Can the coronavirus disease 2019 (COVID-19) cause choroiditis and optic neuropathy?

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Abstract
Objectives: We aim to investigate the involvement of the choroid and retinal nerve fiber layer (RNFL) in COVID-19 patients using spectral domain optical coherence tomography.

Methods: This cross-sectional study was conducted between April and June 2020. 40 patients (23 female and 17 male) with COVID-19 and 42 healthy individuals (26 female and 16 male) were included in the study. The OCT scans were performed 4 weeks after the COVID-19 diagnosis.

Results: In the COVID-19 group, in the right eyes, the mean nasal choroidal thickness was 295.70 ± 7.046 μm (p = 0.017), mean subfoveal choroidal thickness was 333.25 ± 6.353 μm (p = 0.003), mean temporal choroidal thickness was 296.63 ± 6.324 μm (p = 0.039), and mean RNFL was 89.23 ± 1.30 μm (p = 0.227). In the left eyes, mean nasal choroidal thickness was 287.88 ± 9.033 μm (p = 0.267), mean subfoveal choroidal thickness was 333.80 ± 9.457 μm (p = 0.013), mean temporal choroidal thickness was 298.50 ± 9.158 μm (p = 0.079), and mean RNFL was 89.48 ± 1.289 μm (p = 0.092). Compared with the control group, the patient group had significant thickening of the choroidal thickness in all quadrants of the right eyes, and significant thickening of the subfoveal choroidal thickness in the left eyes. There was no significant difference in the RNFL thickness between groups (p > 0.05).

Conclusion: COVID-19 may cause a subclinical involvement in the choroidal layer.

Keywords
COVID-19, choroid, retinal nerve fiber layer, SARS-CoV-2, choroiditis

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Introduction
The coronavirus epidemic that started in China spread rapidly worldwide and resulted in a significant number of deaths.1 Coronaviruses (CoVs) are enveloped, single-stranded RNA viruses. These CoVs cause respiratory tract infections and patients can have a wide clinical spectrum from sore throat to pneumonia.1,2,3 Coronavirus are known to cause infections in areas other than the respiratory tract, including the gastrointestinal

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It has been reported that the retinal renin-angiotensin system (RAS) plays important role in the neurotransmision of retinal ganglion cells, intraocular pressure control, and the pathogenesis of vasoproliferative disorders. In addition, ACE-2 has been known to play a role in the recruitment of inflammatory cells by increasing the vascular permeability. An affected choroid and retinal nerve fiber layer (RNFL) can be expected in the acute phase due to an impaired retinal RAS caused by COVID-19. Therefore, more research should be carried out to investigate the ocular findings of SARS-CoV-2 via ACE-2, especially in the posterior segment.

Some studies reported neurological involvement such as taste and smell disorders in SARS-CoV-2 patients and mentioned virus neurotropism. Animal models showed that SARS-CoV and MERS-CoV can enter the brain, possibly via olfactory nerves, and rapidly spread to specific brain areas including the thalamus and brainstem. At the same time, the damage caused by inflammatory or immune-related molecules such as cytokines detected in SARS-CoV-2 infected patients may cause neurological findings. These reports prompted us to consider investigating the effects of the disease on the optic nerve.

The hyperinflammatory response is important in the development of acute respiratory distress syndrome (ARDS), which plays a critical role in the prognosis of COVID-19, and the release of uncontrolled cytokines is involved in the development of many complications. Extensive alveolar damage has been reported with destruction of epithelial and endothelial cells in ARDS pathogenesis in COVID-19. Also, some studies such as the one conducted by Chung et al. found that choroidal thickness may increase in patients with systemic inflammation even without active ocular findings in Behçet disease. Thereby, ocular vascular structures may be affected due to vasculopathy, inflammation, and endothelial cell dysfunction in the pathogenesis of COVID-19. Another situation that supports that vascular structures are affected in COVID-19, thus the choroid may be affected is Kawasaki-like disease. It has been reported that children with COVID-19 have hyperinflammatory conditions and/or signs of Kawasaki-like illness. Kawasaki is an acute inflammatory pediatric vasculitis involving small, medium-sized vessels, often self-limiting, which may cause arterial complications such as coronary artery aneurysm.

