COVID-19: more than a respiratory virus, an optical coherence tomography study

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Abstract

Purpose The purpose of this study is to investigate anatomic and morphologic features of inner and outer retinal layers in patients recovered from COVID-19 with Spectral Domain Optical Coherence Tomography (SD-OCT), whether correlate with any symptoms during disease process.

Methods 32 patients recovered from COVID-19 and age- and gender-matched 36 healthy controls were included in this cross-sectional study. Ganglion cell-inner plexiform layer, macular and peripapiller retinal nerve fiber layer (RNFL), inner nuclear layer (INL), outer nuclear layer (ONL), outer plexiform layer (OPL) and the outer retinal hyperreflective bands including external limiting membrane (ELM), ellipsoid zone (EZ) and interdigitation zone (IZ) were examined with SD-OCT. The differences of each retinal layers thickness among subgroup analysis of ocular pain and headache were also compared.

Results Macular RNFL of inner and outer nasal and outer inferior quadrants were thinner in COVID-19 patients compared to healthy control group ($p = 0.046$, $p = 0.014$ and $p = 0.016$, respectively). Thinning in outer superior quadrant of GCIPL and INL quadrants were detected in patients with headache ($p = 0.026$ and $p = 0.01$). Superonasal and inferotemporal sectors of pRNFL were thinner in patients with ocular pain compared to patients without ocular pain ($p = 0.024$ and $p = 0.015$). Integrity of EZ, ELM and IZ was evaluated as continuous line and protected on each OCT scans.

Conclusion The study demonstrated convincing evidence that SARS-CoV-2 can affect the inner and outer retinal layers, with subclinical localized alterations, particularly in patients with headache and ocular pain symptoms during COVID-19 period.

Keywords SARS-CoV-2 · COVID-19 · Eye · Retina · Optic coherence tomography · Headache

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Introduction

Novel coronavirus disease (COVID-19) caused by respiratory syndrome coronavirus 2 (SARS-CoV-2) agent, first reported in Wuhan, China, in December 2019 [1–3], along with the fast spread [4] to whole world was declared as pandemic by the World Health

Organisation [5, 6]. Although it is defined as a respiratory virus, since the angiotensin-converting enzyme II (ACE-2), which the agent attaches [3], is expressed widely in the human body, the disease has the potential to damage many tissues and organs.

As the pandemic period continues, the scientific publications pointing ocular involvement have been increased. Ocular involvement can be in different clinical presentations. At the beginning of the pandemic, the publications were mainly about the anterior segment involvement [7–9] of the disease and the discussion was whether the transmission is possible from ocular surface [10] and how the best protection should be [11]. Recent studies are evolved to represent retinal involvement of SARS-CoV-2 infection in the ongoing process.

Retina can be affected by viral infections either with direct cytopathic effect of the virus on retinal neurons as in the case of cytomegalovirus [12], or secondary with a damage to the microvasculature when the virus targets the vascular endothelium like in HIV retinopathy [13]. Furthermore, SARS-CoV-2 has been detected in the retina of the deceased patients with COVID-19 [14].

Prothrombotic state and immune-mediated reactions triggered by COVID-19 infection can lead to retinal damage by endothelial dysfunction, which can cause cotton wool spots, edema and retinal hemorrhage clinically [15, 16].

Spectral domain optical coherence tomography (SD-OCT) is a non-invasive imaging technique that is useful for demonstrating subclinical retinal changes in systemic conditions such as diabetes mellitus [17, 18] and Alzheimer's disease [19, 20], and viral infections as well [21, 22].

The aim of this study is to investigate anatomic and morphologic features of inner and outer retinal layers with OCT in patients, recovered from COVID-19 with OCT, whether correlate with any symptom during disease process.

