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Evaluation of the Vascular Network with Optical Coherens Tomography Angiography in Multiple Sclerosis and its Relationship with the Clinic

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ABSTRACT

Introduction: Optical Coherence Tomography Angiography (OCTA) is an examination that is increasingly used in neurodegenerative diseases. This study in multiple sclerosis (MS) patients; It aims to reveal the presence of vascular involvement in the retina and optic nerve and its relationship with disease-related clinical parameters with the help of OCTA.

Methods: One eye of 49 MS patients and 28 healthy controls were included in the study. Retinal, optic nerve head (ONH) and foveal vascular measurements were performed using OCTA. In the patient group, 23 people without a history of optic neuritis (ON-) and 26 people with a history of optic neuritis (ON+) were compared among themselves and with the healthy group in terms of retinal and ONH blood supply parameters. Detailed ONH vascular measurements using OCTA in the participants were compared with MS-related clinical data.

Results: In the parameters we examined for ONH vascular evaluation, OCTA measurements were statistically significantly lower in the patient group than in the healthy group. In addition, a similar reduction was noted in some retinal superficial and deep capillary plexus densities. When the ON+ group was compared with the ON− group, there was no significant difference between these two groups; There was a significant decrease in ONH vascular density and some retinal vascular layer densities in the ON+ group compared to the healthy group. In addition, while there was no correlation between EDSS value and CSF findings and OCTA data, it was observed that vascular involvement was significantly higher in the group with higher number of attacks and years of disease, decreased visual acuity, and impaired visual evoked potential (VEP) measurement.

Conclusion: In our study, it was observed that vascular involvement of the ONH was correlated with many disease-related parameters, especially the history of ON.

Keywords: Multiple sclerosis, optical coherence tomography angiography, optic neuritis, vessel density

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INTRODUCTION

Multiple sclerosis (MS) is a disease progressing with inflammation, demyelination, gliosis and widespread axonal degeneration in the central nervous system. Generally, MS begins in young adulthood (1). Optic neuritis (ON) is the most common ocular finding of MS (2).

Today, data on the use of optical coherence tomography (OCT) in MS is increasing (3). With the help of OCT, MS and ON-related axon damage can be evaluated. By using optical coherence tomography angiography (OCTA), which was developed as an extension of OCT, the difference in signal between static and nonstatic tissues is calculated by detecting the motion contrast of erythrocytes in vascular structures. In the microvascular network, the same section is displayed many times, three-dimensional images are obtained by detecting the temporal differences between the scans. Artifacts caused by eye movements during shooting can be corrected with the help of software. Microvascular structure and optic nerve head (ONH) perfusion in various layers of the retina and choroid such as the superficial and deep capillary plexus (SCP and DCP), outer retina and choriocapillaris in the parafoveal and perifoveal regions can be visualized in detail via OCTA (4–6), OCTA is a non-contrast, non-invasive, easily reproducible, short-term and inexpensive examination (7,8).

Highlights

- **Early detection of microvascular damage with OCTA may offer rapid diagnosis in MS.**
- **OCTA can be used to evaluate progression and treatment response in MS.**
- **A significant decrease in ONH vessel density was observed with OCTA measurement in patients with MS.**

Perfusion measurements in MS accelerate the detection of optic nerve damage and OCTA may be an additional retinal marker in the evaluation of ON. Retinal microcirculatory disorder detected in patients with MS is considered as evidence of microvascular dysfunction in MS (9). With this study, we aimed to determine the relationship between the number of attacks, visual evoked potential (VEP) value, visual acuity

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(VA) examination, presence of oligoclonal band (OCB), immunoglobulin G (IgG) index positivity, expanded disability status scale (EDSS) and the diagnostic importance of OCTA findings in MS patients, besides confirming the presence of vascular abnormalities in MS, OCTA findings in MS patients with and without ON.

