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Inherited thrombophilic risk factors in a large cohort of individuals referred to Italian thrombophilia centers: distinct roles in different clinical settings

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Background and Objectives. Despite inherited thrombophilic risk factors being strongly associated with vein thrombosis, decisions on whether to screen subjects for these factors vary in different clinical settings.

Design and Methods. We calculated the prevalence of inherited thrombophilic risk factors in a large cohort of patients (n=1,238) with different clinical manifestations of vein thromboembolism. In the present cohort, screening for inherited thrombophilia was worthwhile among patients who developed vein thrombosis of the leg or cerebral vein thrombosis. Carriers of FV Leiden or FII A^{20210} mutation more frequently had had deep vein thrombosis of the leg (OR: 4.35; 95% CI: 3.39-5.60), superficial vein thrombosis (OR: 3.34; 95% CI: 2.06-5.41), or cerebral vein thrombosis (OR: 2.77; 95% CI: 1.10-6.96).

Results. The screening program appeared to have a limited relevance in patients with isolated pulmonary embolism (OR: 2.13; 95% CI: 1.28-3.54), or mesenteric vein thrombosis (OR: 2.05; 95% CI: 1.22-3.44).

Interpretation and Conclusions. The lack of association with inherited thrombophilia does not justify routine screening of patients with thrombosis of the upper extremities or with retinal vein thrombosis.

Key words: screening program, vein thrombosis, inherited thrombophilia

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Venous thrombosis is the third most common cardiovascular disease after ischemic heart disease and stroke.[1] In addition to circumstantial predisposing factors, genetic abnormalities of components of the coagulation pathway leading to hypercoagulability have been found in subjects who have suffered from thromboembolic disease.[2] In patients from different ethnic groups, a common mutation within the gene of the coagulation factor V (FV Leiden mutation),[3] leading to resistance to activated protein C, has been found in up to 20% of cases of unselected patients with deep venous thrombosis.[4] A common mutation, a G-to-A transition at nucleotide position 20210, within the prothrombin (FII) gene locus has been described, the A allele carriership being associated with a higher risk of venous thrombosis and accounting for up to 14% of deep vein thromboses.[5-7]

Predisposing factors are known to interact cumulatively in determining high-risk conditions.[2] A significant subset of thrombophilic patients has multiple genetic risk factors and interactions between co-inherited genetic abnormalities have previously been reported for deficiencies of several clotting factors.[8–15] This has been shown to be a particularly important contributing factor to the highly variable thrombotic risk associated with deficiencies of natural anticoagulants.

Depending on the different clinical manifestations of vein thromboembolism, the prevalence of inherited coagulation abnormalities varies, suggesting pathogenic differences.[16-19] These data support the hypothesis that mechanistic differences are involved in the pathogenesis of thrombosis in different clinical settings.

Thus, before considering whether is advisable to investigate a subject for inherited risk factors, we need to know the prevalence of these risk factors in the different clinical settings.

We, therefore, calculated the prevalence of inherited thrombophilic risk factors in a large cohort of patients with different clinical manifestations of vein thromboembolism referred for a thrombophilic work-up.

Design and Methods

After approval from the local Ethics Committees, this study was carried out according to the Principles of the Declaration of Helsinki; informed consent was obtained from all subjects.

Patients

We retrospectively investigated 1,443 patients, 692 men and 751 women (median age: 46.0 years, range: 3-90), with documented venous thrombosis, who had been referred between May 1996 and May 2000, for a thrombophilic work-up, to one of three Italian Thrombosis Centers: the *IRCCS Casa Sollievo della Sofferenza*, San Giovanni Rotondo (FG); the *A. Cardarelli Hospital*, Naples; and the *G. Moscati Hospital*, Avellino. The protocol for the work-up was similar in the different Centers and included testing for deficiencies of antithrombin, protein C, and protein S either before the start or after the termination of the anticoagulation. In addition, all patients were tested for the presence of factor V Leiden and FII A^{20210} mutations. One hundred and ninety-nine patients (13.8%) had had at least one previous thrombotic event. Because these patients constitute a group that is likely to have a greater susceptibility to thromboembolic episodes, they were excluded from the analysis. Since risk profiles for thrombosis disorders during childhood are different from those in older patients, individuals ≤13 years old (n=3) were excluded from the analysis. Six blood specimens could not be typed. Thus, 1,238 patients, 607 men and 631 women (median age: 45.0 years, range: 14-90), were analyzed.

