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The Evaluation of Choroidal Vascular Changes Associated with Vascular Dysregulation in Patients with Multiple Sclerosis Using Enhanced Depth Imaging Optical Coherence Tomography

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Abstract

Purpose: To evaluate the choroidal thickness (CT) in patients with Multiple Sclerosis (MS) using enhanced depth imaging optical coherence tomography (EDI-OCT) and comparing it with healthy subjects.

Material/Methods: Sixty-four eyes of 32 patients with MS (22 women, 10 men, mean age: 37.5 ± 8.21 years) were enrolled in this study. Their choroidal thickness was measured using EDI-OCT, and compared with healthy subjects. CT was measured at fovea and at four extrafoveal points.

Results: The mean subfoveal choroidal thickness was 327.01 ± 64.60 μm in MS patients and 365.3 ± 99.14 μm in controls (p=0.019). Significant differences were found at points temporal 500 μm, temporal 1000 μm and nasal 500 μm to the fovea between patients and control group (p=0.018, 0.003 and 0.03, respectively).

Conclusions: Patients with MS had thinner choroids when compared to normal subjects. The decrease in mean choroidal thickness in MS patients compared to controls may be related to vascular dysregulation or inflammatory pathology of MS. Further prospective studies are needed to evaluate the choroidal thickness in MS patients.

Keywords: Choroidal thickness; Endothelin-1; Enhanced depth imaging optical coherence tomography; Multiple sclerosis; Vascular dysregulation

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS). The pathogenetic changes in MS result from the remodelling of the blood-brain barrier associated with endotheliopathy due to the effect of activated $CD4^+$ T-cells [1-5]. In the initial phases, endotheliopathy caused by the adhesion of activated T lymphocytes is observed within the blood-brain barrier, and these lesions can lead to vascular dysregulation [2,6-8]. Vascular dysregulation leads to excessive vasoconstriction or insufficient vasodilatation, resulting in vasospasm mediated by endothelin-1 (ET-1) [8].

ET-1 is mainly synthesized by human vascular endothelial cells, and is a powerful physiological vasoconstrictor widely distributed in the body, including the glia, neurons, and eye in the CNS [9]. It contributes to the basal constrictive tone of systemic vessels and may contribute to autoregulation of ocular blood flow and ocular vessel tone, especially in the choroid and optic nerve head. In MS, ET-1 not only regulates the vascular wall tension, but may also act as a proinflammatory mediator, including its effect on the proliferation of astrocytes with an associated increase in the production of metalloproteases, which are involved in the remodeling of the extracellular matrix and the blood-brain barrier [5,8,9].

Haufschild et al [10] reported increased ET-1 plasma levels in MS patients. This might decrease ocular blood flow and contribute to the loss of retinal ganglion cells and their axons [1], to subclinical visual field defects [12], to narrower retinal arterioles and wider venules [13] and to increased rigidity of the retinal vessels [14].

The choroid, being the most vascular tissue of the eye, plays a very important role in pathogenesis of a variety of chorioretinal disorders. The retinal and choroidal pathologic changes are evaluated routinely by fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT) in daily practice. Indocyanine green angiography has been used for many years to analyze the perfusion of the choroid; however, it does not provide any structural analysis of this deep tissue [15].

Recently the introduction of the spectral-domain OCT (SD-OCT) improved not only retinal image resolution, but some instrumental setups now allow a better visualization of the choroid as well. The Spectralis (Heidelberg Engineering, Heidelberg, Germany) incorporating software, with its enhanced depth imaging (EDI) technology allows for the good quality imaging of the choroid, permitting the qualitative and quantitative analysis of this layer. EDIready devices gained great significance in the detection of inflammatory processes involving the choroid [16-19].

In this present study, we hypothesized that vascular dysregulation and vasoactive inflammatory mediators produced in the course of MS patients might yield changes in choroidal blood flow and thickness. We use EDI SD-OCT to examine the choroid of MS patients and to compare the findings with age-matched, sex-matched, and axial length-matched healthy subjects.

Material and Methods

This comparative study consisted of 32 patients (22 female and 10 male) with precise MS diagnosis according to McDonald [20] criteria that were referred from neurology clinics and 32 (20 female and 12 male) control cases. The controls consisted of patients who had been admitted to the ophthalmology outpatient department for routine ophthalmic examination. All patients in the control group had no ocular disease and were age-, sex- and axial length-matched with the study group. Procedures adhered to the tenets of the Declaration of Helsinki, and the Local Ethics Committee approved the protocol.

