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Risk Factors and Recurrence Rate of Primary Deep Vein Thrombosis of the Upper Extremities

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Background—One third of cases of upper-extremity deep vein thrombosis (DVT) are primary, ie, they occur in the absence of central venous catheters or cancer. Risk factors for primary upper-extremity DVT are not well established, and the recurrence rate is unknown.

Methods and Results—We studied 115 primary upper-extremity DVT patients and 797 healthy controls for the presence of thrombophilia due to factor V Leiden, prothrombin G20210A, antithrombin, protein C, protein S deficiency, and hyperhomocysteinemia. Transient risk factors for venous thromboembolism were recorded. Recurrent upper-extremity DVT was evaluated prospectively over a median of 5.1 years of follow-up. The adjusted odds ratio for upper-extremity DVT was 6.2 (95% CI 2.5 to 15.7) for factor V Leiden, 5.0 (95% CI 2.0 to 12.2) for prothrombin G20210A, and 4.9 (95% CI 1.1 to 22.0) for the anticoagulant protein deficiencies. Hyperhomocysteinemia and oral contraceptives were not associated with upper-extremity DVT. However, in women with factor V Leiden or prothrombin G20210A who were taking oral contraceptives, the odds ratio for upper-extremity DVT was increased up to 13.6 (95% CI 2.7 to 67.3). The recurrence rate was 4.4% patient-years in patients with thrombophilia and 1.6% patient-years in those without thrombophilia. The hazard ratio for recurrent upper-extremity DVT in patients with thrombophilia compared with those without was 2.7 (95% CI 0.7 to 9.8).

Conclusions—Inherited thrombophilia is associated with an increased risk of upper-extremity DVT. Oral contraceptives increase the risk only when combined with inherited thrombophilia. The recurrence rate of primary upper-extremity DVT is low but tends to be higher in patients with thrombophilia than in those without. (*Circulation*. 2004;110:566-570.)

Key Words: thrombosis ■ thrombophilia ■ risk factors

Upper-extremity deep vein thrombosis (DVT) is a rare manifestation of venous thromboembolic disease, accounting for ≈4% of all cases.¹ In the past few decades, the clinical importance of upper-extremity DVT has increased because of the wider use of central venous catheters and the development of ultrasonography as a simple and accurate objective diagnostic method.² In addition to indwelling catheters, another common risk factor for upper-extremity DVT is cancer.³ Primary upper-extremity DVT, ie, that which occurs in the absence of the aforementioned risk factors, is recognized in ≈30% of cases.⁴ Because of the relative rarity of the disease, only studies with small sample sizes are available, and therefore, at variance with lower-extremity DVT, knowledge on risk factors for this thrombotic manifestation is limited. Whether thrombophilia due to deficiencies of the natural anticoagulant proteins antithrombin, protein C, and protein S; gain-of-function mutations in coagulation factor V and the prothrombin gene; or the metabolic abnormality hyperhomocysteinemia is associated with an increased risk of

primary upper-extremity DVT remains a matter of debate.^{2,5-11} In addition, data on oral contraceptives as risk factor for primary upper-extremity DVT are scanty and controversial,^{2,5,7-9,11} whereas their role in lower-limb DVT¹² and cerebral vein thrombosis¹³ is well established. Moreover, the rate of recurrence of upper-extremity DVT is unknown. The aim of this case-control study was to investigate the role of potential risk factors and to evaluate the recurrence rate after a period of anticoagulant therapy in a large series of patients with primary upper-extremity DVT.

Methods

Patients

One hundred sixty-seven patients referred between January 1994 and February 2003 to the Thrombosis Center of the Ospedale Maggiore Policlinico of Milan for a thrombophilia screening after a first episode of upper-extremity DVT were considered for the study. Patients were asked to bring to the center the diagnostic documentation of their thrombotic episodes. Eighteen patients were subsequently excluded because thrombosis was related to central venous

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catheters (n=12) or cancer (n=6: 3 lymphoma with mediastinal involvement, 1 breast, 1 lung, and 1 liver cancer); 17 were excluded because of incomplete thrombophilia screening, 12 because of previous DVT of the lower extremity, 3 because the diagnosis was uncertain, and 2 because they were relatives of patients previously diagnosed as having an inherited thrombophilic abnormality. In 5 patients, more than 1 exclusion criterion was present. Therefore, 115 patients with a first, objectively confirmed episode of primary upper-extremity DVT were included in the study; 26 of them had been part of a previous study of thrombosis risk factors in primary upper-extremity DVT,⁵ which was limited by the small sample size. Diagnosis was made in 90 cases by Doppler ultrasound examination, in 22 by contrast venography, and in 3 by computed tomography venography. Upper-extremity DVT involved the axillary and/or subclavian veins in 91 patients, the axillary and/or subclavian veins and the brachial vein in 20, and the brachial vein only in 4. Thrombosis occurred in the dominant arm in 64 patients (56%). Symptomatic pulmonary embolism as an early complication of upper-extremity DVT occurred in 2 (1.7%) of the 115 patients and was diagnosed by ventilation/perfusion lung scan in 1 patient and computed tomography in the other.