Material and methods

This study was approved by the Yildirim Beyazit University Medical School Committee of Clinical Trials and Ethics (Ankara, Turkey). All research procedures were performed in accordance with the Declaration of Helsinki. Written informed consent

was obtained from the subjects with local institutional review board requirements. Between November and December 2020, patients recovered from COVID-19 were assessed by spectral domain optical coherence tomography (SD-OCT) for evaluating thickness of each retinal layers and peripapiller nerve fiber layers and by color fundus photographs in retina department of Ankara City Hospital, a tertiary referral education and research hospital, Ankara, Turkey. Consecutive 32 patients and age- and gender-matched 36 healthy controls were recruited in this cross-sectional study. All patients were healthcare professionals, recovered from confirmed COVID-19, either by showing viral genome in nasopharyngeal swab by reverse transcriptase polymerase chain reaction (RT-PCR), or by an antibody test of SARS-CoV-2 infection. Patients with any systemic or ocular diseases were excluded from the study. Also more than $\pm$ 3 diopter spherical equivalent of refractive errors and use of any topical medication within last three months were exclusion criteria of the study.

Demographic and anamnestic data were collected by the same physician performing the examination. Each subject underwent a detailed ophthalmological examination including anterior segment and fundus slit lamp examination.

Optical coherence tomography

The SD-OCT (Heidelberg Engineering, Heidelberg, Germany) images were performed by an experienced technician, and OCT scans were assessed by two experienced clinicians independently without informed about study group of participants. Total retinal thickness was measured by using Macula Map X–Y scanning protocol. The Macula Map scan pattern evaluates 6×6 mm area centered on the fovea. Thickness of macular ganglion cell–inner plexiform layer (GCIPL) complex, macular retinal nerve fiber layer (RNFL), inner nuclear layer (INL), outer plexiform layer (OPL), and outer nuclear layer (ONL) was segmented automatically and measured by the caliper tool embedded in SD-OCT system (Fig. 1a). These layers were studied in three concentric rings centered in the fovea: central (1 mm), inner ring (1–3 mm) and outer ring (3–6 mm) which were determined by the Early Treatment Diabetic Retinopathy Study (ETDRS) [23].
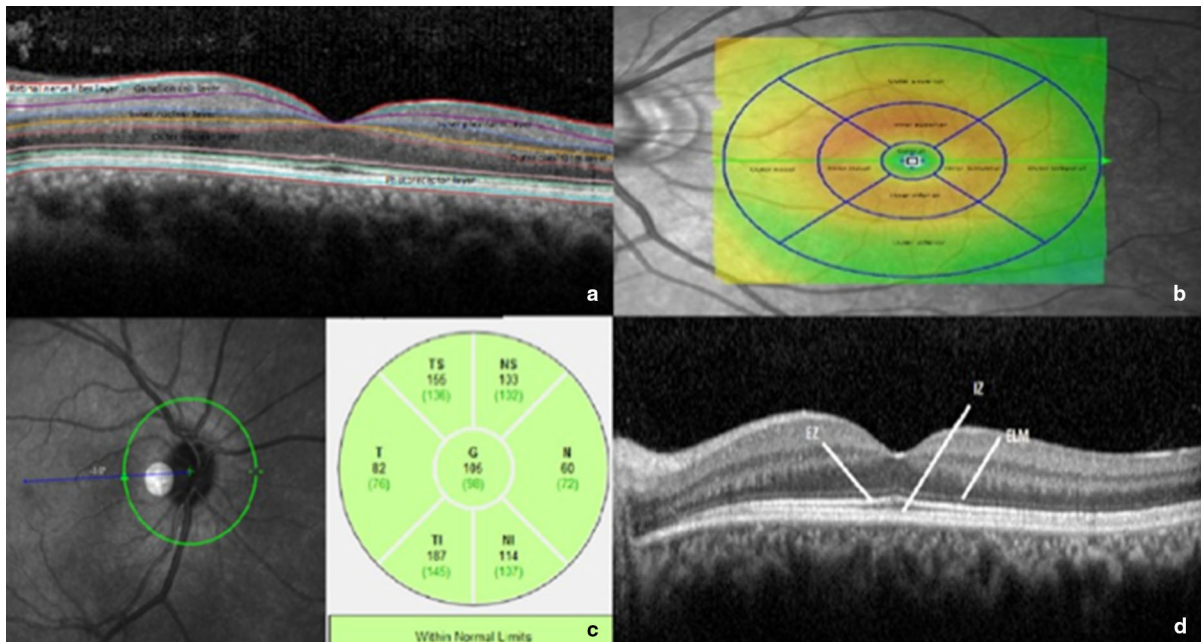
Fig. 1 a. A cross-sectional view of macula SD-OCT scan demonstrating the macular layer segmentation included in the study. **b.** ETDRS grid; the central circle is with a diameter of 1 mm. The inner ring consists of the four quadrants surrounding the central circle with a diameter of 1–3 mm. The outer ring consists of the four quadrants surrounding the inner ring, with a diameter of 3–6 mm. **c.** Analysis of peripapillary RNFL thickness; thickness of all quadrants was included in the study. **d.** Healthy OCT scan of three hyperreflective bands analyzed in the study. Early Treatment of Diabetic Retinopathy Study: ETDRS, ELM: external limiting membrane, EZ: ellipsoid zone, IZ: interdigitation zone

