The risk of recurrent venous thromboembolism in patients with inherited deficiency of natural anticoagulants antithrombin, protein C and protein S

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Few data are available on the risk of recurrent venous thromboembolism (VTE) associated with the rare inherited deficiencies of natural anticoagulants. We studied 602 patients with previous VTE: the incidence of first recurrence in the absence of anticoagulation was retrospectively estimated in 64 patients with deficiency of antithrombin (AT, n=14), protein C (PC, n=28), or protein S (PS, n=22) and 538 with no known defect, who acted as the reference group. After adjustment for sex, age, and circumstances of the first event, AT deficiency resulted an independent risk factor for recurrence (hazard ratio 1.9, 95% CI 1.0-3.9); the carriers of PC or PS deficiency had a marginal increase in risk (hazard ratio 1.4, 95% CI 0.9-2.2). In conclusion, patients with AT deficiency are potential candidates for long-term oral anticoagulation.

Key words: inherited thrombophilia, antithrombin deficiency, protein C deficiency, protein S deficiency, recurrent venous thromboembolism.

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Inherited deficiencies of natural anticoagulants antithrombin (AT), protein C (PC), and protein S (PS) are present in less than 10% of patients with venous thromboembolism (VTE),[1] but patients with these deficiencies are considered at higher risk for VTE.[2-6] Many experts suggest oral anticoagulation for an indefinite duration for such patients after a first spontaneous VTE, especially for individuals with AT deficiency.[7-11] In contrast, others consider knowledge of such alterations not useful for deciding the duration of anticoagulant treatment.[12,13] Indeed, few data concerning the risk of recurrence in such patients are available.[14-20] This study was aimed at estimating the long-term risk of recurrent VTE in patients with inherited deficiency of natural anticoagulants.

Design and Methods

Patients and laboratory methods

From November 1994 to November 2004, 1380 unrelated patients with previous deep venous thrombosis (DVT) of the legs and/or pulmonary embolism (PE) were referred to our Thrombosis Centers. A preliminary evaluation had ruled out patients with overt cancer or chronic myeloproliferative disorders. All patients were interviewed about their medical history before laboratory testing, so that diagnoses of first or recurrent VTE were recorded blinded to the results. The presence of circumstantial risk factors at the time of all episodes of VTE, such as surgery, pregnancy and puerperium, oral contraceptive intake, hormone replacement therapy, trauma, leg cast, prolonged bed immobilization, long travel, was recorded; in the absence of the aforementioned risk factors, VTE was labeled as spontaneous. All patients underwent laboratory screening for thrombophilia, including measurement of AT heparin cofactor and PC functional activities, free PS antigen, search for the factor V Leiden (FVL) and the prothrombin (PT) 20210A polymorphisms, and search for antiphospholipid antibodies (aPL, i.e. lupus anticoagulant and anticardiolipin antibodies). AT, PC, or PS deficiency was considered inherited only in the presence of normal liver and renal functions and in the case of levels below the normal range also in a first-degree relative. All patients had been referred by general practitioners without any preliminary laboratory investigation or immediately after a laboratory result raising the suspicion of thrombophilia. Thus, the duration of antithrombotic prophylaxis after the first VTE was decided by the primary care physicians in the years preceding referral to the Thrombosis Centers without knowledge of the patients' thrombophilia status.

Study end points

The medical records of the patients were examined by at least two physicians before knowledge of the laboratory results. The diagnosis of first or recurrent VTE was adjudicated only in the case of unanimous consensus. The diagnosis of VTE was based only on results of objective investigations: phlebography, compression or color Doppler ultrasonography for DVT, perfusion lung

scanning, computed tomography (CT), or magnetic resonance imaging (MRI) for PE. Objectively established contralateral DVT and PE were computed as recurrences. Ipsilateral DVT was adjudicated recurrent if the results of the objective tests were worse than those obtained in a preceding test,[21] if the thrombus was diagnosed in another venous district of the leg, or if a new course of anticoagulant treatment was started. The following manifestations were also defined as recurrences: objectively proven DVT of the arm, occlusion of cerebral or abdominal veins diagnosed with CT or MRI, thrombosis of the great saphenous vein of the leg not involved in the first manifestation and objectively diagnosed with ultrasonography. Only the episodes that occurred more than three months after the first VTE were computed as recurrences.