Inclusion criteria for MS patients; We included MS patients who fulfilled the following criteria; diagnosed according to McDonald criteria; age older than 18 years; best-corrected visual acuity over 0.2 (on the Snellen visual acuity scale); refractive error within a ± 5 spherical diopter range, with less than ± 3 cylinder diopters.

Inclusion criteria for control cases were age older than 18 years, best-corrected visual acuity over 0.8 or better (on the Snellen visual acuity scale), refractive error within a ± 5 spherical diopter range, with less than ± 3 cylinder diopters.

Exclusion criteria for patients with MS and control cases.

- Patients with congenital or acquired retinal disorder, previous ocular trauma or ocular surgery,
- Patients with a history of any ocular inflammatory disease such as uveitis,
- Patients with a history of any chronic drug use, including analgesics, sildenafil, decongestants and antihistamines,
- Patients with glaucoma,
- Patients with MS that had acute episode of ON,
- Patients with diabetes mellutis, systemic hypertension, cardiovascular disease, any other coexisting systemic disease, were excluded due to the possible influence on choroidal thickness [21-23].
- Patients not sufficiently cooperative for OCT measurements, and all eyes with a refractive spherical equivalent (myopic or hyperopic) >5 D or with high astigmatism (>3 D) were also excluded from this study (In order to reduce the effect of refractive error on OCT testing),
- Three MS patients and 2 control subjects were also excluded because of high variability of OCT measurements between the 2 examiners.

Demographic features of the individuals were recorded. In addition, all the individuals underwent a detailed ophthalmic examination, including auto kerato-refractometry (Topcon RK 8000PA, auto-refractometer, Topcon, Tokyo, Japan), best corrected visual acuity testing, slit-lamp biomicroscopy, intraocular pressure measurement by Goldmann applanation tonometry, dilated fundus examination, axial length measurement with the IOL Master (version 3.02, Carl Zeiss, Meditec, Jena, Germany) and choroidal thickness measurements by OCT. All OCT measurements were performed with a Spectralis HRA +OCT (Heidelberg Engineering, Heidelberg, Germany).

OCT measurements by EDI SD-OCT

Choroidal image was performed using SD-OCT with EDI mode. (Scan pattern: enhanced depth imaging; Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg, Germany). The EDI image was averaged for 100 scans using the automatic averaging and eye tracking system. At the macula, we scanned the horizontal sections across the center of the fovea. The choroidal thickness was defined as the distance between the hyper-reflective line corresponding to the retinal pigment epithelium and the inner surface of the sclera, and was measured with the Heidelberg Eye Explorer software (version 1.7.0.0, Heidelberg Engineering, Heidelberg, Germany). At the macular region, measurements were performed manually at the subfovea site and at the sites 0.5 and 1 mm to the fovea temporally and nasally along the horizontal sections (Figure 1).

All OCT measurements were performed at the same time of the day, in the morning (between 09:00 and 10:00 am) to avoid diurnal fluctuations. For each eye, the choroidal thickness at the fovea was measured independently by two blinded clinicians (M.K. and ZA), and the mean values were recorded. Eyes with more than a 10 % difference in measurements between the interpreters were excluded from the study.

Statistical analyses

Statistical analyses were performed with SPSS for Windows 17.0 (SPSS Inc. Chicago, IL, USA). Data were analysed by independent samples t test. The categorical variables between the groups were analyzed by using χ^2 test. p value<0.05 was considered statistically significant.

Results

The mean age was 37.50 ± 8.21 years (range, 20-53 years) in MS patients and 36.05 ± 8.14 years (range, 22-51 years) in controls. The difference between groups was not statistically significant (p=0.382). The male/female distribution of the both groups was similar (p=0.69). The mean disease duration was 6.04 ± 2.04 (range, 3 to 10 years) years in patients with MS. Of the 32 MS patients, 8 (25 %) had bilateral ON history, 10 (31.2 %) had unilateral ON history and 14 (43.8 %) had no ON history. The mean refractive error was -1.54 ± 1.08 D (range, -3.0 to + 2.25 D) in patient with MS and -1.24 ± 1.1 D (range, -2.25 to + 2.0 D) in controls. There was no significant difference with respect to mean refractive error between patients with MS and controls (p=0.583). Axial length was collected from patients with MS, with an average of 23.18 ± 2.06 mm (range 22 to 25 mm); On the other side, the control group average was 23.47 ± 2.04 mm (range 22 to 25 mm) (p=0.456). All patients had no evidence of inflammation revealed by slit-lamp biomicroscopy and dilated fundus examination. The demographic and clinical information for each group are summarized in Table 1.

