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Research Article

Analysis of Choroidal Macular Thickness in Early Post-Covid-19 Patients

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Abstract

Purpose: Corona Virus Disease 2019 (COVID-19) is considered a critical global health challenge. Several investigations have suggested vascular dysfunction caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, but regarding ophthalmic involvement, only few data are available. Our aim was to evaluate the choroidal involvement in post-COVID-19 patients.

Methods: 40 eyes from 40 patients with previous SARS-CoV-2 infection and 40 eyes from 40 age matched controls were included. Choroidal measurements were made using Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT) at 13 different locations: at central fovea and at intervals of 500µm to 1500µm away from the fovea in the temporal, nasal, superior and inferior regions.

Results: Post-COVID-19 patients showed a significant increase in choroidal thickness compared with the control group for all the regions analyzed (all $p < 0.01$). In the Post-COVID-19 group, the choroid is thickest subfoveally and thinnest 1500µm nasal from fovea. In both groups, the superior and temporal macular choroid has been measured thicker than the inferior and nasal macular choroid, respectively.

Conclusion: Our results cautiously suggest that post-COVID-19 patients showed an increase in choroidal thickness compared to control groups. This choroidal thickening may reflect the importance of vascular factors in the pathogenesis of SARS-CoV-2 infection.

Keywords: Choroid; COVID-19; Hemodynamic Changes; Ocular Circulation; Retina; SARS-CoV-2

Introduction

The World Health Organization (WHO) initially used the term 2019 Novel Coronavirus in late December 2019, to refer to the coronavirus disease that affected a cluster of patients with severe pneumonia of unknown cause in Wuhan, China [1,2]. The term was revised it officially as COVID-19, and the virus is now also commonly known as a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), because of the association with severe acute respiratory syndrome coronavirus (SARS-CoV) [3-5]. Because of high spread severity, mortality and morbidity, the COVID-19 has been declared by the WHO a global pandemic in early March 2020, being the one of the most sever medical challenges in the last decades [6]. Apart from pulmonary disease, the SARS-CoV-2 also affects other organs including, cardiovascular, neurological, gastrointestinal, urinary, and olfactory systems [4,7]. Regarding the eye, only few data are currently available and are yet to be discovered all the ophthalmological involvement in SARS-CoV-2 infections. Several information is gradually expanding, namely related to the ocular symptomatic findings of the disease, such as conjunctivitis, uveitis, retinitis/chorioretinitis and optic neuritis [8,9]. In addition,

other ophthalmological studies have been focused on the mechanisms for the ocular transmission, highlighting the nasolacrimal system as a conduit between the eye and respiratory tract, remaining incompletely understood the role of the lacrimal gland in hematogenous spread [10-12]. Nevertheless, although some studies are now emerging, the effects in the eye caused by the infection, especially regarding the posterior segment involvement are very few. As there is growing evidence suggesting SARS-CoV-2 facility to affecting the vascular endothelium causing macro and microcirculatory impairments, and as being a choroid a predominantly vascular tissue in the eye, the main objective of the present study was to investigate the possible choroidal involvement in COVID-19 patients, providing real-world data on ocular findings regarding SARS-CoV-2 infection.

Methods

Observational case-control study performed at Centro Hospitalar Entre o Douro e Vouga (CHEDV), Santa Maria da Feira, Portugal. This investigation has been implemented in accordance with the Declaration of Helsinki and its later amendments and the experimental protocol was approved by the Ethics Committee of CHEDV. All participants provided written informed consent to participate in the study.

Study design and patients selection

The post-COVID-19 group involved 40 patients who were infected and recovered from SARS-CoV-2 infection from 1 March 2020 to 1 June 2020, recruited at 3rd month from hospital discharge. All clinical data regarding the SARS-CoV-2 diagnosis and clinical course were analyzed by accessing patients records. SARS-CoV-2 infection was diagnosed by oropharyngeal swabs performed at CHEDV, which were positive for the SARS-CoV-2 genome. Cure was attested by the achievement of one or two consecutive negative test results from the oropharyngeal swabs, with concurrent complete resolution of symptoms (if any). The Control group consisted of 40 patients randomly selected from the Optical Coherence Tomography (OCT) Normal Database, created in our Ophthalmology Department, before the era of COVID-19, which consisted of healthy patients recruited from the general ophthalmology consultation or hospital workers who respected exclusion and inclusion criteria. Exclusion criteria for both groups were presence of congenital eye disorders, presence of significant lens opacities or any macular disease, choroidal atrophy, high myopia (> 6D), exudative age-related macular degeneration, previous episode of central serous chorioretinopathy, previous diagnosis of glaucoma, acquired or hereditary optic neuropathy, demyelinating and neurodegenerative disorders, evidence of vitreoretinal disease, uveitis and keratoconus. In the control group, all the patients had a normal anterior segment ophthalmic examination, a BCVA of 20/25 Senllen scale or better, no history of intraocular surgery, or any retinal pathological feature. Each patient underwent an evaluation of best-corrected visual acuity (BCVA), biomicroscopy, fundus examination with a +90 D lens and performed an Enhanced Depth Imaging Optical Coherence Tomography (EDI-OCT) to evaluate the choroidal thickness (CT). One eye for each patient was chosen randomly to undergo the examination.