The diagnosis of vein thrombosis was objectively confirmed. All patients diagnosed as having pulmonary embolism also had the deep veins of their legs evaluated. A complete clinical summary with emphasis on personal history of circumstantial risk factors of vein thromboembolism (surgery, immobilization, pregnancy, post-partum, trauma, oral contraception, varicose veins, malignancy, strenuous muscular activity of the involved extremity, anatomic abnormalities) was obtained from all patients.

Controls

While patients were being recruited, 1,329 apparently healthy employees of the *Casa Sollievo della Sofferenza Hospital*, San Giovanni Rotondo, Southern Italy, 578 men and 751 women; median age 37.0 years, range 22-66, were interviewed as controls. Families of these controls have been resident in the region for at least two generations and all four of their grandparents were born in Italy. A history of vein thromboembolism was determined by a structured questionnaire validated for the retrospective diagnosis of vein thrombosis.[20] Five subjects, 4 women and 1 man, had documented evidence of vein thromboembolism after their enrollment and were excluded from the analysis. All subjects underwent testing for the presence of factor V Leiden and FII A^{20210} mutations, whereas the presence of a deficiency of one natural anticoagulant was not evaluated. Twenty blood specimens could not be typed. Thus, 1,304 apparently healthy subjects (576 men and 743 women; median age 36.0 years, range 22-66) without a clinical history of vein thromboembolism served as controls.

Blood collection and coagulation tests

Blood samples were collected into vacuum tubes containing 0.129 M trisodium citrate and centrifuged at 2,000 g for 15 min to obtain platelet-poor plasma. This was frozen and stored at -70°C until assayed. Antithrombin, protein C, amidolytic and immunologic tests (Behring, Marburg, Germany), and total and free protein S antigen (ELISA, Diagnostica Stago, Asnières, France) were determined in all patients.[7] Clotting assays were performed on a KC4 Amelung coagulometer (Amelung, Germany).

DNA extraction and analysis

DNA was extracted from peripheral blood leukocytes according to standard protocols.[7] Factor V Leiden mutation was detected as previously described.[10] The G->A mutation of the FII gene was assayed according to Poort *et al*.[5]

Statistical analysis

All the analyses were performed according to the Statistical Package for Social Science (SPSS 6.1 for Apple Macintosh®). Differences in proportions were tested by the chi-squared statistic or Fisher's exact test, as appropriate. All the analyses were performed after grouping homozygous and heterozygous carriers of the FV Leiden as well as those of the FII A^{20210} mutation. Odds ratio (OR) and 95%-confidence intervals (CI) were calculated when appropriate. A 5% two-tailed significance level was used for all tests.

Results

Clinical characteristics of patients

The presenting thrombotic episode was: deep vein thrombosis in one leg in 679 (54.8%) patients (319 men and 360 women); superficial vein thrombosis in one leg in 105 (8.5%) patients (39 men and 66 women); thrombosis of the upper extremities in 77 (6.2%) patients (34 men and 43 women); isolated thrombosis of mesenteric veins in 119 (9.6%) patients (67 men and 52 women); isolated pulmonary embolism in 121 (9.8%)

Table 1. Prevalence of FV Leiden and FII A^{20210} gene mutations in the different clinical settings.

Groups	*No mutations*	*FV Leiden*	*FII A^{20210}*	*Both mutations*	*p§*
Deep vein thrombosis in one leg (n=679)	475 (70.0%)	117 (17.2%)	68 (10.0%)	19 (2.8%)	<0.0001*
Superficial vein thrombosis in one leg (n=105)	79 (75.2%)	17 (16.2%)	8 (7.6%)	1 (1.0%)	<0.0001*
Thrombosis of the upper extremities (n=77)	68 (88.3%)	3 (3.9%)	5 (6.5%)	1 (1.3%)	n. s.*
Isolated thrombosis of mesenteric veins (n=119)	99 (83.2%)	6 (5.0%)	10 (8.4%)	4 (3.4%)	0.0055*
Isolated pulmonary embolism (n=121)	100 (82.6%)	13 (10.7%)	8 (6.6%)	-----	0.0029*
Retinal vein thrombosis (n=109)	96 (88.1%)	5 (4.6%)	8 (7.3%)	-----	n. s.*
Cerebral vein thrombosis (n=28)	22 (78.6%)	-----	6 (21.4%)	-----	0.0379*#
General population (n=1304)	1187 (91.0%)	60 (4.6%)	56 (4.3%)	1 (0.1%)	Ref.

