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Original Article

Evaluation of Mean Platelet Volume in Patients With Behcet's Disease as an Indicator of Vascular Thrombosis

Hatice Ataş, MD[1*]; Filiz Canpolat, MD[1]; Fatma Eskioglu, MD[1]

University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Dermatology, Ankara, Turkey

Abstract

Background: Patients with Behçet's disease (BD) are recognized with increased risk for venous and/or arterial thrombosis. Thrombotic tendency of BD is not known. Vascular injury, loss and dysfunction/hyperfunction of endothelial cells are believed to play a role in thrombosis development. Injury and inflammation due to vasculitis can cause platelet response with increase in mean platelet volume (MPV) and thrombosis in BD. In this study, we aimed to compare the levels of MPV between patients with BD and healthy controls, and also show its effect on thrombosis.

Methods: One hundred patients with BD and 100 healthy controls were evaluated for MPV levels with clinical findings in age-gender matched case-control study. The variables of patients and controls were compared and correlated using chi-square, Mann-Whitney U and Spearman tests. Logistic regression analysis was used to determine independent predictors of vascular involvement and thrombosis.

Results: Mean MPV was significantly higher in patients with BD than healthy controls (MPV; Patients: 9.2 ± 0.9 [7.3–12.9] vs. Controls: 8.2 ± 0.6 [6.8–10.6] fl; $P<0.0001$). Platelets levels were lower than controls, but not significantly (236 ± 52.3 [112–451] vs. 245 ± 52.8 [141–467] x10^9/L, $P=0.55$). Negative correlation was found between platelet count and MPV in patients (r = -0.51, $P=0.01$). Presence of erythema nodosum (EN) and MPV were determined as predictors for vascular involvement and thrombosis (EN: $P<0.0001$, OR [95% CI] = 35.4 [6.3–178.2]; MPV: $P<0.0001$, OR [95% CI] = 12.8 [4.1–24.3]).

Conclusion: MPV is a simple measurement for indirect monitoring of platelet activity and thrombotic potential. MPV and EN may be independent risk factors for vascular thrombosis in BD. Patients with higher MPV levels and EN in BD, might have been pursued closely for enhancing thrombosis. We advise to check the MPV and put the patients on anticoagulation if it is high.

Keywords: Behcet's disease, Mean platelet volume, Thrombosis, Vascular

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Introduction

Behcet's disease (BD) is a kind of variable vessel vasculitis with unknown aetiology characterized by oral or genital aphthous ulcerations and uveitis.[1–3] Vascular thrombosis is one of the hallmarks of this disease. It may occur both in veins and arteries, but in the literature, venous involvement with varying ratios is reported nearly 6 times higher in cases with BD in large series of studies (13.8% vs. 2.4%).[4] It occurs especially in deep or superficial veins of the lower extremities.

Pathogenesis of thrombosis in BD is not completely understood, but various mechanisms have been suggested for the increased risk of thrombosis in BD. Impaired fibrinolysis, increased clotting factors, and abnormal platelet function are some of them. BD should be evaluated as a hypercoagulable/prothrombotic state due to tendency to the thrombosis.[5]

Platelets play an important role in the integrity of normal homeostasis. Mean platelet volume (MPV) is the indicator for platelets function. The large platelets which contain more dense granules are more potent and thrombogenic than smaller platelets.[6] Vascular risk factors such as hypercholesterolemia, diabetes mellitus (DM) and hypertension may contribute to MPV increase. Conflicting results are presented in the literature regarding increased and decreased levels of MPV in BD.[7,8] In this study, due to hypercoagulable/prethrombotic state with high incidence rate of thrombosis, we studied MPV and thrombosis in BD. We aimed to compare the levels of MPV between patients with BD and healthy controls, and show the effect of MPV and activity of disease on thrombosis.

Material and Methods

Subjects

This was an age-gender matched case-control study. One hundred patients with BD who were diagnosed according to the International Criteria for BD (ICBD)[9] and admitted to the outpatient clinic of dermatology for medical examinations (52 female, 48 male with a mean age of 39.7 ± 11.1), and 100 healthy age-gender matched controls (54 female, 46 male, with a mean age of 39.2

*Corresponding Author: Hatice Ataş, MD; Department of Dermatology, University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey. Tel: +90-312-5962083, Email: drhaticeartik@gmail.com

± 11.3) were evaluated in this study. Controls over 18 years old were recruited from patients who were referred for minimal dermatological problems such as nevus in order to avoid bias to the study results. Controls had no systemic disease(s) and didn't use tobacco. Controls with oral aphthous ulcers were excluded from the study, because of the fact that patients with recurrent aphthous stomatitis may develop BD in course of time. Clinical and demographic features of patients such as age, gender, beginning and duration of disease, oral aphthous, genital ulcers, ocular lesions, joint, vascular, neurologic, gastrointestinal and genitourinary involvement, results of pathergy test and skin lesions such as papulopustular eruption, thrombophlebitis and erythema nodosum (EN), and treatment and activity of disease were recorded. Exclusion criteria for this study were cardiovascular disease(s), hypertension, obesity, dyslipidemia, smoking, diabetes mellitus, inflammatory colon disease, renal hepatic failure, haematological and immunological disorders, active infectious disease, malignancy and use of any drug for any disease. Ocular involvement can be rare among our BD patients due to the fact that patients with severe ocular involvement might have been referred to departments such as ophthalmology.