METHOD

Forty-nine patients aged 18–60 years, who applied to Ankara Bilkent City Hospital neurology outpatient clinic between 30.06.2020–31.09.2020 and who were diagnosed with MS for at least 1 year according to the revised McDonald 2017 diagnostic criteria, were included in the study. A control group of 28 people was selected among healthy volunteers with similar age ranges.

Those with cognitive impairment were excluded from the study, as they could not cooperate with OCTA. In addition, steroid use in the last 30 days, MS attack in the last 60 days, a history of disease that may cause retinal, fovea or optic nerve damage, refractive error of more than +3 or -6 diopters, still having an ON attack, and systemic diseases that may cause vascular involvement were defined as exclusion criteria in the study. Our study was carried out in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ankara Bilkent City Hospital Ethics Committee (26.03.2020/E-1-20-408) and informed consent was obtained from all participants.

In our study, OCTA data of MS patients and healthy groups were compared. Patients were divided into groups according to whether they had a previous ON or not; ON+, ON- and healthy groups were compared among themselves in terms of OCTA parameters. The OCTA measurement results of the subgroups formed by parameters such as EDSS value, total number of attacks, disease duration, VA, OCB positivity, IgG index and VEP results were compared. Because of the fact that the patients in our study were predominantly in the relapsing remitting (RRMS) subtype and the number of patients with progressive MS was low, a comparison of OCTA measurements between the disease subtypes was not realized.

A detailed ophthalmological examination including VA, refraction evaluations, fundus examination and intraocular pressure measurements was performed by an experienced ophthalmologist in the patient and healthy group included in the study.

Optical Coherence Tomography Angiography

Optical coherence tomography angiography images were obtained via Optovue AngioVue® (Optovue, Inc., Fremont, CA) Data analysis was performed with Optovue RTVue software version 3.5. Evaluation of OCTA images was performed by an ophthalmologist specializing in OCTA.

In one eye of the patient and control group participants, superficial whole image vessel density (WI-SVD), superficial foveal vessel density (F-SVD), deep whole image vessel density (WI-DVD), deep foveal vessel density (F-DVD), retinal whole image vessel density (WI-RVD), retinal fovea vessel density (F-RVD), choriocapillaris whole image vessel density (WI-CVD), choriocapillaris fovea vessel density (F-CVD), choriocapillaris parafovea vessel density (PAR-VD) and choriocapillaris perifovea vessel density (PER-VD) values being retinal blood supply parameters were recorded via OCTA. Measurements on being ONH blood supply parameters whole image peripapillary vessel density (WI-PPVD), intradisc vessel density (ID-VD), peripapillary vessel density (PPVD), upper half peripapillary vessel density (UH-PPVD) and lower half peripapillary vessel density (LH-PPVD); finally, acircularity index (AI), foveal density (FD) and foveal avascular zone (FAZ) were made.

In our study, we targeted to present a descriptive and detailed overview of the changes in retinal and optic nerve vascular density because of MS disease.

Statistical Analysis

The data were analyzed using IBM Statistical Package for Social Sciences (SPSS) program version 23. Fitness to normal distribution was examined by Kolmogorov Smirnov and Shapiro Wilk. Independent samples t-test was used to compare the normally distributed independent paired groups, and one-way analysis of variance was used for the triplet groups. Paired samples t-test was used to compare normally distributed dependent data. Mann-Whitney U test was used to compare data that were not normally distributed and Kruskal-Wallis test was used for the triplet groups. Wilcoxon test was used to compare dependent data that did not show normal distribution. Data compatible with normal distribution were presented average ± standard deviation. Data that did not present normal distribution were given as median. Chi-square test was used to compare categorical data by group. Categorical data were presented as frequency. The level of significance was $p<0.050$.

RESULTS

In our study, one eye of 49 patients with MS and one eye of 28 healthy controls were evaluated. The gender and age distributions of the cases included in the study; while 72.2% (n=39) of the patient group was female, 56.5% (n=13) of the healthy group was male. While the age average is 37.98±9.71 in the patient group, it is 42.11±8.68 in the health group.