§χ squared test; #two-tailed Fisher's exact test. Ref.: references.

patients (66 men and 55 women); retinal vein thrombosis in 109 (8.8%) patients (69 men and 40 women); and thrombosis of a cerebral vein in 28 (2.3%) patients (13 men and 15 women). An episode of pulmonary embolism was diagnosed in 221 (17.9%) patients (103 men and 118 women). Of these, 193 individuals (94 men and 99 women) had already suffered from an objectively confirmed deep vein thrombosis, 23 (8 men and 15 women) superficial vein thrombosis, 4 women thrombosis of the upper extremities, and 1 man isolated thrombosis of a mesenteric vein.

Circumstantial thrombophilic risk factors were registered in 598 patients (48.3%): 372 (54.8%) with deep vein thrombosis in one leg, 37 (35.2%) with superficial vein thrombosis in one leg, 26 (33.8%) with thrombosis of the upper extremities, 62 (52.1%) with isolated thrombosis of mesenteric veins, 35 (62.0%) with isolated pulmonary embolism, 9 (8.3%) with retinal vein thrombosis, and 17 (60.7%) with cerebral vein thrombosis.

Prevalence of inherited thrombophilic risk factors

The distributions of FV Leiden and FII A^{20210} mutations according to the type of clinical manifestations of vein thromboembolism are reported in Table 1. Overall, 8 patients (6 men and 2 women) were homozygotes for the FV Leiden mutation: 6 had had deep vein thrombosis in one leg, 1 superficial vein thrombosis in one leg, and 1 (who also carried a FII A^{20210} allele) isolated thrombosis of a mesenteric vein. Concerning the FII A^{20210} gene variant, 5 patients (1 also carried a FV Leiden allele) were homozygotes; all of them had had deep vein thrombosis in one leg. Among patients with deep vein thrombosis in one leg, 204 (30.0%) carried at least one of these gene variants. Similar figures were observed in the group of patients with superficial vein thrombosis in one leg (n=26; 24.8%) and among patients with cerebral vein thrombosis (n=6; 21.4%). Lower prevalences were obtained in the other patient groups, cases with thrombosis of the upper extremities having the lowest percentage (n=9; 11.7%). The prevalence of FV Leiden and FII A^{20210} gene variants was significantly higher in all settings of patients except those with thrombosis of the upper extremities or retinal vein thrombosis (Table 1). The risk estimate of having a thrombotic event was 4.35 (95% CI: 3.39-5.60) among patients with deep vein thrombosis in one leg, 3.34 (95% CI: 2.06-5.41) in the group of patients with superficial vein thrombosis in one leg, 2.05 (95% CI: 1.22-3.44) in patients with isolated thrombosis of mesenteric veins, 2.13 (95% CI: 1.28-3.54) in patients with isolated pulmonary embolism, and 2.77 (95% CI: 1.10-6.96) among patients with cerebral vein thrombosis. No difference was observed among patients with thrombosis of the upper extremities (OR: 1.34; 95% CI: 0.65-2.76) or with retinal vein thrombosis (OR: 1.37; 95% CI: 0.75-2.53).

Among different clinical settings of patients, the group of subjects with deep vein thrombosis in one leg showed a significantly higher prevalence of FV Leiden and FII A^{20210} gene variants than patients with thrombosis of the upper extremities (p=0.0007), with isolated thrombosis of mesenteric veins (p=0.0030), with isolated pulmonary embolism (p=0.0042), or with retinal vein thrombosis (p<0.0001).

A deficiency of one natural anticoagulant was shown in 29 (19 men and 10 women) subjects (Table 2). None of the patients who had had a thrombosis of the upper extremities, isolated pulmonary embolism, or a superficial vein thrombosis in one leg displayed a deficiency of one of the natural anticoagulants.

When compared with the prevalence in subjects

Table 2. Prevalence of natural anticoagulant deficiencies in the different clinical settings.

Groups	*None*	*Antithrombin*	*Protein C*	*Protein S*
Deep vein thrombosis in one leg (n=679)	655 (96.4%)	4 (0.6%)	10 (1.5%)	10 (1.5%)
Superficial vein thrombosis in one leg (n=105)	105 (100.0%)	–	–	–
Thrombosis of the upper extremities (n=77)	77 (100.0%)	–	–	–
Isolated thrombosis of mesenteric veins (n=115)	111 (96.6%)	–	4 (3.4%)	–
Isolated pulmonary embolism (n=121)	121 (100.0%)	–	–	–
Retinal vein thrombosis (n=109)	109 (100.0%)	–	–	–
Cerebral vein thrombosis (n=28)	27 (96.4%)	–	–	1 (3.6%)
General population (n=1304)	–	n. e.	n. e.	n. e.

n. e.: not evaluated.

without venous thrombosis, the prevalence of inherited thrombophilic risk factors was significantly higher in all clinical settings of patients except those with thrombosis of the upper extremities or retinal vein thrombosis (data not shown). In addition, the latter two groups, as well as patients with isolated thrombosis of a mesenteric vein or isolated pulmonary embolism, showed a significantly lower prevalence of inherited thrombophilic risk factors than patients with deep vein thrombosis in one leg (data not shown).

