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Retinal microvascular and perfusional disruption in paediatric COVID-19: A case-control optical coherence tomography angiography study

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ABSTRACT

Purpose: To investigate the short-term effect of coronavirus 2019 (COVID-19) on the retinal capillary network and choroid in children.

Materials and methods: This prospective, cross-sectional, case-control study included 19 recovered COVID-19 pediatric patients and 20 healthy children. Macular thickness, choroidal thickness, vessel density (VD), perfusion density (PD), and foveal avascular zone (FAZ) values were obtained. Central vessel and perfusion densities were measured at the central 6-mm area, and the values were compared among three subgroups according to location.

Results: The mean ages of patients and controls were 12. 42 ± 3.3 years and 13.35 ± 1.2 years, respectively. Significant differences were observed between the two groups in terms of inner, outer, and full VD, as well as inner and full PD. No significant differences in center VD and PD were observed between groups. Although it was not evident in analysis of choroidal values, inflammatory sites were thickened. FAZ area significantly differed between groups ($p < 0.05$).

Conclusions: Retinal microvascularity was impaired in the acute phase of disease in recovered COVID-19 patients aged 10–15 years. However, the microvascularity impairment was subclinical. The choroid was thickened because of inflammation during the acute phase of disease. pediatric COVID-19 patients should undergo follow up via optical coherence tomography angiography to detect subclinical and asymptomatic retinal changes. Long-term follow-up studies are needed to validate these findings.

Introduction

Coronavirus 2019 (COVID-19) disease is a global public health issue caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which first appeared in Wuhan, China in December 2019, and has been declared a pandemic by the World Health Organization [1]. SARS-CoV-2 is an enveloped, single-stranded RNA virus [1]. At the beginning of the pandemic, respiratory disease (e.g., pneumonia) was emphasised; however, COVID-19 may cause various clinical symptoms, including multiple organ failure. The multi-organ involvement in COVID-19 may be explained by the viral proliferation cycle. Angiotensin-converting enzyme-2 (ACE-2) receptors provide a route of cellular entry for SARS-CoV-2 [2,3]. Because ACE-2 receptors are present on multiple organs (e.g., eyes, lungs, liver, heart, and kidneys), COVID-19 may affect multiple organs [4,5]. COVID-19 can also cause coagulopathies. Endothelial dysfunction initiates coagulopathy by causing an increase in thrombin production and fibrinolysis [6]. COVID-19 can involve any organ that is within the reach of the vascular system.

Previous studies have identified ophthalmological involvement in COVID-19 patients. In particular, cases of conjunctivitis have been reported in children and adults with COVID-19 [7,8]. Although some studies have reported posterior segment involvement in COVID-19 patients, such involvement mostly occurs in adults [9,10]. Here, we used optical coherence tomography angiography (OCTA) to examine posterior segment involvement in children with COVID-19. OCTA is a new

Abbreviations: ACE-2, Angiotensin-Converting Enzyme-2; ANJ-2, Angiotensin-2; COVID-19, Coronavirus 2019; CRP, C-Reactive Protein; FAZ, Fovea Avascular Zone; MAV, Mean Artery Diameter; MT, Macular Thickness; MVD, Mean Vein Diameter; OCTA, Optical Coherence Tomography Angiography; PCR, Polymerase Chain Reaction; PD, Perfusion Density; VD, Vessel Density.

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generation of non-invasive devices, which displays blood flow with high resolution in the retina and choroid, thereby providing information regarding ischemia.

Although most previous studies have exclusively included adults, some reviews and clinical follow-up studies have suggested that posterior segment involvement has a better prognosis in children than in adults [11,12]. Thus, we aimed to investigate chorioretinal changes that occur in the acute phase of COVID-19 in children.