Inner and outer rings were segmented into four quadrants (inner/outer superior, inner/outer inferior, inner/outer nasal, and inner/outer temporal) (Fig. 1b).

Peripapiller retinal nerve fiber layer (pRNFL) thickness was obtained from a circular scan with a diameter of 3.4 mm positioning on middle of the optic disc center. pRNFL was automatically segmented as central, temporal, inferotemporal, superotemporal, nasal, superonasal, and inferonasal quadrants (Fig. 1c).

The three hyperreflective outer retinal bands external limitan membrane (ELM), ellipsoid zone (EZ) and interdigitation zone (IZ) were identified according to the classification by International Nomenclature for Optical Coherence Tomography panel [24].

The disruption of ELM, IZ, and EZ was determined as the loss of the continuous back-reflection line that characterizes each layer. The disruption of these layers was interpreted in the central 1 mm of the three consecutive horizontal scans, and the median scan was located in the fovea. The disruption of the foveal ELM, EZ, and IZ was graded as line not visible, disrupted in at least one scan (band defect) and continuous line (intact band) (Fig. 1d).

Statistical analysis

All analyses and calculations were performed via IBM SPSS Statistics 22.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp.). The distributions of the continuous variables in subgroups were examined by Shapiro–Wilk's test and normality plots. OCT measurements were summarized by mean $\pm$ standard deviation (mean $\pm$ sd). Categorical variables were reported as frequency (%), and comparison of categorical variables between groups was determined by using Chi-squared test. The means of OCT measurements between groups were compared by independent-sample t test or Mann–Whitney U test. A p-value < 0.05 was considered as statistically significant.

Results

A total of 32 patients were included in the study, 14 (43.8%) male, with mean age of 36.72 + − 9.98 years. None of the patients required hospitalization, and only two patients (6.2%) had pulmonary involvement. None of the patients had any systemic or ocular comorbidities. The mean time between confirmatory examination of COVID-19 (positive RT-PCR test for SARS-CoV-2) and eye examination was 60.5 ± 38.6 days.

The control group consisted of 36 healthy individuals mean age of 36.47 + − 9.98, 12 (33.4%) of male. During the acute phase of the infection, main ocular symptom was ocular pain, 12 of the patients (37.5%) suffering from. Thickness of outer temporal quadrant of macular RNFL was 17.58 ± 1.37 μm in patients with ocular pain and 18.8 ± 1.19 μm in patients without ocular pain and thinner in patients with ocular pain ($p = 0.009$). Superonasal and inferotemporal sectors of pRNFL were 94.75 ± 15.88 μm and 143.9 ± 14.85 μm in patients with ocular pain; 108.2 ± 13.84 μm and 158.83 ± 20.78 μm in patients without ocular pain and decreased in patients with ocular pain ($p = 0.024$ an $p = 0.015$).

Most frequent symptoms were fatigue (81.3%) and myalgia (81.3%) in 26 patients, athralgia (71.9%) and anosmia (71.9%) in 23 patients and headache in 20 patients (62.5%). Clinical features of patients recovered from COVID-19 are shown in Table 1. Outer superior quadrants of GCIPL and INL were thinner, 68.85 ± 9.28 μm and 34.45 ± 3.34 μm in patients with headache; 64.33 ± 5.44 μm and 32.42 ± 2.27 μm in patients without headache ($p = 0.026$ and $p = 0.01$).