Disease onset age, number of attacks and EDSS information in the patient group are given in Table 1. The mean age of onset was 30.8; the mean value of the number of attacks was determined as 3.4 (minimum 0 – maximum 15). The mean EDSS value was calculated as 1.1 and the highest EDSS value was calculated as 6.

Disease-related data in the patient group are given in Table 2. Disease year is less than 10 years in 67.3% of patients. The number of attacks in 75.5% of the patients is less than 5. The EDSS of 71.4% of the patients is below 2. It is positive in 71.4% of the OCB patients. While VEP is normal in 40.8% of patients, it is impaired in both eyes in 38.8% of patients and in one eye in 20.4%. While 89.8% of the patients consist of RRMS and clinically isolated syndrome (CIS) groups, 10.2% were patients of progressive MS (PMS). Those with a history of ON constitute 46.9% of the patients. There is deterioration in VA as a sequellae in 38.8% of the patients.

In Table 3, the eyes of MS patients were compared with the eyes of the healthy group in terms of OCTA parameters. A statistically significant decrease was found in patient group with reference to healthy group in the parameters of blood build up WI-SVD (45.5 (34.2–52.6), p=0.007), F-SVD (15.7 (2.5–47.2), p=0.003), WI-DVD (43.7±5, p=0.049), F-DVD (31.7±7.1, p=0.001) ve F-RVD (30.6±6.8, p=0.013) and in the parameters of optical nerve WI-PPVD (48.2±3.4, p=0.002), ID-VD (45.8±5, p=0.015), PPVD (50.9±4.3, p<0.001), UH-PPVD (51.3±4.3, p<0.001) ve LH-PPVD (50.5 (40.1–60.1), p<0.001). In addition, enlargement in FAZ was observed in the patient group (0.3 (0.06–0.61), p=0.019). No significant difference was observed between the patient and healthy groups in other OCTA parameters examined in our study.

In Table 4, the eyes of MS patients with and without ON were compared with each other and with the healthy group in terms of OCTA parameters. When patients with ON were compared with the healthy group, a statistically significant decrease was found in the retinal blood supply parameters WI-SVD, F-SVD, F-DVD and F-RVD, and the optic nerve blood supply parameters WI-PPVD, PPVD, UH-PPVD and LH-PPVD (respectively

Table 1. Disease related parameters in MS group

	Mean	SD	Median	Minimum	Maximum
Starting age	30.8	8.9	29	15	49
Number of attacks	3.4	2.9	2	0	15
EDSS	1.1	1.5	0	0	6

EDSS: expanded disability status scale; SD: standard deviation.

Table 2. Patient group frequency distribution

		Frequency (n)	Percent (%)
Disease year	<10	33	67.3
	≥10	16	32.7
Number of attacks	<5	37	75.5
	≥5	12	24.5
EDSS	<2	35	71.4
	≥2	14	28.6
OCB	-	7	23.3
	+	23	76.7
VEP	Normal	20	40.8
	Unilaterally impaired	10	20.4
	Bilaterally impaired	19	38.8
MS sub-type	CIS+RRMS	44	89.8
	PMS	5	10.2
ON history	-	26	53.1
	+	23	46.9
Visual disturbance	-	30	61.2
	+	19	38.8

CIS: clinical isolated syndrome; EDSS: expanded disability status scale; MS: multiple sclerosis; OCB: oligoclonal band; ON: optic neuritis; PMS: progressive MS; RRMS: relapsing remitting MS; VEP: visual evoked potential.