Materials and methods

This prospective, cross-sectional, case-control study was approved by the Ethics Board of Izmir Katip Celebi University, Atatürk Training and Research Hospital, Turkey. The case group comprised children of healthcare professionals; all patients in the case group had been diagnosed with COVID-19 on the basis of polymerase chain reaction test findings. These patients were aged 10–15 years and presented with a mild upper respiratory tract infection. No patients required intubation or pediatric intensive care; their recovery was confirmed by negative follow-up polymerase chain reaction test findings. Immediately after confirmation of recovery, each patient underwent detailed ophthalmological examinations and OCTA measurements at the Department of Ophthalmology in Izmir Katip Celebi University, Atatürk Training Research Hospital. Visual acuity and autorefraction measurement values of all patients were recorded. The anterior and posterior segments of patients were carefully examined using a biomicroscope. Patients were excluded if they had current or prior best-corrected visual acuity worse than 20/20, amblyopia, strabismus, intraocular surgery, corneal opacity or dystrophy, premature retinopathy, hereditary retinal dystrophy, hereditary optic neuropathy, or glaucoma. Patients were also excluded if they had diabetes, hypertension, or uveitis; these diseases can affect choroidal vascularity. Oxygen saturation levels, vital signs, and laboratory findings were obtained from medical records. The control group included individuals from the same age group who visited the outpatient clinic for routine examinations and had normal ophthalmological findings.

OCTA images were obtained using an RS-3000 Advance device (NIDEK Co., Ltd., Tokyo, Japan). This device features a wavelength of 880 nm and an A-scan speed of 53,000 per second. The retinal capillary plexus was analysed using AngioScan software (NIDEK Co., Ltd.). Using the fovea as the internal fixation source, macular cube areas of 3 × 3 mm and 6 × 6 mm were created, each consisting of 256 B-scans. The macula was then divided into inner, outer, central, and full subgroups in a 6 × 6-mm area, in accordance with the method used in the Early Treatment Diabetic Retinopathy Study. Vessel density (VD) and perfusion density (PD) measurements were automatically obtained for all subgroups. In addition, the fovea avascular zone (FAZ) area, perimeter, and circularity values were recorded. Four additional choroidal measurements were acquired to determine central foveal thickness, including 600 and 1200 μm (μ) from the center, nasal, and temporal regions. All values were saved in Microsoft Excel format.

Statistical analysis

SPSS software (version 22.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis. The normality of all data was evaluated. Non-normally distributed data were analysed using the non-parametric Mann–Whitney U test. The results were calculated with 95% confidence intervals, and p-values < 0.05 were considered statistically significant.

Results

This study included 19 recovered COVID-19 patients (girls: 7, 36%; boys: 12, 64%) and 20 controls (girls: 10; boys: 10). The mean ages of the patients and controls were 12.42 ± 3.3 years and 13.35 ± 1.2 years, respectively (Table 1); the corresponding mean visual acuities were 1.0 and 0.0 logMAR. Significant differences were observed between patients and controls in terms of C-reactive protein level, D-dimer level, and sedimentation rate ($p= 0.019$, $p= 0.001$, and $p= 0.001$, respectively) (Table 1). Although the choroidal thickness values did not significantly differ between groups, minimal thickening was noted in patients, compared with controls (Fig. 1). For example, choroidal thicknesses measured from the central foveal area in patients and controls were 334.9 ± 33.7 μ and 311.2 ± 17.5 μ, respectively. Although the choroidal thickness values from the nasal and temporal quadrants were not significantly different between patients and controls, the patients exhibited choroidal thickening (Table 2). The central foveal thickness and mean macular thickness in patients were 248.0 ± 16.9 μ and 270.8 ± 66.5 μ, respectively; in controls, they were 267.1 ± 19.8 μ and 305.5 ± 9.2 μ, respectively. These values significantly differed between patients and controls ($p= 0.003$ and $p= 0.001$, respectively). While center VD values did not significantly differ between groups, they were lower in patients than in controls (3.8 ± 0.9 and 4.1 ± 1.1, respectively). The inner, outer, and full VD values were significantly lower in patients than in controls (Table 3). Similar results were observed regarding PD values. Inner and full PD values were significantly lower in patients than in controls (Table 3). center and outer PD values did not significantly differ between patients and controls ($p= 0.496$ and $p= 0.627$, respectively). Additionally, a significant expansion of FAZ area was observed among patients, compared with controls ($p= 0.001$; Fig. 2). The FAZ areas in patients and controls were 1.65 ± 6.1 and 0.4 ± 0.1 mm^2, respectively. Significant differences were also observed between groups in terms of perimeter and circularity values ($p= 0.001$ for both) (Table 3).

Discussion

COVID-19 causes respiratory symptoms, as well as coagulopathy, endotheliopathy, and vasculitis [13,14]. Multiple organ failures may occur in COVID-19 patients because of widespread ACE-2 receptor distribution in various end organs, as well as extensive coagulopathy [15,16]. Anterior and posterior segments reportedly exhibit involvement in COVID-19 patients. In this study, we used capillary OCTA to investigate the retinal effects of COVID-19 in children. Previous studies regarding the retinal effects of COVID-19 have exclusively focused on adults; to our knowledge, this is the first such study to include children.