Controls

The population of controls included 797 healthy individuals who were partners or friends of the whole population of patients, who agreed to accompany them and to be investigated at the Thrombosis Center. Previous thrombosis was excluded in these individuals by use of a structured questionnaire validated for the retrospective diagnosis of thrombosis.¹⁴

Information on transient risk factors for thrombosis, such as oral contraceptive intake and trauma of the upper extremities, was obtained for both patients and controls. A positive family history of venous thrombosis was considered when at least 1 first- or second-degree relative had had objectively documented episodes. Patients were also interviewed about strenuous muscular efforts with the arms in the week preceding symptoms of thrombosis. The same information was not obtained from controls. Women were considered to be taking oral contraceptives if they had taken them until 2 weeks or less before thrombosis for patients or at the time of blood sampling for controls. No subject had abnormal liver or renal function or overt autoimmune or neoplastic diseases when they first visited the Thrombosis Center. All subjects were white and gave their informed consent to the study, which was approved by the Institutional Review Board of the University of Milan.

Laboratory Tests

DNA analysis for the 1691 guanine-to-adenine substitution in coagulation factor V gene (factor V Leiden) and for the 20210 guanine-to-adenine substitution in the 3'-untranslated region of the prothrombin gene was performed as described previously.^{15,16} Functional and/or antigenic assays for antithrombin, protein C, and protein S were performed on plasma samples obtained from blood anticoagulated with sodium citrate (3.8% wt/vol), as described previously.¹³ Antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) were diagnosed according to previously described methods¹⁷ and were looked for only in patients, because these tests are not part of the laboratory workup of our control population. Total plasma homocysteine was measured in blood samples anticoagulated with EDTA after overnight fasting and 4 hours after an oral methionine load (3.8 g/m² body surface area), according to previously described methods.¹³ Hyperhomocysteinemia was diagnosed when plasma levels of fasting total homocysteine or their post-methionine-load increments above fasting levels exceeded the 95th percentile of the values obtained in the control group (in men 19.25 and 24.04 nm/mL; in women 14.88 and 24.5 nm/mL, respectively).

Patient Follow-Up

To minimize selection bias, we chose to limit the follow-up analysis only to patients who had the first primary upper-extremity DVT after

January 1991, a time when our Thrombosis Center became fully active and started to assist a similar yearly number of patients. The median time elapsed from the first primary upper-extremity DVT to the visit was 6 months (range 1 month to 5 years). For patients who received oral anticoagulant therapy, the follow-up started after its discontinuation, whereas for those who did not receive this therapy, it started after the event. Patients who were still taking oral anticoagulant therapy at the end of the study were not included in the analysis. The end of follow-up was July 1, 2003, or the date of the recurrent upper-extremity DVT. Patients underwent duplex color ultrasonography when first referred to the Thrombosis Center and, if thrombosis was still present, after 6 months and then annually. Subclavian, axillary, and brachial veins were investigated as described previously.^{2,10} Recanalization was judged complete if a previously abnormal venous segment was normally compressible or for the subclavian vein, which is not easily compressible in the subclavicular fossa, if a normal flow pattern (compared with the contralateral vein) was recorded. In case of symptoms suggestive of recurrence of upper-extremity DVT, patients were instructed to return to the Thrombosis Center for objective examination. Recurrent upper-extremity DVT was diagnosed if a previously compressible venous segment could no longer be compressed or if, in the presence of symptoms of recurrence, a previously nonocclusive thrombus had changed into an occlusive one at ultrasound examination.

