To cite this article: Aydin n, Tufek M, Capraz M, Nalcacioglu. Are the optic nerve head parameters and retinal nerve fiber layer thickness affected in patients who had a mild Covid- 19 infection?. Turk J Clin Lab 2023; 4: 658-664

Research Article

Are the optic nerve head parameters and retinal nerve fiber layer thickness affected in patients who had a mild Covid- 19 infection?

Hafif Covid-19 enfeksiyonu geçiren hastalarda optik sinir başı parametreleri ve retina sinir lifi tabakası kalınlığı etkilenir mi?

Nihat Aydin[1], Melek Tufek*[1], Mustafa Capraz[2], Pinar Nalcacioglu[3]

[1]Department of Ophthalmology, Amasya University, Sabuncuoglu Serefeddin Education and Research Hospital, Amasya, Turkey

[2]Department of Internal Medicine, Amasya University, Sabuncuoglu Serefeddin Education and Research Hospital, Amasya, Turkey

[3]Department of Ophthalmology, Yildirim Beyazit University Medical School, Ankara, Turkey

ABSTRACT

Aim: The aim of this study was to evaluate the peripapillary retinal nerve fiber layer (RNFL) thickness and optic nerve head (ONH) parameters by using a spectral domain optical coherence tomography (SD-OCT) device in patients who had a history of a mild-COVID-19 infection.

Material and Methods: This prospective cross-sectional study included 70 patients who had a history of a mild COVID-19 infection and 65 healthy individuals. After detailed ophthalmological examination, the peripapillary RNFL thickness and ONH parameters were measured with the SD-OCT device in all patients.

Results: No significant difference was present between the groups in terms of age and gender (p=0.907, p=0.979, respectively). The mean, superior, inferior, nasal, and temporal peripapillary RNFL thicknesses were not statistically significantly different between the groups (p=0.797, p=0.488, p=0.079, p=0.820, p=0.820, respectively). Regarding the ONH parameters, no significant difference was found between the groups in terms of disc area, cup area, rim area, cup/disc ratio, horizontal and vertical cup/disc ratio and cup and rim volume (p=0.239, p=0.995, p=0.522, p=0.959, p=0.716, p= 0.873, p=0.476, p=0.701, respectively).

Coclusion: No significant difference was found between the patients who had a mild COVID-19 infection and the control group in terms of the peripapillary RNFL thickness and ONH parameters. However, the results may vary according to the severity of the infection and the acute and long-term data.

Key words: COVID-19, peripapillary retinal nerve fiber layer thickness, optic nerve head parameters, optic coherence tomography,

Corresponding Author*: Melek Tufek, Department of Ophthalmology, Amasya University, Sabuncuoğlu Serefeddin Education and Research Hospital, Amasya, Turkey,
E-mail: melektfk@hotmail.com
Orcid: 0000-0001-5516-7412
Doi: 10.18663/tjcl.1268946
Recevied: 21.03.2023 accepted: 09.11.2023

TJCL Volume 14 Number 4 p: 658-664

ÖZ

Amaç: Bu çalışmanın amacı hafif COVID-19 enfeksiyonu geçiren hastalarda peripapiller retina sinir lifi tabakası (RSLT) kalınlığı ve optik sinir başı (OSB) parametrelerini, spektral domain optik koherens tomografi (SD-OKT) cihazı kullanarak değerlendirmektir.

Gereç ve Yöntemler: Bu prospektif cross-sectional çalışmaya hafif COVID -19 enfeksiyonu geçirmiş 70 hasta ile 65 sağlıklı birey dahil edildi. Ayrıntılı oftalmolojik muayene sonrası tüm hastalara SD-OKT cihazı ile peripapiller RSLT kalınlığı ve OSB parametrelerinin ölçümleri yapıldı.

Bulgular: Gruplar arasında yaş ve cinsiyet açısından anlamlı farklılık yoktu (p=0.907, p=0.979, sırasıyla). Ortalama, superior, inferior, nazal ve temporal peripapiller RSLT kalınlığı, gruplar arasında istatistiksel açıdan anlamlı değildi (p=0.797, p=0.488, p=0.079, p=0.820, p=0.820, sırasıyla). OSB parametrelerine bakıldığında disc alanı, cup alanı, rim alanı, cup/disc oranı, horizontal ve vertical cup/disc oranı, cup ve rim volume açısından gruplar arasında anlamlı farklılık tespit edilmedi (p=0.239, p= 0.995, p=0.522, p=0.959, p=0.716, p= 0.873, p=0.476, p=0.701, sırasıyla).