There were no anterior or posterior segment findings in patients. Evaluating color fundus photographs of each subjects to detect subtle or apparent retinal findings, no central or peripheral retinal abnormalities were observed. There was no difference in all quadrants of total retinal thickness between groups ($p > 0.05$, in each comparison). Macular retina nerve fiber layer of inner and outer nasal and outer inferior quadrants was thinner in COVID-19 patients compared to healthy control group ($p = 0.046$, $p = 0.014$, and $p = 0.016$, respectively).

Inner temporal quadrant of GCIPL was 85.39 ± 10.74 μm, thinner in patients and 89.18 ± 7.67 μm in healthy controls, and the differences was significant ($p = 0.018$). Central thickness of INL, ONL, and pRNFL was significantly thinner in patients recovered from COVID-19 when compared to healthy controls ($p = 0.031$, $p = 0.007$ and $p = 0.013$, respectively). Reduced thickness of inner nasal quadrants of both OPL and ONL and outer nasal quadrant of OPL was determined in patients compared to controls ($p = 0.004$, $p = 0.004$ and $p = 0.017$, respectively). There was no difference in all quadrants of total retinal thickness between groups ($p > 0.05$, in each comparison). Comparison of iner and outer retinal layers between patients recovered form COVID-19 and healthy controls by OCT is shown in Table 2.

There was no OCT scan completely or incompletely invisible of ELM, IZ, and EZ; therefore hyperreflective bands were evaluated as continuous line and protected on each OCT scans.

Discussion

Retinal findings of COVID-19 infection are of interest. Marinho et al. reported focal hyperreflective areas in the inner retina and also subtle cotton wool spots in a small amount patients with confirmed COVID-19 infection [25]. On the other hand, Vasvas et al. submitted that the hyperreflective areas on OCT scans could represent normal retinal vessels and cotton wool spots could represent myelinated nerve fiber layer or might be related to other retinal pathologies [26]. Subsequently, a case of papillophlebitis [27] and two cases of paracentral acute middle maculopathy and acute macular neuroretinopathy [28] were reported.

A study has reported flame-shaped hemorrhages and cotton wool spots in hospitalized severe COVID-19 patients [29], and another study has reported cotton wool spots in patients hospitalized for COVID-19 pneumonia [30].

These studies showed that coronaviruses might induce various retinal pathologies. In this study, color fundus photographs of each subjects were taken to evaluate retinal abnormalities. Nevertheless, in our study we observed no subtle or apparent central or peripheral retinal findings such as vascular abnormalities or cotton wool spots determined by color fundus photographs or OCT scans. In many studies, ophthalmologic manifestations and retinal findings are reported to be related to severity of COVID-19

Table 1 Clinical features of patients recovered from COVID-19

(n,% / mean ± SD)	Patients recovered from COVID-19 (32)
Days since symptoms onset	60.5 ± 38.6
Duration of PCR + time (day)	11.03 ± 0.6
Ocular pain −/+	20 (62.5%)/12 (37.5%)
Headache −/+	12 (37.5%)/20 (62.5%)
Fever −/+	23 (71.9%)/9 (28.1%)
Cough −/+	22 (68.8%)/10 (31.2%)
Dyspne −/+	25 (78.1%)/7 (21.9%)
Fatigue −/+	6 (18.8%)/26 (81.3%)
Myalgia−/+	6 (18.8%)/26 (81.3%)
Arthralgia −/+	9 (28.2%)/23 (71.9%)
Anosmi −/+	9 (28.1%)/23 (71.9%)
Agesuia −/+	10 (31.3%)/22 (68.7%)
Involvement of lung −/+	30 (93.8%)/2 (6.2%)
Treatment agent	
No treatment	2 (6.3%)
Favipiravir	12 (37.5%)
Hydroxychloroquine	12 (37.5%)
Favipiravir and hydroxychloroquine	6 (18.8%)

infection [29–32]. Nevertheless, retinal findings such as hemorrhages, cotton wool spots and vascular changes seem to be time dependent [31, 32]. Clinical features of patients recruited in this study, such as longer duration of post-COVID period until capturing OCT images, no requirement of hospitalization during COVID period, or relatively mild to moderate symptoms of COVID, might reflect the severity of disease, and less severe COVID-19 infection of our cases might explain the invisibility of these retinal findings.

