Original Article

Relation between platelet indices and branch retinal vein occlusion in hypertensive patients

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Backgroud: Branch retinal vein occlusion (BRVO) is the second most common retinal vascular disease after diabetic retinopathy. To date, the studies were unable to elucidate the mechanism of the thrombosis leading to the entity; particularly the relation between thrombocyte aggregation and retinal vein occlusion is still unclear. Mean platelet volume (MPV) is a determinant of rate of platelet production and activation, both of which are indices of function of platelets. The relation between MPV and BRVO has not been studied before. The aim was to evaluate MPV in BRVO. **Materials and Methods:** Forty patients were included in the study. Forty six age and sex matched hypertensive volunteers were recruited as the control group. **Results:** MPV values were significantly higher in BRVO patients compared with the control subjects (8.01 ± 0.79vs 7.52 ± 0.32fL, respectively; $P < 0.001$). **Conclusion:** MPV is significantly higher in patients hypertensive BRVO patients and further investigations regarding its potentially use as a prognostic biomarker in patients with BRVO are needed.

Key words: Branch retinal vein occlusion, mean platelet volume, platelet activation, retinal vein occlusion

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Retinal vein occlusions (RVOs) constitute the second most common cause of retinal vascular disease after diabetic retinopathy, with a prevalence between 1% -2% in subjects older than 40 years of age.[1] Many patients with RVO suffer irreversible visual loss.[2] The pathogenesis is multifactorial and still unclear. The classic risk factors related to RVO are, diabetes, hypertension, age, smoking and hyperlipidemia, which are especially common in patients with branch RVO (BRVO).[3] Open-angle glaucoma or other conditions inducing increased intraocular pressure are established local predisposing factors.[3]

Atherosclerosis and/or hypertensive changes, both surmised as major causes of pathophysiology, cause endothelial dysfunction[4] and thrombocyte activation[5] leading to branch retinal vein occlusion (BRVO). Mean platelet volume (MPV) is a simple and easily measured parameter assayed in auto analyzers. It is a determinant of the rate of platelet production and activation, both of which are indices of the function of platelets.[6] In comparison to smaller platelets, larger platelets have more granules, thus aggregating much more readily with collagen. In addition, the latter have higher levels of thromboxane A2 and can express more glycoprotein Ib and IIb/IIIa receptors, which are other determinants for platelet activation.

Studies related to the platelets in RVO pathogenesis also reported increased platelet activation and aggregation,[7-10] suggesting an eventual alteration with MPV. Thrombosis, indeed, may bear the crucial role for RVO. Platelet count and MPV may be related with the thrombosis in RVO. The relation between MPV and branch retinal vein occlusion (BRVO) has not been studied before. Therefore the aim of this study was to investigate MPV and platelet count in patients with BRVO.

Materials and Methods

Study population and sample size measurement

The present study had a prospective case–control design. Sample size equation for continuous variables of Dell *et al*, was applied.[11] According to this formula, $\left(n = 1 + 2C\left(\frac{s}{d}\right)^2\right)$ where n was the sample size, C was the equation constant with 0.8 power and two sided $\alpha = 0.05$, s was the standard deviation of MPV in Turkish people[12] and d was the effect size (which was taken as 1). 36 was the sample size of a single group. Therefore, we designed a 1:1 case control study with groups of 40. Forty consecutive hypertensive patients with BRVO (27 females, 13 males with a mean age 62.9 ± 7.1 years) who were admitted to our institute between August 2011and March 2012 were included in the study. The control group consisted of 46 consecutive sex and age-matched hypertensive subjects (33 females, 13 males with a mean age 60.2 ± 7.1 years) who visited the Ophthalmology outpatient clinic with presbyopia. The duration of visual symptoms, ocular medication and ocular history were recorded. A complete ophthalmic evaluation of both eyes was done, including best corrected visual acuity (BCVA), slit lamp examination, applanation tonometry, fundus biomicroscopy and fluorescein angiography. Participants had signed an informed consent and the Ethics Committee of Duzce University had approved the study protocol. Each participant received detailed information and provided informed consent before inclusion. All control subjects also underwent standard ophthalmic evaluation, including BCVA, slit lamp examination, applanation tonometry and fundus examination. All subjects underwent detailed physical examination. Medical conditions, including diabetes, systemic hypertension, cardiovascular status, decreased renal function, relevant drug history and

