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Retinal nerve fiber layer thickness and peripapillary vasculature of post-COVID-19 patients with and without olfactory/gustatory dysfunction symptoms

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Abstract:

PURPOSE: We aimed to compare retinal nerve fiber layer (RNFL) thickness and peripapillary vessel density values between COVID-19 patients with or without olfactory/gustatory dysfunction symptoms and healthy controls.

MATERIALS AND METHODS: We evaluated RNFL and radial peripapillary capillary vessel density (RPC-VD) values of 41 patients who had COVID-19 history and age- and gender-matched control group including 31 healthy individuals with optical coherence tomography angiography. First, post-COVID-19 group's and control group's RNFL and RPC-VD values were compared, then post-COVID-19 patients were divided into subgroups according to the presence (subgroup-A) and absence (subgroup-B) of olfactory/gustatory dysfunction symptoms, and same parameters were analyzed for subgroups.

RESULTS: Forty-one eyes of 41 post-COVID-19 patients and 31 eyes of 31 age- and gender-matched healthy controls were included in this cross-sectional study. In RNFL analysis, inferior sector thickness was found significantly lower in post-COVID-19 patients by comparison with control group ($P = 0.041$). In subgroup analyses, COVID-19 patients who first presented with olfactory/gustatory dysfunction symptoms had higher peripapillary and whole image optic disc capillary density ($P = 0.011$ and $P = 0.002$) compared to those who had not had these symptoms.

CONCLUSION: Lower RPC-VD and RNFL thickness were detected in COVID-19 patients compared to healthy controls. Higher Disc-VD values were found in COVID-19 patients with chemosensorial dysfunction (CSD) symptoms compared to those who had not had these symptoms probably due to milder disease course in COVID-19 with CSD. Sectorial RNFL attenuation in COVID-19 might have occurred secondary to peripapillary capillary circulation defect.

Keywords:

Ageusia, anosmia, COVID-19, optical coherence tomography angiography, retinal nerve fiber layer

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Introduction

Coronaviruses are RNA viruses that have been described in 1960s. The shape of this genera is spherical, and they have club-like peplomers which project from viral capsid. These projections contribute to the virulence by providing adhesion and give rise to entitle this group of viruses as "Corona."[1]

Coronavirus infections dominantly develop as upper or lower respiratory tract diseases. Gastrointestinal, neurological, and cardiovascular manifestations may also be seen. The main clinical symptoms of COVID-19 are fever, cough, dyspnea,

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myalgia, and fatigue. However, various organs and systems can be affected by COVID-19.

Especially in European countries, olfactory and gustatory dysfunction in COVID-19 patients was reported in increased numbers by otorhinolaryngology residents. Many of the researches showed that anosmia and other olfactory dysfunction symptoms or ageusia might be early findings of COVID-19 patients, especially in mild-to-moderate cases.[2] There is no certain information about the pathogenesis of this entity but several theories suggest that it is either neurologic or secondary to mucosal disease.[2]

COVID-19-related ophthalmologic findings were reported by several case series and retrospective studies. Most of these findings were related to the anterior segment such as conjunctivitis or corneal involvement. However, retinal findings like microhemorrhages and cotton wool spots and optical coherence tomography (OCT) changes like hyperreflective lesions at ganglion cell and inner plexiform layers were also reported.[3,4]

The aim of this study is to determine whether there is a change in retinal nerve fiber layer (RNFL) thickness and peripapillary vessel density in COVID-19 patients presented with and without olfactory/gustatory dysfunction symptoms. This study is based on the theory of optic nerve involvement in COVID-19 patients similar to the effect of virus on olfactory bulbus that leads to olfactory dysfunction.

Materials and Methods

Consecutive patients with COVID-19 infection history who were interned or treated without hospitalization at Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty from April 1, 2021, to May 1, 2021, were included in the study. COVID-19 was diagnosed by Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) test that detected the virus through nasal and oropharyngeal swabs. The patients with two successive positive swabs were accepted as COVID-19. Forty-one eyes of 41 post-COVID-19 patients and 31 eyes of 31 age- and gender-matched healthy controls were included in this cross-sectional study. Post-COVID-19 group was recruited at least 2 months later from their hospital discharge. Age- and gender-matched healthy control group has been formed.