Activity of Disease

Activity of disease was determined by both clinical and laboratory findings. In clinical evaluation, patients who had worsening clinical symptoms at the time of the study, and also had three of the major criteria (oral ulcers, genital ulceration, eye lesions, skin lesions, and positive pathergy test) were considered to be in the active period of the disease.

Presence of thrombosis: Thrombosis was confirmed with clinical findings, Doppler ultrasonography and/or angiography.

Laboratory Analysis

Blood samples were drawn after a fasting period of 12 hours. MPV was collected in tubes with citrate in order to rule out the formation of platelet aggregation with ethylenediaminetetraacetate (EDTA).[10] Blood samples were centrifuged within one hour after sampling. Beckman Coulter LH 700 Haematology Analyser based on light scattering impedance and conductivity (VCS technology) was used to measure complete blood cell count and other haematological parameters. The normal range of MPV in our haematology laboratory was 7.2 to 10.8 fl.

Statistical Analysis

Statistical analyses were performed using SPSS software, version 15. The variables of patients and controls were investigated using analytic methods to determine whether or not they are normally distributed. Descriptive analyses were done using mean ± standard deviation (SD). For discontinuous variables such as gender, chi-square test was used. For continuous variables such as MPV and platelet counts of patients and controls, Mann-Whitney U test was used. Correlation analysis was performed using Spearman test. Factors such as age, gender, activity of BD, onset and duration of BD, percentage of oral aphthous ulcers, genital ulcers, papulopustular eruptions, involvement of eyes, involvement of vascular regions, EN, pathergy positivity, using a treatment such as colchicine, cyclosporine, steroid, interferon with *P* value less than 0.2 shown by univariate analyses to be associated with vascular involvement were further entered into the multivariate analysis of logistic regression analysis to determine independent predictors of vascular involvement and thrombosis. A *P* value of less than 0.05 was considered to show a statistically significant result.

Results

The demographic features were summarized in Table 1. Mean MPV was significantly higher in patients with BD than healthy controls (9.2 ± 0.9 [range: 7.3–12.9] vs. 8.2 ± 0.6 [range: 6.8–10.6] fl; $P < 0.0001$). Platelets levels were lower than controls, but there was no significant difference (236 ± 52.3 [range: 112 – 451] vs. 245 ± 52.8 [range: 141–467] $\times 10^9$/L, $P = 0.55$). A negative correlation was found between platelet count and MPV in patients ($r = 0.51$, $P = 0.01$) (Table 2). Presence of EN and MPV were determined as predictors for vascular involvement and thrombosis (EN: $P < 0.0001$, OR [95% CI] = 35.4 (6.3–178.2); MPV: $P < 0.0001$, OR [95% CI] = 12.8 [4.1–24.3]) (Table 3). Mean MPV was 8.5 ± 0.5 (Range: 7.3-9.1) fl in patients with EN (n = 7) and 9.2 ± 0.8 (range: 7.6–12.9) fl in patients without EN (n = 93), $P = 0.019$. MPV was 9.8±1.2 (range: 8.7-12.9) fl in patients with vascular involvement (n = 15) and 9.1 ± 0.5 (range: 7.3-11.1) fl in others (n=85), $P = 0.017$. Twenty-seven percent of patients (n = 27) had active disease(s). Mean MPV was not found significant between active (n = 27) and inactive disease(s) (n = 73), respectively (MPV: 9 ± 1.1 [Range: 7.7–11.1] fl vs. 9.3 ± 0.8 [range: 7.6–12.9] fl $P = 0.44$). Other parameters such as status of pathergy test, treatment use, other site involvement and past history features were not significant for MPV ($P > 0.05$).