Statistical Analysis

Continuous variables are presented as median and range. The age difference between patients and controls was calculated by the Mann-Whitney *U* test. ORs and 95% CIs were used as a measure of the association between primary upper-extremity DVT and various types of thrombophilia. An unconditional logistic regression analysis was used to adjust ORs for possible confounders, such as age (continuous variable), gender, and the presence of other causes of thrombophilia (categorical variables). Interaction between inherited thrombophilia and oral contraceptive intake or hyperhomocysteinemia and between oral contraceptive intake and hyperhomocysteinemia was evaluated by stratification of patients and controls into 4 groups, according to the presence or absence of the specific risk factors and using the group without specific risk factors as the reference. The incidence of recurrent upper-extremity DVT was calculated by dividing the number of events by the sum of patient-years of observation. To estimate the cumulative probability of recurrent upper-extremity DVT in patients with and without thrombophilia, a survival analysis was performed by the Kaplan-Meier method and with a Cox proportional hazards model, which allows adjustment for confounding variables, such as age at first event, gender, length of follow-up, and presence or absence of recanalization after the first event. The final hazard ratio (and its 95% CI), adjusted for the other variables in the model, expresses the risk of recurrent upper-extremity DVT in patients with thrombophilia compared with those without.

Results

Risk Factors

The main characteristics of the study population and the prevalence of thrombophilia are shown in Table 1. The median age at first visit to the Thrombosis Center was 35 years (range 14 to 61 years) in patients and 44 years (range 12 to 73 years) in controls ($P<0.001$). Heterozygosity for factor V Leiden and prothrombin G20210A increased the risk for upper-extremity DVT by factors of 6 and 5, respectively. No homozygous carrier of either mutation was found in patients or controls. The presence of antithrombin, protein C, or protein S deficiency (considered together) was associated with an ≈ 5 -fold increase in the risk of the disease, whereas no association was found for hyperhomocysteinemia (Table

TABLE 1. General Characteristics, Type of Thrombophilia, and Transient Risk Factors for Upper-Extremity DVT in the Study Population

	Patients (n=115)	Controls (n=797)	OR (95% CI)	OR* (95% CI)
Male/female, n	41/74	363/434		
Positive family history of venous thrombosis, n (%)	18 (16)	141 (18)		
Median age at thrombosis, y (range)	32 (14–61)	...		
With thrombophilia, n (%)				
Factor V Leiden	10 (9)	22 (3)	3.4 (1.5–7.3)	6.2 (2.5–15.7)
Prothrombin G20210A	11 (10)	25 (3)	3.3 (1.6–7.0)	5.0 (2.0–12.2)
Antithrombin, protein C, or protein S deficiency	3 (3)†	8 (0.8)‡	3.2 (0.8–12.3)	4.9 (1.1–22.0)
Antiphospholipid antibodies	8 (7)	Not investigated
Hyperhomocysteinemia	8 (7)	72 (9)	0.7 (0.3–1.6)	0.8 (0.3–1.9)
With transient risk factors, n (%)				
Strenuous muscular effort	29 (25)	Not investigated
Trauma of upper limb	5 (4)	0
Oral contraceptive use§	23 (34)	85 (30)	1.2 (0.7–2.2)	...

*Each variable adjusted for the others, age, and gender.

†One antithrombin deficiency, 1 protein C deficiency, and 1 protein S deficiency.

‡Seven with antithrombin deficiency and 1 with protein S deficiency.

§Percentage calculated based on the number of women of reproductive age (65 patients and 288 controls).

1). Because homocysteine plasma levels may be influenced by gender and age, we performed separate analyses for men and women and for 2 age categories (below and above the median age of the study population [43 years]), without finding a significant association (data not shown). The OR for thrombophilia and hyperhomocysteinemia did not change after the exclusion of the 26 patients who were part of our previous study.⁵ In terms of transient risk factors, strenuous muscular efforts with the arms were recorded in one fourth of patients and the use of oral contraceptives in one third. Efforts were sports related in 15 patients (8 weightlifting, 3 rowing, 2 tennis, and 2 volley) and related to unusual strenuous exercise in another 14 (7 lifting heavy weights, 4 prolonged above-shoulders extension, 3 repeated abduction). The overall prevalence of thrombophilia was similar in patients who did or did not undergo strenuous muscular efforts, being 31% and 33%, respectively. The prevalence of oral contraceptive users was similar in patients and controls (34% and 30%, respectively), with no association between this transient risk factor and upper-extremity DVT (Table 1). Such risk factors as surgery, pregnancy or puerperium, and prolonged immo-

bilization, frequently found in patients with lower-extremity DVT, were never recorded in our patients.

Table 2 shows that when women were stratified according to the presence of the most common causes of thrombophilia, ie, factor V Leiden or prothrombin G20210A, and the use of oral contraceptives, the OR for upper-extremity DVT increased nearly 14-fold in the group sharing both the genetic and transient risk factors compared with the group with neither risk factor. This figure was similar for the interaction of the separate mutations and oral contraceptive use (not shown). The OR (adjusted for age and gender) for the combination of factor V Leiden or prothrombin G20210A and hyperhomocysteinemia (1.7 [95% CI 0.2 to 14.5]) and the OR (adjusted for age and the presence of factor V Leiden or prothrombin G20210A) for the combination of hyperhomocysteinemia and oral contraceptives (1.8 [95% CI 0.3 to 9.7]) were not statistically significant.

