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Optic nerve and macular optical coherence tomography in recovered COVID-19 patients

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Abstract

Purpose: To investigate the peripapillary retinal nerve fiber layer thickness (RNFLT), macular RNFLT, ganglion cell layer (GCL), and inner plexiform layer (IPL) thickness in recovered COVID-19 patients compared to controls.

Methods: Patients previously diagnosed with COVID-19 were included, while healthy patients formed the historic control group. All patients underwent an ophthalmological examination, including macular and optic nerve optical coherence tomography. In the case group, socio-demographic data, medical history, and neurological symptoms were collected.

Results: One hundred sixty patients were included; 90 recovered COVID-19 patients and 70 controls. COVID-19 patients presented increases in global RNFLT (mean difference 4.3; CI95% 0.8 to 7.7), nasal superior (mean difference 6.9; CI95% 0.4 to 13.4), and nasal inferior (mean difference 10.2; CI95% 2.4 to 18.1) sectors of peripapillary RNFLT. Macular RNFL showed decreases in COVID-19 patients in volume (mean difference −0.05; CI95% −0.08 to −0.02), superior inner (mean difference −1.4; CI95% −2.5 to −0.4), nasal inner (mean difference −1.1; CI95% −1.8 to −0.3), and nasal outer (mean difference −4.7; CI95% −7.0 to −2.4) quadrants. COVID-19 patients presented increased GCL thickness in volume (mean difference 0.04; CI95% 0.01 to 0.07), superior outer (mean difference 2.1; CI95% 0.8 to 3.3), nasal outer (mean difference 2.5; CI95% 1.1 to 4.0), and inferior outer (mean difference1.2; CI95% 0.1 to 2.4) quadrants. COVID-19 patients with anosmia and ageusia presented an increase in peripapillary RNFLT and macular GCL compared to patients without these symptoms.

Conclusions: SARS-CoV-2 may affect the optic nerve and cause changes in the retinal layers once the infection has resolved.

Keywords

COVID, coronavirus, optical coherence tomography, optic nerve

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Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which causes the coronavirus disease 2019 (COVID-19) emerged in Wuhan, China in December 2019 and is having devastating consequences worldwide.[1]

COVID-19 has shown clinical manifestations at nearly all levels, although its major clinical finding is pneumonia, which may eventually lead to an immense respiratory distress. Ground glass opacities and consolidations are common lung computed tomography abnormalities in COVID-19 pneumonia, which express acute lung injury.[2] Common symptoms include fatigue, fever, cough, and diarrhea, as well as characteristic laboratory findings such as elevated serum levels of leucocytes, D-dimer, C-reactive protein, procalcitonin, IL-6, urea, and creatinine, among others.[3,4]

Neurologic manifestations have also been reported in a notable proportion of patients. Several studies hypothesize that the virus may penetrate the central nervous system (CNS) producing neurological complications, including anosmia, ageusia, encephalopathy, headache, ataxia, epileptic seizures, and cerebrovascular disease.[5,6]

Regarding the ocular involvement, ocular surface disorders have been described, mainly conjunctivitis which has been reported in around 10% of patients.[7] However, little is known about how it affects the retina and the optic nerve as part of the CNS.[8]

Optical coherence tomography (OCT) is a non-invasive imaging technique that obtains detailed images of the retina using low-coherence light. It is a reliable and reproducible method for measuring retinal layers and detecting changes in layer thickness with a high level of resolution.[9] This technique has been successfully used to monitor changes in the retinal layers in a number of ophthalmological and neurological diseases, such as glaucoma, multiple sclerosis, and Alzheimer disease.[10,11]

Currently there are no studies that have investigated the effect of COVID-19 on the optic nerve and the macula. The primary objective was to evaluate the peripapillary retinal nerve fiber layer thickness (RNFLT), macular RNFLT, ganglion cell layer (GCL), and inner plexiform layer (IPL) thickness in patients with COVID-19 compared to healthy controls. The secondary objective was to study the relation between macular and optic nerve findings and neurological symptoms.