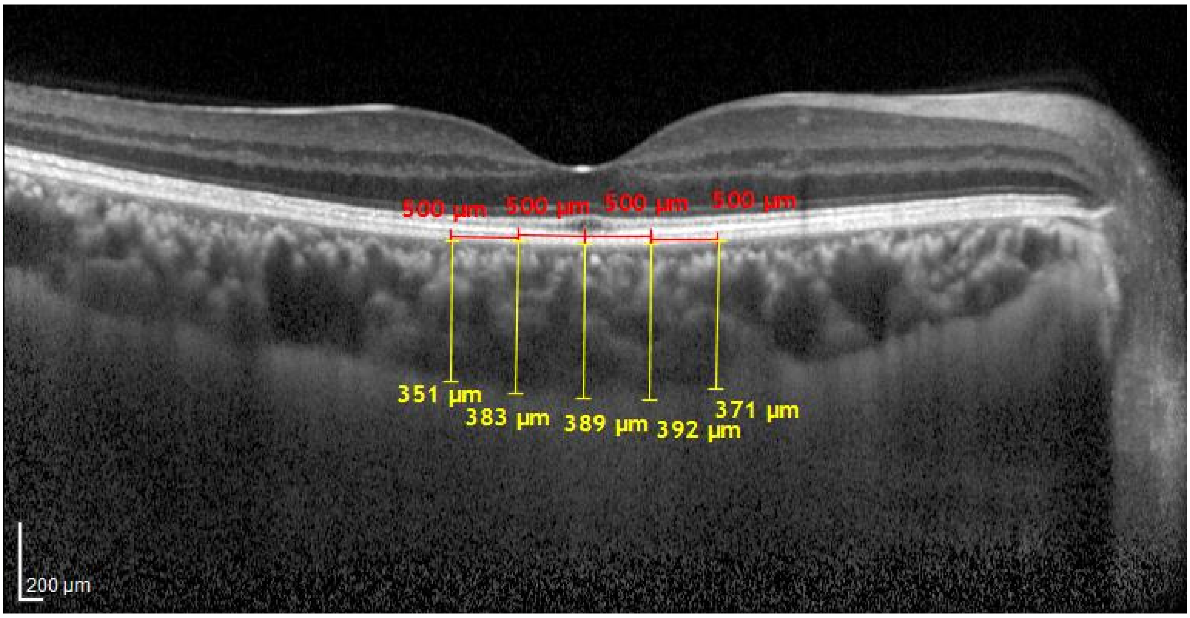

Figure 1: The CT measurements at macular region. The CT measurements at macular region were performed by horizontal EDI-OCT scanning. SFCT and CT 0.5 mm and 1mm temporal (T), nasal (N), to the center of macular fovea were measured between the hyperreflective line corresponding to the RPE and the inner surface of the sclera.

	Patients	**Controls**	**P value**
Age (yrs) mean ±SD	37.50 ± 8.21 (20-53)	36.05 ± 8.14 (22-51)	0.382
Gender (Male/Female)	22/10	20/12	0.690
BCVA mean ±SD	0.95 ± 0.42 (0.7–1)	1.0±0.0	0.875
Duration of disease (years)	6.04 ± 2.04 (3–10)	-	Na*
Axial length (mm) mean ± SD	23.18 ± 2.06 (22-24)	23.47 ± 2.04 (22-24)	0.456
Refractive error (mean diopters)	-1.54 ± 1.08 D (-3.0 to + 2.25)	-1.24 ± 1.1 D (-2.25 to + 2.0)	0.583
Na*: Not applicable, BCVA, best corrected visual acuity			

Table1: Characteristics of patients with multiple sclerosis and control group.

