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The Prevalence of Hereditary Thrombophilia in the Trakya Region of Turkey

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Abstract

The prevalences of deficiencies in antithrombin III (AT III), protein C (PC), protein S (PS) and in the activated protein C (APC) resistance in the thrombotic population of the Trakya region, Turkey were investigated. 37 patients with venous thrombosis (VT) and 17 patients with arterial thrombosis (ArT) were included in this study. The mean ages of the patients with VT and ArT were 46 years (range 20−70) and 38 years (range 32−40), respectively. The activity of AT III was measured by commercially available immuno-turbidimetric assay. The activities of PC and PS were determined by coagulometric assay. The APC resistance was measured using a modified APTT-based clotting assay. Among the VT patients, there were 2 cases (5.4%) with AT III, 5 (13.51%) with PC deficiency, 5 (13.51%) with PS deficiency and 2 (5.4%) with APC resistance. In the ArT patient group, there was 1 patient (5.88%) with AT III, 3 (17.64%) with PC deficiency,1 (5.88%) with PS deficiency and no APC resistant patients, while there was one (2.08%) with PC deficiency and one (2.08%) with APC resistance in the control group (49 persons, mean age 41 years). The relative risk of thrombosis (odds ratio) was 1.7 in the deficiency of PC and 5.6 in the deficiency of PS. The data presented suggests that the prevalences of AT III, PC and PS deficiencies causing thrombophilia in the Trakya region of Turkey are higher than in other reported studies while the APC resistance is lower than in others. Further studies including more patients would be required to clarify these discrepancies.

Key Words: Venous thrombosis, arterial thrombosis, natural inhibitors, activated protein C resistance, Turkish population

INTRODUCTION

Antithrombin III (AT III) deficiency, alterations of the protein C system (PC), activated protein C (APC) resistance, prothrombin gene mutation (G20210A) and hyperhomocysteinemia are the most frequently recognized causes of hereditary thrombophilia.[1-4] Several studies focusing on the laboratory evaluation of patients with thromboembolic disease have been published,[5-10] however, the reported prevalence of different causes of thrombophilia is highly variable, probably due to different patient selection criteria or to geographical reasons.

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The population of the Trakya region of Turkey is composed of residents and the immigrants from Western Trakya and the Balkans due to its geographic location as a bridge between Europe and Asia. Because of this reason, the Trakya region is important for the epidemiologic studies of hereditary diseases. In this study, we investigated the frequencies of deficiencies of AT III, PC and protein S (PS) and APC resistance, as well as determined the risk factors and odds ratios in patients with venous thrombosis (VT) or arterial thrombosis (ArT) in this region.

MATERIALS AND METHODS

Patients were selected from the files of the Hematology, Cardiology and Cardiovascular Surgery Departments of Trakya University from 1995 to 1997. All of our patients orginated from the Trakya region (geographic location was the only selection criteria). A total of 54 patients, 37 with VT of any localization, and 17 with ArT, 14 with myocardial infarction, 2

with ischemic cerebrovascular disease and 1 with peripheral vascular disease were included (Table 1).

Patients with a previous history of chronic or malignant diseases, liver chirrosis, coumarin or other medications usage, or those who had prolonged of APTT were excluded from this study. The patients were examined after the last thrombotic event and had not taken coumarin for at least 3 months. The control group had no biological relationships with those of the study group. All of the control group were healthy volunteers.

A standardized medical history was obtained and a short physical examination was completed. We used ultrasonograpy for the diagnosis of deep vein thrombosis (DVT). Thrombosis in other unusual sites was diagnosed by the examination of newly occuring neurologic signs and of computed tomography for sinuous VT, by ophthalmic examination for retinal VT, by electrocardiography and the levels of cardiac enzymes for myocardial infarction and by angiography for peripheral arterial thrombosis.

We used the classification of risk factors which was proposed by the "Ad Hoc Committee on Reporting Standards of the Joint Council of the Society for Vascular Surgery and The North American Chapter of the International Society for Cardiovascular Surgery" for VTE[11] and the "MONICA" study for ArT.[12] We could not carry out the familial studies.