Methods

Subjects and setting

This case-control study was conducted at the Hospital Clinico San Carlos, a tertiary hospital sited in Madrid (Spain). The study was approved by the hospital's Clinical Research Ethics Committee and was conducted in accordance with the Helsinki Declaration. All patients provided written informed consent.

The case group was formed by patients with COVID-19 who presented in the hospital's Emergency Department (ED) between 23 and 29 March, 2020 and successfully recovered from the infection. The inclusion criteria were: between 18 and 70 years of age; SARS-CoV-2 infection confirmed by positive reverse transcriptase–polymerase chain reaction (RT-PCR) test from nasopharyngeal swab, and written informed consent.

Patients were asked to come to the hospital for the study if inclusion criteria were met. Those patients, still presenting symptoms, on quarantine, unable to attend the hospital due to general health status, as well as those with concomitant psychiatric, neurological, or ophthalmological diseases were excluded. The latter included optic nerve head disease (including glaucoma and congenital optic nerve head abnormalities), macular disease, retinal vascular disorders, high myopia (refractive error greater than six diopters), uveitis, and history of previous ophthalmic procedures other than cataract surgery and capsulotomy.

The control group was formed by historic healthy controls recruited for a normative database in 2018. Due to the difficulty in obtaining controls and being certain of no history of virus infection (specificity and sensitivity of diagnostic tests is not 100% and a high prevalence of asymptomatic patients has been reported), it was decided to use historical controls within the same age group from previous studies that had undergone the same tests (same device and same software). Controls were between 18 and 70 years of age and without ophthalmological pathology (the same criteria that were applied to the study group). The control group was matched by age, sex, and refraction.

Patients unable or unwilling to give consent as well as those with media opacity and poor-quality images were excluded from both groups.

Ophthalmologic exam and optic nerve imaging

All patients underwent an ophthalmological examination, including slit-lamp biomicroscopy, funduscopy, and OCT. These exams were performed 4 weeks after COVID-19 diagnosis in order to fully comply mandatory isolation in the case group and from January 2018 to June 2018 in the historic controls.

The Spectralis-OCT (Heidelberg Engineering, Heidelberg, Germany) was used to obtain the structural measurements of the retina.

Macular OCT was performed using a dense macular cube protocol, where a 6×6 mm area on the retina was scanned. With the ETDRS macular scan, nine ETDRS macular areas are scanned (including a central 1 mm circle, and inner and outer rings measuring 3 and 6 mm in diameter), central, and average layer thickness are analyzed (Figure 1). In the macular area, RNFLT (between the inner limiting membrane and the GCL), GCL thickness (between RNFL and the IPL), and IPL thickness (between

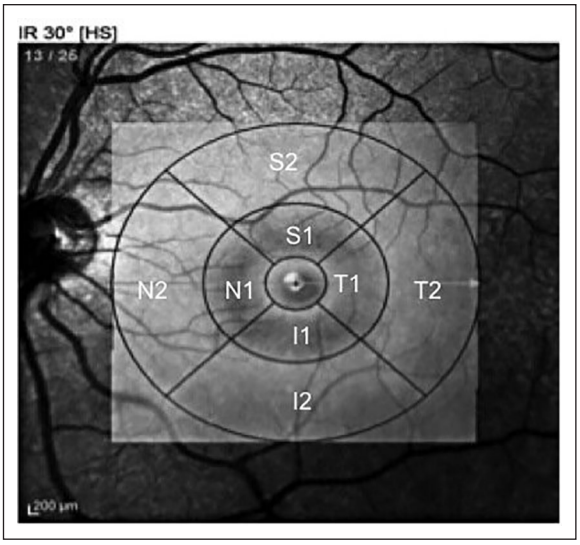

Figure 1. Macular sectors of the optical coherence tomography map.
T: temporal; S: superior; I: inferior; N: nasal; 1: inner sector; 2: outer sector.