Recurrence Rate

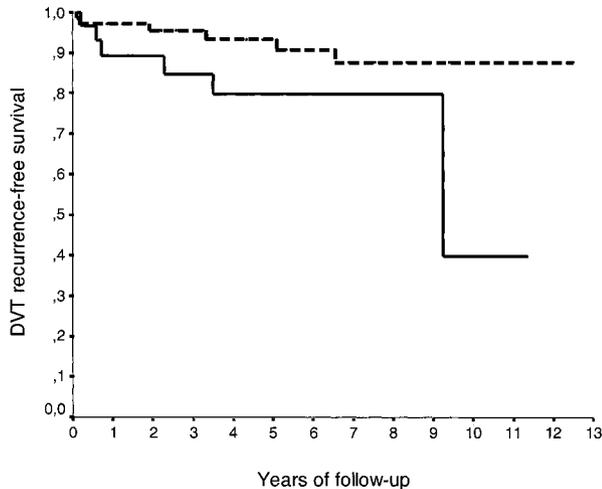
The incidence of recurrent symptomatic upper-extremity DVT was calculated for 98 patients who had the first event

TABLE 2. Interaction Between Factor V Leiden or Prothrombin G20210A and Use of Oral Contraceptives in Determining Risk of Upper-Extremity DVT in 65 Patients and 288 Controls of Reproductive Age

Factor V Leiden or Prothrombin G20210A	Oral Contraceptive Use*	Patients	Controls	OR (95% CI)	OR† (95% CI)
No	No	35	191	1 (Reference)	1 (Reference)
No	Yes	18	82	1.2 (0.6–2.2)	1.0 (0.5–2.0)
Yes	No	7	10	3.8 (1.4–10.7)	4.2 (1.4–12.6)
Yes	Yes	5	3	9.1 (2.1–39.8)	13.6 (2.7–67.3)

*Information on oral contraceptive use was missing for 2 controls.

†Adjusted for age.



Kaplan-Meier curves showing cumulative probability of remaining free from recurrent primary upper-extremity DVT after first episode in patients with (—) and without (----) thrombophilia.

after January 1991. Seventy-seven patients received oral anticoagulant therapy for a mean of 6 months (median 5 months), whereas 14 received subcutaneous heparin and 7 took antiplatelet agents for no longer than 3 months. Eight additional patients were not included because they were still taking oral anticoagulant therapy at the end of the study. A complete recanalization of the first DVT was observed in 65 patients (66%), whereas in the remaining 33 (34%), a residual vein thrombosis was detected. On the whole, there were 12 symptomatic, objectively documented episodes of recurrence (12%), 9 ipsilateral and 3 contralateral, over the median period of follow-up of 5.1 years (range 2 months to 12.5 years). Six of these episodes occurred in patients with thrombophilia and 6 in those without. Seven patients with ipsilateral recurrence had previously shown a complete recanalization of the first event. No patient experienced a recurrence during the oral anticoagulant period and made a strenuous muscular effort before the second event. One patient developed breast cancer during the follow-up period. The overall annual incidence of recurrence of upper-extremity DVT was 2.4% (95% CI 1.2% to 4.0%). In patients with and without thrombophilia, it was 4.4% (95% CI 1.5% to 8.8%) and 1.6% (95% CI 0.6% to 3.2%), respectively. The Figure shows the breakdown of recurrence rate in patients with and without thrombophilia. Overall, the cumulative probability of recurrence-free survival was 95% at 1 year and 89% at 5 years of follow-up. In patients with thrombophilia, such probability was 89% at 1 year and 80% at 5 years, and in those without thrombophilia, it was 97% and 93%, respectively. The hazard ratio for recurrent upper-extremity DVT, adjusted for age at the first event, length of follow-up, gender, and recanalization, in patients with thrombophilia compared with those without was not statistically significant (2.7 [95% CI 0.7 to 9.8]). The hazard ratio for recurrence in patients with lack of recanalization versus those with recanalization was also not statistically significant (0.8 [95% CI 0.2 to 3.3]). These results did not change substantially if thrombophilia was restricted to inherited coagulation abnormalities only, ie,

if the metabolic disorder hyperhomocysteinemia was excluded.