Sonuçlar: Hafif COVID-19 enfeksiyonu geçiren hastalarla kontrol grubu arasında peripapiller RSLT kalınlığı ve OSB parametreleri açısından anlamlı farklılık tespit edilmedi. Ancak bulduğumuz bu sonuçlar enfeksiyonun şiddeti ile enfeksiyonun akut ve uzun dönem verilerine göre değişkenlik gösterebilir.

Anahtar Kelimeler: COVID-19, peripapiller retina sinir lifi tabakası kalınlığı, optik sinir başı parametreleri, optik koherens tomografi

Introduction

Coronavirus disease 2019 (COVID-19) infection, caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus, which emerged in the city Wuhan in China and spread globally was later declared a pandemic by the World Health Organization (WHO). The SARS-CoV-2 virus is an enveloped, single-stranded RNA virus [1, 2]. Although COVID-19 infection mostly progresses with respiratory system findings such as fever, cough, and dyspnea, many neurological and ophthalmological symptoms are also encountered [3, 4]. The angiotensin-converting enzyme (ACE)-2 receptor is the main entry receptor of SARS-CoV-2 into the body, and neurons and glial cells are targeted by the virus because they express ACE-2 [5]. ACE-2 receptor activation has also been detected in the aqueous humor, retina, ciliary body, vitreous, and inner nuclear layer, and the photoreceptors, and Müllerian and ganglion cells [6]. Conjunctivitis, keratoconjunctivitis, episcleritis, uveitis, retinitis, retinal vascular occlusion as well as optic neuritis, viral encephalitis, cerebrovascular disease, acute transverse myelitis, leukoencephalopathy, toxic encephalopathy, acute disseminated encephalomyelitis have been reported in COVID-19 patients [4, 7]. Another target tissue of the SARS-CoV-2 virus is the vascular endothelium. The endothelium is responsible for immunological response regulation, the inflammatory balance, hemodynamic stability, and hemostasis through thrombotic and fibrinolytic pathways in healthy individuals [8]. Ischemic lesions such as cotton wool spots and microhemorrhages have been observed in the retina after thrombosis and inflammation caused by direct invasion of the endothelial cells [9, 10]. Besides, hyperreflective lesions have been detected in the inner plexiform layer (IPL) and ganglion cell layer (GCL), more prominently in the papillomacular bundle, during imaging performed with spectral domain optical coherence tomography (SD-OCT) [10].

The retinal nerve fiber layer (RNFL) consists of neuronal axon bundles. Structural changes due to loss of ganglion cell axons occur in the RNFL in ocular diseases such as glaucoma and in conditions such as aging. The SD-OCT device is a non-invasive method used to measure RNFL thickness and evaluate the structural features of the optic nerve [11]. Our aim in this study was to detect the changes in the optic nerve head (ONH) parameters and peripapillary RNFL thickness in patients with a history of a mild COVID-19 infection with the SD-OCT device and compare them with a healthy control group since SARS-Cov-2 has been reported to be a neurotropic virus [5] with retinal and optic nerve involvement in previous studies [10, 12]. Material and Methods This prospective cross-sectional study was conducted at the Sabuncuoğlu Şerefeddin Training and Research Hospital between March 2022 and September 2022. The study was approved by the Ethics Committee of Amasya University. All research procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects.

The 70 eyes of 70 patients who had a history of a mild COVID-19

infection and the 65 eyes of 65 age- and gender-matched healthy individuals were included in the study. The patients were divided into 2 groups. Group 1 consisted of patients who had received a diagnosis of COVID-19 infection at the Sabuncuoğlu Şerefeddin Training and Research Hospital's Infectious Disease Outpatient Department and had then been referred to the Ophthalmology Outpatients Department after their treatment was completed, while Group 2 included healthy individuals with a negative rRT-PCR test and without any symptoms. Mild COVID-19 infection was defined as symptoms such as fever, cough, sore throat, malaise, muscle pain, headache, and the loss of taste and smell; no dyspnea or lung involvement findings on imaging; no need for hospitalization; a blood oxygen saturation value in room air (SpO2) of >93%; and no need for oxygen support or systemic steroid treatment. A detailed history of ocular and systemic disease was obtained from all patients.The diagnosis of COVID-19 infection was made by detecting the viral genome in a nasopharyngeal swab sample with the rRT-PCR test. Ophthalmological examination and SD-OCT were performed within 2 weeks to 3 months after rRT-PCR test positivity. All patients had negative PCR tests and were asymptomatic during the ophthalmologic examination. The demographic characteristics of all participants and the clinical course of their disease were recorded.