Patients with systemic diseases that could affect the RNFL and OCT angiography (OCTA) results such as diabetes mellitus and systemic hypertension, cerebrovascular diseases, peripheral vascular diseases, any type of cardiovascular and neurologic diseases and hemoglobinopathies were excluded from the study. Ocular pathologies that cause disruption on retinal layers such as posterior uveitis, hereditary retinal disorders, optic nerve abnormalities, and eyes with any type of glaucoma or with elevated intraocular pressure (IOP) (above 21 mmHg) values were excluded. The right eyes of all participants were included in the study. All patients in the study had 20/20 visual acuity because we aimed to look for preclinical RNFL and retinal peripapillary capillary (RPC) abnormalities in COVID-19 individuals with and without symptoms of olfactory and gustatory dysfunction. Patients with any type of COVID-19 vaccination were excluded for reducing the confounding factors. Individuals that did not have any ocular pathology, any symptoms of COVID-19, any risky contact anamnesis in addition to consecutive two negative oropharyngeal and nasopharyngeal swabs in the past 1 month were included as healthy controls. Post-COVID-19 group had no ocular symptoms during their hospitalization and after their discharge. The post-COVID-19 group was separated into two subgroups based on whether they had olfactory or gustatory symptoms. Anosmia, ageusia, hyposmia, and hypogeusia were accepted as olfactory and gustatory symptoms. Patients in subgroup-A presented to the emergency department with olfactory or gustatory complaints. Olfactory/gustatory dysfunction onset patients formed the subgroup-A to strengthen the symptom presence. The patients who developed the symptoms during the course were not included to prevent complicated symptom description in anamnesis and misdiagnosis. Patients in subgroup-B did not develop olfactory/gustatory dysfunction symptoms during the course or after recovery. The study was conducted according to the Declaration of Helsinki and informed consent was obtained from the patients or their legal guardians. Ethical approval was obtained from the Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Clinical Researches Ethics Committee (Date: August 21, 2020, number: 101288).

All patients in this study underwent a complete ophthalmologic examination including slit lamp biomicroscopy, IOP measurement, and dilated fundus examination. Treatments for COVID-19 during the hospitalization such as antithrombotic and anticoagulant drugs were recorded. Computed tomography (CT) and polymerase chain reaction (PCR) results of patients were noted. Other systemic disorders that could alter the course of infection were recorded.

Each individual was scanned with OCTA just after pupillary dilatation with 1% tropicamide and 2.5% phenylephrine. OCTA images were obtained with RTVue XR Avanti (Optovue, Inc., Fremont, CA, USA). This device works with an A-scan rate of 70.000 per second and an 840 nm light source. HD Angio Disc 4.5 mm × 4.5 mm scans were used to evaluate RNFL thickness in average

peripapillary and four sectors (superior, inferior, nasal, and temporal) and RPC small vessel density values. Vertical and horizontal cup/disc ratios also were calculated with the help of this procedure and eyes with cup/disc ratio above 0.5 were excluded. Scans below 5/10 scan quality, discontinuous vessel pattern, and haziness appearance scans were not included in the study.

Statistical analysis

Normal distribution was evaluated with Shapiro–Wilk test. A Chi-square test or Fisher's test was used for comparing the ratios of the groups. Student's *t*-test or Mann–Whitney *U*-test was used for the comparison of the mean values. $P < 0.05$ were accepted as statistically significant. SPSS version 21.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis.