During the COVID-19 pandemic, there have been reports of neurological involvement, such as decreased taste and smell disorders in SARS-CoV-2 patients. These reports prompted us to consider investigating the ocular findings of SARS-CoV-2 via ACE-2, especially in the posterior segment.

A priori power analysis was executed by using G*Power 3.1. The comparison between groups needs to test the difference between two independent group means. The analysis was performed using a one-tailed test, a strong effect size (d = 0.85) and an alpha of 0.05, and resulted in a sample size of minimum 37 patients for each group to achieve a power of 0.95. The study group was formed from 40 patients who were referred to the ophthalmology clinic 4 weeks after the diagnosis of COVID-19 by the infectious diseases department of Niğde Ömer Halisdemir University Hospital, and 42 healthy individuals with negative PCR tests were included as the control group. Real-time reverse transcriptase-polymerase chain reaction was used to confirm the clinical diagnosis of COVID-19. After determining the age and gender distribution of the COVID-19 patient group, healthy volunteers compatible with the patient group were selected. Informed consent form was signed by all participants. The OCT scans of COVID-19 patients were performed 4 weeks after the diagnosis. Pre-imaging PCR tests of all patients were negative and no patients had symptoms. The patients did not have any complaints about eye problems. COVID-19 patients with comorbid diseases such as diabetes mellitus and hypertension were not included in the study. None of the patients had hospitalization. The participants in the control group were selected from volunteers, patients with refractive errors, and relatives of the patients.

In line with the current literature findings such as virus neurotropism and hyperinflammation; we aimed to observe the possible changes in the choroidal RNFL thickness in patients diagnosed with COVID-19 4 weeks after the diagnosis.

Material and methods

This cross-sectional study was conducted between April and June 2020. It was approved by the Ethics Review Board of Niğde Ömer Halisdemir University Hospital (Ethics No: 2020/54), and written consent was obtained from the patients before the eye examination. In addition, approval was obtained from the Ministry of Health of the Republic of Turkey in order to perform the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

A priori power analysis was executed by using G*Power 3.1. The comparison between groups needs to test the difference between two independent group means. The analysis was performed using a one-tailed test, a strong effect size (d = 0.85) and an alpha of 0.05, and resulted in a sample size of minimum 37 patients for each group to achieve a power of 0.95. The study group was formed from 40 patients who were referred to the ophthalmology clinic 4 weeks after the diagnosis of COVID-19 by the infectious diseases department of Niğde Ömer Halisdemir University Hospital, and 42 healthy individuals with negative PCR tests were included as the control group. Real-time reverse transcriptase-polymerase chain reaction was used to confirm the clinical diagnosis of COVID-19. After determining the age and gender distribution of the COVID-19 patient group, healthy volunteers compatible with the patient group were selected. Informed consent form was signed by all participants. The OCT scans of COVID-19 patients were performed 4 weeks after the diagnosis. Pre-imaging PCR tests of all patients were negative and no patients had symptoms. The patients did not have any complaints about eye problems. COVID-19 patients with comorbid diseases such as diabetes mellitus and hypertension were not included in the study. None of the patients had hospitalization. The participants in the control group were selected from volunteers, patients with refractive errors, and relatives of the patients.
Demographic characteristics and clinical information including age, gender, and disease duration of all cases were recorded. Ophthalmoscopic examination including detailed medical history, best-corrected visual acuity, color vision, eye movements, slit lamp biomicroscopic anterior segment examination, ocular pressure measurement with Goldmann applanation tonometer, and dilated fundus examination was performed (by KRZ). All patients were examined by a single ophthalmologist. The right and left eyes of the patients were compared separately between the patient and control groups.

Patients with myopic, hyperopic, or astigmatic refractive errors greater than 3.0 diopters, an ocular disease such as uveitis; retinal and choroidal diseases, optic nerve pathologies, strabismus or amblyopia; a history of ocular trauma or surgery were excluded from the study. Those who were under 18, pregnant, or breastfeeding were also excluded.

**Measurement of choroidal thickness using optical coherence tomography**

Cirrus HD-OCT (Carl Zeiss Meditec Inc., Dublin, CA, USA) was used and performed after the dilation of pupils with 5% tropicamide.

