ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Optical Coherence Tomography Angiographic Assessment of Polycythaemia Vera-Related Retinal Microvascular Morphological Changes: A Cross-Sectional Case-Control Study

Polisitemia Vera ile İlişkili Retina Mikrovasküler Morfolojik Değişikliklerin Optik Koherens Tomografi Anjiyografik Değerlendirmesi: Kesitsel Olgu-Kontrol Çalışması

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Abstract of this study was accepted for oral presentation at the 20th EVRS Meeting, scheduled for June 04-07, 2020 at the Teatro Filarmonico Verona-Italy, which was cancelled due to the COVID-19 pandemic.

ABSTRACT Objective: To assess polycythaemia vera (PV)-related retinal microvascular morphological changes using optical coherence tomography angiography (OCTA). **Material and Methods:** In this cross-sectional case-control study, 30 PV patients (Group 1) and 30 healthy individuals (Group 2) underwent a comprehensive ophthalmological examination, followed by OCTA acquisition in Angio Retina mode (6x6 mm). Macular superficial and deep vascular plexus vessel densities (VDs) in foveal, parafoveal, and perifoveal, as well as foveal avascular zone (FAZ) area, FAZ perimeter, and foveal VD in 300-µm wide region around FAZ (FD-300) were automatically analysed using AngioVue Analytics software. Sequential measurements were compared for statistical significance. **Results:** Mean ages were 46.97±3.20 and 47.42±2.55 years in Groups 1 and 2, respectively (p=0.350). Group 1 had significantly increased superficial foveal VD than Group 2 (p=0.032). Besides, Group 1 had non-significantly increased VDs than Group 2 in the following areas: superficial whole (p=0.468), superficial parafoveal (p=0.692), deep foveal (p=0.752), deep perifoveal (p=0.369), FAZ perimeter (p=0.209), and FD-300 (p=0.914). The FAZ area decreased non-significantly in Group 1 compared to Group 2 (p=0.529). **Conclusion:** PV appears to be associated with considerable retinal microvascular morphological changes, indicating a potential hyperviscosity impact on retinal VDs that would necessitate careful consideration during PV patient evaluation.

Keywords: Hyperviscosity syndrome; optical coherence tomography angiography; retinal microvasculature; polycythaemia vera; vessel density

ÖZET Amaç: Bu çalışmanın amacı, polisitemia vera (PV) ile ilişkili retinal mikrovasküler morfolojik değişiklikleri optik koherens tomografi anjiyografi (OKTA) ile değerlendirmektir. **Gereç ve Yöntemler:** Bu kesitsel olgu-kontrol çalışmasında, 30 PV hastası (Grup 1) ve 30 sağlıklı bireye (Grup 2) kapsamlı bir oftalmolojik muayene yapıldıktan sonra Anjiyo Retina modunda (6x6 mm) OKTA alımı gerçekleştirildi. Foveal, parafoveal ve perifoveal maküler yüzeysel ve derin vasküler pleksus damar yoğunlukları ve foveal avasküler bölge alanı, foveal avasküler bölge çevresi ve foveal avasküler bölge etrafındaki 300 µm genişliğindeki bölgede foveal damar yoğunluğu (FD-300) AngioVue Analytics yazılımı ile otomatik olarak analiz edildi. Sıralı ölçümler istatistiksel anlamlılık için karşılaştırıldı. **Bulgular:** Grup 1 ve 2'de yaş ortalamaları sırasıyla 46,97±3,20 ve 47,42±2,55 idi (p=0,350). Grup 1'de yüzeysel foveal damar yoğunluğu, Grup 2'ye göre anlamlı derecede yüksekti (p=0,032). Ayrıca Grup 1'in şu alanlarda Grup 2'ye göre anlamlı olmayan şekilde yüksek damar yoğunlukları vardı: yüzeysel bütün (whole) (p=0,468), yüzeysel parafoveal (p=0,692), derin foveal (p=0,752), derin perifoveal (p=0,369), foveal avasküler bölge çevresi (p=0,209) ve FD-300 (p=0,914). Foveal avasküler bölge alanı Grup 1'de Grup 2'ye göre anlamlı olmayan şekilde azaldı (p=0,529). **Sonuç:** PV, önemli retinal mikrovasküler morfolojik değişikliklerle ilişkili görünmektedir. Bu bulgu, retinal damar yoğunlukları üzerinde PV hasta değerlendirmesi sırasında dikkatli bir şekilde düşünülmesini gerektirecek potansiyel bir hiperviskozite etkisine işaret etmektedir.