Statistical analysis

The patients with deficiency of a natural anticoagulant were compared with those with no apparent cause of thrombophilia. The interval from the first VTE to a recurrence (uncensored observations) or to referral to the centers (censored observations) was analyzed according to the method of Kaplan and Meier. Differences between groups were estimated by Fisher's exact test, the χ^2 test, the Mann-Whitney test, the Kruskall-Wallis test, or the log-rank test, used when appropriate. p values ≤ 0.05 were considered statistically significant. The relative risk of recurrence was estimated as a hazard ratio (HR) by a Cox regression model. The HR was adjusted with recurrent VTE as the dependent variable and other factors possibly predictive of recurrence as covariates: male sex, advanced age, first spontaneous event, and first pulmonary embolism. All dichotomous variables were coded as 1 if present, 0 otherwise. Age at the first VTE was categorized as a dichotomous variable (1 if >45 years, 0 otherwise).

Results and Discussion

Clinical features

Of the initial 1380 patients, those carrying FVL (n=262), PT20210A (n=133), combined inherited defects (n=42) or aPL (n=61) were excluded. Among the remaining patients, another 280 were excluded because they were referred on the occasion of a first acute VTE, or had received more than 6 months of antithrombotic prophylaxis after the first VTE, or had stopped prophylaxis before referral within a time shorter than 12 months. Of these 280 excluded patients 24 had deficiency of a natural anticoagulant, and 256 had no known defect.

The clinical features of the 602 patients suitable for inclusion in this study are reported in Table 1: 64 had inherited deficiency of a natural anticoagulant and 538 had normal levels of natural anticoagulants and absence of FVL and PT20210A (reference group). The ratio between the patients with deficiency of a natural anticoagulant and those with no known defect was similar in those admitted to the analysis and in those excluded (0.09 and 0.11, respectively). The patients with deficiency of a natural anticoagulant and the reference group did not differ in sex distribution, rate of spontaneous first events, or interval from the first VTE to recurrence or referral. The age at the first event was lower in the patients with deficiency of a natural anticoagulant (p<0.001). Separate analysis of the patients carrying AT, PC, or PS deficiency showed homogeneity with respect to all the parameters indicated above.

Table 1. Main clinical features of the investigated groups.

	AT deficieny n=14	*PC deficiency n= 28*	*PS deficiency n=22*	*Total patients n=64*	*Reference group n=538*
Sex male/female	8/6	10/18	11/11	29/35	227/311
Sex ratio	1.33	0.55	1.00	0.82	0.72
Age at first VTE, years					
Mean	32	32	36	33	46
Median	30	30	34	31	43
Range	14 - 58	0 - 68	18 - 59	0 - 68	11 - 95
Interval from first VTE to recurrence or referral, years					
Mean	8	8	5	7	6
Median	5	3	2	3.5	4
Range	1 - 33	1 - 49	1 - 20	1 - 49	1 - 41
First DVT of the legs no. of patients (%)	8 (57)	20 (72)	18 (82)	46 (72)	422 (79)
First DVT + PE no. of patients (%)	6 (43)	6 (21)	4 (18)	16 (25)	82 (15)
First PE - no. of patients (%)	0	2 (7)	0	2 (3)	34 (6)
Spontaneous first VTE no. of patients (%)	5 (36)	10 (36)	13 (59)	28 (44)	222 (41)
Provoked first VTE overall no. of patients (%)	9 (64)	18 (64)	9 (41)	36 (56)	316 (59)
Oral contraceptive use no. of female patients/total (%)	1/6 (17)	5/18 (28)	2/11 (18)	8/35 (23)	54/311 (17)
Pregnancy or puerperium no. of female patients/total (%)	3/6 (50)	4/18 (22)	1/11 (9)	8/35 (23)	66/311 (21)
Transient risk factors no. of patients (%)	5 (36)	9 (32)	6 (27)	20 (31)	196 (36)
Patient-years at risk after the first VTE	109	215	108	432	3210
Overall recurrences no. of patients (%)	9 (64)	14 (50)	8 (36)	31 (48)	149 (28)
Spontaneous recurrences no./total recurrences (%)	7/9 (78)	12/14 (86)	6/8 (75)	25/31 (81)	110/149 (74)
Recurrent VTE/100 patient-years at risk	8.2	6.5	7.4	7.2	4.6

Venous thromboembolism (VTE) includes deep venous thrombosis of the legs (DVT) with or without pulmonary embolism (PE) and isolated PE. Transient risk factors include surgery, trauma, leg cast, prolonged bed immobilization (> 10 days), long travel (> 8 hours).