HD five Line Raster protocol was reduced to a single line and shot. Enhanced-depth imaging (EDI) mode in Cirrus HD-OCT was used for shooting. Images with signal strength lower than six were excluded in the study. Choroidal thickness was manually measured as the vertical distance between the retinal pigment epithelium and the sclera. The first measurement was carried out under the center of the fovea. The subfoveal choroidal thickness and choroidal thicknesses at 500 µm intervals temporal and nasal points from the fovea up to 2000 µm were measured. The subfoveal measurement, an average of the four temporal measurements and average of the four nasal measurements were used for the study. Measurements were repeated by two independent persons (first measurement was performed by KRZ, second measurement was performed by GYB). Both observers measured in black and white scans. The retinal pigment epithelium (RPE) hyperreflective band was accepted as the beginning and the continuous white line coming to the inner surface of the sclera as the ending. The color setting of the device was used to make the starting and ending point more specific. Observers made one measurement each, the measurements were compared, and the discordant measurements were re-evaluated (Figure 1).

**Measurement of retinal nerve fiber layer thickness using optical coherence tomography**

After pupil dilation, OCT examination was performed. RNFL thickness was measured using the Spectral Domain Cirrus OCT Model 400 (Carl Zeiss Meditec, Jena, Germany). A scan signal strength of six or greater was accepted in the study. In the peripapillary RNFL measurement,
three-dimensional (3D) cube OCT data were obtained using the “Optic Disc Cube 200 × 200 Scan” pattern, which performed raster scanning in a 6 × 6 mm square centered on the optic nerve head. After creating an RNFL thickness map from this dataset, the software determined the disk center automatically and then extracted a circumpapillary circle (3.4 mm in diameter) from the cube dataset for RNFL thickness measurement.

**Statistical analysis**

Data were analyzed using STATA 14 package program. Numerical variables were expressed in mean ± standard deviation [minimum-maximum] values. Categorical variables were presented with numbers and percentages. The normality of numerical variables was examined using the Kolmogorov–Smirnov test and homogeneity of variances was examined with the Levene test. The difference between the groups in terms of numerical variables, the parametric test assumptions, and independent groups were tested with t-test. If there was no difference between the groups and the parametric test assumptions were not met, the Mann–Whitney U test was used. The level of significance was taken as $p < 0.05$.

**Results**

The COVID-19 patient group included 23 women (57.5%) and 17 men (42.5%), and the control group consisted of 26 women (61.90%) and 16 men (38.10%). There was no significant difference in terms of sex among the two groups ($p = 0.684$). The mean age of the COVID-19 group and the control group was 33.9 ± 13.3 and 34.9 ± 11.4 years, respectively. There was no significant difference in mean age among the two groups ($p = 0.707$). The numbers of smokers were similar in two groups ($p = 0.584$).

Subfoveal choroidal thickness, mean nasal choroidal thickness, mean temporal choroidal thickness, and RNFL values for the right eyes were presented in Table 1. In the COVID-19 group, the mean nasal choroidal thickness was 295.70 ± 7046 μm ($p = 0.017$), the mean subfoveal choroidal thickness was 333.25 ± 6353 μm ($p = 0.003$), the mean temporal choroidal thickness was 296.63 ± 6324 μm ($p = 0.039$), and the mean RNFL thickness was 89.23 ± 1.30 μm ($p = 0.227$). In the control group, the mean nasal choroidal thickness was 268.60 ± 8,488 μm, the mean subfoveal choroidal thickness was 304.00 ± 7,131 μm, the mean temporal choroidal thickness was 275.69 ± 7,653 μm, and the mean RNFL thickness was 91.40 ± 1234 μm.

Subfoveal choroidal thickness, mean nasal choroidal thickness, mean temporal choroidal thickness, and RNFL values for the left eyes were presented in Table 2. In the COVID-19 group, mean nasal choroidal thickness was 287.88 ± 9033 μm ($p = 0.267$), mean subfoveal choroidal thickness was 333.80 ± 9457 μm ($p = 0.013$), mean temporal choroidal thickness was 298.50 ± 9159 μm ($p = 0.079$), and the mean RNFL thickness was 89.48 ± 1289 μm ($p = 0.092$). In the control group, the mean nasal choroidal thickness was 274.74 ± 7,574 μm, the mean subfoveal choroidal thickness was 304.50 ± 6,696 μm, the mean temporal choroidal thickness was 277.21 ± 7,750 μm, and the mean RNFL thickness was 92.45 ± 1.18 μm.