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presence of blood dyscrasias were also recorded. Blood pressure was measured in the sitting position on the right arm and the mean of two recordings at least 3 min apart was recorded.

Exclusion criteria included history of diabetes, glaucoma, blood dyscrasias, renal failure, hepatic disorders, malignancy and history of drug use (non-steroid anti-inflammatory drugs, anticoagulant medications and oral contraceptives). Patients with BRVO who had a history of vasculitis were also excluded.

Branch RVO was diagnosed by ophthalmoscopic fundus examination revealing venous dilatation and tortuosity with intraretinal hemorrhages in a wedge-shaped region, with the apex of the wedge pointing towards an arteriovenous crossing point.

Patients and controls were considered hypertensive if their blood pressure was greater than 140 mmHg systolic or 90 mmHg diastolic or if they had already been treated with antihypertensive drugs.

Biochemical measurements

Blood samples were drawn from the antecubital vein by careful vein puncture in a 21-G sterile syringe without stasis bet 08.00 to 10.00am after a fasting period of 12h. Glucose, creatinine and lipid profiles were determined by standard methods. Mean platelet volume was measured in a blood sample collected in dipotassium ethylenediaminetetraacetic acid (EDTA) tubes. An automatic blood counter (Cell-Dyn 3700 [Abbott Diagnostics, Santa Clara, CA, USA]) was used for whole blood. MPV was measured within 30 minutes to prevent EDTA induced swelling. The expected values for MPV in our laboratory ranged from 6.9 to 10.8 fL.

Statistical analysis

Data were analyzed with the Statistical Package for Social Sciences (SPSS) software version 12.0 (SPSS Inc., Chicago, Illinois, USA) for Windows. Continuous variables from the study groups were reported as mean ± SD and categorical variables as percentages. To compare continuous variables, the Student's *t*-test or Mann–Whitney U test were used when appropriate. Categorical variables were compared with the Chi-squared test. Statistical significance was defined as *P* value of less than 0.05.

Results

Clinical features and laboratory characteristics of the patients and the control group are shown in Table 1. There were no statistically significant differences between the two groups with respect to age, gender, systolic and diastolic blood pressures, and levels of glucose, creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin, white blood cell (WBC) and platelet count. Mean platelet volume was significantly higher among patients with BRVO when compared with the control group (8.01 ± 0.79 vs 7.52 ± 0.32 fL, respectively; $P < 0.001$) [Table 2]. Platelet count was lower in the control group but the difference did not reach a statistically significant level.

Table 1: Comparison of the clinical and laboratory characteristics of the patients with BRVO and control participants

	BRVO (*n* = 40)	Control (*n* = 46)	*P*
Age (years)	62.9 ± 7.1	60.2 ± 7.1	0.73
Sex (M/F)	13/27	13/33	0.67
SBP (mm Hg)	157.4 ± 12.4	154.1 ± 13.3	0.25
DBP (mm Hg)	90.1 ± 7.3	89.4 ± 11.3	0.07
Smoking (%)	11 (27.5%)	9 (19.6%)	0.75
Glucose (mg/dL)	98.8 ± 8.5	97.1 ± 8.9	0.38
Creatinine (mg/dL)	0.9 ± 0.3	0.8 ± 0.2	0.13
Total cholesterol (mg/dL)	194.0 ± 39.4	208.5 ± 42.0	0.10
LDL-cholesterol (mg/dL)	118.1 ± 39.2	129.6 ± 31.9	0.14
HDL-cholesterol (mg/dL)	45.3 ± 10.8	47.6 ± 10.5	0.33
ALT (IU/L)	16.4 ± 6.8	17.9 ± 7.0	0.32
AST (IU/L)	18.0 ± 5.7	19.8 ± 5.6	0.13