GCL and the inner nuclear layer) were obtained using the device's software.

The optic nerve head was scanned and peripapillary RNFL thickness measurements were made using a circular scan pattern which was centered on the optic nerve. The Spectralis OCT software calculates RNFLT as a result of automated segmentation. RNFL measurements were noted globally and in the six quadrants (superior temporal, temporal, inferior temporal, superior nasal, nasal, inferior nasal).

A single experienced physician carried out all OCT examinations. Only OCT images with a signal strength level above the recommended signal strength level ($>$7/10) were obtained. One eye per patient, which was randomly selected, was included.

Comparison between neurological symptoms and ophthalmologic parameters in COVID-19

Socio-demographic data (age, sex, and race), medical history (hypertension, diabetes mellitus, dyslipidemia), and clinical severity at ED presentation were collected.

Clinical data was obtained from the electronic medical records, and two physicians (NGV and BBB) checked the data on the neurological symptoms (dizziness, headache, ageusia, anosmia). Electronic medical records were checked for COVID-19 symptoms and questioning on the examination day was used to confirm this.

Statistical methods

Data analysis was performed using SPSS software, version 24.00 (IBM, New Castle, NY, USA), and STATA version 15.1 (Stata Corp, College Station, TX, USA). Continuous variables are presented as mean and standard deviation (SD), while numbers and percentages are used for categorical variables. Differences in age and sex between groups were compared using the Chi^2 test and *t*-student test. Variables normality was evaluated using Kolmogorov-Smirnov test.

For the primary objective, investigation of the differences in the OCT variables between the control group and the patients with COVID-19, a *t*-student test was performed. For the secondary objective, comparison between the group of patients with and without neurological symptoms, a *t*-student test was performed. Statistical significance was established in 0.05.

Results

The study comprised a total of 160 patients; 90 of them recovered from SARS-CoV-2 infection and 70 healthy historical controls.

Of the 584 patients diagnosed with COVID-19 in the ED, 234 patients met the inclusion criteria. Of those, 7 patients died, 19 patients were still admitted to the COVID-19 unit; 13 patients were unable to return to the hospital due to their clinical situation; 12 patients still presented respiratory symptoms after discharge; 29 patients had concomitant ocular disorders, 11 patients did not give consent and 49 patients were lost to follow-up after emergency department discharge. Four patients were excluded because the OCT image did not meet the quality criteria (signal strength, segmentation error, loss of fixation, and motion artifacts).

Among the 70 control subjects included, 30 patients (43%) were male and 40 patients were female (57%), being the mean age 55.5 years (SD 14.9 years), and the mean refractive error −0.36 Dp (SD 1.53 Dp). The main clinical characteristics of the patients with resolved SARS-CoV-2 infection are shown in Table 1. Mean age of the case group was 55.5 years (SD 8.9 years), 49% of patients being male and mean refractive error −0.49 Dp (SD 1.78 Dp). Fifty-three patients (59%) presented anosmia or ageusia as COVID-19 symptoms and 55 (61%) presented headache or dizziness. No statistically significant differences in the sex, age, and refractive error between both groups were noted ($p > 0.05$).

Funduscopic examination of recovered COVID-19 patients included was unremarkable, not showing visible optic disc oedema/swelling, nor related clinical features. None of the patients included in our study reported visual loss.

Tables 2 and 3 depict the distribution and univariable analysis of the OCT parameters in the control and case group. Post-COVID-19 patients showed statistically significant increases in the global RNFLT (mean difference 4.3; CI95% 0.8 to 7.7), as well as superior nasal (mean