Bilateral subfoveal choroidal thickness and the nasal and temporal choroidal thickness of the right eyes were statistically significantly thicker. There was no significant difference in the RNFL thickness between groups ($p > 0.05$).

**Table 1.** Choroidal thickness and retinal nerve fiber layer thickness values for the right eyes.

|                                | COVID-19 group (n = 40) | Control group (n = 42) | p     |
|--------------------------------|--------------------------|------------------------|-------|
| Mean nasal choroidal thickness  | 295.70 ± 7046            | 268.60 ± 8488          | 0.017*|
| (μm)                           |                          |                        |       |
| Subfoveal choroidal thickness   | 333.25 ± 6353            | 304 ± 7131             | 0.003*|
| (μm)                           |                          |                        |       |
| Mean temporal choroidal thickness| 296.63 ± 6324           | 275.69 ± 7653          | 0.039*|
| (μm)                           |                          |                        |       |
| RNFL thickness                  | 89.23 ± 1.30             | 91.40 ± 1.23           | 0.227 |
| (μm)                           |                          |                        |       |

RNFL: retinal nerve fiber layer.

**Table 2.** Choroidal thickness and retinal nerve fiber layer thickness values for the left eyes.

|                                | COVID-19 group (n = 40) | Control group (n = 42) | p     |
|--------------------------------|--------------------------|------------------------|-------|
| Mean nasal choroidal thickness  | 287.88 ± 9033            | 274.74 ± 7574          | 0.267 |
| (μm)                           |                          |                        |       |
| Subfoveal choroidal thickness   | 333.80 ± 9457            | 304.5 ± 6.69           | 0.013*|
| (μm)                           |                          |                        |       |
| Mean temporal choroidal thickness| 298.50 ± 9159           | 277.21 ± 7.74          | 0.079 |
| (μm)                           |                          |                        |       |
| RNFL thickness                  | 89.48 ± 1289             | 92.45 ± 1.18           | 0.092 |
| (μm)                           |                          |                        |       |

RNFL: retinal nerve fiber layer.
Discussion

Spectral Domain OCT is a non-invasive imaging technique that has an important role in the diagnosis and follow-up of many inflammatory and degenerative ocular diseases and is useful for demonstrating viral infection. There are studies examining RNFL in recent studies in COVID-19 patients. Burgos-Blasco et al. sought to examine the RNFL changes in COVID-19 patients. In a study including five participants, only patients with old RNFL values were included and there was an increase in new RNFL thicknesses. The patients were examined 4 weeks after the diagnosis, as in our study. The thickening, reported by Burgos-Blasco et al., was not statistically significant, and they did not fully explain this thickening. They indicated that this may be a residue of a possible inflammation. Optic neuritis cases related to COVID-19 have began to be reported, and RNFL thinning is an expected finding in the chronic period of optic neuritis cases. Although we did not find a significant difference, the RNFL thickness was thinner in the COVID-19 group. This early thinning is not statistically significant, but if the thinning continues in the future, perhaps an optic nerve damage can be detected. However, we think that longer follow-up is required to prove this finding. Our study is different from the study of Burgos-Blasco et al. in that the number of patients was high and both eyes were examined. However, we made a comparison with the control group because we could not reach the old RNFL measurements of the same patients as in the study conducted by Burgos-Blasco et al.