Anahtar Kelimeler: Hiperviskozite sendromu; optik koherens tomografi anjiyografi; retina mikrovaskülatür; polisitemia vera; damar yoğunluğu

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Polycythaemia vera (PV) has been officially classified as a major form of myeloproliferative neoplasms. It is diagnosed by the 95-98% of presence of a JAK2V617F mutation, as well as an increase in haemoglobin/haematocrit above the threshold level defined by the 2016 World Health Organization revised criteria (>16.5 g/dL/49% for males and >16 g/dL/48% for females).[1-3] This condition, also known as primary polycythaemia, is characterized by an erythrocytosis of unknown origin in the bone marrow.[4,5]

Given the systemic and haematological nature of PV, many tissues and organs are likely to be affected. Patients are predisposed to thrombotic and haemorrhagic events, as well as leukemic transformation, which are the leading causes of morbidity and mortality.[3,5-8] Other symptoms, including ophthalmic, which are more often incorrectly identified as being caused by other ocular disorders, vary greatly and are frequently induced by haematological issues. These ophthalmic symptoms range from monocular vision loss due to retinal ischemia and papilledema, to combined retinal vein occlusion and anterior ischemic optic neuropathy.[9-11] In patients suffering from PV, the current treatment goal is to prevent potential thromboembolic complications and alleviate subsequent systemic and ocular symptoms.[12]

Optical coherence tomography angiography (OCTA) is a relatively novel non-invasive imaging technique that allows for visualisation of the retinochoroidal capillary networks as well as foveal avascular zone (FAZ) without using exogenous dye. It is also possible to diagnose retinal ischemic diseases with clinically undetectable fundus lesions.[13] This technique is increasingly being used in diagnosis and evaluation of the vascular-related retinal or choroidal diseases, including diabetic retinopathy, choroidal neovascularization, and retinal vein occlusion.[14-16]

Overall, understanding ophthalmic involvement in PV is critical for these patients and clinicians. Since PV patients are commonly overlooked until they manifest significant thromboembolic complications, an ophthalmologist's role could be critical. To the best of our knowledge, no studies have been published that have investigated adverse ocular complications, specifically retinal microvascular morphological changes caused by PV, using OCTA as a novel non-invasive diagnostic tool.

As a result, the purpose of this study was to assess PV-related retinal microvascular morphological changes using OCTA, and compare the findings with age- and gender-matched healthy individuals.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

This cross-sectional case-control single-centred study included 30 PV patients (Group 1) who were followed up at Afyonkarahisar Health Sciences University Hospital, Department of Haematology, and 30 healthy individuals (Group 2) who came to our ophthalmology department for routine eye exams. The Helsinki Declaration's tenets were followed in all procedures. The Afyonkarahisar Health Sciences University Ethics Committee approved this study with the following approval number and date: 2011-KAEK-2/October 4, 2019. Prior to the study, written informed consent was obtained.

OPHTHALMOLOGICAL EXAMINATION AND OCTA ACQUISITION

A thorough ophthalmological examination was performed, which included measurements of best-corrected visual acuity and Goldmann applanation tonometry, as well as anterior and posterior segment slit-lamp biomicroscopy before and after full pupil dilation.

The same clinician performed spectral-domain OCTA scanning in Angio Retina mode (6x6 mm) on all participants under standard conditions. Eye movement artefacts were reduced by an eye-tracking mode and eliminated by motion correction technology. All scans were reviewed to ensure proper segmentation and image quality (Quality Index ≥7), and scans with low quality were excluded. The RTVue-XR version 2017.1.0.155 program from AngioVue Analytics (Optovue, Inc., Fremont, California, USA) automatically quantified vessel density (VD) in the superficial retinal layer [superficial vascular plexus (SVP)] and deep retinal layer [deep vascular plexus (DVP)]. The AngioVue Analytics program also automatically quantified the central macular thickness, defined as the average thick-

ness of the central 1 mm^2 fovea region, the parafovea macula thickness, the average retinal thickness of the 6x6 mm region, and the superior and inferior hemifields. Flow area of a 3-mm diameter circle was determined. FAZ area, FAZ perimeter, and foveal VD in 300 µm wide regions around FAZ (FD-300) were also obtained using the software's FAZ mode.

STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS (version 18, SPSS Inc., Chicago, IL, USA) and Microsoft Excel (Microsoft Corp., Redmond, Washington, USA). The Shapiro-Wilk test was used to determine the distribution of all parameters. In addition, since the data were identified as having a normal distribution, an independent sample t-test was used in the data analysis. $p<0.05$ were considered statistically significant.

RESULTS

The male-to-female ratio among the 60 participants was 1:1. Groups 1 and 2 had mean ages of 46.97±3.20 and 47.42±2.55 years, respectively (p=0.350). There was no statistically significant difference in intraocular pressure (p=0.159) or axial length (p=0.206) between groups 1 and 2 (Table 1).

RETINAL VD ANALYSIS

Compared to Group 2, Group 1 had statistically significantly increased VD in the superficial foveal area (p=0.032). As shown in Table 2, with the exception of DVP parafoveal area, all other retinal VDs increased non-significantly in Group 1 versus Group 2.

CAPILLARY FLOW AND FAZ ANALYSES

Compared to Group 2, Group 1 had non-significant decreases in outer retinal (p=0.751), choriocapillary flow (p=0.092), and FAZ area (p=0.529) (Table 3 and Table 4). The FAZ perimeter (p=0.209) and FD-300 (p=0.914) were higher in Group 1 than in Group 2, though the difference was not statistically significant (Table 4, Figure 1).

TABLE 1: Demographic characteristics of Groups 1 and 2.

Parameter	Group 1 (n=30)	Group 2 (n=30)	p value*
Gender (male:female)	14:16	15:15	0.883
Intraocular pressure (mmHg)	14.06±2.81	13.71±2.38	0.159
Best-corrected visual acuity (logMAR)	0.0±0.0	0.0±0.0	1.000
Axial length (mm)	21.58±2.09	21.19±1.49	0.206

*Independent t-test results; Group 1, Polycythaemia vera patients; Group 2, Healthy individuals; LogMAR: Logarithm of the Minimum Angle of Resolution.

TABLE 2: Comparison of the retinal VD parameters between Groups 1 and 2.

Parameters	Groups	n	Mean density values (%)	p value*
Whole superficial	Group 1	30	51.7±2.8	0.468
	Group 2	30	50.8±3.5	
Foveal superficial	Group 1	30	23.2±4.5	**0.032**
	Group 2	30	19.1±5.8	
Parafoveal superficial	Group 1	30	53.4±2.4	0.692
	Group 2	30	53.0±4.1	
Perifoveal superficial	Group 1	30	52.4±1.2	0.304
	Group 2	30	53.3±3.1	
Whole deep	Group 1	30	55.3±2.4	0.694
	Group 2	30	54.8±3.9	
Foveal deep	Group 1	30	41.4±3.1	0.752
	Group 2	30	40.7±5,0	
Parafoveal deep	Group 1	30	56.7±2.1	0.426
	Group 2	30	57.4±3.3	
Perifoveal deep	Group 1	30	56.9±1.7	0.369
	Group 2	30	55.8±4.4	

*Independent sample t-test results; p<0.05 was considered statistically significant and was bolded; VD: Vessel density; Group 1, Polycythaemia vera patients; Group 2, Healthy individuals.

TABLE 3: Comparison of capillary flow values between Groups 1 and 2.

Parameters	Groups	n	Mean flow area values (%)	p value*
Outer retinal flow area	Group 1	30	8.60±1.04	0.751
	Group 2	30	8.97±9.68	
Choriocapillary flow area	Group 1	30	18.73±0.72	0.092
	Group 2	30	19.15±0.51	

*Independent sample t-test results; Group 1, Polycythaemia vera patients; Group 2, Healthy individuals.

DISCUSSION

This study, which we believe is the first of its kind to use a novel non-invasive OCTA technique to assess morphological changes caused by PV in the retinal microvascular system, revealed PV-related haematological hyperviscosity evidenced by a tendency for VD increase in almost all central retina, particularly the foveal area, though statistical significance varied.

TABLE 4: Comparison of FAZ parameters between groups 1 and 2.

