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Assessment of macular microcirculation in patients with multiple sclerosis by swept-source optical coherence tomography angiography

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ABSTRACT

Objective: To investigate the changes in the retinal microcirculation in multiple sclerosis (MS) patients by swept-source optical coherence tomography angiography (SS-OCTA).

Patients and Methods: Thirty-seven patients with relapsing-remitting MS and 40 healthy volunteers were included into this cross-sectional study. Clinical history, Expanded Disability Status Scale and duration of MS were collected. SS-OCTA by deep range imaging (DRI) OCT measurements were performed on all subjects. Macular perfusion parameters including superficial and deep foveal avascular zones (FAZs, FAZd, respectively) (%), vascular densities of superficial capillary plexus (SCP) (%), deep capillary plexus (DCP) (%) and choriocapillaris (CC) (%) were compared with healthy subjects.

Results: Vascular densities of SCP, DCP and CC were found to be statistically lower in the study group compared to the control group ($p = 0.02$, $p = 0.03$, $p = 0.03$, respectively). FAZs and FAZd, areas were significantly higher in the study group ($p = 0.02$, $p = 0.02$, respectively). Central macular thickness and subfoveal choroidal thickness were significantly lower than in the control group ($p = 0.015$, $p = 0.047$, respectively).

Conclusion: Evaluation of retinal blood flow in patients with MS is useful both for understanding the physiopathology of the disease and in the clinical follow-up.

Keywords: Multiple sclerosis, Retinal vasculature, Vascular density, Macular perfusion, Swept-source optical coherence tomography angiography

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic and demyelinating disease in the central nervous system (CNS), associated with autoimmune mechanisms [1]. The primary cause of MS is unclear, but immunologic, environmental, infectious and genetic factors may contribute to the development of MS [2]. Cell-mediated and humoral immune systems agents attack CNS myelin or oligodendrocytes, causing neurodegeneration and neurological disability. Approximately, 2.5 million people worldwide are affected, most of them between the ages of 20-40 [3].

Multiple sclerosis especially affects the periventricular area, pons and spinal cord on the CNS [4]. Weakness in the extremities, sensory symptoms, ataxia, cognitive complaints and visual disturbance may occur as a result of axonal damage. Ophthalmological signs are impaired visual acuity, visual field defect, internuclear ophthalmoplegia or a relative afferent pupillary defect in MS. Ocular related symptoms such as optic neuropathy, retinal vasculitis and intermediate uveitis may occur in the course of MS [5].

The McDonald criteria with information from magnetic resonance imaging (MRI), examination of the cerebrospinal fluid, potential evoked visual tests, optical coherence tomography (OCT) and cognitive tests are used for the diagnosis of MS [6]. Disease-modifying therapies (DMTs) such as interferon beta-1a, interferon beta-1b, teriflunomide, daclizumab, natalizumab, fingolimod, etc. may be used after acute attacks [7].

Vascular structures may be affected in MS pathophysiology [8]. Cerebral hypoperfusion was reported in MS patients [9,10]. Recently, some studies showed retinal vascular density (VD) reduction in MS [11-13]. However, there is still a need for further investigation regarding vascular changes in MS.

Retinal micro vascularization can be evaluated quantitatively with developing technology. Swept-source optical coherence

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tomography angiography (SS-OCTA) devices can provide detailed imaging of the retinal vascular network by sequential optical coherence scans of a particular retinal region, based on the motion contrast of erythrocytes in vascular structures and processing [14]. It evaluates retinal micro vascularization non-invasively, without the necessity for intravenous contrast material which can cause adverse reactions [15]. There are a few studies comparing the microvascular findings of MS patients with the healthy group using swept-source deep range imaging (DRI) OCT Triton device in the literature [16,17]. The aim of this study is to measure macular perfusion in patients with MS using OCTA and to compare our results with the existing literature.

