, the risk of venous thrombosis can increase several times.[37] Genetic abnormalities associated with inferior vena cava anomalies include prothrombin G20210A, factor V Leiden (R506Q), MTHFR C677T mutation, and antithrombin III deficiency.[35–42] We have observed three patients with congenital abnormalities of the inferior vena cava (one agenesia and two left-sided). The younger patient was 21 years old. Thrombophilia was detected in two patients with these congenital abnormalities.

Bloom and colleagues demonstrated that the overall risk of venous thrombosis for cancer was increased 7-fold and that this risk was greatly increased with distal metastasis.[43] The risk of venous thrombosis was increased 2-fold in cancer patients with factor V Leiden mutation and 2.5-fold in cancer patients with prothrombin mutation compared with noncarriers.[43]

The incidence of venous thrombosis increases among women using oral contraceptives and increases significantly in those women who are also carriers of thrombophilia. Administration of oral contraceptives increases the risk of venous thrombosis 16-fold in patients heterozygous for prothrombin mutation and 20- to 35-fold in patients heterozygous for factor V Leiden mutation.[44–46] Factor V Leiden mutation increases also the risk of venous thrombosis in women receiving hormonal therapy.[47–48]

Pregnant women have an estimated five times increased risk of developing venous thrombosis comparing to nonpregnant women of similar age.[49,50] The risk was highest during the third trimester and the first six weeks after delivery.[50] The prevalence of thrombophilic defects in women with venous thrombosis during pregnancy and puerperium is very high and varies between 39.5% and 53.5%.[51–53] Pregnant women with inherited thrombophilia have a venous thrombosis risk ranging between 3.4 and 15.2.[54]

Mutation factor V Leiden is the most commonly observed inherited genetic factor in pregnant women.[54] This mutation, essentially in its homozygote form, increases the risk of venous thrombosis 34-fold compared to pregnant women without the mutation and 52-fold compared to nonpregnant women without the mutation.[50,55] Prothrombin G20210A mutation in pregnant women increases the risk of venous thrombosis 31-fold compared to nonpregnant women without thrombophilia.[50]

The evidence of association between prolonged air travel and venous thrombosis has not been clearly established. However, it seems that the risk of venous thrombosis is significant when the flight exceeds 5,000 km or 12 hours duration.[56] In a recent study, the authors demonstrated that prolonged air travel for more than 5,000 km before major surgery significantly increases the risk of perioperative venous thrombosis.[56] Another study has indicated that 72% of individuals with travel-related DVT have associated coagulation defects.[57] These findings illustrate the importance of genetic thrombophilic testing in all patients with venous thrombosis associated with long-haul air travel.

In this study, 92% of patients with venous thrombosis and young age, spontaneous, recurrent, or extensive

venous thrombosis, familial history of VTE, pregnancy, estroprogestative treatment, and long-haul air travel screened for thrombophilia were positive. Either treated with short- or long-term antivitamin K, none of the 25 patients with vein thrombosis and thrombophilia had recurrence or complications related to VTE. Assessment of acquired and genetic risk factors for venous thrombosis in these patients allowed them to avoid thrombogenic treatment (estroprogestative treatment), to prevent venous thrombosis in high-risk conditions (pregnancy, surgery, and long-haul air travel), and oral anticoagulation could be extended for prolonged periods in patients with severe thrombophilia or persistent risk factors (cancer, heart failure, immobilization, etc.).

A recent study demonstrated that 29% of patients with proximal deep vein thrombosis had thrombophilia, which is an independent predictor of persistent residual venous thrombosis.[58] Long-term antivitamin K should be considered in patients with more than one episode of recurrent VTE, in venous thrombosis with continuous risk factor, in idiopathic calf vein thrombosis, and in significant thrombophilia: antithrombin III deficiency (homozygote), protein C or S deficiency (homozygote), homozygote prothrombin or factor V Leiden mutation, and combined heterozygote prothrombin and factor V Leiden mutation.

Conclusions

Mutation factor V Leiden (R506Q) (10%), followed by MTHFR C677T (9.3%) were the most commonly observed inherited genetic abnormalities in this study. Defining risk factors and screening for thrombophilia when indicated reduced recurrence rate and complications related to VTE. Thrombophilia should be screened in:

- Spontaneous DVT.
- DVT in young patients (aged less than 50 years).
- DVT with risk factor of oral contraceptive, estrogen replacement therapy, or pregnancy.
- Familial history of VTE.
- Extended or recurrent DVT.
- Recurrent superficial thrombophlebitis without cancer or varicose veins.
- Children with DVT.
- DVT associated with long-haul air travel.
- DVT associated with congenital abnormalities of the inferior vena cava.
- Asymptomatic first degree relatives of individuals with proven symptomatic thrombophilia. This is particularly important for women of child-bearing age.

Disclosure

This work was presented as "Is thrombophilia a major risk factor for deep vein thrombosis of lower extremities in Lebanese patients?" by Drs Kreidy, Irani-Hakime, and Almawi at the XXIII World Congress of the International Union of Angiology held in Athens, Greece, June 21–25, 2008. This scientific work won the first prize of the International Angiology Scientific Activities and Congress Organization (IASACO) as the best oral communication presented during the XXIII World Congress of the International Union of Angiology. The authors report no conflicts of interest in this work.

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