Discussion

Despite inherited thrombophilic risk factors being strongly associated with venous thrombosis, decisions on who to screen for these risk factors are complex and vary in different clinical settings. We investigated whether the prevalences of inherited thrombophilic risk factors, natural anticoagulant deficiency, FV Leiden and FII A^{20210} gene mutations, vary significantly in different clinical settings of patients with venous thrombosis.

Patients with deep vein thrombosis in one leg had, as would be expected, a significantly higher prevalence of inherited risk factors than did apparently healthy individuals from a general population. The prevalence was, however, also significantly higher than that recorded in patients with thrombosis of the upper extremities, retinal vein thrombosis as well as in cases with isolated thrombosis of a mesenteric vein or isolated pulmonary embolism. Patients with cerebral vein thrombosis had a significantly higher prevalence of inherited thrombophilic risk factors than did asymptomatic subjects. The prevalence was similar to that observed in patients with deep vein thrombosis in one leg and consistent with previous findings.[21,22]

The prevalences of inherited coagulation abnormalities, anticoagulant factors, FV Leiden and FII A^{20210} mutations have been reported to be significantly different depending on the extremities involved (upper/lower).[7,23] In some[19,24,25] but not all studies,[26] the prevalence of inherited thrombophilic risk factors among patients with retinal vein thrombosis was comparable to that among controls. The present report extends these data in large groups of patients with thrombosis of the upper extremities or retinal veins, and further suggests mechanistic differences in the pathogenesis of venous thrombotic events in different districts.

A hypercoagulable state has been found in patients with mesenteric vein thrombosis or Budd Chiari syndrome.[27-29] In the present work, the prevalence of inherited thrombophilic risk factors in patients with mesenteric vein thrombosis was higher than that in controls, but lower than the prevalence in patients with deep vein thrombosis in one leg. Thus, present data further strengthen the hypothesis that inherited thrombophilia plays a significant role in the pathogenesis of thrombosis of mesenteric veins.

A series of studies reported a lower prevalence of resistance to activated protein C,[16] or of FV Leiden mutation[17,18,30] in patients presenting with isolated pulmonary embolism. The prevalence of FV Leiden and FII A^{A20210} mutations was significantly different from that recorded in controls. However, this prevalence was significantly lower than that in patients with deep vein thrombosis in one leg. In addition, none of the patients who had had an isolated pulmonary embolism showed a natural anticoagulant deficiency. Thus, inherited abnormalities of the coagulation pathway seem to play a minor role in the occurrence of isolated pulmonary embolism.

Inherited natural anticoagulant deficiencies were mainly found in patients with deep vein thrombosis in one leg, few cases being observed in different settings. Prevalences of inherited natural anticoagulant deficiencies were rather low when compared to prevalences reported in some studies in unselected patients[31] but similar to others observed in different clinical settings.[32,33] However, in spite of these differences, similar prevalences

of FV Leiden and FII A^{20210} mutations were found, further supporting the findings of the present report.

We conclude that screening for inherited thrombophilic risk factors can identify high-risk individuals among patients who have had a venous thrombosis of the leg or cerebral vein thrombosis. On the other hand, our data suggest that screening programs have less relevance in patients with isolated pulmonary embolism or mesenteric vein thrombosis. The lack of association with inherited thrombophilic risk factors does not justify routine screening of patients with thrombosis of the upper extremities or with retinal vein thrombosis, or in asymptomatic individuals without a family history of venous thrombosis.

Contributions and Acknowledgments

MM was responsible for the conception and design of the study, analysis and interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted. VB was responsible for the conception and design of the study, interpretation of data, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted. AC was responsible for the conception and design of the study, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted. MLP was responsible for the conception and design of the study, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted. EG was responsible for the conception and design, analysis and interpretation of data, revising it critically for important intellectual content, and final approval of the version to be submitted. GDM was responsible for the conception and design of the study, drafting the article, revising it critically for important intellectual content, and final approval of the version to be submitted.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

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Potential implications for clinical practice

Screening programs for inherited thrombophilic risk factors are useful in patients who have suffered from vein thrombosis in one leg or cerebral vein thrombosis. The screening is not justified in patients with thrombosis of the upper extremities or with retinal vein thrombosis.

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