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Platelet Activation in Ocular Behçet's Patients with Posterior Segment Involvement

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Abstract:

PURPOSE: The aim of the present study was to assess platelet activation by analyzing three platelet activation parameters in ocular Behçet's disease (BD): mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT).

METHODS: Twenty-nine patients with active ocular BD (Group 1), 40 patients with inactive ocular BD (Group 2), and 40 healthy adult individuals serving as controls (Group 3) were evaluated. All of the individuals had been performed the complete ophthalmologic evaluation. The levels of MPV, PDW, and PCT were measured in each group.

RESULTS: The mean MPV level was 8.40 ± 0.97 in Group 1, 8.32 ± 1.04 in Group 2, and 7.77 ± 0.72 in Group 3. The mean PDW level was 15.12 ± 1.09 in Group 1, 14.97 ± 1.02 in Group 2, and 14.52 ± 0.82 in Group 3. The mean PCT level was 0.23 ± 0.07 in Group 1, 0.21 ± 0.04 in Group 2, and 0.18 ± 0.03 in Group 3. MPV, PDW, and PCT levels were significantly higher in ocular BD patients than controls ($P < 0.05$).

CONCLUSION: Platelet activation may affect vascular occlusion in ocular Behçet's patients with posterior segment involvement. This result may be important in evaluating ocular BD patients.

Keywords:

Behçet's disease, mean platelet volume, ocular involvement, platelet distribution width, plateletcrit

Introduction

Behçet's disease (BD) is a multisystemic vasculitic disease characterized by occlusive vascular involvement.[1] Ocular BD varies from 40% to 70% and it is usually bilateral.[2] In 25% of BD patients, visual acuity decreases because of active disease.[3] In the majority of BD patients, vasculitis predominantly affects retinal veins.[4] BD can affect both arterioles and venules and is the solely systemic vasculitis affecting both concurrently.[5]

Procoagulant hemostatic abnormalities are frequently considered in vascular disease formation of BD.[6] The alterations in the platelet parameters may affect hemostatic/prothrombotic status in a given patient. The association of platelet markers with many pathological conditions has been reported. There is an increased risk of myocardial infarction and stroke with an increase in the level of mean platelet volume (MPV).[7] In addition, an increase in MPV level has been shown in patients with diabetic retinopathy.[8] To our knowledge, a study of platelet activation parameters, including platelet distribution width (PDW) and plateletcrit (PCT) parameters, has not been previously published in ocular BD patients.

The purpose of this study was to evaluate platelet activation in patients with both active and inactive ocular BD and to compare these values with healthy individuals.

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Methods

The study included 69 Behçet's patients who were evaluated between May 2015 and January 2017. Approval for the study was granted by the local ethics committee, informed consent was obtained from all participants, and it was conducted in accordance with the Declaration of Helsinki. Patients consisted of Turkish Caucasians and the study is registered, number ACTRN12616001178437.

BD diagnosis and classification were carried out according to the International Study Group criteria.[9] Based on the criteria of the International Uveitis Study Group, patients were divided into groups (posterior, middle, anterior, and panuveitis).[10] The current activity form for BD patients was used to evaluate the disease activity. The cases with oral, skin, and/or genital lesions were accepted as active diseases. Patients with no lesions for at least 2 months were considered inactive diseases. Ocular activity status of all BD patients was evaluated according to the findings of the examination.

Active patients were determined according to clinical examination findings. BD patients with periarteritis, periphlebitis, disc edema, macular/retinal edema, papillitis, cells, and white retinal infiltrates in the vitreous were named active patients. Patients who did not show these findings for at least 2 months were referred to as inactive BD. Intraretinal infiltrates were accepted as signs of active retinal phlebitis. Beside, retinal hemorrhages, microaneurysms, telangiectatic abnormalities, and retinal arteritis were accepted as signs of active disease. However, patients with occluded/narrowed retinal vessels were accepted as inactive. On fundus fluorescein angiography, macular edema, vascular leakage, papillitis, branch or central retinal vein occlusion, avascular ischemic areas, and neovascularization were investigated. Macular edema was also assessed by optical coherence tomography. Inactive BD cases are also far from the BD systemic symptoms and laboratory evaluations.

Patients were divided into three groups according to ocular examination findings. Group 1 consisted of 29 ocular BD patients within the active period, Group 2 included 40 ocular BD patients within the inactive period, and Group 3 consisted of 40 patients who had no history of ocular or systemic disease and was selected as the control group. All individuals included in the study, including healthy volunteers, had no history of thrombosis in their family or personal history. Furthermore, the validated questionnaire was administered and confirmed the absence of thrombotic events.[11]

Cases with systemic and ocular diseases other than BD were excluded from the study. Smoking and drinking habits were also excluded from the study. In order to standardize the hemostatic system parameter measurements, all blood sampling was done in the morning hours after at least 8 h of fasting. The complete blood count (CBC) sample was collected in ethylenediaminetetraacetic acid vacuum tubes with minimum stasis and examined in 60 min. The routine values in whole blood analysis were measured. Those whose hemoglobin, hematocrit, red blood cell count, white blood cell count, and platelet cell count were outside the normal range values were excluded from the study. Routinely measured MPV, PDW, and PCT values in CBC examination were evaluated. Furthermore, the biochemical sample was collected in a lithium heparin tube with gel. Cases whose liver, kidney function tests, and electrolyte levels were not within normal range values were also excluded from the study. The same analyzers were used in all sampling.

