The Evaluation of Coagulation Parameters and Vessel Involvement in Behcet' s Disease.
A Clinical Experience of Behcet' s Disease: Study of 152 Cases

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Abstract- Behcet´s disease (BD) is accepted as a systemic vasculitis. Vasculitis is observed predominantly on the venous system. Vessel involvement is frequently seen in males. This study was planned retrospectively evaluate demographic features, clinical features, vessel involvements in BD. Furthermore, we aimed to prospectively compare consecutively chosen patients with and without thrombosis and healthy volunteers in terms of their biochemical, immunological, coagulation parameters. One hundred fifty-two Behcet´s patients were retrospectively evaluated. Blood samples were collected from 52 consecutively chosen patients and 41 healthy subjects. Papulopustular skin lesions, eye involvement and venous lesions were detected frequent in males. In terms of evaluated parameters (biochemical parameters, coagulation parameters, C-reactive protein, erythrocyte sedimentation rate, anticardiolipin antibodies, antinuclear antibody positivity) was not found a significant difference among groups (patients without thrombosis, healthy control subjects, patients with thrombosis). We detected statistically significant difference in terms of factor V levels between patient and control group. The tendency to thrombosis in patients with BD is well known. The endothelial lesion, increased procoagulant activity, hypofibrinolysis were found to be responsible from these events. In our study, there was no significant difference in terms of coagulation parameters between the patients without and with thrombosis.

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Keywords: Behcet´s Disease; Coagulation parameters; Thrombosis; Vessel involvement

İntroduction

Behcet´s Disease (BD) is a systematic vasculitis of unknown origin, which mainly affects young adults. It is observed in the Mediterranean, Middle Eastern countries and Japan. The prevalence has been reported as 80-370/100.000 in Turkey, 13.2/100.000 in Japan, 21/100.000 among Turks living in Germany and 0.64/100.000 in England, 17/100.000 in Iraq, 120/100,000 among the Arabs living in Israel, 6.4/100.000 in Spain, 7.1/100.000 in France and 8.6/100.000 in the United States, 0.24/100.000 in Northern Italy (1-4). Male sex and early development of the disease (<25 years) are poor prognostic factors.6 Although it has been reported to be a male-dominant disease in the Middle East, there are different results in Japan (1,6,7). Ocular diseases, aneurism, folliculitis, thrombophlebitis and neurological diseases are found more common in males, but erythema nodosum is observed commonly in females (8,9). Also, patterns of the disease can vary depending on the geographical location. Gastrointestinal involvement is not common in Turkey, and It is commonly reported in the Far East. Moreover, pathergy positivity is frequent in endemic countries in contrast to European countries and America (3).

Viral infection (HSV-1), some streptococcus strains, and environmental factors are considered to be responsible in etiopathogenesis of BD. Studies involving mitochondrial DNA show that there is a gene exchange between East Asians and Europeans (10).

Today, the diagnosis of Behcet's disease is

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established in accordance with the criteria determined by the International Study Group (ISG) in 1990 (11). Oral aphthous ulcers are the initial and most common symptom of the disease. However, genital ulcers are the second most common symptom of the disease. Ocular lesions (anterior uveitis, cataract, posterior uveitis, and retinal vasculitis) are seen in 50% of the patients (in males and younger patients) (12). Central nervous system involvement (parenchymal/vascular) is seen more often than peripheral nerve or muscle involvements (3). Neurologic involvement appears more often in European and American patients (9,13).