ACE-2 is a cell entry receptor for SARS-CoV-2 to initiate inflammation and pathologic processes [3]. ACE-2 has been detected in human neural retina [33], ganglion cells, cells of inner nuclear layer, photoreceptors [34], and vascularized retinal pigment epithelium and choroid [35]. Therefore, alterations in these various retinal layers might be expected during COVID period. In this study, SD-OCT was used to compare the thickness of each retinal layer of patients recovered from COVID-19 infection with age- and gender-matched healthy subjects and decrease in the localized retinal thickness was determined. Thinning in inner temporal quadrant of GCIPL thickness and central quadrant of INL, ONL and pRNFL thickness was detected.

After reports of microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection [36, 37], optical coherence tomography angiography (OCTA) analysis was performed in recovered COVID-19 patients versus age-matched controls to evaluate retinal vascular involvement. Abrishami et al. determined reduced vessel density in superficial and deep capillary plexus of the foveal and parafoveal regions regardless of hospitalization [38], and Savastano et al. identified reduced perfusion density of the radial peripapillary capillary plexus (RPCP) [39]. Reduction in RPCP reflects the impairment of homeostasis and function of retinal ganglion cells and their axons that is correlated to thinning of RNFL thickness in glaucoma patients [40]. Thinning of inner temporal quadrant of GCIPL, central pRNFL and inner nasal, outer nasal and inferior quadrants of macular RNFL thickness in patients recovered from COVID-19 compared with healthy subjects was detected in this study. The localized subclinical axonal damage might be related to reduction in RPCP. Ornek et al. also demonstrated localized thinning of pRNFL in patients with COVID-19 [41] which was consistent with our study.

To the best of our knowledge, there have been no studies published on determining structural properties

Table 2 Comparison of inner and outer retinal layers between patients recovered from COVID-19 and healthy controls

	Patients recovered from COVID-19 (32)	Healthy controls (36)	*p*-value
Age (years, mean ± SD)	36.72 ± 9.98	36.47 ± 9.98	0.902
Gender (female/male, %)	18/14	24/12	0.378
	(56.2%/43.8%)	(66.6%/33.4%)	
Total retina (μm, mean ± SD)			
Central	269.89 ± 21.25	274.82 ± 19.81	0.164
Inner superior	288.8 ± 17.68	289.81 ± 15.03	0.720
Inner nasal	340.45 ± 15.51	346.33 ± 16.45	0.034
Inner inferior	336.75 ± 14.49	341.89 ± 15.64	0.05
Inner temporal	325.28 ± 15.91	329.67 ± 15.86	0.110
Outer superior	308.08 ± 12.24	308.65 ± 11.78	0.781
Outer nasal	316.03 ± 16.45	319.86 ± 13.18	0.135
Outer inferior	307.3 ± 13.11	309.83 ± 14.74	0.294
Outer temporal	288.80 ± 17.68	289.81 ± 15.03	0.720
Macular NFL (μm, mean ± SD)			
Central	12.51 ± 2.69	12.69 ± 1.85	0.649
Inner superior	18.29 ± 2	18.27 ± 1.37	0.948
Inner nasal	20.78 ± 2.57	21.8 ± 3.25	**0.046**
Inner inferior	23.4 ± 2.76	23.91 ± 3.5	0.352
Inner temporal	16.65 ± 1.43	16.88 ± 1.35	0.334
Outer superior	37.15 ± 5.32	38.79 ± 5.32	0.076
Outer nasal	49.2 ± 8.78	52.8 ± 8.01	**0.014**
Outer inferior	36.85 ± 5.23	39.05 ± 5.27	**0.016**
Outer temporal	18.29 ± 2	18.27 ± 1.37	0.948
GCIPL (μm, mean ± SD)			
Central	37.71 ± 10.38	38.77 ± 8.20	0.514
Inner superior	70.15 ± 8.14	71.27 ± 6.99	0.389
Inner nasal	93.40 ± 9.63	95.54 ± 7.58	0.151
Inner inferior	91.31 ± 8.20	93.63 ± 7.15	0.080
Inner temporal	85.39 ± 10.74	89.18 ± 7.67	**0.018**
Outer superior	67.85 ± 7.24	66.75 ± 4.76	0.300
Outer nasal	68.96 ± 7.50	68.23 ± 4.93	0.498
Outer inferior	72.39 ± 7.47	72.37 ± 6.18	0.989
Outer temporal	70.16 ± 8.14	71.28 ± 6.99	0.389
INL (μm, mean ± SD)			
Central	17.97 ± 4.38	20.16 ± 6.84	**0.031**
Inner superior	33.83 ± 2.76	33.82 ± 2.82	0.986
Inner nasal	39.67 ± 4.18	39.63 ± 3.59	0.944
Inner inferior	39.89 ± 3.75	39.94 ± 4.41	0.939
Inner temporal	37.17 ± 3.28	37.06 ± 3.96	0.862
Outer superior	33.86 ± 2.81	33.51 ± 2.62	0.461
Outer nasal	34.53 ± 2.70	34.11 ± 2.27	0.327
Outer inferior	35.38 ± 2.93	35.29 ± 2.92	0.869
Outer temporal	33.83 ± 2.76	33.82 ± 2.82	0.986
OPL (μm, mean ± SD)			

