Why are male patients with Behçet's disease prone to thrombosis? A rotational thromboelastographic analysis

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ABSTRACT

Objective. *To investigate whether there is a difference between male and female patients with Behçet's disease (BD) in terms of hypercoagulability by using modified rotational thromboelastograhic (ROTEM) analysis.*

Methods. *126 BD patients (71 male, 55 female; mean age: 41±9 yrs) who met ISSG criteria for BD were included into the study. 23 patients with vasculitis (16 female, 7 male; mean age 49±16 yrs), and 25 healthy individuals (11 female, 14 male; mean age: 37±10 yrs) were included to the study as disease and healthy control (HC) group, respectively. Clotting time (CT), clot formation time (CFT) and maximum clot firmness (MCF) were determined by INTEM and EXTEM analyses. As a marker of vascular endothelial injury, along with inflammatory markers, vWFag levels were investigated in patients and HC group.*

Results. *Extem-CFT was shorter in only vasculitic group compared to HC group. Intem-CFT was found to be shorter in BD patients and vasculitis group compared to HC. Intem-MCF was significantly longer in male BD patients than female BD patients. Extem-CFT was found to be shorter in male BD patients compared to female BD patients. Extem-MCF was statistically longer in male BD patients. In inactive male BD patients, while Intem-CFT was shorter than HC individuals, Intem-MCF and Extem-MCF were statistically longer than HC ($p<0.02$, $p<0.03$), respectively. However, no significant differences were found between inactive female BD patients and HC in terms of all ROTEM parameters.*

Conclusion. *These results support that male BD patients have a hypercoagulable state compared to female BD patients, which may explain why male patients are prone to thrombotic complications.*

Introduction

Behçet's disease (BD) is a multisystem inflammatory disorder characterised by recurrent oral ulcers, genital ulcers, and ocular involvement. The major histological features of BD lesions are characterised by vasculitis with perivascular lymphocyte, monocyte and neutrophils infiltration (1). Vasculitis and thrombotic events are often seen together in BD patients. Although the pathogenesis of vascular thrombosis in BD is not well known, vasculitis and endothelial dysfunction are supposed to cause thrombosis. Defective fibrinolysis (2), increased thrombin generation (3), activated platelets (4) and increased procoagulant microparticles (5) are also suggested to be causes of thrombosis in BD patients. Although BD is a vasculitic disorder, it differs from other vasculitic diseases due to increased thrombotic events. Another interesting aspect of BD is that vascular thrombosis is more commonly seen in male BD patients.

ROTEM is a viscoelastometric clotting test to evaluate the kinetics of clot formation and fibrinolysis, which provides global information on cellular and soluble procoagulant/anticoagulant protein interactions. We and other authors previously reported that BD patients, even in the absence of thrombosis, had a pro-thrombotic state, which was evaluated by Rotational Thromboelastography (ROTEM) (6, 7). However, in these studies, ROTEM parameters were not compared between female and male BD patients. We do not know why thrombosis is more commonly seen in male BD patients compared to female BD patients. Thus, the present study aims to inves-

tigate why male BD patients are more prone to develop thrombosis with the aid of ROTEM analysis.

Methods

Patients

126 BD patients (71 male, 55 female; mean age: 41±9 yrs) who met ISSG criteria (8) for BD were included into our study at the Department of Rheumatology, Eskişehir Osmangazi University, Turkey. BD group was divided into 3 subgroups as non-thrombotic (n=73), acute thrombotic (n=25) and chronic thrombotic group (n=28). As disease control and healthy control group, 23 patients with vasculitis (4 temporal arteritis, 4 Takayasu's arteritis, 1 eosinophilic granulomatosis with polyangiitis, 12 granulomatosis with polyangiitis, 1 Buerger's diease, 1 polyarteritis nodosa) (16 female, 7 male; mean age 49±16 yrs), and 25 healthy individuals (11 female, 14 male; mean age: 37±10 yrs) were included to study. The diagnosis of vasculitis was made according to relevant classification criteria in each disease control patient. Informed consent was obtained from all patients and control groups according to the Declaration of Helsinki. The study was approved by local ethics committee.