Table 3. Patient and healthy group comparison

	Patient	Healthy	P
WI-SVD	45.5 (34.2–52.6)	48.1 (39–53,1)	0.007
F-SVD	15.7 (2.5–47.2)	21.2 (8.2–32)	0.003
WI-DVD	43.7±5	46.1±4.8	0.049
F-DVD	31.7±7.1	37.6±8	0.001
WI-RVD	50.1 (36.4–56.1)	51.3 (45.3–55.9)	0.097
F-RVD	30.6±6.8	34.7±6.7	0.013
WI-CVD	70.6 (41.9–75)	69.2 (59.3–74.2)	0.619
F-CVD	66.4 (33.5–76.4)	66.1. 46. 73.1	0.920
PAR-VD	68.9 (34.9–75.1)	67.9 (59.5–73.9)	0.828
PER-VD	71.6 (42.4–76.7)	69.9 (58.7–75.4)	0.452
WI-PPVD	48.2±3.4	50.5±2	0.002
ID-VD	45.8±5	48.9±5.6	0.015
PPVD	50.9±4.3	54.4±2.1	<0.001
UH-PPVD	51.3±4.3	54.4±2.3	<0.001
LH-PPVD	50.5 (40.1–60.1)	54.3 (50.9–59.7)	<0.001
AI	1.09 (1.05–1.28)	1.09 (1.05–1.36)	0.737
FD	51.1 (32.2–58.5)	52.1 (40.3–58.9)	0.357
FAZ	0.3 (0.06–0.61)	0.23 (0.08–0.49)	0.019

AI: acircularity index; FAZ: foveal avascular zone; FD: foveal density; F-CVD: choriocapillaris fovea vessel density; F-DVD: deep foveal vessel density; F-RVD: retinal fovea vessel density; F-SVD: superficial foveal vessel density; ID-VD: intradisc vessel density; LH-PPVD: lower half peripapillary vessel density; PAR-VD: choriocapillaris parafovea vessel density; PER-VD: choriocapillaris perifovea vessel density; PPVD: peripapillary vessel density; UH-PPVD: upper half peripapillary vessel density; WI-CVD: choriocapillaris whole image vessel density; WI-DVD: deep whole image vessel density; WI-PPVD: whole image peripapillary vessel density; WI-RVD: retinal whole image vessel density; WI-SVD: superficial whole image vessel density.

Table 4. Comparison of ON - and ON + group vs. healthy group

	Optic Neuritis -	Optic Neuritis +	Healthy	p
WI-SVD	46.2 (43–50.9) [ab]	45.5 (34.2–52.6) [a]	48.1 (39–53.1) [b]	0.021
F-SVD	15.2±4.2[ab]	15.9±8.4[a]	20.8±7[b]	0.032
WI-DVD	43.5±3.8	43.7±5.1	46.1±4.8	0.146
F-DVD	32.2±2.6[ab]	31.6±7.4[a]	37.6±8[b]	0.006
WI-RVD	50.4±3	49.5±4.1	51.2±3	0.167
F-RVD	30.8±4.7[ab]	30.6±7[a]	34.7±6.7[b]	0.048
WI-CVD	62.7±12	67±9.4	69±3.4	0.264
F-CVD	59.7±14.2	62.3±11.6	63.8±7.1	0.689
PAR-VD	61.4±13.2	65.4±9.3	67.6±3.5	0.257
PER-VD	63.2±11.8	68±9.6	69.7±3.6	0.284
WI-PPVD	48.4±2.6[ab]	48.2±3.5[a]	50.5±2[b]	0.008
ID-VD	44.9±6.3	45.9±4.9	48.9±5.6	0.050
PPVD	51.8 (49.3–54.5) [ab]	50.6 (41.1–59.5) [a]	54.2 (50.5–59.4) [b]	0.001
UH-PPVD	51.9 (48.4–53.9) [ab]	50.8 (42.1–59.9) [a]	54.4 (50.2–59.1) [b]	0.005
LH-PPVD	52.2±3.8[ab]	50.2±4.6[a]	54.4±2.1[b]	<0.001
AI	1.1 (1.05–1.1)	1.1 (1.1–1.28)	1.09 (1.05–1.36)	0.945
FD	51.8 (50.9–58.5)	50.9 (32.2–58.5)	52.1 (40.3–58.9)	0.358
FAZ	0.3 (0.06–0.4)	0.3 (0.1–0.6)	0.23 (0.08–0.49)	0.065