Image acquisition and choroidal segmentation

Image acquisition of OCT was performed without pharmacological pupillary dilation. All subjects underwent the spectral-domain (SD) OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) imaging of the macula (6-mm horizontal line scan centered on the fovea) executed in the EDI mode, a preset software-driven algorithm that produces an upright enhanced choroidal image, performed by two experienced operators (L.D. and S.V.). Only images with a quality score greater than 25 were considered. To prevent circadian variations, we made the OCT exams at the same time of the day, between 3 p.m. and 6 p.m. The CT was measured from the external part of outer retinal pigment epithelium, identified by the hyperreflective line, to the choroidal scleral interface recognized by the presence of a hyporeflective line (Figure 1). These measurements were made using a manual tool included in the software (calliper), in the subfoveal choroid and at 500 µm intervals from the fovea to 1500 µm nasal; 1500 µm temporal; 1500 µm superior; and 1500 µm inferior (13 locations).

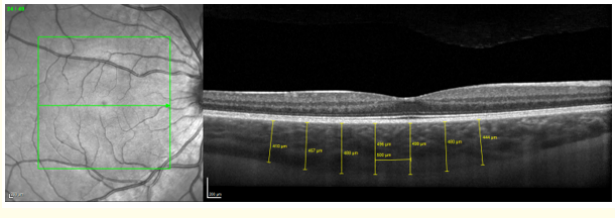

Figure 1: Representative method of the choroidal thickness measurements on the OCT horizontal scan. The measurements were made manually using the Caliper, centered in the fovea and at 500 µm intervals up to 1500 µm. We performed 7 measurements on each horizontal scan, 3 of them located in each quadrant, namely, nasal, temporal, superior and inferior.

Statistical analysis

Data was analyzed using SPSS software for Macintosh (IBM® SPSS® Statistics v. 26.0, Ontario, Canada). Descriptive statistics were calculated. The t-test was used to perform univariate comparisons between the groups. For correlation analysis between the variables, Spearman's Test was used. Alpha and beta values were used at 5% and 20%, respectively. Level of statistical significance was set at $p < 0.05$.

Results

40 eyes from 40 patients with previous confirmed SARS-CoV-2 disease (26 females; mean age [years ± SD] 38.00 ± 9.95 and 40 eyes from 40 age matched controls (28 females; mean age 40.20 ± 8.95) were included. The demographic, clinical, and ophthalmologic characteristics are summarized in table 1. There were no statistical differences between patients and the Control group for the refractive error and mean best corrected visual acuity was 20/20 (0.98 ± 0.04 decimal scale) and 20/20 (1.00 ± 0.00 decimal scale) in the Post-COVID-19 group and control group, respectively. The subfoveal CT was 349.90 ± 85.50 µm in the Post-COVID-19 group and 278.78 ± 57.27 µm in the Control group ($p < 0.001$). The CT in the different quadrants (temporal, nasal, inferior and superior) was significantly different among the groups, being thicker in all regions analyzed in the Post-COVID-19 group (all $p < 0.001$). For the Post-COVID-19 group, the choroid is thickest subfoveally (349.90 ± 85.59 µm) and thinnest 1500 µm nasal from fovea (329.63 ± 75.26 µm). The superior and temporal macular choroid has been measured thicker than the inferior and nasal macular choroid, respectively. In the Control Group, the choroid is thickest 500 µm superior from fovea (286.73 ± 58.98 µm) and thinner 1500 µm nasal from fovea (242.60 ± 62.32 µm). In the Control group, the superior and temporal macular choroid has also been measured thicker than the inferior and nasal macular choroid, respectively. The biggest difference in the mean choroidal thickness between the groups is 91.95 µm, occurring 1500 µm temporal from fovea, (340.35 ± 88.73.59 µm) in the Post-COVID-19 Group vs. (248.40 ± 74.20 µm) in the control group. The values are more similar 500 µm superior from fovea, with mean difference of 57.92 µm between the groups (344.65 ± 68.34 µm) in the Post-COVID-19 group vs. (286.73 ± 58.98 µm) in the Control Group. Independently from the group, age was negatively associated with CT in all locations, without statistical significance (Table 2).