Activity criteria

If a patient had 2 or more BD-related manifestations, he or she was considered to be active.

Exclusion criteria were as follows: preexisting haematological or coagulation disorders, those taking anticoagulation and anti-agregan, those with liver disease or renal dysfunction, use of oral contraceptives, uncontrolled hypertension, diabetes, hyperlipidemia, coronary artery disease.

Analysis of Rotational Thromboelastography (ROTEM®)

The formation and stability of blood clot were evaluated by TEG studies, using ROTEM (ROTEG 05 Pentapharm, Munich, Germany). All samples were analysed within 30-90 min of blood collection. INTEM: 20 µl extract of rabbit brain as contact activator, partial thromboplastin phospholipid and ellagic acid were used for the intrinsic system activation (in-TEMM®; Pentapharm, Munich, Germany). EXTEM: Extract of rabbit brain 20 µl tissue factor was used for extrinsic pathway activation (ex-TEM®; Pentapharm, Munich, Germany). Clotting time (CT) defines the latency time from the start of analysis until initial clot formation. CT provides information about thrombin generation prior the deposition of fibrin strands. Clot formation time (CFT) shows the time from initial clot formation until fixed clot strength (20-mm amplitude). CFT depends on clotting factors, platelets, and fibrinogen level. Maximum clot firmness (MCF) means the maximum clot strength and mainly depends on the platelets and the fibrinogen level.

vWFag levels were evaluated by Siemens BCS XP with vWFag Reagent kit. The erytrocyte sedimentation rate (ESR) was determined automatically by the vacuplusESR-120 device (Len Med-Medical, Ankara, Turkey), C-reactive protein (C-RP) by Siemens (Enlargen, Germany).Fibrinogen levels were analysed by Siemens Multifibrin U October kit.

Statistical analysis

Whole data analyses were made by IBM-SPSS 21,0 packaged software. Descriptive statistics belonging to continuous variables were given in the form of average±standard deviation or median (Q_1-Q_3). Categorical variables were given in the form of frequency and percentages (%). The availability of continuous variables to the normal distribution was investigated with Shapiro-Wilk normality test. In the comparisons of dual groups, test was used for those who show availability to the normal distribution in independent examples; Mann-Whitney U test, for those who do not show availability to the normal distribution. On the other hand, in the comparisons of three or more independent groups, single direction variance analysis (Oneway ANOVA) or Kruskall Wallis-H test were used. Tukey or Dunn's test were used for multiple comparisons not available to the normal distribution. While the magnitude and aspect of the relation among continuous variables were investigated by Spearman correlation test, this relation was obtained by using Chi-Square analysis in data sets formed categorically. Multiple linear regressionswere used to evaluate among variables relevant to each other. $p<0.05$ probability value was accepted as significant.

Table I. The comparison of ROTEM$^{M®}$ data among groups.

	BD (n=126)	Vasculitic Gr (n=23)	Healthy Gr (n=25)	p1	p2	p3
EXTEM						
CT (sec)	82 (68-128)	79.5 (61-121)	97 (76-114)	ns	ns	ns
CFT (sec)	89.2 ± 26.7	74.6 ± 26	103 ± 28.6	ns	**	ns
MCF (mm)	64.2 ± 5.6	68.6 ± 7.2	60.7 ± 4.46	*	***	*
INTEM						
CT (sec)	190 (168-211)	175 (158-197)	189(159-213)	ns	ns	ns
CFT (sec)	80 (69-93)	61 (48-90)	100 (84-120)	**	***	ns
MCF (mm)	62 (59-66)	66 (61.5-72)	58 (55-63)	**	***	*

Results are shown as the mean ± SD, the median and range (25^{th} -75^{th}percentile)
*p value<0.05, **p value<0.01; ***p value<0.001
p1: BD pts *vs*. healthy control; p2: Vasculitic Gr *vs*. healthy control; p3: BD patients *vs*. Vasculitic Gr.