[a, b] There was no difference between the groups with the same letter.
AI: acircularity index; FAZ: foveal avascular zone; FD: foveal density; F-CVD: choriocapillaris fovea vessel density; F-DVD: deep foveal vessel density; F-RVD: retinal fovea vessel density; F-SVD: superficial foveal vessel density; ID-VD: intradisc vessel density; LH-PPVD: lower half peripapillary vessel density; PAR-VD: choriocapillaris parafovea vessel density; PER-VD: choriocapillaris perifovea vessel density; PPVD: peripapillary vessel density; UH-PPVD: upper half peripapillary vessel density; WI-CVD: Choriocapillaris whole image vessel density; WI-DVD: deep whole image vessel density; WI-PPVD: whole image peripapillary vessel density; WI-RVD: retinal whole image vessel density; WI-SVD: superficial whole image vessel density.

Table 5. Variation of ONH vascular densities according to disease parameters

	EDSS <2	EDSS ≥2	p	<5 Attacks	≥5 Attacks	p	
WI-PPVD	48.7±3.2	46.9±3.7	0.089	49±2.9	45.9±3.8	0.005	
ID-VD	46.5±4.9	44±4.7	0.107	46.1±5	44.9±4.8	0.455	
PPVD	51.3±4.2	49.8±4.6	0.257	51.7±3.8	48.3±4.8	0.015	
UH-PPVD	51.7±4.4	50.5±4.1	0.419	52.1±4	48.9±4.6	0.025	
LH-PPVD	51±4.1	48.9±5.3	0.148	51.3±3.9	47.5±5.3	0.011	
	<10 year	**≥10 Years**	**p**				
WI-PPVD	49.1±2.8	46.5±3.9	0.025				
ID-VD	45.6±5	46.2±4.9	0.683				
PPVD	52±3.4	48.6±5.2	0.028				
UH-PPVD	52.4±3.5	49.1±5.1	0.031				
LH-PPVD	51.4±3.7	48.2±5.3	0.018				
	VA impaired	**VA normal**	**p**	**Normal VEP**	**Unilaterally impaired VEP**	**Bilaterally impaired VEP**	**p**
WI-PPVD	46.8±3.4	49.1±3.1	0.020	50±3.2[a]	46.7±3.7b	47.2±2.7[b]	0.009
ID-VD	46.2±5.1	45.6±4.9	0.677	45.1±5.2	45.8±5.9	46.5±4.3	0.667
PPVD	48.8±4.5	52.2±3.7	0.006	53.4±4[a]	49±4.5[b]	49.2±3.3[b]	0.002
UH-PPVD	49.3±4.6	52.6±3.6	0.007	53.6±4.3[a]	49.9±4.4[b]	49.7±3.2[b]	0.005
LH-PPVD	48.4±4.7	51.7±4	0.011	53±4.1[a]	48.1±4.9[b]	48.9±3.5[b]	0.002
	OCB -	**OCB +**	**p**	**IgG index -**	**IgG index +**	**p**	
WI-PPVD	49.6±2.5	45.8±3.6	0.013	49±3	46.4±4.3	0.067	
ID-VD	45.9±4.2	42.9±3.5	0.166	46.3±4.3	42.8±4.2	0.043	
PPVD	52.3±3.1	48.8±6.4	0.104	51.5±3.8	49.3±6.1	0.233	
UH-PPVD	53±2.8	49.7±6.4	0.106	52.2±3.7	50±6	0.229	
LH-PPVD	51.5±3.9	47.8±6.6	0.128	50.9±4.1	48.5±6.3	0.290	