2. PATIENTS and METHODS

Study participants

This retrospective and cross-sectional study was performed on MS patients who had referred to the Selcuk University Faculty of Medicine, Department of Ophthalmology from January 2020 to March 2020. The research protocols were applied in accordance with the principles of the Declaration of Helsinki and was approved by Selcuk University's Institutional Review Board and Ethics Committee (Protocol No: 2020/177). All participants gave written informed consent.

Clinical data

Patients with relapsing-remitting MS applying to the Faculty of Medicine, Department of Neurology, Selcuk University, were advised routine eye examinations according to the 2010 McDonald criteria [6]. Those aged 18-65 and with an Extended Disability Status Scale score below 6 (mobile without support) were enrolled into the study. Detailed ophthalmological examination was performed including auto refractometer (Tonoref III, Nidec Co. Ltd, Aichi, Japan) measurement, best corrected visual acuity (BCVA) as measured on the standard Snellen chart, intraocular pressure (IOP) (mmHg) measured by Goldmann applanation tonometry, slit lamp and fundus examination using a +90 D lens after pharmacological dilatation with 1% tropicamide for each patient. After physical examination, OCTA was performed in participants with full vision and no pathological findings were determined in the examination. The exclusion criteria were having an additional systemic disease other than MS, BCVA under 20/50, high refractive correction (higher than +3 or – 3 dioptre spherical equivalent), low quality images in OCTA, any ophthalmological pathology (Glaucoma, diabetic retinopathy, hypertensive retinopathy, retinal vascular diseases, uveitis, amblyopia etc.), history of intraocular surgery and history of optic neuritis in the 6 months prior to enrolment in the study. After the evaluation of the including and excluding criteria, 37 MS patients were included in this study. The control group consisted of 40 age and sex matched healthy individuals. The right eye of each individual was assessed.

Optical coherence tomography angiography technique

We obtained OCTA images with the SS DRI OCT Triton (Topcon Corp, Tokyo, Japan) device. The participants were then asked to rest for ten minutes. All parameters were measured by one experienced operator (S.E.) using SS-OCTA which operates a 1.050 nm wavelength light source and 100,000 A Scan/s [18]. We used OCTA function to obtain 6 × 6 mm cubes focused on the fovea (Figure 1). The OCTA software (IMAGEnet 6 V.1.14.8538) system did the macular segmentation which consists of four 'en face' OCT slabs: (1) superficial vascular complex (SVC) is defined as from 2.6 µm below the internal limiting membrane (ILM) to the 15.6 µm below the inner plexiform layer (IPL); (2) deep vascular complex (DVC) is defined as from IPL offset of 15.6 µm to the IPL offset of 70.2 µm and (3) choriocapillaris vascular complex (CC) is identified as from BM to 10.4 µm under the Bruch's membrane (BM) [19].

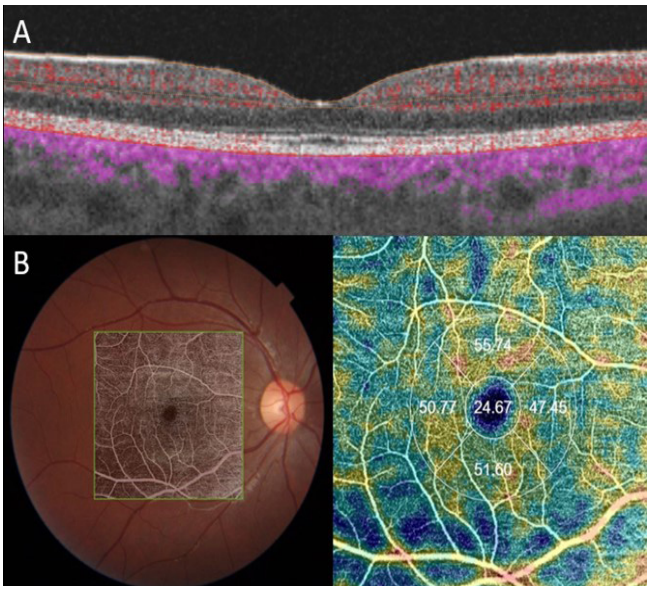

Figure 1. *Image of optical coherence tomography angiography measurement in 6x6mm area with grid centered in macula. Superficial vascular plexus density is shown with color lines (A). On density map with grid divided in five areas; central, nasal, interior, temporal and superior with number of percentages of vessel density are demonstrated (B).*