Behcet´s disease is a vasculitis which can affect vessels of all types and sizes. Vascular involvement occurs more often in males and is the most common cause of death in young male patients. Approximately, in 25% of the patients there are large arterial and venous vessel involvement (15). Vascular involvement patterns can be in the form of superficial thrombophlebitis, deep vein thrombosis, and occlusion and aneurisms of larger arteries. Venous involvement is more frequent (approximately 20-40%) according to arterial involvement. Vessel involvement usually occurs in the first five years of the disease. Thrombosis can be detected in the subclavian, femoral, popliteal, hepatic vein, cerebral venous sinus (16). Vena cava thrombosis, pulmonary arterial aneurysm, dural sinus thrombosis, and abdominal aorta aneurysms appear with descending frequency (17). Pulmonary arterial aneurysm, the Budd-Chiari syndrome, and vena cava thrombosis are linked to increased mortality. Superficial thrombophlebitis may appear along with inferior vena cava and lower extremity deep vein thrombosis. Vasculitis developing by immunological mechanisms causes endothelium activation and thus, It can occur the predisposition for thrombosis (18). Arterial involvement is a rare occurrence compared to venous involvement and can have more serious results. Males have arterial involvement more common. The common arterial involvement type is aneurysm, and It recurs often after surgery (19). Arterial aneurisms have a high risk for mortality. Generally, arterial aneurisms appear in the aorta and pulmonary arteries. Behcet´s disease is the most frequent acquired cause of pulmonary arterial aneurysms (16). It can cause fatal hemoptysis in young male patients. Pulmonary arterial aneurysms are often bilateral, and there are accompanying to venous thrombosis in 80% of these patients. Intracardiac thrombosis is rare, and It can be detected located in the right ventricle among the young male patients.

It is believed that endothelial activation linked to vasculitis is responsible for the predisposition to thrombosis (18) Fibrinolysis is associated with some procoagulant gene mutations, hyperactive coagulation, hypoactive anticoagulant mechanisms. Thus, these mechanisms may result in the predisposition to thrombosis. The heterozygote factor V Leiden mutation and heterozygote prothrombin gene mutation frequency has been reported as 37.5% and 31.3% among Behcet´s patients, respectively. There are detected hereditary prothrombotic mutations in about 56% of Behcet´s patients. It suggest that there is a possible relationship between the development of thrombosis and gene mutations (20-23). Briefly, immunological defect and consequently endothelial activation rather than primary degeneration are responsible for thrombosis. Conditions such as endothelial damage, increased procoagulant activity, hyperfibrinolysis may contribute thrombosis.

Materials and Methods

One hundred and fifty-two patients were diagnosed "Behcet´s Disease" according to the criteria of the International Study Group. These patients were retrospectively evaluated in terms of demographics, clinical features and types of vessel involvement. All subjects gave their informed consent to the study protocol that was

conducted according to the guidelines of the Declaration of Helsinki, and had been approved by the local Ethic Committee. The blood samples were collected from 52 Behcet´s patients who were selected sequentially and 41 healthy volunteers. Types of vascular involvement were recorded. Superficial thrombophlebitis was identified with clinical findings (pain along the vein, swellings, and nonbacterial inflammations). Deep vein thromboses were detected using venography and angio-computed tomography, Doppler ultrasonography (Toshiba SSA 27AA, Tokyo, Japan). Aneurysms and/or some thrombotic lesions were evaluated using computed tomography (HITACHI W 450, Tokyo, Japan), angiography (AXIOM MULTI STAR SIEMENS, Germany), and angio-computed tomography.

The blood samples were placed in tubes containing 3.2% citrate, they were centrifuged at 3000 rotations for 10 minutes. The plasma samples were evaluated in terms of coagulation parameters (prothrombin time, activated partial thromboplastin time, fibrinogen, international normalized ratio, Protein C, Protein S, Activated protein C resistance, factor V, antithrombin) by using the fully automatic coagulation machine "STA Compact". The

Von Willebrant factor was measured quantitatively (Liatest vWF TAMPON/Buffer vWF Latex). The Anticardiolipin antibodies (ACA) were analyzed using the fully automatic "THA-HD4" microeliza tool with the "AESKULIZA Cardiolipin-GM, REF 7204" kit. The samples were placed in contact with the "BIOCHIP" slides for antinuclear antibodies evaluation (ANA). The evaluation was conducted with fluorescent microscopy. In the statistical evaluation, the group distribution was found to be normal using the One-Sample Kolmogorov-Smirnov test. The "independent t" test was used to determine the significant difference between the groups. The values of $P<0.05$ were deemed significant. Arithmetic means were calculated using standard methods.