Discussion

The study of this large series of patients with primary upper-extremity DVT, which investigated the prevalence of underlying risk factors and the rate of recurrent events, shows that inherited thrombophilia is associated with an increased risk of primary upper-extremity DVT. A 5- to 6-fold increased risk was found in carriers of thrombophilia due to deficiencies of the naturally occurring anticoagulant proteins antithrombin, protein C, or protein S and to the gain-of-function factor V Leiden or prothrombin mutations. In contrast, the metabolic abnormality hyperhomocysteinemia and the use of oral contraceptives, known to be associated with an increased risk of DVT of the lower extremities and of cerebral vein thrombosis,¹⁸ were not associated with primary upper-limb DVT. However, a multiplicative interaction between the use of oral contraceptives and the most common inherited thrombophilic abnormalities, factor V Leiden or prothrombin mutation, was observed, with an increased risk for the disease up to 14-fold. Patients with thrombophilia were more likely to have symptomatic recurrence than those without, for an incidence of 4.4% and 1.6% per year, respectively.

Strenuous muscular effort with the arms was a common predisposing condition, present in one fourth of the patients. This is in agreement with what was reported in the largest series to date of 51 patients with primary upper-extremity DVT.⁷ We could not calculate the risk associated with strenuous muscular effort in the present study because the corresponding information was not included among those the data we routinely collect in individuals who make up our control population. However, at variance with the study by Héron et al,⁷ thrombophilia was equally distributed among patients with and without a history of strenuous muscular effort. Data on thrombophilia in the literature are conflicting, perhaps because of different selection criteria for patients and the limited sample size of most studies.^{2,5-11} In a previous study of only 36 patients with primary upper-extremity DVT,⁵ we reported a statistically nonsignificant trend toward an association between the disease and all the inherited thrombophilic abnormalities taken together (factor V Leiden and antithrombin, protein C, and protein S deficiency). To date, the role of hyperhomocysteinemia has been investigated only in that study,⁵ and the role of the prothrombin mutation has only been investigated in 2 additional case-control studies, which showed an association with primary upper-extremity DVT in 48 patients¹¹ and with primary or secondary upper-extremity DVT in 55 patients.¹⁹ The prevalence of antiphospholipid antibodies in patients with upper-limb DVT varies from 3.7% to 26.8%.^{2,7,9,11} Although we could not calculate the risk associated with this acquired thrombophilic condition because it was not investigated in control subjects, we found a prevalence similar to that reported in patients with upper-limb¹¹ or lower-limb^{20,21} DVT. Recently, an OR of ≈6 in favor of an association between oral contraceptive intake and primary upper-extremity DVT has been reported.¹¹ The data from the present study failed to confirm such an

association and are in agreement with the low prevalence of oral contraceptive use reported by others.^{2,9} However, a synergistic effect was found between oral contraceptive intake and thrombophilia in increasing the risk of upper-extremity DVT. A similar interaction is already well established for patients with lower-extremity DVT, although in these patients, oral contraceptives alone are associated with an increased risk. Compared with DVT of the lower extremities, upper-extremity DVT recurs less frequently. A study of patients with a first, idiopathic episode of lower-extremity DVT estimated a 5.0% annual incidence of recurrence after discontinuation of anticoagulant therapy,²² whereas in the present study, it was 2.4%.

One of the limitations of the present study is that patients referred for thrombophilia screening to a specialized center are selected. We believe we minimized such bias by excluding from the follow-up analysis patients who had the first event before the Thrombosis Center had become a national referral for thrombosis patients. The average yearly number of patients referred to the center after 1991 was similar, and there is no reason to think that patients with a higher probability to have thrombophilia were preferentially referred to us. In addition, a positive family history for venous thrombosis was not a selection bias, because this was similar among patients and controls. Diagnostic bias should have been limited by review of the diagnostic documentation of thrombotic episodes and the adoption of strict criteria for diagnosis of recurrent upper-extremity DVT. In particular, a recurrent event at the same venous segment only partially obstructed by thrombus occurred in 2 patients only.

In conclusion, the present study provides evidence that the risk of first primary upper-extremity DVT is higher in individuals with inherited thrombophilia than in those without. The risk of recurrent events appears to be higher in such individuals, but not so high as to suggest the extension of anticoagulant treatment, which in the present series had a mean duration of 6 months. The metabolic abnormality hyperhomocysteinemia and the use of oral contraceptives per se are not associated with an increased risk for this site of DVT, which strengthens the concept that risk factors may play a different role in determining venous thrombosis in different sites.²³ However, women with inherited thrombophilia have a much greater risk of upper-extremity DVT if they also use oral contraceptives. Therefore, discontinuation of oral contraceptives after a first episode of upper-extremity DVT should be recommended in women with inherited thrombophilia.

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