M/F: Male to female, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase. *P* value is for comparison between control and study population

Table 2: Comparison of the platelet indices of the patients with BRVO and control participants

	BRVO (*n* = 40)	Control (*n* = 46)	*P*
WBC ($\times 10^3$ mg/dL)	6.98 ± 1.34	7.02 ± 1.50	0.89
Hemoglobin (g/dL)	12.92 ± 1.34	12.87 ± 1.27	0.87
Platelet count ($\times 10^9$)	250.70 ± 45.67	272.02 ± 61.48	0.07
MPV (fL)	8.01 ± 0.79	7.52 ± 0.32	< 0.001

WBC: White blood cell, MPV: Mean platelet volume. *P* value is for comparison between control and study population

Discussion

The present study showed that MPV was significantly higher in patients with BRVO. Thrombosis may develop due to endothelial injury, abnormal fibrinolysis, procoagulant activation and platelet abnormalities.[7-10] Abnormal platelet aggregability and *in vivo* platelet function has been reported, suggesting that platelet aggregation might be an important sequel to endothelial swelling, thus leading to the occlusion.[13] Robinson *et al.*, showed that there is a link between platelet activation and endothelium-dependent vasomotor dysfunction.[14] Indeed, some studies have suggested that in dysfunctional states, platelet activation and aggregation can occur on the surface of the intact endothelium.[15]

Histological studies showed that endothelial injury, presenting as endothelial proliferation, may lead to BRVO.[16] An esteemed relation between BRVO and retinal arteriolar disease was discovered.[17,18] Being the risk factors for BRVO, hypertension and atherosclerosis cause thickening of the arteriolar wall. Thickened artery compresses the vein within a common adventitial sheath inducing turbulence, endothelial damage and thrombosis of retinal venous tree.[18]

MPV is a marker for platelet function. Large platelets contain more dense granules and produce more thromboxane A2 and larger platelets are enzymatically more active with respect to the prothrombotic activity than the smaller ones.[5] MPV is related to increased platelet aggregation, increased thromboxane synthesis, release of β-thromboglobulin, and over expression of adhesion force molecules, which are other

determinants for platelet activity.[19] Increase in MPV was also seen in cardiovascular risk factors including smoking, diabetes mellitus, hypertension and hypercholesterolemia.[20-22] Higher MPV levels have been identified as an independent risk factor for death or recurrent vascular events after MI and coronary artery disease.[23]

In the present study, platelet count was insignificantly decreased in BRVO. To our knowledge, this is the first study showing such an interaction. It is highly probable that the prothrombotic state accounts for venous thrombosis. A role for active platelets and coagulation factors in the venous system is supposed in the basis of the hypothesis.[24] The mechanism set forth for increased platelet activation in BRVO is likely of atherosclerosis and vascular endothelial dysfunction lead to platelet activation and consequently to local thrombosis and inflammation.[25]

Platelets have a crucial role in the pathophysiology of atherothrombotic cardiovascular diseases. MPV increase was shown in cardiovascular disease and this increase has a role in the mechanism.[25] MPV was also higher in patients with hypertension in comparison to the control subjects.[22] In the present study, the patients and controls were hypertensives so as to abolish the confounding effect of hypertension on MPV. These data suggest that MPV is significantly higher in patients hypertensive BRVO patients and further investigations regarding its potentially use as a prognostic biomarker in patients with BRVO are needed.

Limitations of the study

The cohort is relatively small and larger studies are warranted. This observation may be accepted as a start of new investigations on MPV and BRVO.

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