Table 2. Relative risk of recurrent venous thromboembolism according to the clinical and laboratory parameters.

	Univariate hazard ratio (95% CI)	*Log-rank test (p)*	*Multivariate hazard ratio (95% CI*	*Log-rank test (p)*
AT, PC, PS deficiency (vs. reference group)	1.5 (1.0-2.2)	0.01	1.5 (1.0-2.3)	0.03
AT deficiency (vs. reference group)	1.9 (1.0-3.8)	0.05	1.9 (1.0-3.9)	0.05
PC or PS deficiency (vs. reference group)	1.4 (0.9-2.2)	0.13	1.4 (0.9-2.2)	0.14
Sex (male vs. female)	1.6 (1.2-2.1)	0.001	1.4 (1.0-1.9)	0.03
Age > 45 years at the first event (vs. age < 45 years)	1.4 (1.0-2.0)	0.02	1.3 (0.9-1.9)	0.10
First spontaneous event (vs. first provoked event)	1.6 (1.2-2.2)	< 0.001	1.4 (1.0-1.9)	0.03
First pulmonary embolism (vs. no pulmonary embolism)	0.9 (0.6-1.2)	0.40	0.9 (0.6-1.3)	0.59

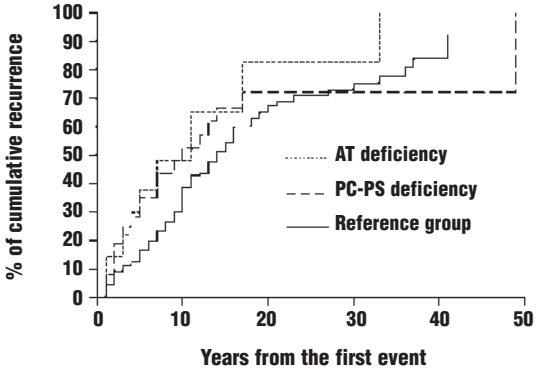

Figure 1. Cumulative incidence of recurrent venous thromboembolism (VTE) after a first episode of deep venous thrombosis and/or pulmonary embolism in patients with antithrombin (AT), protein C (PC), and protein S (PS) deficiency and in patients of the reference group (normal levels of AT, PC, PS and wildtype factor V and factor II genotypes).

Incidence of recurrent venous thromboembolic events

Recurrent VTE occurred in 180 patients (in 3% of cases during the period of oral anticoagulation); the cumulative incidence of recurrence in the whole cohort was 28.4% by 8 years after the first event, which fits with that found for the same time interval in a prospective cohort of consecutive patients.[16] At the time of referral, the rate of recurrence was 48.4% in patients with deficiency of a natural anticoagulant, and 27.7% in the reference patients (p=0.001), with no difference among the subgroups of patients with AT, PC, or PS deficiency (p=0.25) (Table 1). A late recurrence occurred more than 10 years after the first event in 12.5% of patients with deficiency of a natural anticoagulant and in 7.6% of the reference patients (p=0.22).

Current clinical practice offers patients with previous VTE short-term antithrombotic prophylaxis during surgery or pregnancy and puerperium, and discourages the use of oral contraceptives. Accordingly, the large majority of recurrences occurred spontaneously both in the patients with deficiency of a natural anticoagulant and in the reference group (80.6% and 73.8% of the recurrences, respectively, p=0.50). Recurrences were mostly DVT of the legs and/or PE (87.1% in the study group and 87.9% in the reference group, p=1.00). The incidence of recurrent VTE/100 patient-years was 7.2 in patients with deficiency of a natural anticoagulant and 4.6 in the reference patients (Table 1). The likelihood of recurrence was 1.5-fold higher among patients with a natural anticoagulant deficiency (Table 2). In a separate analysis the risk of recurrence was 1.9-fold increased among the carriers of AT deficiency, bordering statistical significance; the risk was not significantly increased among carriers of PC or PS deficiency (Table 2, Figure 1).