Discussion

BD is a relapsing vasculitis in which orogenital ulceration is a prominent feature.[11] Patients with BD are recognized with increased risk for venous and/or arterial thrombosis. Therefore, it has been termed as a hypercoagulable prethrombotic state.[12] The exact pathogenic mechanism

Table 1. Demographic Features of Subjects

	Patients	Controls	*P*
Subjects, No.	100	100	
Gender, No. (%)			
Female	52 (52)	54 (54)	0.86
Male	48 (48)	46 (46)	
Age (y), mean ± SD (range)	39.7 ± 11.1 (18–66)	39.2 ± 11.3 (18–62)	0.83
Beginning age of disease, y	30.6 ± 7.7 (16–50)		
Duration of disease, y	9.1 ± 6.6 (0–30)		
MPV, fl	9.2 ± 0.9 (7.3–12.9)	8.2 ± 0.6 (6.8–10.6)	< 0.0001
Platelets, × 10^9/L	236 ± 52.3 (112–451)	245 ± 52.8 (141–467)	0.55
Presence of aphthous lesion, No. (%)	67 (67)		
Presence of genital ulcer, No. (%)	12 (12)		
Papulopustular eruption, No. (%)	22 (22)		
Presence of erythema nodosum, No. (%)	7 (7)		
Presence of ocular involvement, No. (%)	4 (4)		
Presence of joint involvement, No. (%)	60 (60)		
Presence of vascular involvement, No. (%)	15 (15		
Presence of neurological involvement, No. (%)	7 (7)		
Presence of gastrointestinal involvement, No. (%)	8 (8)		
Presence of genitourinary involvement, No. (%)	3 (3)		
Undergone systemic treatment, No. (%)	96 (96)		
Pathergy test positivity, No. (%)	21 (21)		
Presence of active disease, No. (%)	27 (27)		

Abbreviations: SD, standart deviation; MPV, mean platelets volume.

Table 2. Significant Linear Correlation Between MPV and Platelets in Patients With BD

Parameters	*r*	*P* Value
MPV-platelets	-0.51	0.001

Abbreviation: BD, Behcet's disease; MPV, mean platelets volume.
$P<0.05$ is significant.

underlying thrombotic tendency of BD is still unknown.

A number of mechanisms have been implicated to account for high incidence of thrombosis. Endothelial cell injury and resultant endothelial loss and/or dysfunction/hyperfunction seem to be some key events in the prethrombotic state of BD. Normal haemostatic

Table 3. Effects of Some Predictors on Vascular Involvement and Thrombosis in Univariate and Multivariate Analyses

Predictor	Reference Category	Univariate Analysis			Multivariate Analysis		
		P	OR	95% CI	*P*	OR	95% CI
Increase in age		0.42	0.94	0.8–1.1			
Gender	Male	0.24	2.4	0.55–10.6			
Increase in duration of disease		0.85	1.1	0.9–1.2			
Increase in MPV		< 0.0001	7.6	2.1–15.3	< 0.0001	12.8	4.1–24.3
Increase in platelet		0.61	0.98	0.91–1.1			
Presence of aphthous lesion	Yes	0.49	1.8	0.34–9.5			
Presence of genital ulcer	Yes	0.98	0.97	0.1–9.2			
Presence of papulopustular eruption	Yes	0.41	1.9	0.41–8.8			
Presence of ocular involvement	Yes	0.37	3.1	0.25–39.3			
Presence of joint involvement	Yes	0.25	2.6	0.5–14.2			
Presence of neurological involvement	Yes	0.54	2.1	0.2–22.5			
Presence of gastrointestinal involvement	Yes	0.71	1.5	0.15–15.5			
Presence of genitourinary involvement	Yes	0.98	0.95	0.2–12.8			
Pathergy test positivity	Yes	0.33	2.2	0.46–10.1			
Presence of active disease	Yes	0.79	0.8	0.15–4.2			
Presence of erythema nodosum	Yes	< 0.0001	11.3	2.1–6.8	< 0.0001	35.4	6.3–178.2
Undergone treatment	Yes	0.75	0.68	0.1–7.9			

Abbreviation: MPV: mean platelets volume.
$P<0.05$ = significant; CI: confidence intervals were estimated using logistic regression model; OR: odds ratio was estimated using logistic regression model. Simple: first was selected to evaluate the effect of the categorical predictors.

response is initiated when endothelial damage disrupts the vascular endothelial lining, and blood is exposed to subendothelial connective tissues.[5] Hypofibrinolysis and defective fibrinolytic response are proposed as a part of generalized cell dysfunction in BD.[13]

Platelets have a central role in the pathogenesis of thromboembolic diseases. In BD, platelets are active and more reactive than normal controls which may contribute to the thrombotic tendency.[14] It could be speculated that three factors may contribute to increased platelet activation: both arterial and venous wall injuries, circulating inducers of platelet activation, and genetic predisposition. However, the difference in platelets levels between patients and controls is clinically unimportant.