Results

In our study, there were 152 patients with Behcet´s disease. It was detected 69 female patients, 83 male patients. The mean age of the patients and the control group were 32.48±8.88 (years) and 31.9±11.86 (years), respectively. There was no significant difference for mean ages between patients and control group (Table 1). Similarly, there was not a significant difference in terms of age between gender.

The family histories of our patients contained Behcet´s disease, Familial Mediterranean Fever, Ankylosing Spondylitis, Rheumatoid Arthritis (respectively; 15.1%, 1.3%, 1.3%, 1.3). Clinical findings of the patients were evaluated (Table 2). Clinical features such as papulopustular skin lesions, ocular involvement, posterior uveitis and loss of vision were detected in male patients. There was a significant difference between genders in terms of these findings ($P<0.05$). It was detected vascular involvement in 17.8% of the patients (n=27). The mean age of onset was 23.78±8.97 (years) for patients with vascular involvement.

Table 1. Demographical findings of the Behcet´s patients and the control group.

Demographical findings	Behcet´s diseases (n=152)	Control group (n=41)
Male/Female ratio	1.2	0.8
Mean age (years)	32.48±8.88	31.9±11.86
Mean age of onset (years)	24.61±8.08	-
Mean age of diagnosis (years)	28.66±8.25	-
The duration between the onset and diagnosis (months)	46.45±47.69	-

Table 2. Evaluation of the clinical findings in the patient group.

Clinical findings which were positive at the time of diagnosis	Total	(n=152)
Oral aphthae	152	(100%)
Genital ulcers	112	(73.7%)
Extragenital ulcers	5	(3.3%)
Dermatological manifestations	122	(80.3%)
Papulopustular lesions	103	(67.8%)
Erythema nodosum	47	(30.9%)
Uveitis	37	(24.3%)
Arthritis	24	(15.8%)
Arthralgia	16	(10.5%)
Thrombophlebitis	19	(12.5%)
Cardiac involvement	0	(0%)
Lung involvement	0	(0%)
Central nervous system involvement	0	(0%)
Aneurism	0	(0%)
Gastrointestinal system involvement	1	(0.7%)
Thrombosis	4	(2.6%)
Pathergy	49	(32.2%)

Table 3. Demographical findings of patients with deep vein thrombosis, locations of the thrombosis and methods of screening.

	Total (n=9) **Male/female ratio: 8/1**
Mean age of onset (years)	24.78±8.98
Mean age of diagnosis (years)	27.89±7.59
Duration from onset to diagnosis (months)	20.56±14.01
Portal vein thrombosis	2 (22.2%)
Right main femoral vein thrombosis	1 (11.11%)
Right internal jugular- right tibialis posterior vein thrombosis	1 (11.11%)
Right internal jugular-right axillary- right subclavian vein thrombosis	1 (11.11%)
Left femoral-left popliteal vein thrombosis	1 (11.11%)
Right popliteal vein thrombosis	1 (11.11%)
Right main femoral–saphenous vein thrombosis	1 (11.11%)
Left popliteal vein thrombosis	1 (11.11%)
Doppler ultrasonography	8 (88.89%)
Venography	1 (11.11%)

Aneurysms (n=3), thrombosis (n=9), thrombophlebitis (n=25), thrombosis accompanying thrombophlebitis (n=9) was detected. Twenty-two of 27 patients with vessel involvement were male (81.5%), and 5 of 27 patients were female (18.5%). There was a significant difference between genders (P=0.002). Twenty-four patients had venous involvement and 3 patients had arterial involvement. In male patients was found venous involvement dominance (P=0.01). There was no difference between patients with and without vessel involvement in terms of clinical features. Nine of the 152 Behçet´s patients had deep vein thrombosis. Demographical findings of these patients, locations of thrombosis and the screening methods are demonstrated below (Table 3).