Exclusion criteria were a history of COVID-19 infection with hospitalization or systemic steroid therapy; diabetes, systemic hypertension, or neurodegenerative disease; previous intraocular surgery; a history of ocular trauma, glaucoma, optic neuritis, congenital optic disc anomaly, or retinal and choroidal disease; age < 18 years; pregnancy; a refractive error > ± 2 diopters (D); corneal or lens opacities that prevented SD-OCT imaging; and a history of smoking.

All participants underwent a detailed ophthalmologic examination including best-corrected visual acuity (BCVA) with the Snellen chart, anterior segment and dilated fundus examination with the slit-lamp, central corneal thickness (CCT) measurement with the Nidek UP-1000 (Nidek Co., Ltd., Aichi, Japan), and intraocular pressure (IOP) measurement with the Goldmann applanation tonometer. The right eye of all participants was included in the study. The SD-OCT device (3D OCT-2000, Topcon, Japan) was used for the measurement of peripapillary RNFL thickness and ONH parameters. OCT scans were performed by an experienced technician after pupil dilation and images were evaluated at different time intervals by two experienced physicians (NA, MT), with the groups masked. Sections with a signal strength index < 6/10 were excluded. Optic disc scanning was performed within a 6X6 mm2 area during the analysis of ONH parameters. Thanks to the software, the end of the retinal pigment epithelium, choriocapillaris and photoreceptors was considered the beginning of the ONH with the disc borders being determined automatically. Peripapillary RNFL thickness was measured with an automatic computer algorithm after the user placed a 3.4 mm diameter circle around the disc at an equal distance to all quadrants, and the average of three consecutive circular scans was taken (Figure 1). ONH parameters including the mean, superior, inferior, nasal and temporal peripapillary RNFL thicknesses in addition to the disc area, rim area, cup area, cup/disc ratio, vertical and horizontal cup/disc ratio, and cup and rim volume values of all patients were recorded.

Statistical analysis

Statistical analysis was performed using the SPSS software for Windows, version 22 (SPSS Inc., Chicago, IL, USA). The continuous variables were reported as mean±standard deviation while the categorical variables were summarized with the use of frequencies. The normality of all data samples was checked with the Kolmogorov–Smirnov test. Only the right eye values were used for statistical purposes. The chi-square test was used in the analysis of categorical variables. The independent t-test for paired data was used to compare the parameters between the two groups when the normality criteria were met. The Mann-Whitney U test was performed if the data distribution was not normal. A p value <0.05 was accepted as statistically significant.

Results

The 135 eyes of 135 patients were included in this study. Group 1 consisted of 70 patients (40 females, 30 males) and Group 2 of 65 patients (37 females, 28 males). The mean age was 45.4±12.6 years in Group 1 and 45.2±9.8 years in Group 2. No significant difference was present between the groups in terms of age or gender (p=0.907, p=0.979, respectively). Besides, no significant difference was observed in terms of IOP, BCVA, refractive error, and CCT (p=0.814, p=0.335, p=0.865, p=0.750, respectively). The demographic and clinical characteristics of the patients are summarized in Table-1.

Comparison of the groups in terms of peripapillary RNFL thickness revealed that the mean, superior, inferior, nasal, and temporal RNFL thickness values were lower in Group 1 than Group 2 but without statistical significance (p=0.797, p=0.488, p=0.079, p=0.820, p=0,820, respectively). Besides, no

significant difference was found between the groups in terms of ONH parameters including disc area, cup area, rim area, cup/disc ratio, horizontal and vertical cup/disc ratio, and cup and rim volume (p=0.239, p=0.995, p=0.522, p=0.959, p=0.716, p= 0.873, p=0.476, p=0.701, respectively). Data regarding peripapillary RNFL thickness and ONH parameters have been summarized in Table-2 and Table-3.