GNU Image Manipulation Program (GIMP) 2.8.14 was used to analyse quantitatively the VD of the SVC, DVC and CC as VDs, VDd and VDc, respectively. Superficial foveal avascular zone (FAZs) and deep foveal avascular zone (FAZd) were measured separately. VD was measured as the percentage of the vascularized tissue in the grid centred in macula. The subfoveal choroidal thickness (SFCT) and central macular thickness (CMT, respectively) analyses were performed for the eyes of all subjects in 9 regions of the macula. Macula sections were identified objectively with radii of 0.5 mm (center 1 mm), 0.5 to 1.5 mm (inner ring), and 1.5 to 3.0 mm (outer ring). CMT and SFCT values were obtained from central 1 mm measurements. Only the right eye of each subject enrolled in the study, was included in the analysis. All measurements were performed at the same time interval of the day. Two experienced observers examined two consecutive scans of a subject to detect interobserver reproducibility at different

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times. The mean value of two independent measurements was used for each OCTA parameter. Patients with any pathologic condition detected in structural OCT scans, or if the Image Quality Index (IQI) was under 70, were excluded to avoid inaccuracy in the measurements due to image artifact [15].

Statistical Analysis

Data on demographic features, VDs of three vascular plexus, FAZs, FAZd, CMT, SFCT and disease duration were collected as mean ± standard deviation (SD). Normality for each variable for groups was measured using the Kolmogorov–Smirnov test. Categorical data were compared between groups using Pearson's chi-square test; independent samples test was used for variables with normal distribution and the Mann-Whitney U test was used for variables with abnormal distribution for comparison of means between groups using Statistical Package for the Social Sciences (version 26.0; SPSS Inc., Chicago, IL). Spearman correlation coefficient was used for correlation between variables. P values of less than 0.05 were noted as statistically significant.

3. RESULTS

There were 37 MS patients with an average age of 36.2 ± 12.1 years. The healthy control group was comprised of 40 individuals with a mean age of 35.6 ± 14.6 years. The mean onset time of the disease in the study group was 22.4 ± 5.1 (months). The age and gender distribution of the participants in both groups did not show any significant difference significantly ($p > 0.05$; Table I). Demographic data of MS patients and healthy controls and OCTA parameters are demonstrated in Table I.

FAZs and FAZd values were increased significantly in MS patients compared to the control group (p=0.026; p=0.022, respectively). VDs central value was found to be significantly decreased (p=0.02) in the MS cases compared to the control group. In the case group, the VDs superior and VDs temporal values were significantly lower than in the control group ($p = 0.04$; $p = 0.01$, respectively). However, VDs inferior and VDs nasal value did not change significantly ($p>0.05$).

VDd central value was found to be significantly lower than in the control group ($p = 0.03$). In addition, VDd inferior and VDd nasal values were significantly lower in MS cases than in the control group ($p = 0.01$; $p = 0.02$), while VDd superior and VDd temporal values did not vary significantly ($p>0.05$).

In MS patients, VDc central, VDc superior, VDc temporal, VDc inferior and VDd nasal values were significantly lower than in the control group ($p<0.05$, each of them). CMT and SFCT values were significantly lower in the MS group ($p = 0.015$; $p = 0.047$, respectively). Also, CMT and SFCT values correlated with the duration of MS onset time ($r= -0.335$; $p = 0.043$ and $r= -0.452$; $p=0.005$).