	Post-COVID-19 group	Control Group
Number of eyes	40	40
Sex (female/male)	26/14	28/12
Age	38.00 ± 9.95	40.20 ± 8.95
Mean BCVA	0.98 ± 0.04	1.00 ± 0.00
Hydroxychloroquine	5	-
ICU	1	-
Hospitalization	5	-
Choroidal thickness		
Sub-foveal*	349.90 ± 85.50	278.78 ± 57.27
Temporal*		
500	346.65 ± 83.41	274.25 ± 58.99
1000	349.28 ± 90.59	263.20 ± 70.25
1500	340.35 ± 88.73	248.40 ± 74.20
Nasal*		
500	346.30 ± 76.89	274.23 ± 57.01
1000	340.10 ± 78.68	261.05 ± 58.91
1500	329.63 ± 75.26	242.60 ± 62.32
Inferior*		
500	337.28 ± 90.00	272.35 ± 64.30
1000	355.70 ± 90.92	269.85 ± 70.75
1500	340.90 ± 82.50	269.40 ± 73.74
Superior*		
500	344.65 ± 68.34	286.73 ± 58.98
1000	343.65 ± 78.34	284.50 ± 68.04
1500	347.33 ± 71.02	286.68 ± 62.75

Table 1: Demographic and clinical characteristics of Covid-19-group and control group.

Age described as mean years ± SD (standard deviation); BCVA: Best Corrected Visual Acuity (mean decimal scale ± SD); ICU: Intensive Care Unit; Choroidal thickness described as mean µm ± SD. *$p < 0.01$.

Spearman Correlations														
		AGE	**Central**	**T1**	**T2**	**T3**	**N1**	**N2**	**N3**	**I1**	**I2**	**I3**	**S1**	**S2**	**S3**
Age	Spearman's rho	-													
	p-value	-													
Central	Spearman's rho	-0.141	-												
	p-value	0.211	-												
T1	Spearman's rho	-0.152	0.942	-											
	p-value	0.180	< .001	-											
T2	Spearman's rho	-0.128	0.904	0.967	-										
	p-value	0.259	< .001	< .001	-										
T3	Spearman's rho	-0.098	0.832	0.926	0.955	-									
	p-value	0.386	< .001	< .001	< .001	-									
N1	Spearman's rho	-0.105	0.936	0.888	0.853	0.799	-								
	p-value	0.352	< .001	< .001	< .001	< .001	-								
N2	Spearman's rho	-0.076	0.891	0.815	0.778	0.724	0.943	-							
	p-value	0.502	< .001	< .001	< .001	< .001	< .001	-							
N3	Spearman's rho	-0.057	0.839	0.772	0.755	0.698	0.892	0.947	-						
	p-value	0.614	< .001	< .001	< .001	< .001	< .001	< .001	-						
I1	Spearman's rho	-0.113	0.843	0.857	0.824	0.800	0.826	0.811	0.766	-					
	p-value	0.317	< .001	< .001	< .001	< .001	< .001	< .001	< .001	-					
I2	Spearman's rho	-0.152	0.807	0.828	0.803	0.775	0.782	0.796	0.757	0.896	-				
	p-value	0.178	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	-				
I3	Spearman's rho	-0.199	0.761	0.798	0.780	0.794	0.767	0.766	0.755	0.866	0.900	-			
	p-value	0.077	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	-			
S1	Spearman's rho	-0.163	0.830	0.823	0.819	0.755	0.795	0.752	0.756	0.786	0.757	0.775	-		
	p-value	0.148	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	-		
S2	Spearman's rho	-0.100	0.854	0.819	0.797	0.739	0.814	0.785	0.797	0.797	0.751	0.773	0.869	-	
	p-value	0.379	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	-	
S3	Spearman's rho	-0.151	0.835	0.826		0.768	0.770	0.735	0.727	0.771	0.760	0.773	0.824	0.855	-
	p-value	0.180	< .001	< .001		< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	< .001	-

Table 2: Correlations between age and choroidal thickness measurements.

T: Temporal Quadrant; N: Nasal Quadrant; I: Inferior Quadrante; S: Superior Quadrant.