Results

Forty-one eyes of 41 post-COVID-19 patients and 31 eyes of 31 age- and gender-matched healthy controls were included in this cross-sectional study. Eighteen of post-COVID-19 patients had olfactory/gustatory dysfunction signs (subgroup-A) and 23 of them (subgroup-B) did not have. In post-COVID-19 group, 22 (54%) were male and 19 (46%) were female. The mean age of post-COVID-19 group was 40.71 ± 13.02 years and control group was 37.67 ± 10.43 years. Age and gender distribution did not differ significantly between post-COVID-19 and control groups ($P = 0.691$ and $P = 0.634$, respectively). In subgroups of COVID-19, the mean age of subgroup A was 41.67 ± 14.84 and subgroup-B was 39.96 ± 11.70 ($P = 0.682$). The mean age and ocular characteristics of groups are given in Table 1. One patient in subgroup-A and one patient in subgroup-B had controlled hypothyroidism. One patient in subgroup-A had treated breast cancer history. The mean duration between symptom onset and OCTA analysis was 88 days.

In post-COVID-19 group, all of the patients had positive PCR results. But while 19 of 41 (46%) had COVID suspicious pneumonia signs in CT, 22 of 41 (54%) were CT negative. Among 41 post-COVID-19 patients, 8 patients had taken acetylsalicylic acid and 20 patients had taken enoxaparin sodium during the treatment. All patients in post-COVID 19 group were treated with oral anti-COVID medication (Favipiravir). In subgroup-A, all patients had both olfactory and gustatory dysfunction symptoms. There was no patient with isolated olfactory or gustatory dysfunction symptoms. Clinical characteristics of the patients in post-COVID-19 group and subgroups are given in Table 2.

Inferior sector RNFL thickness was found significantly lower in post-COVID-19 group by comparison with the control group ($P = 0.041$). There was no significant difference in other sectors and peripapillary average RNFL thickness. However, RNFL thicknesses in all sectors and average were thinner in post-COVID-19 group. In RPC small vessel density analysis, only inside disc small vessel density was found significantly lower ($P = 0.002$) in post-COVID-19 group compared to the control group. RNFL thickness analysis and RPC small vessel density analysis between post-COVID-19 group and control group are given in Table 3.

In comparisons of subgroups, no significant difference was found in RNFL thickness but all sectors of Subgroup-B (except nasal sector) had thinner RNFL values. Peripapillary and whole image RPC small vessel density were found significantly higher in subgroup-A ($P = 0.011$ and $P = 0.002$, respectively) compared to subgroup-B. RNFL thickness analysis and RPC small vessel density analysis between subgroups are given in Table 3. Images of RPC analysis of subgroups and control group are given in Figure 1. In a comparison of subgroups and control group, only inferior RNFL significantly differed between subgroup B and controls ($P = 0.028$). Inside disc vessel density (VD) differed between subgroup-A, subgroup-B, and controls ($P = 0.016$ and $P = 0.004$, respectively).

Discussion

Growing numbers of case series and retrospective studies have been published about COVID-19-related olfactory

Table 1: Age and ocular characteristics of groups

	Subgroup-A	Subgroup-B	Control group	*P*
Age	41.67±14.84	39.96±11.70	37.67±10.43	0.525
IOP	15.11±1.85	15.39±1.97	14.93±1.95	0.694
AL	24.01±0.49	24.03±0.43	23.87±0.41	0.388
Refractive status (SE)	0.11±0.79	0.07±0.92	0.11±0.89	0.982

IOP=Intraocular pressure, AL=Axial length, SE=Spheric equivalent

Table 2: Clinical characteristics in post-COVID-19 group, subgroup-A and subgroup-B (Chi-square test)

Clinical characteristics	Post-COVID-19 Group	Subgroup-A	Subgroup-B	*P*
COVID-19 related CT-Findings	19	6	13	0.245
Hospitalization need	21	7	14	0.279
Antithrombotic treatment	8	4	4	-
Anticoagulant treatment	20	5	15	0.039
Total number of patients	41	18	23	

CT=Computed tomography

Table 3: Comparison of superior, temporal, inferior, nasal and average retina nerve fiber layer thickness thickness and radial peripapillary capillary density in between post-COVID-19 patients and healthy controls and between subgroups