Behcet´s patients with superficial thrombophlebitis were evaluated, and It was detected 25 patients (21 male patients, 4 female patients). It was shown aneurysm in 1 female and 2 male patients. Ages of diagnosis in patients with aneurysms were found 10 (years) (female), 37 (years) (male) and 31 (years) (male). The locations of the aneurysm were detected as the abdominal aorta and the left iliac artery (in the female patient), the ascending aorta (in first male patient), the right popliteal artery and the deep femoral artery (in other male patient).

There was a significant difference in terms of factor V levels between 52 Behcet´s patients and 41 healthy (P<0.05). It was not detected significant difference between patients and control group in terms of other parameters (uric acid, triglyceride, total cholesterol, HDL, LDL and VLDL), hemoglobin, hematocrit, platelet counts, prothrombin time, activated partial thromboplastin time, fibrinogen, International normalized ratio, Protein C, Protein S, Activated protein C resistance, antithrombin III, Von Willebrand factor, C-reactive protein, erythrocyte sedimentation rate, anticardiolipin antibodies, and antinuclear antibody positivity). Moreover, there was no significant difference detected between patients with or without thrombosis in terms of their biochemical parameters, coagulation parameters, C-reactive protein, erythrocyte sedimentation rate, anticardiolipin antibodies, and the antinuclear antibodies. Also, there was no significant relationship between patients with or without thrombosis in terms of tobacco use.

Discussion

Male/female ratio was 1.2 in our study. It was detected male predominance in other countries (Asia, Middle East and Mediterranean countries) (24). In a recent study conducted in the United States, It was reported a high incidence among women (25). The male/female ratio was 1.03 in a study conducted in Turkey by Tursen *et al.* (26) and It is reflect the general situation for Mediterranean countries.

In our study, the mean age of onset for Behçet´s disease was 24.6 (years). Clinical features such as papulopustular skin lesions, ocular involvements, posterior uveitis, loss of vision, and vascular involvement were found to be more common among males. In terms of neurological, articular, and gastrointestinal system involvement, there was no significant difference between male and female. In the

studies conducted, the age of onset for Behçet´s disease was reported as the 20s. Bang *et al.* (27) reported the age of onset as 33.1 (years) in males and 33.3 (years) in females. Moreover, the mean age of onset for males with poor prognostic factors (ocular, neurological and vascular involvement) was found more younger than females. In some studies, It was reported that male gender and age (<25 years) are associated with poor prognosis (5,28,29).

In some studies, erythema nodosum was found more common among females (5,26,30,31). Conversely, we did not detected significant difference between male and female. In our study, the frequency of erythema nodosum was found as 35.53% similar to literature (25,32). Papulopustular lesions appear frequent in male patients (26). Similarly, papulopustular skin lesions were detected in 73.68% of the patients and male dominance was present in this study. Pathergy positivity was detected 40-98% in the Mediterranean and Far Eastern countries. It was reported as 56% in the study conducted by Tursen *et al.* (26). In our study, pathergy positivity was found 50.66%, and there was not significant difference between male and female.

Ocular involvement was reported around 35-80% in some series.27 This rate was at 55.6% in the study conducted by Salvarani *et al.* (4). In our study, ocular involvement rate was at 29.80%, and there was male-dominance. There are publications that illustrate that ocular involvement is more common among males (5,26). Articular involvement has been detected among 30-70% of Behcet´s patients. İn our study, 42.11% of the patients had joint involvement, and there was no difference between genders. In literature, It was reported similar ratio between genders (26,31,33). Rate of neurologic involvement at Behcet´s patients may 3.2-17%.32 İn the study conducted by Tursen *et al.* (26) neurological involvement rate was 2.3%, and the prevalence was higher in males than females. In our study, 4.6% of the patients had neurological involvement, and there was not difference between females and males. Gastrointestinal system involvement prevalence has been detected about 0-5% in Turkey and Israel (34). İn our study, 1.97% of the patients had gastrointestinal system involvement, and there was no significant difference between females and males. İn the study conducted by Tursen *et al.* (26) was found similar results. Pulmonary involvement occurs in 0.7-7% of Behçet´s patients. Tursen *et al.* (26) reported pulmonary involvement in 1% of the patients. Similarly, the frequency of pulmonary emboli was 0.7% in our study.