Marinho et al. reported that hyperreflective lesions were observed at the level of ganglion cells and more prominent inner plexiform layers in the papillomacular bundle in both eyes in 12 adults examined 11–33 days after the onset of COVID-19 symptoms. Thus, they supported the optic neuritis and retinitis findings suggested in animal models. A case report supporting these findings was presented by Zhou et al. They described optic neuritis and myelitis associated with myelin oligodendrocyte glycoprotein antibody in a young male patient concurrent with COVID-19. SARS-CoV-2 RNA PCR was negative in the patient’s CSF. They explained this situation with secondary immune-based pathogenesis triggered by SARS-CoV-2. Additional reports on COVID-19 presented as Miller Fisher syndrome, polyneuritis cranialis, Guillain-Barré syndrome, and Kawasaki syndrome, in which similar pathogenesis is mentioned, provide specific examples of this virus’s ability to disrupt the immune system. In addition to triggering secondary immunity, viral RNA of SARS-CoV-2 was isolated from cerebrospinal fluid in the presence of altered mental state and meningocencephalitis in a patient with COVID-19 pneumonia from Japan. Similar to the cranial system, there is evidence in the detection of SARS-CoV-2 in the retinal biopsies of patients who died from COVID-19. Thus, the virus can reach the eye through the optic nerve or affect it through other mechanisms such as systemic inflammation. Recently, Rodrigo-Armenteros et al. reported a case of optic neuritis caused by SARS-CoV-2. In our study, no significant change was found in RNFL thickness 30 days after patient’s positive test compared to the control group.

Choroid consists of a vascular network that acts as a blood supply for the outer retina, optic nerve, and avascular fovea. Choroid tissue can rapidly change its thickness in response to a variety of stimuli. Changes in choroidal circulation, autonomic nervous system, or inflammation can cause changes in choroidal thickness. SARS-CoV-2 infection activates a systemic inflammatory response that leads to the release of inflammatory mediators. There is increasing evidence that COVID-19 predisposes to thrombosis in both arterial and venous circulation. Reported findings showed that organ dysfunction in patients with COVID-19 can be caused by immunosuppression, endothelial activation, or direct viral-mediated tissue damage. The presence of ACE-2 receptors in the choroid is well known. Cat CoV and murine CoV mouse hepatitis virus can cause retinal detachment, vasculitis, retinitis, retinal atrophy and optic neuritis, uveitis, and choroiditis. In some recent articles, a Kawasaki-like disease was described in children. In pathogenesis, pulmonary endothelial inflammation possibly mediated by endothelial ACE-2 after SARS-CoV-2 infection increases the inflammatory response in vascular lesions and may cause endothelial dysfunction and vascular dilatation. Considering these information, we wanted to examine the choroidal circulation in patients who have survived COVID-19. Our study is the first to find an increase in choroidal thickness in COVID-19. Although we cannot say that the increase in thickness is choroiditis, we think that it is an inflammatory change in the choroid. The highest level of immune response to COVID-19 has been reported to be around day 8. Therefore, there might be a thicker choroid in the early stages of the disease and we think that if we can visualize the choroid with OCT as soon as the diagnosis was made, there may be a significant change in all quadrants. The choroidal thickening occurring in parallel with the immune response may have decreased after the peak. We think we could see a meaningful thickening in all choroidal parts of the left eyes if the examination had been performed early in our study. This result indicates that COVID-19 may affect the choroid by secondary systemic inflammation or direct viral invasion. We predict that there may be a subclinical choroidal involvement due to the inflammation. But Çetinkaya et al. and Furat et al. did not find a difference between the COVID-19 and control groups in terms of choroidal thickness. A study directly supporting viral invasion was also reported by Casagrande et al. They detected SARS-CoV-2 in retinal biopsies in a postmortem study. According to these reports, it is a high probability
that the retina and choroid will be affected by COVID-19 either directly or with a secondary immune response. In addition to old studies, posterior segment findings will emerge with time.\textsuperscript{17,28}

An important limitation of our study is that we could not use indocyanine green angiography to differentiate it from other diseases with increased choroidal thickness and to prove our findings. Another factor limiting the results of our study was that we could not evaluate COVID-19 patients in the acute phase due to the risk of contagion. In addition, since our patients did not have pre-COVID-19 choroidal and RNFL values, we could not compare them with post-infection values.

**Conclusion**

Our study was the first to find an increase in choroidal thickness in patients with a history of COVID-19. Significant increase in choroidal thickness of both the right and left eyes indicates that the choroid is also subclinically affected during COVID-19 infection. Further studies with more participants in the early and late stages of the disease should be conducted.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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**Ethics approval**

The study protocol was approved by Niğde Ömer Halisdemir University Ethics Committee (Protocol No: 2020/54)

**Informed consent**

Written informed consent was obtained from all subjects before the study.

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