The overall effect of inherited thrombophilia on the risk of recurrent VTE is small;[18,19] the risk for the rare patients with deficiency of a natural anticoagulant is difficult to pick out since it is diluted by the weak effect of the much more frequent polymorphisms FVL and PT20210A. However, the available data suggest that patients with such a deficiency are more prone to recurrences.

In retrospective studies the rate of recurrence after a first VTE among individuals with deficiency of a natural anticoagulant has been reported to range between 36% and 62%,[14,15,17] with an incidence of 4.8 /100 patient-years before diagnosis of thrombophilia.[14] In prospective cohorts, the risk of recurrent VTE was increased by 1.4 to 1.8-fold in the patients with deficiency of a natural anticoagulant.[16,18,19] When analyzed separately, carriers of AT deficiency had a 2.6-fold increased risk of recurrence .[18]

In our study the rate of first recurrent VTE in patients with deficiency of a natural anticoagulant is 48%, with an incidence of 7.2/100 patient-years. This fits with a report from the European Prospective Cohort on Thrombophilia on 73 patients with natural anticoagulant deficiency, which estimated an incidence of recurrent VTE /100 patient-years of 6.4 in the absence of anticoagulation (10.5 for AT deficiency, 5.1 for PC deficiency, and 6.5 for PS deficiency).[20] Our study was retrospective and conducted in patients referred to two specialized centers. Indeed, the clinical management of all the recruited patients after their first VTE was decided by their primary care physicians without knowledge of the thrombophilia status. The diagnosis of first or recurrent VTE was validated by the investigators of the Thrombosis Centers, who were blind to the laboratory results. Moreover, the period after referral to the centers was not considered, because patients with a diagnosis of inherited thrombophilia were likely to be followed

more carefully, whereas patients with no identified cause of thrombophilia in many cases had no further contact with the centers. Finally, the overall incidence of recurrent VTE fits with that found in a long-term prospective study on consecutive patients.[16] Thus, overestimation of the risk of recurrence due to a referral bias or to knowledge of the presence of inherited thrombophilia appears unlikely. For many patients, our study covered a life-long period, so that a number of recurrences could have been missed for the lack of objective documentation or a recall bias could have occurred. Moreover, some patients received long-term anticoagulation on the basis of a clinical diagnosis and were excluded from the analysis, likely producing an underestimation of the risk of recurrent VTE; however, the proportions of patients subsequently diagnosed as having a deficiency in a natural anticoagulant were similar among the subjects excluded from and those admitted to the study. The patients with or without deficiency of natural anticoagulants admitted to the analysis did not differ in sex distribution, rate of first spontaneous VTE, or median observation time. Thus, since the two investigated groups were fully comparable and it is unlikely that possible overestimation or underestimation of the recurrent events or any bias had an unbalanced distribution, the estimate of the relative risk between patients with or without deficiency of natural anticoagulants can be considered reliable.

In conclusion, patients with inherited deficiency of AT, PC, or PS have a moderate 1.5-fold increased risk of recurrent VTE; in particular, symptomatic patients with AT deficiency seem to be candidates for indefinite anticoagulation, given that the incidence of recurrent VTE in such patients is 8.2 /100 patient-years, with a 1.9-fold higher risk than that in patients with no apparent thrombophilia.

VDS conceived and designed the study and was responsible for the statistical analysis, the final interpretation of the data, and the final drafting of the manuscript; VDS, PS, ER, DT, TZ were the physicians responsible for the recruitment and for laboratory screening of the patients, as well as for the adjudication of the thrombotic events; ER, TZ, DT were responsible for the final database collecting the laboratory and clinical data; AP and GL as senior authors critically revised the paper and gave important intellectual contributions. All authors were involved in the final revision of the article, giving contribution to the final interpretation of the data and final approval. The authors declare they have no potential conflicts of interest.

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