JOURNAL OF
CONTEMPORARY MEDICINE
DOI:10.16899/jcm.1081927
J Contemp Med 2022;12(4):495-499

Original Article / Orijinal Araştırma

Optic Nerve and Retinal Layer Measurements with Optical Coherence Tomography in PCR Positive and Negative COVID-19 Patients

PCR Pozitif ve Negatif COVID-19 Hastalarında Optik Koherens Tomografisi ile Optik Sinir ve Retinal Katman Ölçümleri

Nihat Aydin[1], Mustafa Çapraz[2]

[1]Amasya University Sabuncuoğlu Şerefeddin Training and Research Hospital, Eye Diseases, Amasya, Turkey
[2] Amasya University Sabuncuoğlu Şerefeddin Training and Research Hospital, Internal Medicine, Amasya, Turkey

Abstract

Aim: COVID-19 targets all tissue and organ systems, not just the lungs. The optic nerve and retina with extensive microvascular nutrition are prone to viral involvement. Optical coherence tomography is a technology that provides detailed information about both optic nerve and retinal structure. The study was carried out to investigate possible changes in the optic nerve and retinal structure of patients with COVID-19 infection, dividing PCR positivity or negativity.

Material and Method: Thirty PCR positive COVID-19 patients with different ages and varying admission complaints were included in the study. Twenty-five COVID-19 patients who were PCR negative with similar age and gender were selected as a secondary group for comparison. All patients underwent ophthalmologic examination, including slit-lamp biomicroscopy, funduscopy, and Optical Coherence Tomography (OCT). These examinations were performed four weeks after the diagnosis of COVID-19 for full compliance with the mandatory isolation. In addition, Retinal Nerve Fiber Layer Thickness (RNFL), retinal thickness, and retinal volume measurements were performed.

Results: No statistical significance was observed in any parameter between the PCR positive or negative patients when the comparative analysis for both eyes in RFNL measurements. There was a significant difference in retinal thickness measurements between the PCR positive and negative groups regarding left eye central retinal thickness (p=0.047). In addition, there was no statistical difference in retinal volume measurements.

Conclusion: Retinal imaging with optical coherence tomography is a non-invasive, reproducible, and rapid technique in which subclinical or overt retinal pathologies can be detected during COVID-19. Therefore, management of COVID-19 patients should include retinal assessment with close follow-up, especially in patients with headaches and optic pain.

Keywords: Optical coherence tomography, retinal nerve fiber layer thickness, COVID-19, optic nerve

Öz

Amaç: COVID-19 sadece akciğerleri değil tüm doku ve organ sistemlerini hedef almaktadır. Kapsamlı mikrovasküler beslenmeye sahip optik sinir ve retina viral tutuluma yatkındır. Optik koherens tomografi, hem optik sinir hem de retina yapısı hakkında detaylı bilgi veren bir teknolojidir. Çalışma, COVID-19 enfeksiyonu olan PCR pozitif ve negatif hastaların optik sinir ve retina yapısındaki olası değişiklikleri araştırmak amacıyla gerçekleştirilmiştir.

Gereç ve Yöntem: Çalışmaya farklı yaş ve farklı başvuru şikayetlerine sahip PCR pozitif 30 COVID-19 hastası dahil edildi. Benzer yaş ve cinsiyet grubundaki yirmi beş PCR negatif COVID-19 hastası karşılaştırma yapabilmek adına ikincil bir grup olarak tanımlandı. Tüm hastalara yarık lamba biyomikroskopisi, fundoskopi ve Optik koherens tomografi (OCT) dahil oftalmolojik muayene yapıldı. Bu muayeneler, zorunlu izolasyona tam uyum için COVID-19 tanısından dört hafta sonra yapıldı. Ayrıca Retina Sinir Lif Tabaka Kalınlığı (RNFL), retina kalınlığı ve retina hacmi ölçümleri yapıldı.