[a, b] There was no difference between the groups with the same letter.
EDSS: expanded disability status scale; ID-VD: intradisc vessel density; LH-PPVD: lower half peripapillary vessel density; OCB: oligoclonal band; PPVD: peripapillary vessel density; UH-PPVD: upper half peripapillary vessel density; VA: visual acuity; VEP: visual evoked potential; WI-PPVD: whole image peripapillary vessel density.

p1=0.021, p2=0.032, p3=0.006, p4=0.048, p5=0.008, p6=0.001, p7=0.005 ve p8<0, 001). The difference is due to the fact that the ON+ mean value was lower than the healthy group. ON- patient group is not different from other groups. No significant difference was observed between the patients who had ON and who had not ON in other OCTA parameters examined in our study.

In Table 5, the mean vascular densities of the patients for ONH were compared according to EDSS, number of attacks, year of disease, VA, VEP examinations and CSF findings. There was no difference in ONH blood supply parameters according to EDSS value in patients. However, statistically significant decreases in intensity were observed in WI-PPVD, PPVD, UH-PPVD and LH-PPVD measurements in patients with more attacks and years of illness (according to the number of attacks and respectively p1=0.005, p2=0.015, p3=0.025, p4=0.011, and according to the disease year and respectively p1=0.025, p2=0.028, p3=0.031, p4=0.018).

Patients were divided into two groups according to VA examination and compared in terms of OCTA parameters. A significant decrease was detected in WI-PPVD, PPVD, UH-PPVD, LH-PPVD in the group with impaired VA compared to the normal group (respectively p1=0.020, p2=0.006, p3=0.007, p4=0, 011). Whereas there was no significant difference between the VEP unilateral and bilateral impaired groups, when the patients were divided into three groups according to their VEP findings as normal, unilaterally disordered and bilaterally disordered; WI-PPVD, PPVD, UH-PPVD, LH-PPVD were measured lower in both groups compared to the healthy group (respectively p1=0.009, p2=0.002, p3=0.005, p4=0, 002).

When the patients were divided into two groups according to their OCB positive and negative status, WI-PPVD was lower in the OCB positive group (45.8±3.6, p=0, 013). The relationship between index positivity and OCTA parameters was also evaluated, and the mean value of ID-VD (42.8±4.2, p=0.043) in the positive group was lower than the index negative group.

DISCUSSION

In our study, we demonstrated the presence of a significant decrease in the vascular densities of the optic nerve, superficial and deep retinal layers, especially in optic nerve head vascular density, in MS patient compared to healthy controls.

Retinal and cerebral microcirculation present similar features. Both systems contain autoregulation mechanisms to maintain constant blood flow. The blood-retina barrier is similar in structure and function to the blood-brain barrier (10). It was reported that retinal perfusion impairment correlates with cerebral hypoperfusion, more pronounced in demyelinated areas (11). Optical coherence tomography angiography studies have shown that ischemic findings in the DCP, impaired perfusion and neovascularization play an important role in the visual prognosis of patients (12). Therefore, vascular changes in the retina can be used to evaluate the extent of cerebral neuronal and microvascular damage and the progression of neurodegenerative diseases. In the light of this information, it has become possible to comment on future visual performance in patients after ON attack (13). In consideration of the difficulty of accessing the cerebral vascular system, easily accessible retinal measurements can be a guide in neurodegenerative diseases (14). Early detection of microvascular dysfunction can provide rapid diagnosis and treatment in these diseases which are usually diagnosed at the stage of diffuse neuronal damage.