MPV is an important biological variable. Large platelets have higher thrombotic potential.[15,16] In comparison to smaller ones, larger platelets are denser,[17] aggregate more rapidly with collagen,[18] have higher thromboxane A2 level[19] and express more glycoprotein Ib and IIb/IIIa receptors.[20,21] An increased MPV decreases the inhibitory effectiveness of prostocyclins on platelets aggregation and release reaction.[22]

Increase in MPV is now emerging as an independent risk factor for thromboembolism, stroke and myocardial infarction.[23–26] Also increased levels of MPV are identified as a predictor for venous thromboembolism of unprovoked origin.[27]

Venous thrombosis in BD might be due to vasculitis itself or hypercoagulable status whether venous thrombi seem to be caused by inflammation of the vessel wall rather than by a primary clotting abnormality. Systemic immunosuppressive agents are used in an effect to prevent this inflammation.[28] Guideline on thrombosis in BD comes from a recent small study which compares the use of immune suppression and anticoagulation. In this study, the authors suggested that using anticoagulation in BD patients with thrombosis may be unnecessary.[29] Another study showed that taking anticoagulants may be appropriate, at least until the diagnosis is confirmed and inflammation is controlled.[30] Whereas, according to the latest European League Against Rheumatism (EULAR) Guidelines for treatment of BD, the use of anticoagulation is forbidden unless it is proved that the patient has no tendency for hemorrhage and aneurism.[31–33] In our opinion, anticoagulant agents may be used because of high coagulation tendency, until the disease is controlled. Decreasing MPV may indicate the control of the disease.

However, the potential contribution of MPV to development of thrombosis in BD is unclear. Association between BD and MPV levels has been demonstrated in two previous studies with conflicting results.[7,8] Different factors such as time from venepuncture, choice of anticoagulant, sample storage temperature, and/or equipment for measuring MPV can give different results.[34–36] On the other hand, some patients are on treatment for BD which might affect the results. In our study, we found increased MPV levels in patients with BD. In addition, MPV was found significantly higher in BD patients with thrombosis than those without thrombosis. Increased MPV levels may have an association with thrombosis due to large thrombogenic platelets and vascular involvement of disease. In this study, increase in MPV in patients with BD was related to a 12.8-fold increased risk for vascular involvement and thrombosis in multivariate analysis (OR = 12.8, $P < 0.0001$). This might be associated with chronic or controlled inflammatory processes due to vasculitis.[37] Increased MPV in inflammatory status contributes to thrombosis.

There was no difference between active patients and inactive patients with BD for MPV. Some studies show that low MPV and high platelet levels are found in acute course of Familial Mediterranean Fever, ankylosing spondylitis, and rheumatoid arthritis. Cytokines such as IL-1, 3, 4, 6, 11 and TNF-alpha can contribute to this fact. In addition, suppression of acute proinflammatory status of disease can contribute to increase of MPV.[38–40] In our study, we found decreased levels of MPV in EN. This result and negative correlation between MPV and platelets supported the decreased levels of MPV in acute conditions. However, presence of EN in patients with BD was related to a 35.4-fold increased risk for vascular involvement and thrombosis in multivariate analysis (OR = 35.4, $P < 0.0001$). Iinflammatory status of BD is very complex with acute and chronic processes. To sump up, presence of EN and increased MPV levels were found as independent predictors for thrombosis in BD.

Unfortunately, the main limitation of this study is that, there is not any control with other acute, chronic inflammatory and infection diseases to compare to our subjects with BD. In addition, the BD with acute deep vein thrombosis (DVT) could be compared to acute and chronic DVT due to other causes.

In conclusion, MPV which is one of the markers indicating the function of platelets is a simple and easy measurement of indirect monitoring of platelet activity and thrombotic potential. In our study, the significance of MPV was evaluated in BD because of the fact that many studies about MPV had been studied on venous thromboembolism, other vascular diseases (e.g stroke) and vascular disease risk factors such as obesity, DM and metabolic syndrome. Most of our patients were on systemic treatments which could be a limitation in our study. Increased level of MPV was found in patients with BD compared to controls. It may be an independent risk

factor for vascular involvement and thromboembolism in BD. BD patients who have higher MPV levels must be pursued closely for thrombosis. Decreased or increased levels of MPV can indicate disease palliation or progression, respectively. Anticoagulant agents can be used due to high coagulation tendency until the disease is controlled. According to the latest EULAR Guidelines for the treatment of BD, the use of anticoagulation is forbidden unless it is proved that the patient has no tendency for hemorrhage and aneurism. However, we advise to check MPV and put the patient on anticoagulation if it is high, and continue until it reaches the normal level. We also suggest further studies to evaluate the role of MPV on thrombosis in BD.

Authors' Contribution

Study design: HA, FC, FE. Study conduct: HA, FE. Data collection: HA. Data analysis: HA. Data interpretation: HA, FC, FE. Drafting of the manuscript: HA, FC, FE. Revising manuscript content: HA, FC, FE. Approving final version of manuscript: HA, FC, FE. HA takes responsibility for the integrity of the data analysis.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

Ethical approval and informed consent were obtained before beginning the study.

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