Bulgular: RNFL ölçümlerinde her iki göz için karşılaştırmalı analiz yapıldığında PCR pozitif COVID-19 hastaları ile PCR negatif grup arasında herhangi bir parametrede anlamlı fark gözlenmedi. Retina kalınlığı ölçümlerinde sol göz santral retina kalınlığı açısından PCR pozitif ve negatif gruplar arasında anlamlı fark vardı (p=0.047). Bununla birlikte, retina hacim ölçümlerinde istatistiksel bir fark yoktu.

Sonuç: Optik koherens tomografi ile retina görüntüleme, COVID-19 sırasında subklinik veya aşikar retina patolojilerinin tespit edilebildiği, invazif olmayan, tekrarlanabilir ve hızlı bir tekniktir. Bu nedenle COVID-19 hastalarının yönetimi, özellikle baş ağrısı ve oküler ağrısı olan hastalarda yakın takip ile retina değerlendirmesini içermelidir.

Anahtar Kelimeler: Optik koherens tomografi, retina sinir lif tabaka kalınlığı, COVID-19, optik sinir

Corresponding *(İletişim)*: Nihat Aydin, Amasya University Sabuncuoğlu Şerefeddin Training and Research Hospital, Eye Diseases, Amasya, Turkey
E-mail *(E-posta)*: drnihataydin@gmail.com
Received *(Geliş Tarihi)*: 02.03.2022 **Accepted *(Kabul Tarihi)*:** 17.04.2022

INTRODUCTION

COVID-19 is caused by SARS-COV-2, a novel beta coronavirus that has caused a life-threatening infection that has caused millions of deaths worldwide. SARS-COV2 uses a spike protein that binds directly with a strong affinity to human angiotensin-converting enzyme 2 (ACE2) to enter human cells.[1] Although the lungs are the primary site of involvement in COVID-19 infection, problems related to the disease have been detected in various organs. In the COVID-19 infection, which is still not prevented globally, optic surface disorders, mainly conjunctivitis, have been described in approximately 10% of patients.[2] However, little is known about how it affects the retina and the optic nerve as part of the central nervous system (CNS).[3] The human eye has its renin-angiotensin system, located not only on the eye's surface but also in the retina.[4] In addition, several human respiratory viruses (including coronavirus CoV) are neuroinvasive and neurotropic, with potential neuropathological consequences in vulnerable populations. The neurological symptoms seen in patients with viral infections are caused by what is known as a "cytokine storm", which includes pro-inflammatory and anti-inflammatory cytokines as an immune response to viral infection of the CNS. An exaggerated response to infection can lead to meningitis, encephalitis, meningoencephalitis, or death. The COVID-19 pandemic, caused by SARS-CoV 2, is a human respiratory virus that infects the respiratory tract and can cause pneumonia and respiratory failure similar to SARS-CoV, displaying neuroinvasive neurotropic abilities.[5] Optical coherence tomography (OCT) is a promising technology developed to evaluate tissue thickness in vivo, such as the retinal nerve fiber layer (RNFL). This technology was initially designed for fiberoptic use. OCT is a non-invasive imaging technique that obtains detailed retina images using low coherence light. It is a reliable and reproducible method for measuring retinal layers and detecting changes in layer thickness with high resolution.[6] This technique has been used successfully to monitor changes in retinal layers in several ophthalmological and neurological diseases such as glaucoma, multiple sclerosis, and Alzheimer's disease.[7,8] With a prototype instrument, OCT data was reported to correlate with the known topography of human retinas.[9] Reproducibility studies using an OCT prototype have shown standard distributions (SD) of measurement of RNFL and retinal thicknesses of approximately 10 to 20 µm (10%-20%) in normal and glaucomatous eyes.[10,11]

This study evaluated total, superior, and inferior peripapillary retinal nerve fiber layer thickness (RNFL), mean retinal thickness, central retinal thickness, and total retinal volume in COVID-19 patients according to PCR results. Thus, our study is the first in the literature that examines optic nerve and retina measurements according to PCR results in COVID-19 patients.