The vascular lesions usually occur within the first 10 years of the diagnosis of BD. The critical period is the first two years. Vascular involvement is more common among men, and the male/female ratio is 4-5/1. In a study conducted in Beirut between 1980 and 2000, the vessel involvement was reported as 2-46% and male-dominance was detected (32). In a series reported from Amman, the mean age of patients with vessel involvement was reported as 24 (years) and the rise at the vascular involvement frequency was reported in the first 3.8 years of the disease.36 Vascular involvement ratio was reported as 7% and 39.6% in some studies, respectively (26,36). In another study, the possibility of thrombosis was found be higher in younger male patients (35). In our study, the frequency of vessel involvement was 17.7%, and this number was 4.4 times higher in males than females. In Behçet´s patients, venous thrombosis occurs most frequently in the lower extremities. Patients with recurring venous thrombosis in a single extremity or in the lower extremity should be suspected from the inferior vena cava thrombosis. The frequency of thrombosis in our study was 5.9% (nine patients). Arterial involvement occurs less (iliac, popliteal, and femoral arterial aneurysms). In the study of Tohme *et al.* (32) was reported that arterial involvement ratio was as 3,6%. Although arterial thrombosis occurs more less according to aneurysms, there were the contrary reports in studies conducted by Tohme and Le Thi Hung (32,37). The period between the diagnosis of Behçet´s disease and the detection of arterial involvement has been reported to be 3-25 years (38). In our study, the frequency of arterial involvement was 2%. The mean age of onset in patients with arterial involvement was detected as 18.33±12.66 (years). In a study done in Saudi Arabia, 24% of the patients had venous lesions and 18% of the patients had arterial lesions (39). In their study, It was reported that the rates of venous, arterial, combined (arterial and venous) lesions were 85%, 10%, and 5%, respectively. Contrary to this, in studies from North America, Europe and Japan, arterial lesions were reported to be more frequent than venous lesions. In our study, the rates of venous, arterial and combined involvement were found about 16.4%, 2% and 0.6%, respectively. In a study conducted in Korea, thrombophlebitis was the most common venous symptom. It was detected decreasing frequency in the lower extremities (popliteal and superficial femoral veins), superior and inferior vena cava and upper extremities, respectively (40). In our study, It was reported that lower extremity veins (especially the popliteal and femoral veins) were affected. The frequency of thrombophlebitis has been reported as 2.2-

20% in Behçet´s disease. In a study conducted by Tursen *et al.* (26), 10.6% of the patients had thrombophlebitis and the ratio was five times higher among males than females. In our study, 16.4% of all the patients (n=25, male:21, female:4) had thrombophlebitis. This result was in line with results from other studies (5,30,31).

Oxidation of low-density lipoproteins might cause vascular endothelial damage. Vascular endothelial damage could be a factor in the pathogenesis of Behçet´s disease (41). It was not detected significant differences between patients and control group in terms of serum lipid parameters (42). Similarly, there was no significant difference between patients with and without thrombosis in terms of biochemical parameters in this study. In a study, LDL levels were found higher in the patient group than the control group (43).