Previous studies have reported that SARS-CoV-2 infection triggers substantial inflammation [5,17]. The American Physiological Society reported that COVID-19 is a cause of "thromboinflammation," which is consistent with the physiopathology of COVID-19.

Previous clinical studies and case reports have indicated that children are less likely than adults to become infected with SARS-CoV-2; children also exhibit a milder disease course [18,19]. These differences may be explained by a few observations. The number of ACE-2 receptors, used by the SARS-CoV-2 virus to enter the cell [2], decreases with age; this results in failed angiotensin-2 (ANJ-2) catabolism [20,21]. ANJ-2 has vasoconstrictor, fibrotic, and pro-inflammatory effects. SARS-CoV-2 may also downregulate ACE-2 receptors upon entry into the cell [22]. Therefore, ANJ-2 levels may increase again, leading to

Table 1
Demographic and laboratory values of patients with Covid-19 and control group.

Parameters	Covid-19 (n= 19)	Control (n= 20)	P
Age (years)	12.42±3.3	13.35±1.2	*0.588
Gender (Male/Female)	12/7	10/10	*0.341
C-Reactive Protein (CRP) (mg/L)	94.55±84.7	10.57±16.4	**0.019
Sedimentation (mm/hour)	28.21±12.9	6.85+3.7	**0.000
D-dimer (ng/ml)	898.78±645.7	113.30±26.0	**0.000

*Not significant Mann-Whitney U test, **Significant Mann-Whitney U test, Values are presented as means ± standart deviations.

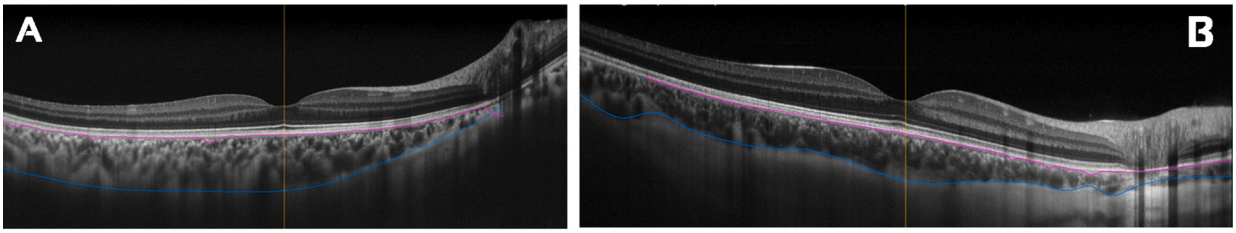

Fig. 1. A, Thickened choroid caused by inflammation in the acute phase of COVID-19; B, normal choroid in controls.

Table 2
Comparison of the choroidal thickness measurements, between the Covid-19 and control groups.

Choroidal thickness	Covid-19 (*n*= 19)	Control (*n*= 20)	*p**
Subfoveal (central) (μ)	334.94±33.7	311.20±17.5	*0.141
Nasal 600 (μ)	317.42±33.8	307.90±23.2	*0.792
Nasal 1200 (μ)	313.47±30.5	303.40±37.7	*0.513
Temporal 600 (μ)	311.26±30.7	301.00±20.8	*0.309
Temporal 1200 (μ)	303.05±25.8	290.50±22.6	*0.120

μ= Micron.
*Not significant Mann-Whitney U test, **Significant Mann-Whitney U test, Values are presented as means ± standart deviations.

Table 3
Comparison of the macular optical coherence tomography angiography measurements, between the Covid-19 and control groups.

Parameters	Covid-19 (*n*= 19)	Control (*n*= 20)	*p**
Foveal MT(μ)	248.05±16.9	267.10±19.8	**0.003
Avarage MT(μ)	270.84±66.5	305.55±9.2	**0.000
Vessel density(mm^{-1})			
Center	3.77±0.9	4.11±1.1	*1.000
Inner	7.62±1.0	8.81±0.8	**0.000
Outer	8.47±1.3	9.99±0.8	**0.000
Full	8.49±0.8	9.06±0.5	**0.013
Perfusion density			
Center	18.91±1.3	20.13±3.5	*0.496
Inner	37.95±2.1	40.40±3.7	**0.015
Outer	48.70±2.7	49.30±3.3	*0.627
Full	39.75±2.2	42.82±2.6	**0.000
Foveal avascular zone			
Area(mm^2)	1.65±6.1	0.40±0.1	**0.000
Perimeter(mm)	2.25±0.4	3.50±0.6	**0.000
Circularity index	0.71±0.0	0.38±0.9	**0.000

*MT=Macular thickness, μ=Micron, mm=Millimeter, *not significant Mann-Whitney U test, **significant Mann-Whitney U test, Values are presented as means ± standart deviations.*

undesirable effects. Because children have higher levels of ACE-2 receptors, the impact of COVID-19 may be limited.