MATERIAL AND METHOD

Subjects

The study included 30 COVID-19 patients of different ages and admission complaints. The SARS-CoV-2 virus genetic material was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) in the nasal swab sample. Twenty-five COVID-19 patients of similar age and sex who were PCR negative were selected as a secondary comparison group. The PCR positive group was formed by patients with COVID-19 who presented in the hospital's Emergency Department (ED) and successfully recovered from the infection between 23 and 29 March 2020. Inclusion criteria were: 18 to 70 years old; SARS-CoV-2 infection was confirmed by a positive reverse transcriptase-polymerase chain reaction (RT-PCR) test from a nasopharyngeal swab and written informed consent. The PCR negative group consisted of patients diagnosed with COVID-19 by clinical examination and lung tomography but did not have SARS-CoV-2 virus in the swab test. Those who had ongoing symptoms were in quarantine, could not go to the hospital due to their general health condition, and had accompanying psychiatric, neurological, or eye diseases were excluded from the study. The individuals volunteered for the study by signing the informed consent form. After the pre-approval from the study by the Republic of Turkey Ministry of Health, ethical approval was obtained from the Amasya University Ethical Board with 13.09.2021-32307 date and number.

Ophthalmologic Exam and Optic Nerve Imaging

All patients underwent ophthalmologic examination, including slit-lamp biomicroscopy, funduscopy, and OCT. These examinations were performed four weeks after the diagnosis of COVID-19 for full compliance with the mandatory isolation. RNFL, retinal thickness, and retinal volume measurements were performed with the Topcon 3D 2000 (3D OCT 2000, Topcon Corporation, Tokio, Japan) OCT device. All peripapillary RNFLT measurements were made using a circular scan pattern centered on the optic nerve. The eye-tracking system allowed any subsequent OCT scan to be scanned precisely at the exact location as the last scan. The OCT software calculated the average RNFLT for the overall global (360 degrees). RNFL measurements were noted globally and in the three quadrants (superior, inferior, total). A single experienced physician carried out all OCT examinations.

Statistics

Data analysis was performed using SPSS version 24.00 (IBM, New Castle, NY, USA). Continuous variables were used as mean and standard deviation (SD), while numbers and percentages were used for categorical variables. Age and gender differences between the groups were compared using the Chi2 and t-student tests. The normality of the variables was evaluated using the Kolmogorov-Smirnov test. Student t-test was used for group comparisons of OCT measurements. Statistical significance was determined as 0.05.

RESULTS

While 43.3% of the PCR positive were women, the mean age group was 46.6±18.2. While 46.6% of the PCR negative group were women, the mean age was 47.3±15.9 years. There was no difference between the groups regarding age and gender (p=0.648 and p=0.716, respectively). No statistical significance was observed in any parameter between the PCR positive and negative patients when the comparative analysis for both eyes in RFNL measurements (**Table 1**).

Table 1. Peripapillary optical coherence tomography (OCT) results in Polymerase Chain Reaction (PCR) positive and negative COVID-19 patients.

Optic Nerve OCT (µm)	PCR positive (n=30)		PCR negative (n=25)		p value
	Mean	SD	Mean	SD	
Rnfl Total - Right	96.2	10.8	93.1	9.9	0.234
Rnfl Total - Left	99.1	8.0	93.3	8.4	0.116
Rnfl Superior - Right	115.5	13.9	103.5	14.4	0.432
Rnfl Superior - Left	116.8	11.7	101.6	11.9	0.537
Rnfl Inferior - Right	116.8	16.1	106.8	16.5	0.678
Rnfl Inferior - Left	123.6	17.1	107.9	17.8	0.719

SD: standard deviation; Rnfl: retinal nerve fiber layer.

There was a significant difference in retinal thickness measurements between the PCR positive and negative groups regarding left eye central retinal thickness (p=0.047). However, there was no statistical difference in retinal volume measurements (**Table 2**).

Table 2. Retinal thickness and volume measurements of Polymerase Chain Reaction (PCR) positive and negative COVID-19 patients.