Results

Analysis of Rotational Thromboelastography (ROTEM®)

Extem-CFT was shorter in only vasculitic group compared to HC group. Intem-CFT was found to be shortened in BD patients and vasculitis group-compared with HC. As a maximal clot firmness (MCF) which reflect the maximum strength of the thrombus, Intem-MCF and Extem-MCF were prolonged in BD patients and vasculitis group (Table I). In subgroup analysis of BD patients, acute thrombotic group had a rapid clot formation time and prolonged maximal clot firmness

Table II. ROTEM results according to gender among BD patients.

	I-CT (sec)	I-CFT (sec)	I-MCF (mm)	E-CT (sec)	E-CFT (sec)	E-MCF (mm)
Male BD pts n=71	186.8 ± 48.3	79.3 ± 22.1	64 (61-67)	98.6 ± 58.9	81.2 ± 21.2	65 (63-69)
Female BD pts n=53	188.4 ± 40.8	86.5 ± 27.2	60.5 (57-64)	117 ± 67.7	96.4 ± 29.1	62.5 (59-66)
p	0.65*	0.11*	0.005	0.07*	0.003*	0.003

*t test; Mann-Whitney U test.

Table III. The comparison of ROTEM data between inactive male BD patients and male HC group.

	I-CT (sec)	I-CFT (sec)	I-MCF (mm)	E-CT (sec)	E-CFT (sec)	E-MCF (mm)
Inactive male BD pts (n=25)	188.4 ± 5	84 (75-106)	59.3 ± 4.4	91 (70-165)	92.2 ± 4.9	60.4 ± 3.4
HC-male (n=14)	195.4 ± 15.8	108 (85-142)	56 ± 3.4	99.5 ± 76-116)	117.1 ± 8.9	57.9 ± 3.2
p	0.95*	0.011	0.021*	0.3*	0.06*	0.038*

*t test; Mann-Whitney-U test.

comparedto non-thrombotic group and chronic thrombotic group (Supplementary Table SI). Active BD patients had a rapid clot formation time and prolonged clot firmnesscompared to inactive BD patients (Supplementary Table SII).

Intem-MCF was significantly longer in male BD patients than female BD patients. Extem-CFT was found to be shorter in male BD patients compared to female BD patients (Table II). Extem-MCF was statistically prolonged in male BD patients. In inactive male BD patients, while Intem-CFT was shorter than HC individuals, Intem-MCF and Extem-MCF were statistically longer than HC ($p<0.02$, $p<0.03$), respectively. However, no significant differences were found between inactive female BD patients and HC in terms of all ROTEM parameters (Table III). In active BD patients, Extem-CFT was shorter ($p<0.02$) and Extem-MCF was significantly longer than those of inactive BD patients ($p<0.005$).

Correlation analysis

In active BD patients, there was a negative correlation between Intem-CFT and platelet (r=-0.58, $p<0.001$), fibrinogen (r=-0.53, $p<0.001$), ESR (r=-0.51, $p<0.001$). Haemoglobin was positively correlated with Intem-CFT (r=0.46, $p<0.001$). Intem-MCF was positively correlated with platelet (r=0.59, $p<0.001$), fibrinogen (r=0.71, $p<0.001$), ESR (r=0.60, $p<0.001$) and negatively correlated with haemoglobin (r=-0.48, $p<0.001$).