The inflammatory component of the aforementioned thromboinflammation is related to ACE-2. Additionally, SARS-CoV-2 may also cause endotheliitis, vasculitis, and a hypercoagulable state. Iba et al. [13] reported that the coagulation cascade is triggered by endotheliopathy caused by direct endothelial infection and the indirect effects of inflammation. In the same study, it was found that D-dimer and fibrinogen levels increased in COVID-19 patients [please check whether part of the sentence is missing] [13]. Endothelial structures in children are less damaged; therefore, the impact of disease may be limited.

Because ACE-2 receptors are also present in the endothelium, SARS-CoV-2 can affect the entire vascular system and involve multiple organs, including the eyes. A previous immunohistochemical study investigated the effects of COVID-19 on the eyes; in 10 eyes of five dead COVID-19 patients, endothelial damage and microthrombi were found in eight eyes. Four patients had microthrombi in choriocapillaris and larger choroidal vessels. These findings were not observed in control eyes, suggesting that they were related to COVID-19 [23]. SARS-CoV-2 RNA was detected in three enucleated eyes of 14 dead COVID-19 patients [24]. The findings thus far suggest ocular involvement in COVID-19 patients.

Previous studies have evaluated the retinal vascular structures of adult COVID-19 patients using OCTA. COVID-19 patients reportedly have abnormal VD. A study of 31 COVID-19 patients reported reduced VD and PD values during the acute phase of disease [9,25–27], similar to the findings in our study. The inner, outer, and full sectors, which remain outside of the center VD and PD, were thinner. center VD was also reduced, although this difference was not statistically significant. These findings imply the presence of microvascular changes in the retina of COVID-19 patients during the acute phase of disease. There are many potential reasons for such changes. Endotheliitis, caused by the pro-inflammatory state during the acute phase of disease, may have triggered these changes. An elevated C-reactive protein level and an elevated sedimentation rate are indicators of inflammation in COVID-19 patients. Similarly, a subclinical hypercoagulable state was triggered by microthrombi and vascular disruption. The presence of an elevated D-dimer level also supports this hypothesis. D-dimer levels were remarkably high in our patients, compared with controls, suggesting a hypercoagulable state among patients. In a study regarding D-dimer levels in adult COVID-19 patients, VD and PD levels were significantly reduced in 48 of 80 patients with D-dimer levels $\geq$ 500 ng/mL [9]. In our study of 19 patients, we did not find such a relationship; however, 11 of our 19 patients had D-dimer levels $>$ 500 ng/mL, with a mean value of 898.7 $\pm$ 645.7. D-dimer levels may affect VD and PD by triggering microthrombosis. The decrease in PD value may be caused by reduced perfusion and a hypercoagulable state. Another reason could be increased vascular fibrosis related to the inflammation and hypoxia that occur in COVID-19. These processes inevitably trigger ischemia. The SERPICO-19 study, conducted in Italy, included 54 COVID-19 patients and 133 controls; it found cotton wool spots in 4 of 19 COVID-19 patients and in zero controls. Cotton wool spots represent ischemic areas. In the same study, vessels around the optic nerve head with diameters of 0.5 and 1 disk were automatically segmented by the software. The software selected four main vessels to obtain the mean artery and mean vein diameters, then automatically calculated these diameters. Significantly increased mean artery and mean vein diameters were found in COVID-19 patients [10]. Vein length was also associated with disease severity. A molecular study of arterial responses under short-term hypoxic conditions demonstrated arterial dilatation mediated by various receptors [28]. In the present study, although patients were examined during the acute phase of disease, the observed changes in PD may have been caused by short-term hypoxia. Similarly, studies that investigated the relationship between retinal veins and oxygen saturation reported a wider diameter of retinal veins under lower arterial oxygen saturation levels [29]. These findings may explain the negative impact of COVID-19-associated ischemia on PD. In our study, we also found increased FAZ area among COVID-19 patients; this was presumably related to temporary ischemia and microthrombi during the acute phase of disease.