Parameters	Groups	n	Mean values	p value*
FAZ area (mm2)	Group 1	30	0.27±0.64	0.529
	Group 2	30	0.29±0.14	
FAZ perimeter (mm)	Group 1	30	2.26±0.37	0.209
	Group 2	30	2.07±0.49	
FD-300 (%)	Group 1	30	53.93±2.34	0.914
	Group 2	30	53.85±4.06	

*Independent sample t-test results; FAZ: Foveal avascular zone; FD-300: Foveal vessel density in 300 µm wide region around FAZ. Group 1: Polycythaemia vera patients; Group 2: Healthy individuals.

PV is a commonly known clinical entity resulting from primary hyperplasia of erythroblastic elements of the bone marrow. It is seldom detected by the internist, and far more seldom by the ophthalmologist, as vision is occasionally impaired. Fundus examination, on the other hand, is likely to reveal early characteristic lesions that are important in the diagnosis. Williamson et al. conducted a comparative investigation of viscosity and coagulation, including activated protein C resistance, between 87 central retinal vein occlusion patients and an age-matched, population-based control group, and found significant reductions in both choroid and retinal blood flow in central retinal vein occlusion patients.[17] Despite the lack of statistical significance, PV patients had consistent decreases in capillary flow values and FAZ area relative to healthy individuals, which could also be explained by the PV's adverse haematological complications.

Hyperviscosity and/or thrombosis are the two main causes of PV-related ophthalmic symptoms.[18] PV may be fatal if left untreated due to cardiovascular thrombotic events or PV progression to myelofibrosis, leukaemia, or myelodysplastic syndromes.[19] Dhrami-Gavazi et al. reported a *JAK2* mutation patient who suffered from central retinal artery occlusion and ipsilateral middle cerebral artery stroke.[20] This also could indicate the consequences of haematological hyperviscosity, as observed in this study in-

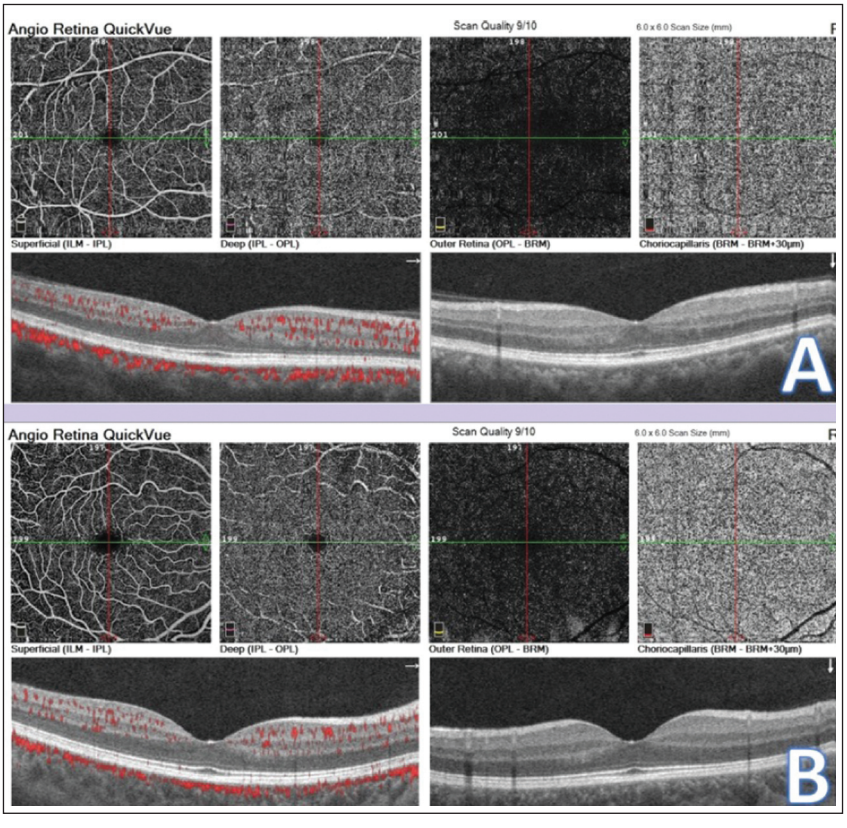

FIGURE 1: Illustrative optical coherence tomography angiography comparison of a polycythaemia vera patient **(A)** and a healthy individual **(B)**.

volving PV patients. As a result, PV management is generally intended to prevent thrombotic incidents and to maintain a steady haematocrit level via periodic phlebotomy.