Table 2 shows the mean central macular thickness and choroidal thickness measurements of patients and controls at each location. The mean subfoveal choroidal thickness (SFCT) was 327.01 ± 64.6 µm in patients with MS and 365.3 ± 99.14 µm in controls. The difference in the SFCT between eyes of patients and controls was significant (p=0.019). Outside the fovea, significant differences were found at points temporal 500 µm, temporal 1000 µm and nasal 500 µm to the fovea between patients and control group (p=0.018, 0.003 and 0.03, respectively). Although patients with MS had lower mean choroidal thickness at point nasal 1000 µm to the fovea than controls, these results did not reach any statistically significance (p=0.160). The mean central macular thickness was 223.32 ± 18.55 µm in MS patients and 228.87 ± 20.09 µm in the controls (p=0.154).

Distance from fovea (mm)	Patients (µm) Mean ± SD 64 eyes	Controls (µm) Mean ± SD 64 eyes	P value
SFCT	327.01 ± 64.6	365.3 ± 99.14	0.019*
T1	321.65 ± 66.99	359.82±94.57	0.018*

T2	311.76 ± 65.96	358.80±92.85	0.003*
N1	314.76 ± 71.41	351.42 ± 99.23	0.031*
N2	307.57 ± 71.06	330.92 ± 96.9	0.160
CMT	223.32 ± 18.55	228.87 ± 20.09	0.154

*Statistically significant. SFCT: Subfoveal choroidal thickness; T1: choroidal thickness at 500 μm temporal to the fovea; T2: choroidal thickness at 1,000 μm temporal to the fovea; N1: choroidal thickness at 500 μm nasal to the fovea; N2: choroidal thickness at, 1000 μm nasal to the fovea; CMT: central macular thickness.

Table 2: The mean choroidal thickness measurements of patients and controls at each location.

Table 3 demonstrated the mean choroidal thickness measurements of MS patients with and without ON. Even If MS with ON eyes had lower choroidal thickness measurements at all points when compared with MS without ON eyes. This difference was not statistically significant ($p>0.05$).

Distance from fovea (mm)	ON (μm) Mean ± SD 26 eyes	Non-ON (μm) Mean ± SD 38 eyes	P value
SFCT	314.53 ± 53.10	335.55 ± 70.93	0.204
T1	312.92 ± 65.45	327.63 ± 68.23	0.393
T2	305.50 ± 57.13	316.05 ± 71.81	0.534
N1	302.96 ± 65.46	322.84 ± 74.98	0.278
N2	301.19 ± 73.19	311.94 ± 70.22	0.556

SFCT: subfoveal choroidal thickness; T1: choroidal thickness at 500 μm temporal to the fovea; T2: choroidal thickness at ,000 μm temporal to the fovea; N1: choroidal thickness at 500 μm nasal to the fovea; N2: choroidal thickness at ,000 μm nasal to the fovea; ON: optic neuritis.

Table 3: The mean choroidal thickness measurements of MS patients with ON and non-ON.

Discussion

Vascular dysregulation refers to the regulation of blood flow that is not adapted to the needs of the respective tissue. If vascular dysregulation is associated with symptoms or signs, the term vascular dysregulation syndrome is used. This syndrome can be primary (primary vascular dysregulation syndrome, PVD syndrome) or secondary to another disease (secondary vascular dysregulation syndrome, SVD syndrome). Vascular dysregulation can involve any organ; however, the eye is particularly often affected. Subjects with PVD tend to suffer more often from tinnitus, muscle cramps, migraine with aura and silent myocardial ischaemia and are at greater risk for altitude sickness. While the main cause of vascular dysregulation is vascular endotheliopathy, dysfunction of the autonomic nervous system is also involved. In contrast, SVD occurs in the context of inflammatory diseases such as multiple sclerosis, retrobulbar neuritis, rheumatoid arthritis, fibromyalgia and giant cell arteritis. The choroid, being the most vascular tissue of the eye, may easily be affected by primary or secondary vascular dysregulations [2,24-26].

Multiple sclerosis is a demyelinating autoimmune disease of the central nervous system with possible involvement of vascular dysregulation secondary to endothelial dysfunction caused by destruction of the vessel wall. The endothelial cells have the ability to modulate local vascular tone by releasing relaxing factors, such as nitric oxide and prostacyclin, or constrictive factors, such as ET-1. It is generally believed that vasospasm is caused by an imbalance between vasodilator and vasoconstrictor mechanisms responsible for regulating vascular tonus [7,27-29]. These mechanisms are very complex, involving local metabolites, circulating hormones, mechanical factors, and autonomic innervation. Among the local metabolites, substances produced by the vascular endothelium play an important role in the local regulation of blood flow. This role is even more important in circulatory beds such as the choroid and optic nerve head, which lack autonomic regulation [7,27,28].

