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Aetiology of Deep Vein Thrombosis in 63 Turkish Patients

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Aim: The aetiology of deep vein thrombosis differs among populations throughout the world. This study examines the aetiology of deep vein thrombosis in Turkish patients.

Materials and Methods: Our study involved the treatment of 63 patients, including follow-up in our outpatient department, between November 2006 and December 2007. There were 29 female and 34 male patients with a mean age of 49.35 + 14.19 (range 25 – 85 years). Deep vein thrombosis was identified using a Doppler-/ duplex sonogram. A small pulmonary embolism was present in 5 patients.

Results: Follow-up was carried out in 58 patients (92.06%). The causes of deep vein thrombosis were detectable in 43 patients (68.25%) by anamnesis and physical examination. Immobilization was present in 33 patients (52.38%). A thrombophilia test was carried out in 29 patients. In 20 patients (31.74%) with the first manifestation of deep vein thrombosis, no cause for deep vein thrombosis could be found in the anamnesis. A thrombophilia test was carried out through analysis of Protein C, Protein S, APCR (Activated Protein C Resistance), and Factor V Leiden in 12 (60%) of these 20 patients. In 11 (91.66%) of these 12 patients, thrombophilia was positive.

Conclusions: The main causes of deep vein thrombosis in the Turkish population were immobilization (52.38%) and thrombophilia (51.72%). The incidence of both causes is approximately equal. In the healthy Turkish population with the first manifestation of deep vein thrombosis, thrombophilia can be positive in 91.66% of patients.

Key Words: Deep vein thrombosis, aetiology, thrombophilia

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Altmış Üç Derin Ven Trombozlu Hastada Etiyoloji

Amaç: Derin ven trombozunun etiyolojisi dünya popülasyonları arasında farklılıklar göstermektedir. Bu çalışmada derin ven trombozlu Türk hastalarındaki derin ven trombozunun etiyolojisi araştırılmaktadır.

Yöntem ve Gereç: Kasım 2006 ve Aralık 2007 tarihleri arsında derin ven trombozlu 63 hasta polikliniğimizde tedavi ve takip edilmiştir. Yaş ortalamaları 49,35 + 14,19 yıl (25 – 85 yıl) olan 29 kadın ve 34 erkek hasta tedavi edilmiştir. Derin ven trombozu tanısı doppler ve duplex sonografiyle konmuştur. Minor pulmoner enfarktüs 5 hastada mevcuttu.

Bulgular: 58 hasta (% 92,06) takiplere katıldı. Derin ven trombozunun nedeni anemnez ve fiziksel muayeneye göre 43 hastada (% 68,25) tesbit edilmiştir. Immobilizasyon 33 hastada mevcuttu (% 52,38). Trombofili testi toplam 29 hastada uygulanabildi. Hayatında ilk defa derin ven trombozu geçiren 20 hastanın (% 31,74) anemnezine göre derin ven trombozu için herhangi bilinen bir risk faktörü yoktu. Bunlardan 12 hastada (% 60) trombofili testi Protein C, Protein S, APCR (Activated Protein C Rezistansı) ve Factor V Leiden analizleriyle yapıldı. Trombofili 12 hastanın 11 inde (% 91,66) pozitif bulunmuştur.

Sonuç: Türk populasyonundaki derin ven trombozunun ana etiolojik faktorleri immobilizasyon (% 52,38) ve thrombofilidir (% 51,72). Her iki nedenin sıklığı ortalama olarak eşittir. Hayatında ilk defa derin ven trombozu gelişen genç sağlıklı Türk populasyonunda trombofili bu hastaların % 91,66' ında pozitif olabilir.

Anahtar Sözcükler: Derin Ven Trombozu, etiyoloji, trombofili

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Introduction

Deep venous thrombosis is a serious clinical condition and can be associated with life threatening pulmonary embolism. Its aetiology is multifactorial, involving mostly immobilization, malignancy, and thrombophilia (1). Inherited thrombophilia as a cause of deep vein thrombosis appears mostly through protein C deficiency, protein S deficiency, activated protein C resistance (APCR), and Factor V Leiden. The distribution

of these parameters and other causes in the world varies among populations (2-5). In this study we present the etiologic factors, especially the rate of thrombophilia, in deep vein thrombosis and its short-term prognosis in the Turkish population.

Materials and Methods

In 63 patients, a deep vein thrombosis was diagnosed by duplex scan (Voluson 730 Pro; General Electric / Austria), and treated and followed up in our outpatient department between November 2006 and December 2007. The following conditions were observed: left subclavian vein thrombosis in 2 patients (3.17%), a mesenterial portal vein thrombosis in 1 patient (1.58%), left iliac vein thrombosis in 5 patients (7.93%), right iliac vein thrombosis in 1 patient (1.58%), left lower extremity deep vein thrombosis in 32 patients (50.79%), right lower extremity deep vein thrombosis in 20 patients (31.74%), and bilateral lower extremity deep vein thrombosis in 2 patients (3.17%) (Table 1).