Optical Coherence Tomography Measurements	PCR + (n=30)		PCR - (n=25)		p value
	Mean	SD	Mean	SD	
Average Retinal Thickness - Right (µm)	272.0	14.5	273.7	12.3	0.301
Average Retinal Thickness - Left (µm)	272.5	15.1	273.5	11.8	0.128
Central Retinal Thickness - Right (µm)	192.6	25.6	191.7	28.3	0.237
Central Retinal Thickness - Left (µm)	202.7	27.5	189.9	22.8	0.047
Total Retinal Volume - Right (µm3)	7.69	0.41	7.56	0.3	0.431
Total Retinal Volume - Left (µm3)	7.71	0.42	7.56	0.3	0.381

SD: standard deviation. +: positive, -: negative.

DISCUSSION

The retinal manifestations of COVID-19 infection are interesting. For example, one study reported fine cotton wool spots and focal hyperreflective areas on the inner retina in a small number of patients with confirmed COVID-19 infection.[12] On the other hand, another study suggested that hyperreflective areas on OCT scans may represent normal retinal vessels, and cotton wool spots may represent myelinated nerve fiber layer or be associated with other retinal pathologies.[13] Thus, these studies have shown that coronaviruses can induce a variety of retinal pathologies.

Table 3. Statistical data of RNFL and retinal measurements by PCR positive and negative group.

Variable	N	N*	Mean	SE Mean	StDev	Minimum	Q1	Median	Q3	Maximum
C RNFL T R	25	5	93.08	2.02	10.12	62.00	90.00	95.00	100.00	104.00
C RNFL T L	25	5	93.32	1.71	8.56	73.00	87.00	95.00	99.00	112.00
C RNFL S R	25	5	103.48	2.95	14.73	65.00	92.50	105.00	113.50	125.00
C RNFL S L	25	5	101.64	2.44	12.19	70.00	93.00	101.00	110.50	127.00
C RNFL I R	25	5	106.84	3.37	16.84	71.00	96.50	105.00	121.50	136.00
C RNFL I L	25	5	107.88	3.64	18.21	66.00	96.00	107.00	125.00	136.00
C ART R	25	5	273.67	2.51	12.55	246.60	264.15	276.20	281.25	298.50
C ART L	25	5	273.47	2.41	12.06	248.70	264.70	275.00	280.70	294.30
C CRT R	25	5	191.72	5.78	28.89	164.00	175.00	184.00	192.00	282.00
C CRT L	25	5	189.92	4.65	23.24	169.00	176.50	183.00	194.50	282.00
C TRV R	25	5	7.5576	0.0620	0.3102	6.9700	7.3050	7.5400	7.7800	8.2900
C TRV L	25	5	7.5624	0.0562	0.2811	7.0300	7.4000	7.5000	7.7600	8.2800
P RNFL T R	30	0	96.23	2.00	10.95	76.00	89.75	94.00	105.25	119.00
P RNFL T L	30	0	99.10	1.49	8.15	84.00	93.00	98.50	105.25	114.00
P RNFL S R	30	0	115.50	2.58	14.13	85.00	108.75	116.00	123.75	143.00
P RNFL S L	30	0	116.80	2.17	11.87	90.00	108.50	115.50	128.00	137.00
P RNFL I R	30	0	116.77	3.00	16.42	85.00	101.00	121.00	129.25	144.00
P RNFL I L	30	0	123.60	3.17	17.34	83.00	112.75	124.50	134.25	161.00
P ART R	30	0	271.97	2.68	14.70	243.20	258.73	272.20	281.38	298.90
P ART L	30	0	272.46	2.80	15.31	238.40	258.65	275.40	283.73	300.00
P CRT R	30	0	192.60	4.76	26.05	158.00	176.00	186.50	203.75	272.00
P CRT L	30	0	202.73	5.11	27.99	164.00	183.75	192.50	224.75	295.00
P TRV R	30	0	7.6887	0.0758	0.4153	6.8800	7.3125	7.7000	7.9525	8.4500
P TRV L	30	0	7.7090	0.0775	0.4243	6.7400	7.3275	7.7850	8.0225	8.4800

C: PCR negative, P: PCR positive, RNFL: retinal nerve fiber layer, ART: average retinal thickness, CRT: central retinal thickness, TRV: total retinal volume, T: total, S: superior, I: inferior, R: right eye, L: left eye, SE: standard error, StDev: standard deviation.