It is thought that cerebral hypoperfusion may play a role in the initiation and progression of the neurodegenerative process (15). Studies have demonstrated that the progression of MS patients with vascular risk factors is faster than the group without (16). In addition to the views that argue that demyelination develops due to vascular dysfunction, there are also studies that argue the opposite. According to these; the demyelinating process spreads to the optic nerve and retinal ganglion cell layer by trans-synaptic degeneration and then ocular vascular endothelial damage occurs (17). Autoregulation mechanisms that come into play secondary to the decreased metabolic activity as a result of the decrease in the number of nerve fibers in ONH and retinal nerve fiber layer (RNFL) may explain the decrease in ONH perfusion (15,18). In other words, it is suggested that the retinal hypoperfusion observed in MS is actually a result of the neurodegenerative process (19). Retinal nerve fiber layer involvement due to retrograde axonal degeneration occurring in optic nerve axons is more pronounced in patients with a history of ON than in other MS patients. Therefore, the perfusion effect in ON+ eyes is expected to be more pronounced than in non-ON+ eyes. It has been demonstrated that retinal microcirculation is impaired in MS patients for whatever reason, and this indicates microvascular dysfunction in MS (9).

Ulusoy et al. found the whole view, upper and lower half-area, parafoveal and perifoveal vessel densities (VD) in the SCP to be significantly lower in RRMS patients with and without ON than in the normal group. In DCP, although all parameters were lower in the patient group, no statistical significance was found. Optic disc parameters were found to be significantly lower in the inferior and temporal VD patient group. There was no significant difference in superficial and deep capillary plexus between ON+ and ON- groups; however, more unperfused area was noted in the ON+ group than in the ON- group in the optic disc area. In addition, while a correlation was observed between OCTA parameters and disease duration, no correlation was found with EDSS scores (20). In our study, when the patients were compared with the healthy group, regardless of whether they had ON or not, significantly lower vascular density was detected statistically in all of the sub-parameters examined in the periparillary capillary layer (WI-PPVD, ID-VD, PPVD, UH-PPVD ve LH-PPVD), as well as in some of the superficial and deep retinal vascular layers (WI-SVD, F-SVD, WI-DVD, F-DVD ve F-RVD). Statistically significant enlargement was detected in FAZ. When our patients are divided into groups as ON+ and - and compared with each other and with the healthy group, a statistically significant decrease was detected in the ON+ group in all of the other ONH blood supply parameters, except for ID-DD, and in some of the superficial and deep vascular plexus measurements (WI-SVD, F-SVD, F-DVD, F-RVD) compared to the healthy group. In the ON- patient group, although the measurement results were lower than the healthy group, no statistically significant difference was observed. In addition, our EDSS and disease year related data were also consistent with this study. In another study, it was reported that the ONH flow index (FI) was significantly reduced in all MS patients compared to healthy controls, more significantly in those with ON+ (21). It was shown in many similar studies that MS patients have decreased vascular plexus densities or flow indices in both ONH and macula compared to the healthy population (22).

Wang et al. found that FI of ONH was significantly lower in ON+ patients compared to controls and ON– groups. As a result of the study, no significant difference was found in parafoveal FIs between these three groups. Therefore, they argued that parafoveal FI is insensitive to MS severity, unlike other OCTA parameters (18). Lanzillo et al. evaluated patients with stable MS after 1 year of follow-up and reported an increase in parafoveal vascular density. In the study of Ulusoy et al., the finding that the VD in the foveal and parafoveal regions was significantly lower in MS patients may suggest that VD is more indicative than FI. In our study, PAR-VD measurements were made to evaluate the parafovea and no difference was detected between the patient and the healthy group in this parameter. In another study, a decrease in parafoveal superficial and deep capillary plexus density compared to healthy controls was noted in

MS patients. With decreased metabolic demand, flow decreases in the SCP and in the DCP blooded by anastomoses (15). In our study, in line with this information, it was observed that the involvement in the deep retinal layer often accompanied that in the superficial layer.