There were 29 female and 34 male patients. Mean age was 49.35 + 14.19 (range 25–85 years). The clinical classification according to the CEAP (C: Clinical Sign; E: Etiologic Classification; A: Anatomic Distribution; P: Pathophysiologic Dysfunction) classification (6) was C3 in 63 patients, C5 in 3 patients, and C6 in 1 patient. A small pulmonary embolism in 5 patients was present in the thorax computed tomogram. For financial reasons, none of the patients, including those with pulmonary embolism, agreed to be hospitalized. We therefore began a therapy with 120 mg/day of enoxaparin sodium administered subcutaneously up to an INR of 2-3 and parallel oral warfarin sodium. Mechanical prophylaxis was achieved by stocking therapy. A warfarin sodium dose was established by INR laboratory tests with the aim of maintaining an INR of 2-3. The patients received follow-up for up to 12 months, with mean follow-up 5 + 2.56 months (range 1–12 months). During follow-up, the patients were called at home and invited to attend our outpatient department for examination. The patients were physically examined and asked about their symptoms.

In cases where a deep vein thrombosis was suspected, this was checked by a Doppler-/ duplex sonogram. In addition to other etiologic factors for deep vein thrombosis, thrombophilia was considered as a cause of deep vein thrombosis especially in younger healthier patients, and an attempt was made to detect this through analysis of protein C (Technochrome; Technoclone GmbH; Vienna /Austria), protein S (Bioclot 300 ACT; Bioclot GmbH; Eidenbach / Germany), activated protein C resistance (APCR) (Date-Behring; Behring GmbH; Marburg / Germany), and Factor V Leiden (Real Time PCR Roche-Light Cycler 2.0; Roche; CA / USA). Blood samples for thrombophilia tests were taken before initiation of the anticoagulant therapy. An analysis of protein C deficiency, protein S deficiency, APCR, and Factor V Leiden could not be performed for some of the patients due to their financial circumstances. Because of increasing costs, the other anticoagulant factors for thrombophilia could not be examined. Thrombophilia test was available for only 29 patients. In patients with positive thrombophilia, a life-long oral anticoagulation therapy with warfarin was advised, if the further thrombophilia tests were also positive in the 6th month. In patients whose thrombophilia was negative or those who was not administered the thrombophilia test , warfarin therapy was continued for 6 months.

Table 1. Distribution of deep vein thrombosis.

	Number	Percent
Left subclavian vein	2	3.17
Mesenterial and portal veins	1	1.58
Left iliac vein thrombosis	5	7.93
Right iliac vein thrombosis	1	1.58
Left lower extremity thrombosis	32	50.79
Right lower extremity thrombosis	20	31.74
Bilateral lower extremity thrombosis	2	3.17

Results

Follow-up was carried out in 58 patients (92.06%). The other 5 patients were contacted by phone, but they did not come for an examination. Two of those 5 patients failed to comply with the advised therapy. No patients died during follow-up. After medical therapy with enoxaparin sodium, warfarin and stocking therapy under outpatient conditions, 44 patients (69.84%) no longer had symptoms in their limbs. Thirteen patients (20.63%) had moderate limb edema. Five patients (7.93%) had limb pain.

Through anamnesis and physical examination, causes of deep vein thrombosis were detectable in 43 patients (68.25%). Immobilization was present in 33 patients (52.38%). Of these 33 patients, immobilization due to surgery was present in 13 patients (39.39%), postpartum in 13 patients (39.39%), and malignancy in 3 patients (9.09%). Four patients (12.12%) with immobilization in their history were mostly older with multi-morbidity. Hereditary history was positive in 5 patients (7.93%). Three patients (4.76%) had taken an oral contraceptive. One patient had Behçet syndrome (1.58%). Another one had a thoracic outlet syndrome (1.58%). In 17 (39.53%) out of 43 patients with detectable cause for deep vein thrombosis in their anamnesis, a thrombophilia test through analysis of Protein C, Protein S, APCR, and Factor V Leiden was carried out. Thrombophilia was positive in 4 (23.52%) of these 17 patients. The causes of deep vein thrombosis are summarized in Table 2.

In 20 patients (31.74%) no cause for deep vein thrombosis could be found in the anamnesis. For 12 of those patients (60%), a thrombophilia test through analysis of Protein C, Protein S, APCR, and Factor V Leiden was carried out. In 11 of these 12 patients (91.66%), thrombophilia was positive.

Table 2. Aetiology of deep vein thrombosis.

	Number	Percent
Immobilization	33	53.38
Surgery	13	39.39
Postpartum	13	39.39
Malignancy	3	9.09
Multi-morbidity	4	12.12
Hereditary	5	7.93
Oral contraceptive	3	4.76
Behçet syndrome	1	1.58
Thoracic outlet syndrome	1	1.58
Thrombophilia	15	23.8
Isolated PCD	3	20
Isolated APCR	4	26.66
Isolated FVL	1	6.66
PCD + APCR	1	6.66
PCD + APCR + FVL	3	20
PCD + PSD + APCR	2	13.33
APCR + FVL	1	6.66
Total combined defect for thrombophilia	7	46.66

PCD: Protein C deficiency, APCR: Activated protein C resistance, FVL: Factor V Leiden, PSD: Protein S deficiency.