Blood (9 ml) was collected from the antecubital vein and was collected in coded plastic tubes containing 1 ml of trisodium citrate-dihydrate (3.8%). Plasma was separated by centrifugation at 1,600×g for 20 min at room temperature and was stored immediately at −70°C until it was assayed. AT III activity was measured with an immunoturbidimetric assay (LIATEST®). PC and free PS were measured by coagulometric assay. The level of modified APC resistance was determined to measure the sensitivity of APTT to APC. We determined the APC sensitivity ratio (APC-SR) and normalized it. Factor II, V, VIII and X coagulant activities were measured by one-stage clotting assay with artificial deficient plasma. The kits and the semi-automated ST4 coagulometer used were from Diagnostica Stago, France.

For statistical analysis, we used the descriptive, one way Anova and Student-t test with SPSS software package.

RESULTS

The patients with VT

The localizations of thrombotic events of these patients are shown in Table 1. The total number of deficiencies of AT III, PC, PS and APC resistance was 14 of the 37 patients (37.43%). PC deficiency in five cases (13.51%), PS deficiency in five cases (13.51%), AT III deficiency in two cases (5.40%) and APC resistance in two cases (5.40%) were determined. There was no combined deficiency. The incidences of these deficiencies and APC resistance are shown in Table 2. The clinical features of the patients are shown in Table 3. The mean age for the first thrombotic event occurring in our patients was 41 years old. The mean age for the first thrombotic event occurring in the deficiencies of AT III, PC and PS were 40, 54, and 27 years old, respectively.

One patient who had PC deficiency had both VT and myocardial infarction. We found one PC deficiency in the control group (1/49; 2.08%). The crude odds ratio for the deficiencies of PC and PS were 1.7 (95% CI; 2.16−3.10) and 5.6 (95% CI; 3.22−9.35), respectively.

We found APC resistance only in two patients with VT (5.40%) and in one person in the control group (1/49; 2.08%). We accepted APC resistance below 1.83 of the APC sensitivity ratio (APC-SR) and 0.53 of the normalized APC-SR. We could not determine

Table 1. Characteristics of Patients with Thrombosis in Trakya Region

Localization of thrombosis	n	Male/ Female	Mean age (yr) (range)
Venous thrombosis (VT)			46 (20−70)
Deep VT	31	13/18	
Retinal VT	4	2/2	
Sinuous VT	2	0/2	
Total	37	15/22	
Arterial thrombosis (ArT)			38 (32−40)
Acute myocardial infarction	14	14/0	
Ischemic CVD	2	1/1	
CVD+Peripheral VD	1	1/0	
Total	17	16/1	
Control group	49	17/32	41 (25−63)

CVD, cerebrovascular disease; VD, vascular disease.

the effect of age and sex on the APC-SR (APC-SR-sex p=0.966; APC-SR-age p=0.967). There was no case of APC resistance combined with other deficiencies.

Table 2. The Incidences of Antithrombin III, Protein C and Protein S Deficiencies and Activated Protein C Resistance in Patients with Thrombosis in Trakya Region

Etiology	Venous thrombosis n (%)	Arterial thrombosis n (%)
AT III deficiency	2 (5.40)	1 (5.88)
PC deficiency	5 (13.51)	3 (17.64)
PS deficiency	5 (13.51)	1 (5.88)
APC resistance	2 (5.40)	0 (0)
Others	23 (62.18)	12 (70.60)
Total	37 (100)	17 (100)

AT, antithrombin III; PC, protein C; PS, protein S; APC, activated protein C.

Familial history, the risk factors and the recurrence of the thrombotic events are shown in Table 3. We could not perform the familial studies.

The patients with ArT

We found 3 patients with deficiency of PC (17.64%), one patient with deficiency of PS (5.88%) and one patient with deficiency of AT III (5.88%). We could not find any patients with APC resistance. The incidences of the deficiencies and the clinical features of the patients are shown in Table 2 and 4, respectively.