	Control Group (*n*=31)	Post-COVID-19 Group (*n*=41)	*P*	Subgroup-A (*n*=18)	Subgroup-B (*n*=23)	*P*
RNFL thickness (μm)						
Superior sector	133.13±14.23	130.63±12.90	0.443	132.05±15.49	129.52±10.68	0.539
Temporal sector	76.13±7.02	74.63±7.37	0.391	76.61±8.11	73.08±6.49	0.130
Inferior sector	144.03±11.77	137.07±15.25	0.041	139.22±14.35	135.39±16.02	0.432
Nasal sector	101.93±14.94	100.63±13.42	0.702	100.38±14.46	100.82±12.87	0.919
Peripapillary average	113.06±8.99	110.29±7.26	0.155	111.72±6.39	109.17±7.82	0.270
RPC density (%)						
Inside disc	51.29±2.99	47.90±5.62	0.002	48.01±6.07	47.82±5.38	0.916
Peripapillary	52.29±3.50	52.83±2.54	0.452	53.96±2.28	51.95±2.43	0.011
Whole image	49.93±2.39	49.59±1.87	0.502	50.57±1.63	48.82±1.69	0.002

RNFL=Retina nerve fiber layer thickness, RPC=Radial peripapillary capillary

and gustatory dysfunction in last years, especially from European countries rather than China.

The pathogenesis of retinal COVID-19 manifestations is still unknown. In a recent research, SARS-COV-2 RNA was isolated from retinal biopsies of three deceased COVID-19 patients in postmortem examination.[5] Theoretically, transportation of SARS-COV-2 to retina might occur in different ways. Neural transportation was thought by some of the researchers. Especially in central nervous system manifestations, viral passage to caudal brain regions via neural transportation was suggested in some articles. Hematogenous spread can be one of the alternative ways too.

It was reported that anosmia could be one of the prominent symptoms of COVID-19 in many studies. In a literature review of the American Academy of Otolaryngology–Head and Neck Surgery that evaluated most of the cohort studies, olfactory dysfunction was suggested as an important predictor for COVID-19, especially in the early stage of the disease. Up to 25% of patients with COVID-19 have been suggested to have olfactory dysfunction without nasal obstruction.[6] The sudden onset of anosmia may indicate a possible neurotrophic side of SARS-COV-2 and similar dysfunction of the optic nerve can project itself as alterations on RNFL or RPC.

Our study was primarily designed to find out any relation between COVID-19 and possible subclinical neuroretinal or neurovascular retinal disease. We found a significant difference in RNFL thickness of inferior sector in post-COVID-19 group compared to healthy controls ($P = 0.041$). This result might indicate a partial or sectorial involvement of RNFL. In subgroups, no differences had been found in sectorial or average peripapillary RNFL thickness values. It could be thought that the existence of olfactory or gustatory dysfunction did not affect RNFL thickness in post-COVID-19 patients according to our results.