Table 2 continued

	Patients recovered from COVID-19 (32)	Healthy controls (36)	*p*-value
Central	27.14 ± 7.87	24.93 ± 5.41	0.062
Inner superior	27.31 ± 2.29	27.72 ± 7.11	0.660
Inner nasal	30.03 ± 4.21	32.70 ± 6.28	**0.004**
Inner inferior	34.64 ± 8.55	33.10 ± 8.36	0.290
Inner temporal	30.41 ± 3.89	30.28 ± 3.78	0.846
Outer superior	28.02 ± 3.84	27.61 ± 3.18	0.504
Outer nasal	27.46 ± 2.34	28.53 ± 2.82	**0.017**
Outer inferior	29.16 ± 4.30	28.19 ± 3.24	0.141
Outer temporal	27.31 ± 2.29	27.72 ± 7.11	0.660
ONL (μm, mean ± SD)			
Central	87.38 ± 11.45	93.31 ± 13.60	**0.007**
Inner superior	58.11 ± 7.39	60.33 ± 7.45	0.084
Inner nasal	72.67 ± 9.96	77.61 ± 9.85	**0.004**
Inner inferior	66.30 ± 11.46	69.88 ± 11.98	0.078
Inner temporal	72.55 ± 7.08	75.15 ± 9.08	0.063
Outer superior	62.09 ± 8.13	62.67 ± 8.08	0.681
Outer nasal	58.69 ± 7.82	60.17 ± 7.38	0.259
Outer inferior	56.39 ± 7.90	58.04 ± 7.56	0.216
Outer temporal	58.11 ± 7.39	60.33 ± 7.45	0.084
Peripapiller RNFL (μm, mean ± SD)			
Central	99.56 ± 8.68	104.19 ± 12.18	**0.013**
Superotemporal	135.50 ± 20.34	138.92 ± 15.85	0.281
Superonasal	71.78 ± 11.38	75.24 ± 11.32	0.079
Nasal	72.17 ± 14.36	76.07 ± 19.50	0.191
Inferonasal	114.56 ± 21.06	119.24 ± 22.87	0.219
Inferotemporal	147.44 ± 18.88	148.54 ± 18.80	0.734
Temporal	781.78 ± 11.38	75.24 ± 11.32	0.079

GCIPL Ganglion cell-inner plexiform layer, *INL* İnner nuclear layer, *NFL* Nerve fiber layer, *ONL* Outer nuclear layer, *OPL* Outer plexiform layer, *RNFL* Retinal nerve fiber layer

of outer retinal hyperreflective bands and qualitative analysis of outer retinal layers in patients recovered from COVID-19 compared with healthy control subjects. Defects in outer retinal layers were described as case reports with acute macular neuroretinitis, paracentral acute middle maculopathy, or outer retinal band abnormalities [28, 42]. In our study, there was no disruption in integrity of external limitan membrane, ellipsoid zone, or interdigitation zone, but localized subclinical thinning in outer retinal layers was prominent in inner nasal quadrant of both outer plexiform

and outer nuclear layers; thinning in outer nasal quadrant of OPL and central quadrant of ONL was also determined.