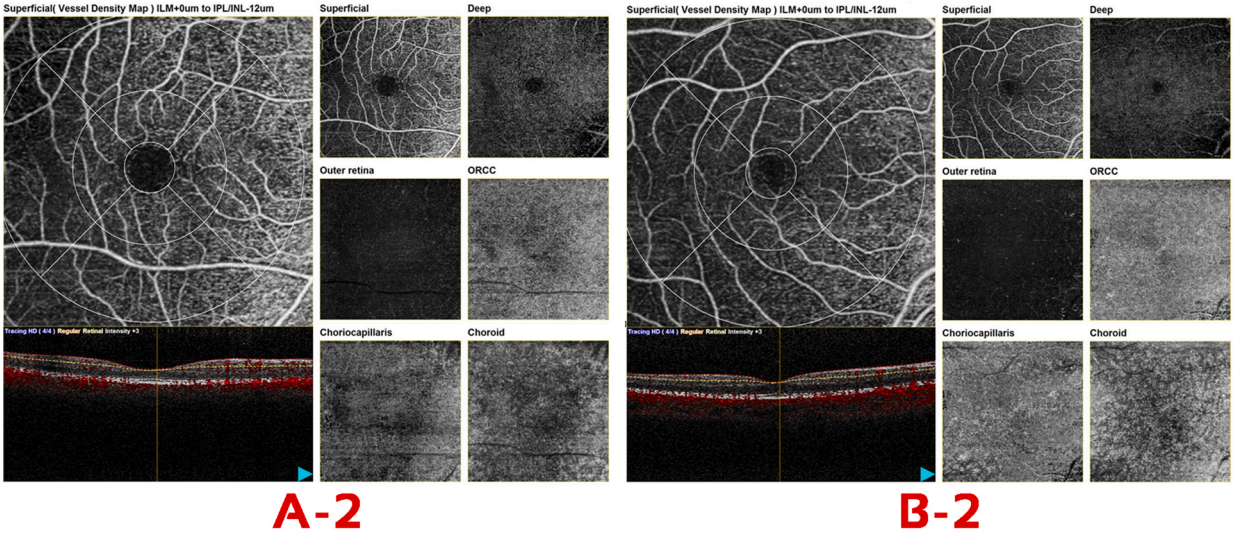

Fig. 2. A2, Foveal avascular zone (FAZ) area may expand in the acute phase of COVID-19 because of temporary ischemia and microthrombi; B2, Normal FAZ area in controls.

In a previously reported case, unilateral panuveitis and optic neuritis occurred prior to pulmonary symptoms. The authors of that report presumed that this progression was caused by inflammation or ischemia; the inflammation may have been caused by direct viral infiltration into ocular or choroidal tissue [30]. In our study, we also investigated the choroid to evaluate its role in the spread of inflammation. Although the difference was not statistically significant, we found increased choroidal thickness in all five measurements performed at intervals between 600 and 1200 μ from the central, nasal, and temporal regions. This implies choroidal inflammation during the acute phase of COVID-19, which may damage the outer retinal layer vasculature. Our findings of reduced central and mean macular thicknesses may represent temporary changes caused by early choroidal inflammation.

As previously mentioned, several factors may explain why these observed changes do not cause clinical symptoms, especially in children. First, higher ACE-2 levels in children enable metabolization of ANJ-2, preventing the clinical symptoms of its anti-fibrotic, anti-inflammatory, and vasodilator effects. Second, the presence of a healthier endothelial structure in children may protect against damage. Although these factors lead to a better prognosis among children, our OCTA findings demonstrate subclinical changes, which suggest the need for ophthalmological follow-up (e.g., detailed posterior segment examinations) among children with COVID-19.

There were some limitations in our study. First, this study included a small sample size. However, it is more difficult to obtain high-signal-strength OCTA images in children than in adults. Second, we only evaluated patients in the acute phase of the disease; we did not investigate long-term changes, which should be the focus of future studies.

In conclusion, COVID-19 patients may exhibit ophthalmological involvement, which merits further investigation. Ophthalmological involvement with COVID-19 affects both the anterior and posterior segments. Therefore, posterior segment examinations should also be performed. Importantly, children can also exhibit subclinical ophthalmological involvement; they should undergo follow-up eye examinations.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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