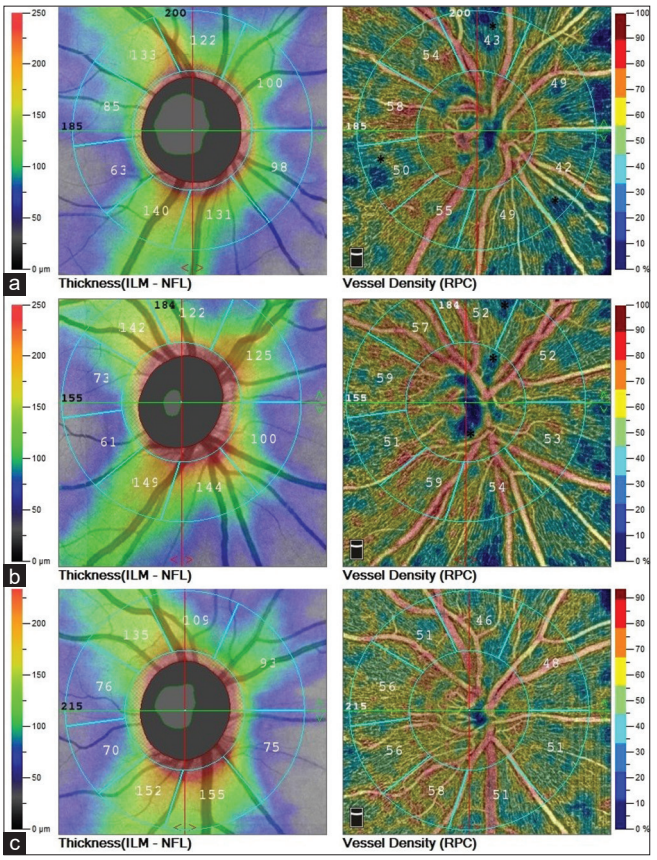

Figure 1: (a) RPC density and RNFL thickness map of a patient in Subgroup-A (b). RPC density and RNFL thickness map of a patient in Subgroup-B (c). RPC density and RNFL thickness map of a healthy individual. Decreased RPC density and more capillary drop-out areas in OCTA were observed in COVID-19 patients by comparison to healthy individuals. Capillary drop-out areas were showed with *. RNFL: Retina nerve fiber layer, RPC: Radial peripapillary capillary

The prevalence of neurologic COVID-19 manifestations was founded less than olfactory or gustatory dysfunction rates in many case series.[7] This condition may be an evidence that supports the primary neural involvement theory. Viral involvement in more caudal neural sites can support this nonhematogenous transmission theory. These observations might approximate us to the primary neuroretinal mechanism.

Two main theories had been asserted for COVID-19-related anosmia among the articles in literature. One of them can be defined as epithelial inflammation theory and the other is primary neural dysfunction.[8]

There are no classical flu-like symptoms which resemble viral rhinitis in most of the COVID-19 cases. Obvious nasal obstruction and nasal discharge are occasional features of the clinical picture but as we mentioned before there are higher rates of anosmia and other olfactory dysfunctional phenomena in many various case series. This is the main contradiction about the association between anosmia and nasal inflammation.[8] Some of the cases with rapid recovery duration may be caused by olfactory epitheliitis without neural involvement. However, inflammation alone cannot explain the cases with a long recovery time of anosmia, incomplete recovery, or refractory anosmia. The virus may invade olfactory bulb and primarily affects neurons or supporting cells. There was an animal model which showed that mice olfactory epithelium was infected by Mouse Hepatitis Virus, and this study revealed the damage in tufted and mitral cells in the olfactory epithelium.[9] Coronavirus-related anosmia was linked to the destruction of these supporting cells that leads to decrease in neuronal growth factors. Hence, the primary target of the virus might be nonneuronal cells in olfactory epithelium or bulb. The exact transmission way for SARS-COV 2 to neural tissues is still widely controversial. Hence, viral entry through the optic nerve to the eye is a contradictory theory.[9,10]

Different rates for olfactory dysfunction were reported in many researches. Qui has reported a significant higher frequency of olfactory dysfunction in mild disease than in severe.[11] Nasal obstruction rates in these studies were found between 12.9% and 46%, significantly lower than the rates of olfactory dysfunction.[12,13]

Olfactory and gustatory dysfunction symptoms were reviewed as outcomes of inflammation at local infection site, not a far tissue manifestation. Hence, neural invasion theory in local inflammation site might be a possible pathogenetic mechanism. However, dissemination of the posterior segment of the eye through ocular surface is hard to explain. Hence, the secondary involvement of RNFL and other layers of retina seems more acceptable theory than local transmission theory through ocular tissues. Viral effect on neuroretinal tissues may arise from microvascular impairment in COVID-19, as a second theory. Retinal manifestations of COVID-19 are still controversial. Marinho *et al*. reported hyperreflective lesions in ganglion cell layer and inner plexiform layer in OCT. Furthermore, they found fundoscopic changes such as cotton wool spots and microhemorrhages in four patients.[3] In this report, OCTA had been obtained from COVID-19 patients after 11–33 days from initial symptoms. The mean duration between symptom-onset and OCTA analysis in our study was 88 days. They reported normal OCTA and ganglion-cell complex results. On the contrary, we found a significant difference (P = 0.002) in inside disc capillary density in post-COVID-19 group compared with the control group. Mean values of whole disc capillary vessel density were lower in post-COVID-19 patients but had no significant difference (P = 0.502). Significantly decreased inside disc RPC small vessel density may bring up another pathogenetic approach which is based on developing a subclinical ischemia in the optic disc area.