In inactive BD patients, Intem-CFT was negatively correlated with fibrinogen (r=-0.46, $p<0.001$), ESR (r=-0.39, $p<0.001$), platelet (r=-0.51, $p<0.001$), and positively correlated with haemoglobin (r=0.44, $p<0.001$). Also, there was a positive correlation between Intem-MCF and fibrinogen (r=0.55, $p<0.001$), ESR (r=0.51; $p<0,001$), platelet (r=0.54, $p<0.001$). A negative correlation exists between Intem-MCF and haemoglobin (r=-0.53, $p<0.001$).

vWFag levels

vWFag levels were significantly high in male BD patients compared to female BD patients (151.9±44.6% *vs*. 121±45%; $p<0.003$). Active BD patients had higher vWFag levels than inactive BD patients 159.9 (99-113%) *vs*. 133.3 (90-157%). No significant differences were found between BD group, vasculitis group in terms of vWFag levels. vWFag levels were high in three main groups of BD compared to healthy group (data not shown).

Acute phase reactants and fibrinogen levels

As was expected, CRP and ESR levels were statistically high in subgroups of BD patients compared to HC. Male BD patients had increased CRP (1.9±3.6 mg/dl *vs*. 0.9±1.4 mg/dl; $p<0.01$) and fibrinogen levels (403±116 mg/dl *vs*. 353±97 mg/dl; $p<0.01$) compared to female BD patients. No significant differences were found between male and female BD patients in terms of ESR. CRP, ESR and fibrinogen levels were significantly high in BD patients with acute thrombosis compared tonon-thrombotic and chronic thrombotic group ($p<0.003$, $p<0.01$, $p<0.03$) respectively.

Discussion

This study is the first study in which the role of the haemostatic mechanisms in the thrombosis encountered in BD was investigated with thromboelastographic analysis according to the sex. In this study, it was demonstrated that male BD patients had a tendency of a faster coagulation and increased clot firmness compared to the female BD patients. The most important finding in this study was that the male patients were in a prothrombotic state even in the inactive stage compared to the healthy males. There were studies reporting that haemostatic mechanism might play a role in the aetiology of the thrombotic events emerged during the progression of the disease. These studies discussed the presence of a defective fibrinolytic system (2); increased thrombin synthesis (3); the changes in the platelet functions (4); the increase of the procoagulant microparticles (5) and the increase of the procoagulant factors (9). In these studies, the factors which might play a role in the coagulation were separately investigated but an overall evaluation of the haemostatic parameters was not committed. Furthermore, while the role of the haemostatic mechanisms was explored the differences in respect of sex were not investigated. We had already shown with the thromboelasto-

graphic technique that the haemostatic mechanism might play a role in the BD thrombi regardless of sex (6). Similarly, Fernandez-Bello *et al*. also showed with thromboelastography that BD patients might have a prothrombotic state (7). Fernandez-Bello *et al*. reported a correlation between the fibrinogen level and Intem-MCF both in BD and control groups. Although, there was a positive correlation between CRP and Intem-MCF, they did not find out a correlation with platelets. Both in active and inactive BD patients, we observed a positive correlation between Intem-MCF and ESR, platelet and fibrinogen. These findings indicated a logical relation between the inflammation and clot firmness. These conflicting results between these two studies might depend on the different subject sizes, different indexes used for the activity evaluation and different involvements of the organs.

In this study, we evaluated haemostatic mechanisms along with the thromboelastographic parameters, whether there was any difference between the male and female BD patients. We found out that the prothrombotic state was encountered more commonly in the male patients compared to the female patients. Until today, there was no other study focused on the patterns and differences of the haemostatic parameters according to sex. Only Macey *et al*. evaluated the influence of age and sex on the platelet and neutrophil functions (10). In this study, CD62P+ percentage was higher both in female and male BD patients compared to the healthy control subjects. However, the neutrophil-platelet aggregates were only higher in the male BD patients compared to the healthy males. There was no difference between the female BD patients and healthy group regarding this parameter. This result indicated that some haemostatic parameters might not have a parallel course among the males and femalesin BD.