difference 6.9; CI95% 0.4 to 13.4) and inferior nasal (mean difference 10.2; CI95% 2.4 to 18.1) sectors of the peripapillary RNFLT (Figure 2). Macular RNFL parameters showed decreases in recovered COVID-19 patients in volume (mean difference −0.05; CI95% −0.08 to −0.02), as well as the superior inner (mean difference −1.4; CI95% −2.5 to −0.4), nasal inner (mean difference −1.1; CI95% −1.8 to −0.3), and nasal outer (mean difference −4.7; CI95% −7.0 to −2.4) quadrants (Figure 3(a)). Comparison of GCL thickness between recovered COVID-19 patients and controls showed increased thickness in the former in volume (mean difference 0.04; CI95% 0.01 to 0.07), superior outer (mean difference 2.1; CI95% 0.8 to 3.3), nasal outer (mean difference 2.5; CI95% 1.1 to 4.0) and inferior outer (mean difference 1.2; CI95% 0.1 to 2.4) quadrants (Figure 3(b)). IPL thickness did not reveal significant differences (global and sectors, all $p > 0.05$).

Table 1. Demographic and clinical characteristics of COVID-19 patients.

	N = 90
Sociodemographic data	
Age, years. Mean (SD)	55.5 (8.9)
Sex, male. No (%)	44 (48.9)
Race	
Caucasic. No (%)	60 (66.7)
Hispanic. No (%)	30 (33.3)
Medical history	
Hypertension No (%)	26 (28.9)
Diabetes mellitus No (%)	8 (8.9)
Dyslipidemia No (%)	25 (27.8)
Neurological symptoms	
Anosmia/ageusia. No (%)	53 (58.9)
Headache/dizziness. No (%)	55 (61.1)
Clinical severity	
Mild. No (%)	31 (34.4)
Moderate. No (%)	23 (25.6)
Severe. No (%)	36 (40.0)

SD: standard deviation.

Post-COVID-19 patients with anosmia and ageusia during the infection presented a significant increase in some regions of peripapillary RNFLT and macular GCL compared to COVID-19 patients who had not referred these symptoms (Table 4). There were no differences in peripapillary RNFL between controls and patients without anosmia or ageusia (global and sectors, all $p > 0.05$). The association between having headache or dizziness and the OCT layers did not reach statistical signification (global and sectors, all $p > 0.05$).

Discussion

Neurological involvement in COVID-19 has already been described and highlights the relevance of considering the neurological impact of SARS-CoV-2. In this study, the peripapillary RNFLT and the inner retina in patients with SARS-CoV-2 infection were analyzed, presenting recovered COVID-19 patients an increase in peripapillary RNFLT and macular GCC compared to controls. Patients with anosmia and ageusia also showed increased peripapillary RNFLT and macular GCL thickness compared to COVID-19 patients without these symptoms during the infection.

Neurological manifestations are described in 30–40% of COVID-19 patients, being CNS manifestations such as dizziness and headache more frequent, followed by peripheral nervous system (PNS) and skeletal muscle injury.[5] Ageusia and anosmia have also been reported as common clinical features, with a frequency ranging from 20% to 90% of patients and are considered highly specific for COVID-19.[5,12–14] In our series, prevalence of neurological manifestations (anosmia/ageusia 59%, headache/dizziness 61%) was slightly higher than in other series, perhaps due to our thoroughness on questioning about these symptoms.

Reports on ocular involvement in SARS-CoV-2 infection are scarce. Invernizzi et al.[15] assessed the presence of retinal alterations in patients with COVID-19 using fundus photographs, detecting hemorrhages (9.25%), cotton wools spots (7.4%), dilated veins (27.7%), and tortuous

Table 2. Peripapillary optical coherence tomography (OCT) results in healthy controls and COVID-19 patients.