Table I. *The demographic characteristics and OCTA parameters of patients with multiple sclerosis and healthy eyes (Control group).*

		MS group				Control group				p	
		Mean±ss /n-%			Median	Mean±ss /n-%			Median		
Age		36.2	±	12.1	31	35.6	±	14.6	28	0.609	m
Gender	Female	23		62.2%		24		60%		0.846	X^2
	Male	14		37.8%		16		40%			
FAZs		175	±	57.4	164.9	150.5	±	67.1	136.2	0.026	m
FAZd		258.2	±	59.7	244.7	240.1	±	124.2	200.9	0.022	m
VDs Central		20.4	±	4.4	21.5	24	±	7.3	22.8	0.02	m
VDs Superior		48.9	±	2.1	48.2	49.5	±	2.8	49.8	0.048	m
VDs Temporal		43.6	±	3.1	42.4	45.4	±	3.5	44.4	0.011	m
VDs Inferior		46.1	±	2.7	44.9	47.8	±	3.8	47.7	0.077	m
VDs Nasal		43.4	±	2.9	43.6	44.6	±	3.6	45.1	0.097	t
VDd Central		18.8	±	6.2	18.7	22.1	±	8	21	0.03	m
VDd Superior		50.6	±	1.8	50.8	50.9	±	3.3	50.9	0.526	m
VDd Temporal		45.5	±	2.7	44.7	46.7	±	3.7	46.5	0.131	m
VDd Inferior		47.2	±	2.8	47	49.1	±	3.6	48.9	0.016	m
VDd Nasal		44.8	±	3.4	45.6	46.8	±	4.1	47.5	0.02	t
VDc Central		22.2	±	4.5	19.9	31.2	±	15.2	23.9	0.034	m
VDc Superior		49	±	2	48.1	50.5	±	3.5	50.4	0.009	m
VDc Temporal		44.7	±	2.2	44.6	47.1	±	5.0	46.8	0.043	m
VDc Inferior		46.5	±	2.7	46.1	49.1	±	4.7	48.3	0.012	m
VDc Nasal		43	±	2.7	43.7	46.2	±	5.4	45.7	0.004	m
CMT		177.9	±	13.1	178	189.1	±	21.8	183	0.015	m
SFCT		250.5	±	43.5	256	298.6	±	87.7	277	0.047	m

m: Mann-Whitney U test / t: Independent Sample t Test / X^2: Chi-squared test. SD: standard deviation; FAZs: superficial foveal avascular zone; FAZd: deep foveal avascular zone; VDs: superficial vascular density; VDd: deep vascular density; VDcc: choriocapillaris vascular density; CMT: central macular thickness; SFCT:subfoveal choroidal thickness. Italicized bold values represent p<0.05.

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4. DISCUSSION

The development of the retina and optic nerve from the diencephalon during the embryological development reveals the similarity of the retina to the cerebral cortex [20]. Thus, pathophysiological changes in the CNS may affect the optic nerve and retina. Retinal microcirculation and CNS vascular structures have similar features. Neuronal metabolic activity plays an essential role in the autoregulation mechanism of these vascular structures with high oxygen concentration [21]. MS, is characterized by autoimmune, demyelinating and chronic inflammatory processes, which can cause vascular dysfunction along with neuroaxonal degeneration. Endothelial dysfunction as a result of chronic inflammation is thought to cause impairment in the vascular system [22]. In the past, parameters that could be used in the diagnosis and follow-up of MS patients were evaluated with the OCT devices [23]. In recent years, it has been aimed to observe vascular change in MS patients with the OCTA device, which provides retinal microvasculature evaluation. Researchers had focused on parameters that could be used in the follow-up of MS patients [12,24-29]. The present study aims to examine the changes in macular perfusion based on the different results seen in the literature through OCTA.