However, our study did not observe subtle or prominent central or peripheral retinal findings, such as vascular abnormalities or cotton wool spots determined by OCT scans. In addition, many studies have reported that ophthalmologic results and retinal findings are associated with the severity of COVID-19 infection.[14,15] However, retinal manifestations such as hemorrhages, cotton swabs, and vascular changes appear time-dependent.[16,17] One research found macular RNFL thickness in patients recovering from COVID-19 compared to healthy subjects.[18] Another study also showed localized thinning of RNFL in patients with COVID-19.[19] In contrast, our study could not observe a different outcome in COVID-19 patients regarding RNFL. Involvement of the inner retinal layers has been reported using OCT in multiple neurodegenerative diseases. Braak's hypothesis regarding its etiology in Parkinson's is that a neurotropic virus invades the nervous system. Interestingly, the preclinical phase of Parkinson's may present olfactory and gastrointestinal symptoms similar to COVID-19.[20] Peripapillary RNFLT and retinal thickness are thinner due to nerve damage in OCT of Parkinson's patients.[21-23] Also, multiple sclerosis can be triggered by an infectious agent, the most likely cause being a virus. Animal models explain that the best method of inducing neuroinflammation is intracranial grafting, which leads to optic nerve inflammation.[24] However, we could not detect the expected changes in retinal thickness and volume measurements in the light of these studies. The most important thing is that positive or negative PCR results did not differentiate the measures. The clinical diagnosis of COVID-19 may be why OCT results are similar. In addition, the fact that we did not distinguish between patient groups and patients in terms of disease severity, although we conducted clinical studies on mild and healed patients, may explain our results.

CONCLUSIONS

This study did not show convincing evidence that SARS-CoV-2 can cause changes in RNFL measurements, retinal thickness, and volume, contrary to literature data. Nevertheless, retinal imaging with optical coherence tomography is a non-invasive, reproducible, and rapid technique in which subclinical or overt retinal pathologies can be detected during COVID-19. Therefore, management of COVID-19 patients should include retinal assessment with close follow-up, especially in patients with headaches and optic pain. The results of studies like this may highlight the pathophysiology of COVID-19, especially in optic involvement with neurological symptoms. However, for a meaningful assessment of the optic nerve and retinal measurements in COVID-19 patients, it is essential to evaluate the clinical course of both the control groups consisting of healthy individuals and the clinical course. In addition, future studies are needed to assess whether these changes in the retinal layers of COVID-19 have lasting and long-term effects.

Limitations

The clinical features of the patients included in this study, such as the relatively long post-COVID time until OCT images are captured, no need for hospitalization during the COVID period, or somewhat mild to moderate COVID symptoms, may reflect disease severity and less severe COVID-19. Conversely, our cases' infection severity and duration may explain the absence of these retinal findings. In addition, the inability to include the control group in our study limited our ability to compare with healthy individuals.