Optic nerve OCT	COVID+ (*n* = 88)		COVID − (*n* = 70)		*p*	Mean differences	CI 95%
	Mean	SD	Mean	SD			
RNFL G (μm)	101.4	10.2	97.1	11.7	**0.015**	4.3	0.8 to 7.7
RNFL T (μm)	70.0	11.3	68.6	13.0	0.467	1.4	−2.4 to 5.2
RNFL TS (μm)	136.1	22.7	132.5	17.8	0.281	3.6	−3.0 to 10.2
RNFL TI (μm)	141.2	22.0	137.5	20.1	0.276	3.7	−3.0 to 10.4
RNFL N (μm)	79.2	13.5	76.0	16.5	0.179	3.2	−1.5 to 7.9
RNFL NS (μm)	112.0	20.4	105.1	21.2	**0.039**	6.9	0.4 to 13.4
RNFL NI (μm)	123.9	24.9	113.6	24.8	**0.011**	10.2	2.4 to 18.1

SD: standard deviation; CI: confidence interval; RNFL: retinal nerve fiber layer; G: global; T: temporal; TS: temporal-superior; TI: temporal-inferior; N: nasal; NS: nasal-superior; NI: nasal inferior.
Significant differences are shown in bold.

Table 3. Macular optical coherence tomography (OCT) in healthy controls and COVID-19 patients.

Macular OCT	COVID+ ($n=90$)		COVID − ($n=70$)		p	Mean differences	CI 95%
	Mean	SD	Mean	SD			
RNFL volume (μm^3)	0.90	0.11	0.95	0.09	**0.002**	−0.05	−0.08 to −0.02
RNFL S1 (μm)	23.8	3.5	25.3	3.3	**0.009**	−1.4	−2.5 to −0.4
RNFL S2 (μm)	36.8	6.1	38.6	5.8	0.059	−1.8	−3.7 to 0.1
RNFL N1 (μm)	20.7	2.5	21.7	2.2	**0.006**	−1.1	−1.8 to −0.3
RNFL N2 (μm)	46.5	7.8	51.2	6.5	**0.000**	−4.7	−7.0 to −2.4
RNFL I1 (μm)	25.2	3.7	26.0	3.4	0.166	−0.8	−1.9 to 0.3
RNFL I2 (μm)	39.5	5.8	41.1	5.3	0.071	−1.6	−3.4 to 0.1
RNFL T1 (μm)	17.7	1.8	17.8	1.2	0.900	−0.1	−0.5 to 0.5
RNFL T2 (μm)	19.2	1.5	19.5	1.5	0.298	−0.3	−0.7 to 0.2
GCL volume (μm^3)	1.09	0.10	1.05	0.11	**0.028**	0.04	0.01 to 0.07
GCL S1 (μm)	51.3	5.9	50.4	6.1	0.371	0.9	−1.0 to 2.7
GCL S2 (μm)	35.4	4.0	33.4	4.0	**0.001**	2.1	0.8 to 3.3
GCL N1 (μm)	50.3	6.5	49.5	5.8	0.410	0.8	−1.1 to 2.8
GCL N2 (μm)	39.0	4.0	36.5	4.9	**0.001**	2.5	1.1 to 4.0
GCL I1 (μm)	51.3	5.3	49.8	6.3	0.098	1.6	−0.3 to 3.4
GCL I2 (μm)	33.6	3.3	32.4	3.8	**0.028**	1.2	0.1 to 2.4
GCL T1 (μm)	46.3	5.6	45.8	5.2	0.622	0.4	−1.3 to 2.1
GCL T2 (μm)	35.9	4.4	35.0	3.9	0.161	0.9	−0.4 to 2.3

SD: standard deviation; CI: confidence interval; RNFL: retinal nerve fiber layer; T: temporal; S: superior; I: inferior; N: nasal; 1: inner sector; 2: outer sector; GCL: ganglion cell layer; IPL: inner plexiform layer.
Significant differences are shown in bold.