The SVC and DVC creates a capillary free zone in the fovea which is associated with ischemia [30]. The current study showed statistically significant FAZs and FAZd enlargement in MS patients. However, Yilmaz et al., did not report any difference in FAZ metrics in the eyes of MS patients [11]. On the other hand, Ulusoy et al., found enlargement of the FAZ, correlated by the reduction in the SVC [26]. Similar to our work, Alzheimer's disease, which is a neurodegenerative disease such as MS, FAZ enlargement, was shown as a result of decreased blood flow [31]. Impaired vascular blood flow might induce FAZ enlargement because of decreased neuron metabolism. It was observed that the increase in the FAZs area was more significant than the FAZd. Because the retinal nerve fibre layer and ganglion cell layer are supplied by the SVC, it is expected to be more affected in MS patients.

VDs values of the central, temporal and superior sectors were statistically significantly lesser than the VD values of the controls. Farci et al., reported significant reduction in all sectors of the SVC [32]. In addition, Ulusoy et al., showed a statistically significant decrease in the superior and inferior sectors of the SVC [26]. In the current study, it was observed that the superior and temporal sectors of the SVC seemed to be primarily affected by MS. There was no significant difference in the inferior and nasal sectors of VDs in the eyes of MS patients than in those of the control group. This is because the mean follow-up period of MS patients included in the study was limited to a short period. If this period had been longer, we could have found a decrease in all sectors of the VDs.

The current study demonstrated a significant decrease in the VD values of the central, inferior and nasal sectors in the VDd, while we did not see any significant change in the superior and temporal sector density values. Similarly, Yilmaz et al. and Feucht et al., found a significant reduction in the VDd values [11,27]. However, Ulusoy et al., did not report any statistical difference, although they found a decrease in VDd [26]. In addition, Farci et al. and Murphy et al., did not detect a significant change in the DVC capillary flow density [28,32]. In another study, it was stated that VD of DVC in MS patients with optic neuritis history were significantly decreased than those in eyes of MS patients without optic neuritis [29]. Although, different results were seen in the literature, we thought that the cerebral impaired vascular architecture in MS patients could affect the VDd in addition to diminished SVC blood flow [33].

In terms of VDc, this study showed a significant decrease in all sectors of MS patients compared to the control group. Cennamo et al., observed that VDc values did not change significantly in the MS groups included [34]. However, Feucht et al., reported that increased VDc values are associated with ongoing inflammatory disease activity [27]. Contrary to Feucht's results, we did not see an increase in VDc. Cerebral hypoperfusion may play a role in the pathogenesis of MS lesions. The current study is the first to show a decrease in all sectors of VDc. Concerning CMT and SFCT values, we found a significant reduction in MS patients. The decrease in CMT was consistant with the results of Waxman et al. and Britze et al. [35,36]. Furthermore, it has been reported that thinning in choroidal thickness is associated with the duration of MS disease [37]. The current data has also supported that there is a relationship between CMT and SFCT with disease duration.

The present study had some important limitations. The small sample size and short follow-up time were the features most lacking. The study did not include the patients'medication data that could alter the results. Additionally, since, cerebral perfusion was not measured, its relationship with retinal microvasculature could not be examined. Future studies should focus on the correlation between cerebral and retinal vascular values to study new follow-up parameters for MS.

The following conclusions can be drawn from the present study: that VD of SVC, DVC and CC measured by SS DRI OCT Triton device are reduced in the eyes of MS patients. In addition, CMT and SFCT values decreased in MS disease and correlated with MS disease onset. OCTA parameters can be a useful additional retinal marker in MS. Further detailed research is needed to investigate the value of OCTA in MS patients and to correlate with ongoing disease activity and cerebral perfusion.

Compliance with Ethical Standards

Ethical approval: The research protocols were applied in accordance with the principles of the Declaration of Helsinki and was approved by Selcuk University's Institutional Review Board and Ethics Committee (Protocol No: 2020/177). All participants gave written informed consent.

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Conflict of interest: Authors have no conflict of interest to declare.

Authors' contributions: SE and YK : Concept, design, data collection and analysis, YK and HG: Supervision, SE and YK: Literature search and writing, SE: Critical review. All authors critically revised the manuscript, approved the final version to be published, and agreed to be accountable for all aspects of the work.

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