What would be the clinical significance of these results? Thrombosis is usually encountered in the lower extremities in BD patients. There are mostly superficial thrombophlebitis and deep vein thrombosis. The involvement of the major vessels might be lethal as well as recurrent (11). Conducted studies demonstrated that thrombi, which might develop at a later stage, could be foreseen with ROTEM parameters (12). Thanks to this significant and predicting feature of thromboelastography, thrombi which might develop at a later stage and might be lethal could be foreseen with serial ROTEM analysis in the young male patients and in patients with superficial thrombophlebitis. This evaluation might be significant in the prevention of the vascular thrombi, which might be fatal. Although, the efficacy of the antithrombotic treatment in BD is under debate for a long time, there was no study with control groups focusing on this topic. Ahn *et al*. conducted a retrospective study and stated that recurrence was more frequently observed in patients receiving anticoagulant agents compared to the patients receiving immunosuppressives (13). However, this study had important limitations like the retrospective design and the limited number of patients who were under antithrombotic treatment. Alibaz *et al*. conducted also a retrospective study on 936 Turkish patients. They observed more recurrence in patients with thrombophilic factors, but this finding was not statistically significant (14). Saadun *et al*. demonstrated that anticoagulant treatment was a safe and effective therapy in cerebral venous thrombosis (15). We had previously shown that recurrence was more frequently observed in BD patients with having more than one thrombophilic factor (16). Nevertheless, these conflicting study findings indicated the necessity of controlled trials focusing on the place of antithrombotic agents in the therapy. At this stage, thromboelastography might be clinically useful to assess the necessity and duration of the anticoagulant treatment.

In this study, the correlation which we determined between the acute phase reactants, fibrinogen and ROTEM parameters indicated that inflammation was determinative in this process. It was not surprising that the anti-inflammatory and immunosuppressive drugs are the main components in the therapy of the thrombosis encountered in BD. Cytokines such as IL-1, IL-8, interferon-γ and cytokines originating from the TH17 cells increased in BD (17). These cytokines caused a procoagulant state while increasing the inflammation (18). We knew for a long time that there was a correlation between inflammation and coagulation. Regarding this correlation, anticoagulant treatment might be useful along with the anti-inflammatory treatment in the suitable BD patients.

vWFag levels can be a sign of endothelial damage in BD patients. In this study, vWFag levels were high in male BD patients compared to female BD patients. And also it was found to have increased in active BD patients compared to inactive BD patients. It has been reported that as an indicator of endothelial cell activation, vWFag levels were found to be increased together with hypercoagulable state in BD patients (19). However it can also increase in active phase of BD rather than vascular involvement (20).

A potential limitation of our study is that thromboelastography was determined cross-sectionally. Serial analysis and long-term assessment would be a good way to find valuable evidence for the role of haemostatic mechanism.Another limitation might be the selected activity index. There is not any generally accepted activity index in Behçet's disease. The activity index which we chose might also not be a reliable method and might decrease the reliability of our results we performed regarding the activity. The limited number of patients in the subgroups might be another factor which decreases the reliability of our results. Another limitation is a lack of reproducibility of the tests due to limited financial sources. However, in our laboratory unit, quality control tests were made at regular intervals using normal control plasma samples with known parameters. Unfortunately, we could not form a homogeneous vasculitic group as a disease control group. A homogeneous vasculitic group would be better to compare ROTEM parameters between the groups.

In conclusion, the results of this study indicate that disease activity provides a pro-coagulant state in BD patients. The presence of positive correlation

between ROTEM parameters and acute phase reactants suggests that there may be a close relationship between inflammation and thrombosis in BD patients. However, male BD patients are prone to thrombotic condition even if they are in inactive period, which could suggest that haemostatic mechanisms may influence development of thrombosis, particularly when there is inflammation. Considering that the predictive value of ROTEM parameters for further thrombosis (21), further studies are needed to ascertain whether pro-thrombotic state in inactive period of BD could herald thrombosis in the presence of inflammation.

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