Data analysis was performed using IBM SPSS version 22.0 for Windows (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp). A one-way analysis of variance was performed to analyze the differences among the three groups. After that, *post hoc* Bonferroni tests were performed. $P < 0.05$ was considered statistically significant.

Results

This study was carried out on 29 patients in Group 1, 40 in Group 2, and 40 in Group 3. There were 25 men (86.2%) and 4 women (13.8%) in Group 1, 37 men (92.5%) and 3 women (7.5%) in Group 2, and 37 men (92.5%) and 3 women (7.5%) in Group 3. The mean age of the patients (mean ± standard deviation) was 31.8 ± 8.2 years, 35.1 ± 11.9 years, and 33.5 ± 7.6 years, respectively, in active ocular BD (16–47 years), inactive ocular BD (18–57 years), and control group (16–47 years). There was no statistically significant difference in age ($P = 0.5$) and gender ($P = 0.6$) assessment among the groups.

The period until the diagnosis of BD was 50.5 ± 18.7 months for active BD and 62.9 ± 19.7 months for inactive BD. Panuveitis was observed in 27 cases of Group 1 (93.1%) and 34 cases of Group 2 (85%); posterior uveitis was observed in two cases of Group 1 (6.9%) and six cases of Group 2 (15%). All forty patients with inactive BD had a previous history of ocular vascular attack.

The symptom of active BD was posterior segment involvement uveitis in 29 cases, oral ulcers in 10, genital ulcers in 2, both oral and genital ulcers in 1, skin lesions in 1, and arthritis in 1 patient.

In the inactive cases of BD in our present cohort, there was also no activity in terms of systemic symptoms and

laboratory evaluations of BD and we evaluated them as an inactive disease.

The posterior segment findings and complications secondary to uveitis in active ocular BD were vascular sheathing (27 patients, 93.1%), vitreous condensation (25 patients, 86.2%), retinal infiltrates (24 patients, 82.7%), cystoid macular edema (17 patients, 58.6%), optic disc edema (8 patients, 27.5%), optic atrophy (6 patients, 20.6%), macular scar (6 patients, 20.6%), and epiretinal membrane (5 patients, 17.2%). The posterior segment finding and complications secondary to uveitis in inactive ocular BD were sclerotic vessels (35 patients, 87.5%), vitreous condensation (31 patients, 77.5%), optic atrophy (18 patients, 45%), macular scar (17 patients, 42.5%), and epiretinal membrane (11 patients, 27.5%).

Treatment options in our patients for uveitic relapses included systemic corticosteroids, azathioprine and/or cyclosporine, interferon therapy, and infliximab/adalimumab therapy. Twenty-seven cases (93.1%) with active ocular BD and 31 cases (77.5%) with inactive ocular BD had a combination of azathioprine and cyclosporine. Interferon therapies were used in six cases (20.6%) with Group 1 and seven cases (17.5%) with Group 2. Three patients (10.3%) were treated with infliximab in Group 1 and six patients (15%) were treated with infliximab in Group 2.

The mean MPV value was 8.40 ± 0.97 in Group 1, 8.32 ± 1.04 in Group 2, and 7.77 ± 0.72 in Group 3 [Table 1]. Statistically significant differences in MPV levels were determined among the three studied groups ($P = 0.005$). In addition, MPV levels were significantly higher in active and inactive BD patients than in healthy controls ($P = 0.001$ and $P = 0.01$, respectively). However, there was no significant alteration between the two groups in the comparison of the active and inactive groups ($P = 0.7$).

The mean serum level of PDW was 15.12 ± 1.09 in Group 1, 14.97 ± 1.02 in Group 2, and 14.52 ± 0.82 in Group 3 [Table 1]. Statistically significant differences in PDW levels were determined among the three groups ($P = 0.02$). Furthermore, PDW levels were statistically higher in patients with active and inactive BD than in healthy controls ($P = 0.001$ and $P = 0.04$, respectively). While there was no significant change between the two groups in the comparisons of patients in the active and inactive groups ($P = 0.54$).

Table 1: The mean values of the Mean Platelet Volume (MPV), Plateletcrit (PCT), and Platelet Distribution Width (PDW) and the comparison of platelet parameters (mean±standard deviation) for groups

	Group 1 (*n*=29)	Group 2 (*n*=40)	Group 3 (*n*=40)	*P*
MPV (fL)	8.40±0.97	8.32±1.04	7.77±0.72	0.005
PDW (%)	15.12±1.09	14.97±1.02	14.52±0.82	0.02
PCT (%)	0.23±0.07	0.21±0.04	0.18±0.03	0.02

MPV: Mean Platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit, SD: Standard deviation

The mean serum PCT value was 0.23 ± 0.07 in Group 1, 0.21 ± 0.04 in Group 2, and 0.18 ± 0.03 in Group 3 [Table 1]. Statistically significant differences in PCT levels were determined among the three groups ($P = 0.02$). Moreover, PCT levels were statistically higher in patients with active BD compared to inactive BD ($P = 0.03$) and healthy controls ($P = 0.01$). On the other hand, there was no significant difference between the patients in the active and inactive groups ($P = 0.52$).