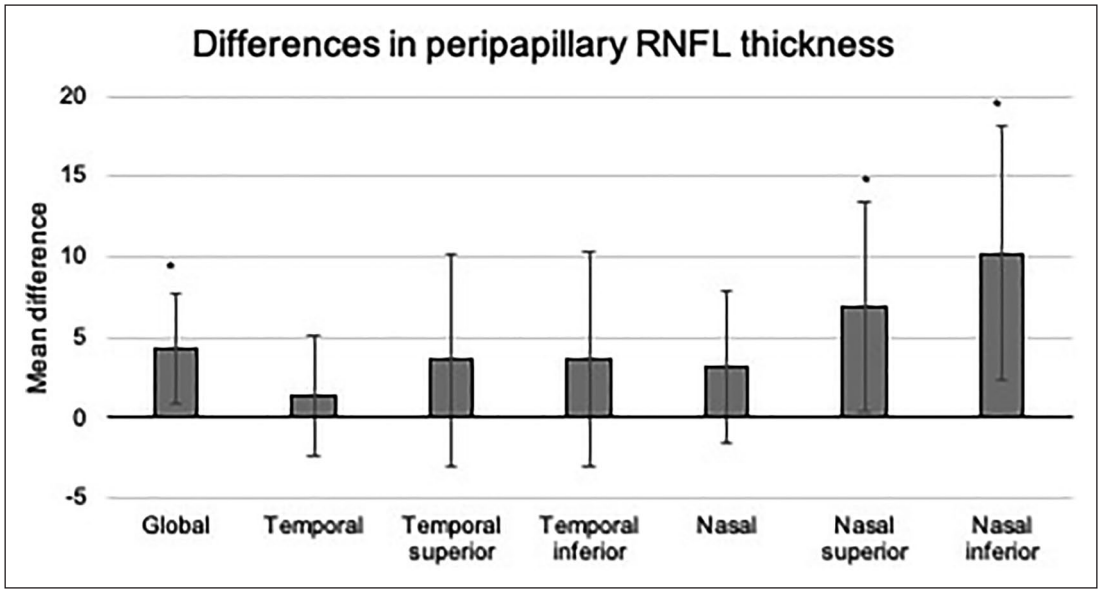

Figure 2. Differences in retinal nerve fiber layer (RNFL) thickness between COVID-19 patients and healthy controls.
RNFL thickness is measured in μm. *$p < 0.05$.

vessels (12.9%). Mean arteries diameter and mean veins diameter were higher in COVID-19 patients compared to unexposed subjects using computer-based analysis, retinal vessels dilation not always being detectable by clinical funduscopic examination. These changes could be due to inflammation, hypoxia or an increase in CO_2.

Savastano et al.[16] evaluated peripapillary RNFL and vascularization of 80 COVID-19 patients compared to 30 healthy controls. Radial peripapillary capillary plexus (RPCP) perfusion density was lower in COVID-19 patients, correlating with age, as well as treatment with lopinavir/ritonavir or antiplatelet therapy. RNFL average thickness was linearly correlated to RPCP flow index and perfusion density within post-COVID-19 group. However, no differences in RNFL average thickness were observed between COVID-19 patients and healthy controls.