The plasma or cerebrospinal fluid levels of ET-1 in patients with MS have been investigated in several studies. Speciale et al. [30] measured increased levels of ET-1 and nitric oxide (NO) in the cerebrospinal fluid of patients with MS, which implies a possible role for these vasoactive substances in the pathogenesis of MS. Pache et al. [31] demonstrated increased ET-1 plasma levels in MS patients and a significant reduction of extraocular blood flow in tandem with elevated plasma levels of the potent vasoconstrictor ET-1 in patients with MS. Haufschild et al. [10] also demonstrated markedly and significantly increased ET-1 plasma levels in MS patients. Apart from its direct vasoconstrictive effect, ET-1 also increases the sensitivity of blood vessels to the action of other vasoconstrictive circulating hormones, such as norepinephrine, 5-hydroxytryptamine and angiotensin II [32-34]. The choroid is regulated mainly by the autonomic nervous system, which is responsive to circulating hormones. Furthermore, the choroid has fenestrated capillaries that permit even larger molecules to escape and to have direct access to smooth muscle cells. Therefore, circulating vasoactive molecules are supposed to have a major impact on the choroid. Thus, vasoconstrictor effects of these vasoactive substances in the circulating blood might be observed on choroidal tissue [35-36]. The resulting response is smooth muscle contraction, which may cause the decrease of the choroid blood flow. Studies using color Doppler imaging have shown in MS patients a decreased blood flow velocity and increased vascular resistance index (RI) in the extraocular vessels, which indicates a reduction of the ocular blood flow in the course of MS [8,37-39].

There is a growing body of evidence suggesting that at least some patients with MS have an altered vascular endothelium function, with an imbalance between endothelium-derived vasodilators and vasoconstrictors that is similarly seen in patients with vascular dysregulation and can lead to vasospasm in MS. Given the fact that ET-1 is a potent vasoconstrictor in ocular vessels, we hypothesized that choroidal blood flow might be reduced in MS patients. In a recent paper, Esen et al. [35] described those choroidal vascular changes in patients with MS using SD-OCT. They found that choroidal thickness was significantly decreased in MS patients when compared to healthy controls and they also found that the difference between the subjects of MS with a history of ON and MS without a history of ON was not significantly different in regard to choroidal thickness, as demonstrated in our study. A possible limitation of their study was the lack of measurement of central macular thickness which would have allowed them to support vascular dysregulation hypothesis. However, our study demonstrated that central macular thickness measurements revealed no significant difference between MS patients and controls. We strongly believe that this data is an important finding that supports our hypothesis. Due to absence of central macular involvement, we suggest that choroidal vascular changes might be assumed as a consequence of systemic vascular dysregulation rather than inflammatory process.

Apart from vascular dysregulation in MS patients, uveitis may also effect the choroidal blood circulation. Patients with MS may present with intermediate uveitis, granulomatous anterior uveitis, posterior and pan-uveitis. Since inflammatory diseases of the choriocapillaris and stromal inflammatory vasculopathy play a role in the pathogenesis of many of the non-infectious uveitis conditions, changes in the normal blood circulation in the choroid are expected [40-42]. During active inflammation the choroidal thickness may change. Inflammatory infiltration could potentially result in increased choroidal thickness, whereas the diminished choroidal circulation may result in reduced choroidal thickness [43-47]. The patients in this study had no a prior uveitis history. So, we could not demonstrate choroidal changes associated with MS uveitis.

There are yet several limitations in this study. Firstly, the number of enrolled subjects was not large. The small population size had limited statistical power to detect small differences in choroidal thickness between MS patients and controls. Secondly, the calculation of average choroidal thickness at macular region was carried out manually due to the lack of automatic software. The objective automated measurements were better to yield convincing results and conclusions.

In conclusion, MS may affect the choroidal circulation, which may cause the reduction of the choroidal thickness. In light of our findings, we feel that choroidal thickness measurements may be used in the evaluation of patients with suspected MS as an additional method. Extensive studies that include patients with MS higher quantities should expand our knowledge on the choroidal vascular change or thickness in patients with MS.

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