DISCUSSION

The main aim of this study was to establish the

Table 3. The Clinical Features of Patients with Venous Thrombosis in Trakya Region

Etiology	No of cases	Kind of VT (n)	Mean age of the first attack (yr)	Cases of recurrent thrombosis	Familial history	Risk factors (n)
AT III Deficiency	2	DVT+SVT (1) RVT (1)	40	1	No	No
PC Deficiency	5	DVT (4) RVT (1)	54	2	Yes (1)	Obesity (1) Surgery (1)
PS Deficiency	5	DVT (5)	27	2	No	Pregnancy (1) Trauma (1)
APC Resistance	2	DVT (2)	42	2	No	No

DVT, deep vein thrombosis; SVT, sinuous venous thrombosis; RVT, retinal vein thrombosis.

Table 4. The Clinical Features of Patients with Arterial Thrombosis in Trakya Region

Etiology	No of cases	Kind of ArT	Mean age of the first attack (yr)	Cases of recurrent thrombosis	Familial history	Risk factors (n)
AT III Deficiency	1	AMI	30	0	Yes	Smoking
PC Deficiency	3	AMI*	40	0	Yes (1)	Smoking (2)
PS Deficiency	1	CVD+PAD	27	1	No	Smoking Hypertension

AMI, acute myocardial infarction; CVD, cerebrovascular disease; PAD, peripheral arterial disease.
* A patient who had both DVT and AMI, (yr): years.

prevalence of biological abnormalities causing thrombophilia in the Trakya region of Turkey. Previously released data on the prevalence of these deficiencies has been conflicting and the rates were reported to range from 4.5% to 32.2%.[5-10] The combined prevalence of deficiencies of AT III, PC and PS were 37.43% in our study. This result was higher than the in other studies. We believe that the reasons for this discrepancy are the difference in patient age between study groups as well as the small numbers in our study consisting of unselected patients. The age limit was 70 years in our study. Grossman et al. reported the prevalence of deficiencies as high as 42.9% but their age limit was 79 years.[13] In addition, other reasons may be geographic localization and genetic variations.

The prevalences of the deficiencies of PC and PS in our study were found to be similar (13.51%), but the frequency of AT III deficiency (5.4%) was lower than the PC and PS deficiencies. The prevalence of the AT III deficiency was similar to that found by Melissari et al.[7] We determined two patients with APC resistance (5.4%). This result was lower than that reported by the international and national studies in other areas.[14-18] This difference may be due to our study limitations, geographic localization and genetic variations.

The relative risk of thrombosis in the patients with PS deficiency was higher than that in the patients with PC deficiency in our study group. However, the effect of PS deficiency on the relative risk of thrombosis in VT is still debatable.[15]

One PC deficiency (2.08%) and one APC resistance (2.08%) were determined in our healthy control group. It was shown that the deficiency of PC and the APC resistance in healthy people are equally important as the other known risk factors for the relative risk of thrombosis.[19,20]

It is known that the biological abnormalities causing thrombophilia are not as important in VT as in ArT. However, we found deficiencies of proteins of the natural inhibitory system in 29.41% of the patients who were younger than 40 years of age (3 PC, one AT III and one PS deficiency). The deficiency of PC occurred more frequently than the deficiency of PS in our group. Although it has been reported that ArT occurs frequently with a deficiency of PS, the effect of the deficiency of PS on ArT is still unclear. The frequency of PC deficiency in our ArT group was higher than the others.[21-23]

In recent years, APC resistance has been an important element in the etiology of hereditary thrombosis. However, there is a conflict in terms of the reported effects of the APC resistance on ArT.[24,25] Many studies reported no effect of the APC resistance on ArT.[26,27] The prevalence of the homozygous resistance to APC increases the frequency of ArT but heterozygous resistance to APC does not. Rosendall et al.[25] reported that resistance to APC could be a risk factor in young smoking women with myocardial infarction. We could not find any patients with APC resistance in our ArT group.

In summary, this study showed that the prevalence of the biologic abnormalities causing thrombophilia in the Trakya region of Turkey was higher than in other studies but APC resistance was lower than other reported international and national studies in our population. We found that the deficiency of PC was an important risk factor for ArT in the thrombotic population of the Trakya region of Turkey. The reasons for these discrepancies may be the limitation of the different patient selection criteria, geographic localization and genetic variations.

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