Discussion

BD is a chronic vasculitis that may decrease in frequency and severity during the clinical course of the disease.[12] This disease is endemic in the Eastern Mediterranean region and Central and Eastern Asian countries, and the highest prevalence rates were reported in Turkey (80–300 per 100,000).[13] The most frequent type of uveitis in ocular BD is panuveitis.[13] Posterior segment involvement is very important in the prognosis of ocular BD. In ocular BD, fundus changes were noted in 82.9% of the patients with ocular involvement.[4] In our patient cohort, panuveitis was the most common kind of uveitis, and panuveitis constituted 88.4% of all posterior segment ocular BD.

Increased risk for both venous and arterial thromboses is defined in BD patients. For this reason, the disease is called a hypercoagulable/prothrombotic state.[14] Increased thrombosis in BD can be attributed to vascular inflammation and endothelial dysfunction.[14]

The platelet activation correlates with increased MPV levels. The increase in the MPV level may affect the vascular occlusion process in ocular BD. An increase in MPV value means a larger platelet size, in which case the platelets are younger, denser, and more active. For this reason, high MPV increases the likelihood of vascular problems.[15] There have been studies reporting that MPV is associated with thrombotic disorders such as cerebral ischemia, peripheral artery disease, and myocardial infarction.[8]

Because the value of PDW does not increase in the case of simple platelet swelling, PDW is a more significant marker than MPV in terms of demonstrating platelet activation.[16] PDW shows changes in platelet size, so it is an indicator of active platelet release.[17] PDW levels can alter in several cases, and thrombocytosis

has been described to be associated with PDW.[17,18] A study showed that PDW is an important marker for the activation of coagulation.[16] For these reasons, it is thought that the increment in PDW value may play a role in BD pathogenesis.

The PCT is considered an indicator of the platelets and is an important screening tool to detect quantitative abnormalities of platelets.[19] The decreased levels of platelets have been described in patients with branch retinal vein occlusion.[20] PCT has been shown to correlate with the level of C-reactive protein in inflammatory conditions.[21]

The increased levels of these parameters may play a role in the pathogenesis of ocular BD with posterior segment involvement. Increments in these parameters may reflect the activation of platelets and may affect vasoactive mediator secretion, like thromboxane A2. As a result of the ongoing process, endothelial dysfunction, vasoconstriction, and inadequate blood flow may occur, leading to microvascular obstruction. Thrombophilic parameters have been shown to change in ocular BD patients.[6] The literature review has shown that all three MPV, PDW, and PCT values were not previously evaluated in ocular BD patients at the same time. Gunduz *et al*.[22] collected the data of 33 BD patients in the active and inactive periods and reported significantly higher MPV values in the active period than the inactive period. Türkcü *et al*.[23] reported a significant difference between MPV values of BD patients and control groups. Furthermore, in the study of Ricart *et al*.,[24] BD patients showed a statistically higher MPV than controls. Uzkeser *et al*.[25] declared that MPV was statistically higher in patients with BD than in the controls. Differently, Ryu *et al*.[26] reported that MPV was significantly lower in patients with BD compared to controls and claimed that MPV may be useful as a marker of BD activity. According to the results of this study, MPV, PDW, and PCT levels were significantly higher in active and inactive ocular BD patients than controls. On the other hand, no significant difference was observed between MPV, PDW, and PCT levels between active and inactive diseases.

There are a few limitations to our study. First, the number of patients is low in this study. Second, the design of the study was not planned for potential risk factors for the development of thrombosis, since the control group was selected from healthy individuals without systemic or ocular disease history. Third, any correlation with other acute phase reactants was not studied in this study. Fourth, Behçet's patients without ocular involvement were not included in the present study. Fifth, some patients with active eye disease also had an active systemic disease, and none of the patients with inactive eye disease had an active systemic disease. Hence, we cannot speculate how the presence or absence of active systemic disease might impact the results.

Conclusion

The results of our study showed that serum MPV, PDW, and PCT levels were significantly higher than those of the control group and may be associated with posterior segment involvement in ocular BD patients. Therefore, the evaluation of platelet parameters may be important in ocular BD. The CBC test including these platelet activation parameters can be performed in every clinic, and this procedure will not add extra costs. Nevertheless, we would like to point out that further comprehensive and broader clinical trials are needed to support these results.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethical Committee of Ankara Diskapi Training and Research Hospital. Furthermore, this study is registered in the Australian New Zealand Clinical Trials Registry, number ACTRN12616001178437.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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