Menke et al., conducted a study on the effects of plasmapheresis on hyperviscosity syndrome-related retinopathy and retinal hemodynamic parameters in Waldenström's macroglobulinaemia patients.[21] They concluded that hyperviscosity could cause a specific type of retinopathy with retinal vein occlusion-like appearance, despite normal retinal blood flow. Patients experienced a decrease in venous diameter and an increase in retinal venous blood flow velocity as a result of therapy. Nonetheless, prior to plasmapheresis, focal vascular constrictions revealed by slit-lamp biomicroscopy and indirect ophthalmoscopy were not associated with significant changes. Similarly, in this study, PV patients were associated with decreases in microvascular morphological parameters, as well as increases in FAZ perimeter and FD-300 parameters with negligible differences relative to healthy individuals. This indicates that the sluggishness of the retinal microcirculatory blood flow could be mainly attributable to haematological hyperviscosity, which is associated with elevated haematocrit in PV.

Crowe et al., found a consistent relationship between these two parameters when they plotted retinal vessel diameter against relative serum viscosity.[22] In both arteries and veins, viscosity decreased proportionally to retinal vessel diameter. Correspondingly, in this study, PV patients had significantly increased VDs in almost all central retina, particularly in the superficial foveal area, relative to healthy individuals. As is well understood, OCTA scanning entails the acquisition and processing of an erythrocyte motion contrast within the vessel. Hence, the authors believe that different measurement values for hyperviscosity syndrome, including PV, could be obtained, particularly in the foveal area. This incidence could also be explained by the observation of a significant increase in only superficial foveal VD values relative to healthy individuals in this study.

The authors acknowledge limitations of this study. Since this study was cross-sectional, the authors were unable to discover prospective haematological implications of PV on the posterior ocular segment on the whole. This study only included people of Turkish descent. As a result, there was no assessment of PV-related morphological changes in retinal microvasculature based on race. There have been reports of racial differences in foveal composition.[23,24] More studies are needed to see if the findings of this study apply to other races. Only one OCTA device was used in this study and the results were interpreted based on this device. Moreover, the sample size was just not high enough for it to improve the efficacy of the study either. Further trials with a larger population determining pre- and post-treatment PV-related adverse complications, as well as a longer follow-up period, may be worthwhile.

CONCLUSION

PV patients frequently experience ophthalmic symptoms, which may be due to an indirect effect on the ocular microvascular structures. This OCTA-based study revealed PV-related substantial retinal VD changes around the foveal area. Thus, PV appears to be associated with increased hyperviscosity in retinal SVP and DVP VDs, necessitating careful systemic and ophthalmic consideration when evaluating PV patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Müberra Akdoğan, Mustafa Doğan, Hamidu Hamisi Gobeka;* ***Design:*** *Müberra Akdoğan, Mustafa Doğan, Hamidu Hamisi Gobek, Anar Elizade, Mehmet Cem Şabaner, Filiz Yavaşoğlu;* ***Control/Supervision:*** *Müberra Akdoğan, Mustafa Doğan, Hamidu Hamisi Gobek, Anar Elizade, Mehmet Cem Şabaner, Filiz Yavaşoğlu;* ***Data Collection and/or Processing:***

Müberra Akdoğan, Mustafa Doğan, Hamidu Hamisi Gobek, Mehmet Cem Şabaner, Filiz Yavaşoğlu; ***Analysis and/or Interpretation:*** *Müberra Akdoğan, Mustafa Doğan, Hamidu Hamisi Gobek, Anar Elizade, Filiz Yavaşoğlu;* ***Literature Review:*** *Müberra Akdoğan, Mustafa Doğan, Anar Elizade, Hamidu Hamisi Gobek, Mehmet Cem Şabaner;* ***Writing the Article:*** *Müberra Akdoğan, Mustafa Doğan, Hamidu Hamisi Gobek, Mehmet Cem Şabaner, Filiz Yavaşoğlu;* ***Critical Review:*** *Müberra Akdoğan, Mustafa Doğan, Hamidu Hamisi Gobek, Filiz Yavaşoğlu;* ***References and Fundings:*** *Müberra Akdoğan, Mustafa Doğan, Filiz Yavaşoğlu;* ***Materials:*** *Müberra Akdoğan, Mustafa Doğan, Filiz Yavaşoğlu.*

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