In the literature, it has been shown that, the effect on DCP and SCP intensities increases significantly as VA deterioration and the frequency of ON attacks increase in patients with neuromyelitis optica spectrum disorder (NMOSD) (23). Macular and peripapillary vascular density reductions have been reported even in cases of NMOSD with a subclinical course (24). In our study, a statistically significant decrease in vascular density in some superficial and deep retinal layers and peripapillary capillary layer was noted in patients who had ON, compared with those who did not, that is compatible with the literature. However, the patients in our study were not grouped in terms of the number of ON attacks, only those with and without a history of ON were differentiated. Therefore, it could not be measured whether ON attack frequency and parameters were affected; this can be considered as one of the limitations of this study.

In another study realized in order to evaluate SCP in patients with ON + and -, it was reported that the difference in density of SCP between the two eyes in patients with a history of ON was greater than in patients with MS without ON. The timing of OCTA measurements after ON is important, as the change in SCP density can be detected at least 1 year after ON (25). The fact that we did not exclude patient whose time between the ON attack and OCTA examiation was less than 1 year from this comparasion can be considered as one of the limitations of the study. However, the involvement of SCP in our ON+ patient group could be clearly demonstrated; when the healthy group was compared, a significant decrease was found in the WI-SVD, F-SVD parameters.

Lanzillo et al. evaluated patients with stable MS after 1 year of follow-up and reported an increase in parafoveal VD. This increase in intensity was thought to be a consequence of the treatment. In addition, parafoveal VD was negatively correlated with EDSS (26). However, there is a need for more comprehensive studies with longer follow-up periods for the purpose of using the VD change as a biomarker in the follow-up of the disease and the quantitative assessment of the patient's response to treatment. Unfortunately, we do not have data on this subject, since control OCTA was not performed in our study for follow-up purposes. There are other examples of literature showing that the reduction in retinal VD correlates with an increase in EDSS (27). Murphy et al. showed that superficial VD was negatively associated with EDSS (28). In the study of Lanzillo et al., an inverse correlation was found between whole image and parafoveal VD and EDSS, but no correlation was observed between disease duration and OCTA parameters (29). In another study, it was found that blood flow velocities were not associated with EDSS scores or disease duration (19). When we compared the vascular measurements of ONH by dividing the patients into two groups as those with EDSS <2 and those with ≥2 in our study, no statistically significant relationship could be found, but we think that the fact that most of our patients consisted of EDSS <2 patients may have an effect on these results. In our study, it was demonstrated that there was a negative correlation between ONH parameters other than ID-VD and disease year; a decrease in these parameters was found in the group with more years of disease. It is a fact that studies with large patient populations are necessary to clarify this relationship because we have a small number of patients with long disease duration.

In our study, the relationship of OCTA parameters with OCB positivity and IgG index levels was also evaluated and in OCB + patients statistically significant low level with reference to the - group was found in the WI-PPVD values; in those with high IgG index, a statistically significant low level was found in the ID-VD values. No information related to these data was found in the literature. We think that understanding whether our data is significant or not will only be possible with the increase in the number of similar studies on the subject in the future.

There are many studies that suggest that evoked potentials may contribute to the early recognition of irreversible damage such as demyelination, axon loss or conduction block (30). In our study, ONH blood flow parameters were found to be significantly lower in patients with unilateral or bilateral VEP dysfunction compared to the healthy group.

As a result; in our study, a statistically significant decrease was observed in many OCTA parameters examined, especially in ONH vascular density in MS patients. The available data on how the patient and some clinically-related parameters that make up the content of our study are reflected in the OCTA findings are limited and studies generally have small sample groups. Therefore, there is a need for standardized studies with a large patient population in the future with OCTA.

Based on the knowledge that retinal vascular changes are a precursor of central involvement in the light of the existing literature, our opinion is that OCTA will have an important place in the follow-up of progression and evaluation of treatment response in MS patients in the future. It would be a correct approach not to consider OCTA as a test that only evaluates retinal vascular involvement in ON cases, but as a potential biomarker that facilitates the follow-up of the neurodegenerative process from the beginning.

Ethics Committee Approval: The study was approved by the Ankara Bilkent City Hospital Ethics Committee (26.03.2020/E-1-20-408).

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