C-reactive protein and erythrocyte sedimentation rate are the activity markers for Behçet disease. In some studies, these parameters was found significant higher in the patients compared to the control group (44,45). In our study, no difference was observed among the groups (patients with thrombosis, patients without thrombosis, control subjects). The fibrinogen level was found to be significantly higher in patients than the control group in some studies (43,45,46). Conversely, Espinosa *et al.* did not detect a significant difference between patients and the control groups (42). İn our study, There was no significantly difference among groups in terms of fibrinogen levels.

The prothrombin time is a test that evaluates the extrinsic coagulation system. Partial thromboplastin time (PT) is a test that reflects the intrinsic coagulation system. In some studies, there was no meaningful difference between the patient and the control groups in terms of PT and APTT (42,46,47). In our study, we did not detect a significant difference among groups. Von Willebrand factor (vWF) affects the platelet aggregation and the primary hemostasis. It is synthesized in the endothelium. High level of vWF is a marker of endothelial damage. There is an unclear relationship between the vWF and the occurrence of atherogenesis - thrombus. In some studies was shown high vWF levels in patients (45,48). In our study and in the study conducted by Akarsu *et al.* (43) There was no significant difference among groups.

Factor V is activated with thrombin as primary under in vivo conditions. The active factor X and the active factor V degrade prothrombin enzymatically. Thrombin occur and thus, intrinsic coagulation could be activated. Active factor V can be inactivated by the active protein C. The exchange of Arginine 506 to Glutamin causes active protein C resistance and thus venous thromboembolism can occur (49). This condition could explain the predisposition to coagulation in Behçet´s disease. In our study, factor V levels were found significantly higher in the patient group compared to the control group. Antithrombin III is a member of the serine protease inhibitor family. It is important as the physiological inhibitor of the blood coagulation proteases. When it is lacking, the risk of thrombosis increases significantly. It was found conflicting results among patients (42,46,47,50). We did not detect a difference among groups.

Lack of Protein C and S can cause in thrombotic degeneration. In some studies, It was not found differences between the patient and control groups in terms of protein C and protein S (43,45-47,51,52). Fuseawa *et al.* (50) reported increased protein C levels in patients. Hampton *et al.* (48) detected significantly lower protein C levels in patients without thrombosis. Navarro *et al.* (53) reported that CRP, fibrinogen, vWF, protein S and antithrombin levels increased, but APC levels decreased (53). We did not detect a significant difference for protein C and protein S in terms of thrombosis. Active protein C resistance (APCR) along with idiopathic venous thromboembolism is a common hereditary defect, and this is a phenotypic reflection of the point mutation in the factor V gene. The frequency of APCR in Behçet´s patients are unclear. It was obtained conflicting results (45,51,53,54). In our study, we did not find a significant difference among groups in terms of APCR.

Anticardiolipin antibodies are related to the clinical severity of the disease. They have an important role for systemic inflammation, procoagulant, proatherogenic activity. The frequency of AKA is 0-47% in Behçet´s patients. It was detected that the prevalence of AKA in patients has been increased. But, there was not correlation between AKA and thrombosis (31,43,51,55-58). In a study conducted in Italy, there was a lack of protein C, S with AKA positivity in patients with deep vein thrombosis (59). In a study conducted by Yasar et al. it was shown that combined thrombophilia caused recurring thrombotic events (60). There was not significant difference in our study in terms of AKA levels.

In conclusion, it is known that there is a predisposition to thrombosis in subjects with Behçet´s disease. Vasculo-Behçet´s is a case with a high risk of mortality and morbidity. These patients may have serious complications. This situation should be

considered for male patients. In patients with thrombosis, thrombophilic risk factors should be evaluated. In accordance with existing literature, we detected male-dominance in terms of vascular and ocular involvement in our study. Vascular endothelial damage could be a factor in the pathogenesis of Behçet´s disease. Atherosclerosis and oxidation of low-density lipoprotein increase the endothelial damage. However, we did not detect a significant difference in terms of active disease markers such as biochemical parameters, C-reactive protein, erythrocyte sedimentation rate, coagulation parameters between patients with and without thrombosis.

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