Table 1. The demographic and clinical characteristics of the subjects

Parameters mean±SD	COVID-19 group (n=70)	Control group (n=65)	p value
Age, years	45.4±12.6		
Sex (%) Female	40 (57.1%)		
Male	30 (42.9%)	45.2±9.8	0.907*
IOP (mmHg)	15.1±2.8	37 (56.9%)	0.979**
Refractive Error (D)	-0.08±0.7	28 (43.1%)	
CCT (µm)	532.1±25.4	-0.08±0.6	0.814***
Visual acuity	1.0 (1.0)	533.5±24.8	0.750*
Duration after COVID 19 (days)	43.9±20.7	1.0 (1.0)	0.335***

IOP: Intraocular pressure, D: Diopter, CCT: Central corneal thickness, *:Independent t-test, **: Chi square test, ***: Mann-Whitney U test

Table 2. Comparison of the peripapillary retinal nerve fiber layer thickness between the groups

Parameters mean±SD	COVID-19 group (n=70)	Control group (n=65)	p value
Mean RNFL (µm)	111.5±10	112.6±11.5	0.797*
Superior RNFL (µm)	135.3±17.2	137.3±15.8	0.488**
Inferior RNFL (µm)	135.7±16.2	140.6±16.3	0.079**
Nasal RNFL (µm)	86.7±15.4	87.2±12.9	0.820**
Temporal RNFL (µm)	80±12.9	80.5±11.5	0.820**

RNFL: retinal nerve fiber layer, *: Mann-Whitney U test, **: Independent t-test

Table 3. Comparison of the optic nerve head parameters between the groups

Parameters mean±SD	COVID-19 group (n=70)	Control group (n=65)	p value
Disc area	2.6±0.5	2.6±0.3	0.239*
Cup area	0.7±0.4	1.9±0.3	0.995**
Rim area	1.9±0.4	0.3±0.1	0.522*
C/D ratio	0.3±0.1	0.5±0.1	0.959**
Horizontal C/D ratio	0.5±0.1	0.5±0.1	0.716*
Vertical C/D ratio	0.5±0.1	0.5±0.1	0.873**
Cup volume	0.15±0.1	0.14±0.1	0.476*
Rim volume	0.6±0.2	0.6±0.2	0.701**

C/D: cup/disc ratio, *: Mann-Whitney U test , **: Independent t-test

Discussion

The SARS-CoV-2 virus is a neurotropic virus and has been observed to involve the optic nerve in humans and animal models [5, 12, 13]. Our aim in this study was to investigate whether SARS-Cov-2 affects the peripapillary RNFL thickness and ONH parameters in patients with mild-COVID-19 infection by using the SD-OCT device, which allows non-invasive evaluation of the optic nerve. Mean peripapillary RNFL and sectoral thickness values were lower in the group with a history of SARS-CoV-2 infection in our study, but this difference was not statistically significant. No significant difference was observed between the groups in terms of ONH parameters either.

The SARS-CoV-2 virus often causes respiratory system findings, and at least one neurological symptom has been reported in more than 90% of the patients. These neurological symptoms may begin before the typical respiratory symptoms or may be the only symptom of SARS-CoV-2 infection in asymptomatic carriers [3]. While the most common of these COVID-19 infection symptoms are headache, confusion, and dizziness, serious life-threatening diseases such as stroke, encephalitis, Miller Fisher Syndrome, Guillain-Barr'e syndrome, acute myelitis, and sinus vein thrombosis can also be encountered [3, 12]. The spread of the virus to the central nervous system (CNS) occurs either through the blood circulation or directly through the nerve endings, and detection of the RNA of SARS-CoV-2 in the cerebrospinal fluid of symptomatic patients indicates the invasion of the virus into the CNS [14, 15]. The SARS-CoV-2 virus has also been shown to cause ocular involvement [4, 10]. As in the CNS, the RNA of the SARS-CoV-2 virus has been found in the retina of patients who have died because of COVID-19 [6].

COVID-19 infection-related optic neuritis cases have also been reported [12, 16]. Direct invasion of the SARS-CoV-2 virus into the optic nerve is mediated by the ACE-2 receptor. This receptor is a highly expressed cell surface receptor in the heart, kidney, and lung, where SARS-CoV-2 enters the host cell; it is also found in retinal vascular endothelial cells, Müller cells, ganglion cells, photoreceptors, and the choroid and ciliary body [6, 17]. Fundus examination of patients with COVID-19 infection has revealed peripapillary flame-shaped hemorrhages and cotton wool spots, peripheral retinal hemorrhages, hard exudates, and retinal sectoral pallor, while OCT imaging has shown hyperreflective lesions in the GCL and IPL [10, 18].