ETHICAL DECLARATIONS

Ethics Committee Approval: After the pre-approval from the study by the Republic of Turkey Ministry of Health, ethical approval was obtained from the Amasya University Ethical Board with 13.09.2021-32307 date and number.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181:271–80.
2. Güemes-Villahoz N, Burgos-Blasco B, García-Feijoó J, et al. Conjunctivitis in COVID-19 patients:frequency and clinical presentation. Graefes Arch Clin Exp Ophthalmol 2020;258:2501–7.
3. Seah I and Agrawal R. Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and optic implications in humans and animals. Ocul Immunol Inflamm 2020;28(3):391–5.
4. Verma A, Shan Z, LeivB, et al. ACE2 and Ang-(1-7) confer protection against the development of diabetic retinopathy. Mol. Ther. 2012;20:28–36.
5. Amesty MA, Alió del Barrio JL, Alió JL. COVID-19 Disease and Ophthalmology: An Update. Ophthalmol. Ther. 2020;9:1–12.
6. Burgos-Blasco B, Guemes-Villahoz N, Donate-Lopez J, et al. Optic nerve analysis in COVID-19 patients. J Med Virol. 2021;93(1):190–1.
7. Medeiros FA, Zangwill LM, Bowd C, et al. Evaluation of retinal nerve fiber layer, optic nerve head, and macular thickness measurements for glaucoma detection using optical coherence tomography. Am J Ophthalmol 2005;139(1):44–55.
8. Lamirel C, Newman NJ, Biousse V. Optical coherence tomography (OCT) in optic neuritis and multiple sclerosis. Rev Neurol (Paris) 2010;166(12):978–86.
9. Hee MR, Izatt JA, Swanson EA, et al. Optical coherence tomography of the human retina. Arch Ophthalmol. 1995;113:325-32.
10. Schuman JS, Hee MR, Puliafito CA, et al. Quantification of nerve fiber layer thickness in normal and glaucomatous eyes using optical coherence tomography. Arch Ophthalmol. 1995;113:586- 96.
11. Baumann M, Gentile RC, Liebmann JM, Ritch R. Reproducibility of retinal thickness measurements in normal eyes using optical coherence tomography. Ophthalmic Surg Lasers. 1998;29:280- 5.

12. Marinho PM, Amarcos AA, Romano AC, Nascimento H, Belfort Jr R. Retinal findings in patients with COVID-19. Lancet 2020;395(10237):1610-6.
13. Vasvas DG, Sarraf D, Sadda SR, et al. Concerns about the interpretation of OCT and fundus findings in COVID-19 patients in recent Lancet publication. Eye (London) 2020;9:1-2.
14. Pereira LA, Soares LCM, Nascimento PA, et al. Retinal findings in hospitalised patients with severe COVID-19. Br J Ophthalmol. 2022;106(1):102-5.
15. Landecho MF, Yuste JR, Gándara E, et al. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease?. J Intern Med. 2021;289(1):116-20.
16. Invernizzi A, Torre A, Parrulli S, et al. Retinal findings in patients with COVID-19:Results from the SERPICO-19 study. E Clinical Medicine 2020;27:100550.
17. Zapata MÁ, Banderas García S, Sánchez-Moltalvá A, et al. Retinal microvascular abnormalities in patients after COVID-19 depending on disease severity. Br J Ophthalmol. 2022;106(4):559-63.
18. Dag Seker E, Erbahceci Timur IE. COVID-19:more than a respiratory virus, an optical coherence tomography study. Int Ophthalmol. 2021;1-10.
19. Ornek K, Temel E, Asıkgarip N, Kocamıs O. Localized retinal nerve fiber layer defect in patients with COVID-19. Arq Bras Oftalmol 2020;83(6):562-3.
20. Santos SF, de Oliveira HL, Yamada ES, et al. The gut and Parkinson's Disease:a bidirectional pathway. Front Neurol 2019;10:574.
21. Aydin TS, Umit D, Nur OM, et al. Optical coherence tomography findings in Parkinson's disease. Kaohsiung J Med Sci 2018;34(3):166–171.
22. Satue M, Obis J, Alarcia R, et al. Retinal and choroidal changes in patients with Parkinson's disease detected by swept-source optical coherence tomography. Curr Eye Res 2018;43(1):109–115.
23. Garcia-Martin E, Larrosa JM, Polo V, et al. Distribution of retinal layer atrophy in patients with Parkinson's disease and association with disease severity and duration. Am J Ophthalmol 2014;157(2):470–478.e2.
24. Singh M, Khan RS, Dine K, et al. Intracranial inoculation is more potent than intranasal inoculation for inducing optic neuritis in the mouse hepatitis virus-induced model of multiple sclerosis. Front Cell Infect Microbiol 2018;8:311.