Discussion

In this study, we used EDI SD-OCT to compare CT in early Post-COVID-19 patients with a control group. Our results showed an overall choroidal thickening in the Post-COVID-19 group, when compared to Control group, in all the different locations evaluated, with statistical significance. From the beginning of COVID-19 era, as a life-threatening disease, most of the investigation has been naturally focused on respiratory tract and vital organs for a survival rate improvement, remaining unclear all the effects on other organs. Regarding the human eye, the most available evidence is concentrated on the ocular surface, in part because of conjunctivitis can be a first sign of the disease, being now emerging the first results of studies about the posterior segment of the eye. The motivation in centering our research on possible ocular retinal alterations, relies on previous studies performed in animals infected by coronavirus. Hooks., *et al.* observed pathological findings on the retina in a mouse coronavirus infection model in 1993 [13]. In both early and late stages of the disease, changes caused by the Coronavirus infection were discovered and corroborated [13,14]. Initially, there was a release of pro inflammatory mediators and infiltration of inflammatory cells. Later, the photoreceptor cells and ganglion cells gradually decrease, and the fibers of the optic nerve became thinner, mainly due to the production of autoantibodies in the retina and retinal pigment epithelial cells [14]. These findings suggest that the autoimmune response may persist after viral infections causing progressive damage to the retina [13,14]. Recently, Paula., *et al*. reported the pathological changes in the retina on human in 12 adults COVID-19 examined 11 - 33 days after the symptom onset [15]. Alfonso Savastano., *et al*. explored the involvement of the retinal capillary microcirculation by using OCT Angiography, focusing on the radial peripapillary capillary plexus, in Post-COVID-19 Patients, and detected a decrease in post SARS-CoV-2 patients compared to controls [16]. Although the growing investigation, studies about the pathological changes caused by the novel coronavirus in the human retina are still lacking. For better understanding the effects in the posterior pole, and as is known microvascular effects and circulatory disfunction in response to SARS-CoV-2 infection, our team focused the research to understand the impact of the disease in the choroidal macular system [17]. The choroid is constituted mainly by blood vessels organized in choriocapillaris, Sattler's and Haller's layers and supplied by the internal carotid artery (ICA) via the ophthalmic and posterior ciliary arteries [18]. Being a densely vascularized structure, its main role is providing oxygen and nutrients to the outer retina, mainly in the foveal avascular zone, and retinal pigment epithelium [18,19]. Several data has been shown that SARS-Cov-2 binds to ACE-2 receptors in type 2 alveolar cells, macrophages, perivascular cells, cardiomyocytes and ACE-2 receptors distributed in various tissues of the eyeballs, causing endothelial cell dysfunction, microvascular and macrovascular disorder, and tissue ischemia in the corresponding localizations, but still unknown all the consequences of the damage [20,21].

To our knowledge, this is the first research study aimed to assess choroidal thickness using EDI- OCT after COVID-19 infection. Our study found that the choroid was thicker in patients with early post-COVID-19 infection, and a presumable mechanism of this enlargement was a possible compensatory vasculature adjustment to prevent retinal and choroidal ischemia, as a result of the diminished blood flow due to a possible ICA endothelial damage, mediated by inflammatory reactions and oxidative stress. Although blood-retinal barrier separates the neural retina from the blood, avoiding the harmful effects of specific components, such as immune complexes and lymphotoxins, the inflammatory cascade could damage the vascular endothelial cells, resulting in the destruction of the endothelial cell barrier and in the increase of choroid's permeability [22].

Although this research highlights new insights regarding the choroidal layer in the COVID-19 patients, the results are affected by some limitations. At first, CT measurements were done manually, although this manual method already showed a high intraobserver and interobserver reproducibility [23]. Second, we don't take into account the hydration status and body mass index that could affect CT measurements. To reduce the bias, we intended to perform the measurements at the same time of the day, we the same two operators, and in the same environment. Besides, our Control group is age and sex-matched to Post-COVID-19 group. In addition, many other factors not controlled in our study can theoretically influence the CT measurements, such as smoking, corticosteroids and glycose or aldosterone levels [24,25]. Lastly, a small number of eyes studied can overestimate the magnitude of the results.

Conclusion

In conclusion, in early post-COVID-19 patients there is an evidence of global thickening of the choroid on EDI-OCT when compared with normal subjects who never have the disease could be explained in part by alterations in choroid hyperpermeability,

probably as a result of molecular and ionic variations. The differences between the groups were particularly visible in temporal and subfoveal segments, while in the superior part, there was less choroidal thickness or volume variations at any points analyzed in this study. The achieved results seems to be an additional topic in the incomplete knowledge about COVID-19 disease. Our observations showed that EDI-OCT could be a potentially valuable tool for assessing both short-term and long-term vascular alterations caused by SARS-CoV-2 infection in thickness and morphology of the choroid. Further longitudinal and prospective studies are required to understand these findings and the persistence of these alterations and to explain this phenomenon and clarify the mechanism behind.

Declarations of Interest

None.

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