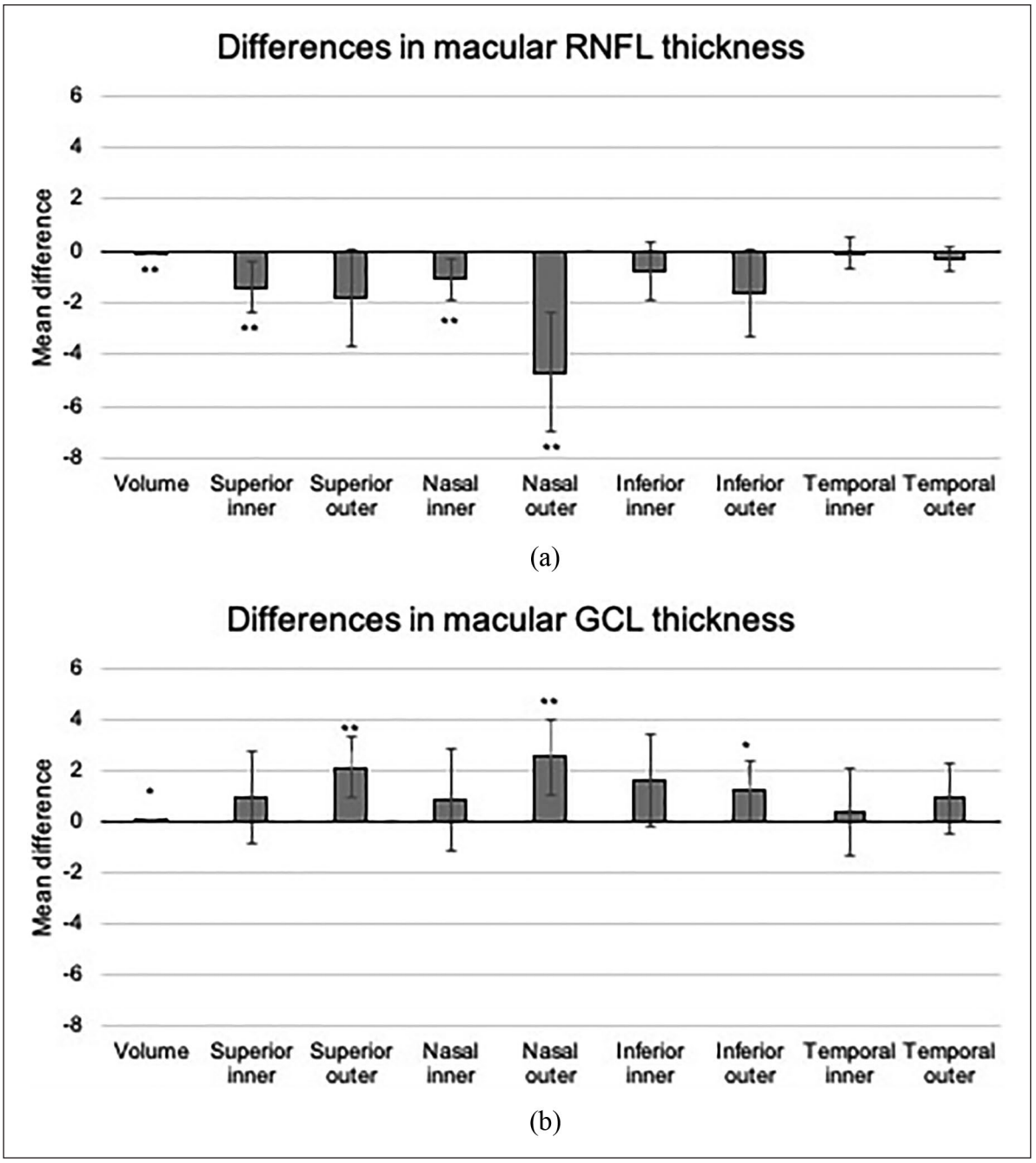

Figure 3. Macular optical coherence tomography analysis showing differences in (a) macular retinal nerve fiber layer (RNFL) thickness and (b) ganglion cell layer (GCL) thickness between COVID-19 patients and healthy controls.
Sectors are measured in μm, volumes are measured in μm^3. *$p < 0.05$. **$p < 0.01$.

Despite its immune-privileged status, the CNS can respond quickly and intensely to virus.[17] Neurotropic viral infections can cause brain parenchyma inflammation, reports of encephalitis caused by SARS-CoV-2 proving this mechanism.[18,19] Our results note increases in peripapillary RNFLT and macular GCL compared to patients without COVID-19, which could suggest an effect of the virus on the optic nerve.[20] This increase is supported by other results from our group that observed an increase in peripapillary RNFLT in recovered COVID-19 patients in comparison to examinations prior to the infection.[9] Our results contrast with those reported by Savastano et al.,[16] but, as they acknowledge, they present a low sample of healthy controls and an asymmetry between groups. In addition, only 6.25% of the subjects required admission to the intensive care unit and 8.8% required non-invasive ventilation, while 40% of the patients in our group presented a severe form of the disease. All of this could explain why differences were detected in the present study.