Thinning of GCIPL and more prominent outer nuclear layer could be in relation to neuroinvasive potential of COVID-19 as central nervous system manifestation [43], described in animal studies [44] or neurologic events associated with SARS-CoV-2 [45]. In an animal study on the murine coronavirus mouse hepatitis virus strain, effects in different retinal layers were demonstrated [46], and virus antigens in inner

and outer retinal layers were detected in another study [47]. Vulnerability of inner layers of retina especially GCIPL rather than outer layers of retina [48] and also decreased vessel density of superficial and deep capillary plexus [38] after COVID-19 infection might explain the alterations of thickness to be more prominent in inner retinal layers and preserved outer retinal bands.

Neurotropism of the virus has been proposed as one of the mechanisms for the neurological and neuro-ophthalmic manifestations [49]. A prominent tropism to neurosensorial retinal layers regardless of inoculation route was observed in murine coronavirus, and gliosis might be seen in affected retinal layers as a result of damage in blood-ocular barrier [46, 50]. Eye seems to be crucial in understanding pathophysiology of SARS-CoV-2 and should be emphasized more [51].

As the COVID-19 pandemic progresses, reports of neurological manifestations are increasing [52, 53]. Headache is the most common neurological symptom of COVID-19 and could be due to direct invasion of SARS-CoV-2 or stimulated trigeminal nerve endings with pro-inflammatory mediators and cytokines in the nasal cavity or trigemino-vascular activation with involvement of the vascular endothelial cells [54]. In our study, outer superior quadrant of GCIPL and INL thickness was reduced in patients with headache (62.5%) compared to patients without headache. Ocular pain was the most frequent ocular symptom in our study, 12 patients (37%) suffering from. This pain was described as a pressure on both eyes. We analyzed that the patients with ocular pain, outer temporal quadrant of macular RNFL, and superonasal and inferotemporal sectors of pRNFL were thinner compared to patients without ocular pain. Although headache and ocular pain are known as nonspecific neurologic symptoms, we determined retinal thickness in subgroup analysis of patients with these symptoms, pointing the subclinic localized damage in macular and peripapiller RNFL, that could regard to neurological involvement and those patients should be followed up closely.

Patients enrolled in the study were with mild to moderate COVID symptoms and without visual complaints; long duration after COVID recovery for ophthalmic evaluation, small sample size and limited age range were limitations of this study. Also evaluating retinal vasculature parameters with an accurate imaging method such as OCT-angiography and evaluating function of outer retinal layer with electrophysiological tests were lack in this study.

In conclusion, this study demonstrated convincing evidence that SARS-CoV-2 can affect the inner and outer retinal layers, with subclinical localized alterations and preserved integrity of outer retinal hyperreflective bands. Retinal imaging by optical coherence tomography is a non-invasive, reproducible, and expeditious technique that subclinic or apparent retinal pathologies might be detected during COVID-19 period. Management of COVID-19 patients should include retinal assessment, with a close follow-up, especially in patients with headache and ocular pain. The results of this study could highlight pathophysiology of COVID-19, especially in ocular involvement with neurological symptoms. Future studies are needed to evaluate whether these alterations of COVID-19 at retinal layers have permanent and long-term effects.

Availability of data and material Supplemental materials for this article are available from the corresponding author on reasonable request.

Declarations

Conflict of ınterest The authors declare that they do not have any conflict of interest.

Ethical approval Approval was obtained from the Ethics Committee of Yildirim Beyazit University, Ankara, Turkey. All procedures performed in the study involving human participants were in accordance with the ethical standards and also with Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

Consent for publication Both authors have agreed to the submission fort this article.

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