Thrombophilia was detected in 15 patients (23.8%) out of a total of 63 patients with positive and non-positive indications for deep vein thrombosis. Isolated Protein C deficiency was present in 3 patients (20%). Isolated APCR was present in 4 patients (26.66%). Isolated Factor V Leiden was present in 1 patient (6.66%). A combined Protein C deficiency and APCR were present in 1 patient (6.66%). Protein C deficiency and APCR and Factor V Leiden were present in 3 patients (20%). Protein C deficiency and Protein S deficiency and APCR were present in 2 patients (13.33%). Protein C deficiency and APCR and Factor V Leiden were present in 3 patients (20%). APCR and Factor V Leiden were present in 1 patient (6.66%).

Discussion

Deep venous thrombosis is a serious clinical condition and can be associated with life threatening pulmonary embolism. Immobilization through multi-morbidity, surgery, trauma, malignancy, use of oral contraceptives, hormonal therapy, antiphospholipid syndrome, myeloprolipherative disorders, polycythaemia vera, central venous catheter, and advanced age are causes of acquired risk factors for deep vein thrombosis (7). Its incidence increases above the age of 60 and increases further with each decade thereafter. In our group of Turkish patients with deep vein thrombosis, the main etiologic cause of deep vein thrombosis was immobilization in 33 out of a total of 63 patients (52.38%). This was due to surgery (39.39%), post partum (39.39%), malignancy (9.09%), and multi-morbidity (12.12%). Hereditary factors were identified by means of anamnesis in 5 patients (7.93%). The patients were asked about the incidence of deep vein thrombosis in parents and siblings. Other causes were rare: Behçet syndrome in 1 patient (1.58%) and thoracic outlet syndrome in 1 patient (1.58%). Myeloprolipherative disorders and polycythaemia vera could not be detected in our patient group by complete blood count and white blood cell differential count.

Several inherited anticoagulant factors that predispose to deep vein thrombosis have been identified (8). A common cause of thrombophilia is Factor V Leiden. A mutation in this factor causes activated protein C resistance (9). On the other hand, natural coagulation inhibitors protein C and protein S deficiencies have been observed in less than 1% of the general population. However, they play a role in 10% of the aetiology of deep vein thrombosis. The incidence of Factor V Leiden is 20%-25% in the first attack of deep vein thrombosis, but 20%-50% in recurrent deep vein thrombosis (10). In Mediterranean countries, it is the main cause of hereditary thrombophilia (11). Aznar et al. reported that Factor V Leiden was positive in 12.2% of a total of 229 patients with deep vein thrombosis examined in Spain (12). This increased to 18.5% for patients less than 45 years old (12). Simkova et al. from Slovakia observed Factor V Leiden in 37% of 350 patients with deep vein thrombosis (13). Gürgey et al. reported that Factor V Leiden was present in 30.8% of 146 Turkish patients (14). Ghosh et al. from western India found 3% of patients under the age of 45 out of a group of 432 patients with deep vein thrombosis (15). Al-Jaou et al. detected only 1 patient who was Factor V Leiden positive from a group of 179 patients in an Arabian population (16). In Chinese patients, malignancy and protein S were the most frequently acquired and congenital causes of venous thrombosis (17). In our patients, thrombophilia was detected in 15 patients (51.72%) out of a total group of 29 patients examined for thrombophilia. In the group in which aetiology was positively detected by anamnesis and physical examination, the thrombophilia test was positive in 4 (23.52%) out of 17 patients. However, in the group in which aetiology was not detected by means of anamnesis and physical examination the so-called healthy population with the first manifestation of deep vein thrombosis, thrombophilia, was observed in 11 patients (91.66%) out of 12 patients examined. In the thrombophilia positive group, we found a combined defect in 7 patients (46.66%) out of 12 patients tested (Table 2). In 5 (17.24%) out of 29 patients, Factor V Leiden was positive. In 11 (37.93%) out of 29 patients, activated protein C resistance was positive. Protein C deficiency was detected in 9 (31.03%) out of 29 patients. Protein S deficiency was observed in 2 (6.89%) out of 29 patients.

The causes of deep vein thrombosis in the Turkish population are immobilization (52.38%) and thrombophilia (51.72%). The incidence of both causes is approximately equal. In the healthy Turkish population with the first manifestation of deep vein thrombosis, thrombophilia is positive in 91.66% of patients. The

combined defect exists in 46.66% of patients. Activated protein C resistance with a total rate of 37.93% and protein C deficiency with a total rate of 31.03% are the most common causes of thrombophilia, whereas Factor V Leiden is recorded in 17.24% and protein S deficiency in 6.89 % of cases.

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