The RNFL consists of the unmyelinated retinal ganglion cell axons that form the optic nerve. The radial peripapillary

capillary (RPC) plexus is parallel to the axons of the RNFL and is responsible for supplying the ganglion cell axons. A positive correlation has been reported between RPC plexus density and RNFL thickness in the human retina [19, 20]. Uğurlu et al. have reported significantly lower RPC plexus values in symptomatic COVID-19 patients than in asymptomatic patients and the control group, and significantly lower thickness values of the RNFL and ganglion cell complex (GCC) layers in the COVID-19 patient group with neurological symptoms compared to the control group [21]. Cennamo et al. have found lower RPC and RNFL values in the group with patients who had COVID-19 infection than the control group [22]. These studies indicate that one of the mechanisms of how COVID-19 infection affects the optic nerve is through the vascular structures since the binding of SARS-CoV-2 to endothelial cells triggers systemic inflammation, thrombosis, and microvascular dysfunction [9]. The microangiopathic changes that develop as a result affect the RNFL thickness and the optic nerve.

SARS-CoV-2 infection causes various degrees of inflammatory response and alveolar damage, and leads to hypoxemia that predisposes to multiple organ and especially CNS dysfunction [23]. The neural retina has high metabolic needs and is highly susceptible to hypoxia. Neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) are expressed in CNS neuronal injuries, and excessive NO production via nNOS and iNOS in the retina during hypoxia has been shown to cause neuronal damage in rats [24]. CNS injuries also cause changes in the microglial cells, which are immunocompetent cells located in the retina that are known to be activated in response to hypoxia [24]. An increase in the number of microglia mediated by interferon γ (INF-γ) also occurs in the outer retinal layers and subretinal space in systemic viral infections and triggers neurodegenerative diseases [25]. All these indicate that changes in RNFL thickness and ONH parameters may occur secondary to the hypoxemia and immunological response caused by COVID-19 infection.

There are various studies on the effect of COVID-19 infection on RNFL and ONH parameters. Various other studies have found no significant difference between the group of patients with a history of COVID-19 infection and healthy individuals in terms of mean peripapillary RNFL, similar to our results [26, 27]. Ozmen et al. have found no significant difference between the groups in terms of RNFL and ganglion cell- inner plexiform layer (GC-IPL) thickness in all quadrants in their study on patients with a history of severe COVID-19 infection [28]. However, Burgos-Blasco et al. have reported an increase in the thickness of the peripapillary RNFL and macular GCL in patients with neurological symptoms such as anosmia and ageusia compared to asymptomatic patients and the control group in their study on early stage COVID-19 patients [29]. Another study found the peripapillary RNFL thickness to be thicker in all quadrants after COVID-19 infection compared to the control group; however, this change was not statistically significant and no such difference was reported between the groups in terms of ONH parameters either [30]. We believe that these differences in the results may be related to the severity of the COVID-19 infection, the presence of neurological symptoms, and the stage of the infection. Besides, the difference in the time elapsed between the diagnosis of COVID-19 infection and the ophthalmological examination and thus the corresponding difference in the level of inflammatory cytokines may also explain the different results.

Our study had various limitations. The first of these was that it was conducted with a small sample group. Another limitation was the lack of acute and chronic COVID-19 infection data of our patients, and that we could not compare them with these data. Besides, only patients with mild-COVID-19 infection were included in our study, and moderate and severe COVID-19 patients who required hospitalization or needed intensive care were excluded. Therefore, we cannot generalize our results to all patients with COVID-19 infection.

Conclusion

Although peripapillary RNFL thickness was lower in the group with patients who had a history of COVID-19 infection in our study, this difference was not statistically significant. There was no significant difference between the groups in terms of ONH parameters either. The fact that our patient group had a history of mild-COVID-19 infection and that we evaluated the post-infection quarterly data may have influenced our results. Therefore, it is necessary to support these results with future studies on larger sample groups and subjects in the acute and late stages of infections of various severity levels.

Funding

No funding was obtained in this study

Disclosure statement

The authors declare that they have no conflict of interest

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