The thromboembolic state during COVID-19 pneumonia was recognized by many articles in current literature. Even anticoagulant therapies and prophylaxis for venous thromboembolism were suggested in most of them.[14,15] Rougier *et al*. found lower capillary perfusion density in inferior sector in patients with nonarteritic ischemic optic neuropathy.[16] Similarly, thinning of the inferior sector in COVID-19 patients can be the result of inadequate vascular support in optic disc, resembling a type of subtle ischemic optic neuropathy.

Savastano evaluated RNFL, retinal peripapillary capillary plexus flow index (RPCP-FI), and perfusion density (RPCP-PD) of 80 COVID-19 patients and 30 controls. RPCP-PD was found significantly lower in COVID-19 patients in this report. Patients that were treated with antiplatelet therapy had lower RPCP-PD and RPCP-FI values. Savastano reported average RNFL thickness which correlated with RPCP-PD and RPCP-FI but no significant difference was reported in RNFL between groups.[17]

In our study, olfactory/gustatory dysfunction symptoms were not found as a deterministic factor for RNFL thickness. However, the significant difference was found in peripapillary and whole image small vessel density of optic disc between subgroups. Higher vessel density in subgroup-A by comparison to subgroup-B might be explained by clinical features of this group. Most of the post-COVID-19 patients with olfactory/gustatory dysfunction symptoms in our study had usually mild disease course without hospitalization or systemic anti-inflammatory treatment. In subgroup-A, six patients were CT+ and 12 were CT−. Eleven of 18 patients followed up without hospitalization during treatment. Only 5 patients needed low-molecular-weight heparin in this subgroup (P = 0.039). In subgroup-B, 13 patients had COVID-19-related pneumonia signs in CT and 10 patients did not. The need of anticoagulant therapy was significantly lower in subgroup-A. Higher VD in peripapillary and whole image was noted in subgroup-A. A higher frequency of olfactory and

gustatory dysfunction symptoms in milder disease course was mentioned above.[11] Systemic inflammatory and thrombotic activation are seen more rare in mild disease. Therefore, higher VD in subgroup-A could be explained with lower thrombotic and inflammatory state of mild COVID-19 cases. The need of anticoagulant therapy might be consider as a risk factor for retinal perfusion reflecting increased procoagulability status in disease course. A similar mechanism for antiplatelets that Savastano reported might support this hypothesis.[17]

RNFL thinning might be secondary to microvascular alterations instead of primary neural involvement in our study. The effects of COVID-19 on microvascular circulation and prothrombotic situation were mentioned in a lot of articles before.[14,18] Decrease in the capillary density of optic disc can cause a subclinical ischemic optic neuropathy, or in other words, RNFL attenuation secondary to ischemia due to prothrombotic situation in COVID-19, like other body parts. COVID-19-related retinal and optic disc effects and their possible pathogenetic factors cannot be explained clearly now.

There were several limitations in our study design. Major limitation was the cross-sectional design of the study. Acute and chronic term changes were not compared with each other. Treatment and diagnostic data of COVID-19 patients have been reached by their medical records. We excluded any systemic vascular diseases initially to reduce the confounding factors, so correlation analysis for these factors was not obtained. Unfortunately, any variant analysis could not be obtained to COVID-19 patients due to variant analysis was not common in our country when the study was performed. The study was conducted in small sample size. Hence, prospective and wider population-based researches are needed to understand complete process of COVID-19-related retinal disease.

Conclusion

SARS-COV-2 should not be highlighted as a virus that only affects the ocular surface. Its effects on the posterior segment must be considered as well. Partial changes in RNFL and vascular structures of the optic disc were detected in this study. To the best of our knowledge, this is the first article that shows a link between COVID-19 and sectorial RNFL alterations. These changes may become clearer in long-term follow-ups in these patients.

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Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

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