Table 4. Optic nerve and macular optical coherence tomography (OCT) in COVID-19 patients with anosmia or ageusia.

	Without symptoms ($n=37$)		With symptoms ($n=53$)		p	Mean differences	CI 95%
	Mean	SD	Mean	SD			
RNFL G (μm)	98.5	10.5	103.4	9.7	**0.026**	−4.9	−9.2 to −0.6
RNFL T (μm)	69.1	9.7	70.6	12.3	0.557	−1.4	−6.3 to 3.4
RNFL TS (μm)	130.4	22.4	140.1	22.3	**0.047**	−9.7	−19.2 to −0.1
RNFL TI (μm)	133.2	19.6	146.7	22.1	**0.004**	−13.5	−22.6 to −4.4
RNFL N (μm)	78.0	14.3	80.0	13.0	0.495	−2	−7.8 to 3.8
RNFL NS (μm)	108.2	22.4	114.6	18.6	0.145	−6.4	−15.1 to 2.3
RNFL NI (μm)	122.1	28.3	125.0	22.5	0.594	−2.9	−13.7 to 7.9
M RNFL volume (μm^3)	0.91	0.11	0.89	0.10	0.448	0.02	−0.03 to 0.06
M RNFL S1 (μm)	24.5	4.0	23.4	3.0	0.132	1.1	−0.3 to 2.6
M RNFL S2 (μm)	36.8	6.7	36.8	5.7	0.979	0.1	−2.6 to 2.7
M RNFL N1 (μm)	21.4	2.9	20.2	2.0	**0.03**	1.2	0.1 to 2.3
M RNFL N2 (μm)	47.9	8.4	45.4	7.2	0.136	2.5	−0.8 to 5.8
M RNFL I1 (μm)	26.2	4.0	24.5	3.3	**0.023**	1.8	0.3 to 3.3
M RNFL I2 (μm)	38.5	5.4	40.2	6.0	0.174	−1.7	−4.1 to 0.8
M RNFL T1 (μm)	18.1	2.3	17.5	1.2	0.110	0.7	−0.1 to 0.4
M RNFL T2 (μm)	19.4	1.4	19.1	1.5	0.309	0.3	−0.3 to 1.0
GCL volume (μm^3)	1.07	0.10	1.09	0.10	0.400	−0.02	−0.06 to 0.02
GCL S1 (μm)	51.1	6.7	51.4	5.3	0.798	−0.3	−2.9 to 2.2
GCL S2 (μm)	35.3	3.9	35.5	4.1	0.772	−0.2	−2.0 to 1.5
GCL N1 (μm)	50.9	5.9	49.8	6.8	0.424	1.1	−1.6 to 3.9
GCL N2 (μm)	38.0	3.9	39.7	3.9	**0.045**	−1.7	−3.4 to −0.1
GCL I1 (μm)	51.5	4.7	51.2	5.6	0.796	0.3	−2.0 to 2.6
GCL I12 (μm)	32.5	3.1	34.5	3.2	**0.004**	−2.0	−3.3 to −0.6
GCL T1 (μm)	45.8	5.8	46.6	5.4	0.529	−0.8	−3.1 to 1.6
GCL T2 (μm)	35.5	4.9	36.2	4.1	0.455	−0.7	−2.6 to 1.2

SD: standard deviation; CI: confidence interval; RNFL: retinal nerve fiber layer; M: macular; T: temporal; S: superior; I: inferior; N: nasal; 1: inner sector; 2: outer sector; GCL: ganglion cell layer; IPL: inner plexiform layer.
Significant differences are shown in bold.

In multiple neurodegenerative diseases involvement of the inner retinal layers using OCT has been reported. In Parkinson, the Braak hypothesis for its etiology is based on a neurotropic virus that invades the nervous system. Interestingly, the preclinical phase of Parkinson may present olfactory and gastrointestinal symptoms, similarly to COVID-19.[21] In OCT of Parkinson patients, peripapillary RNFLT, GCL, IPL, and retinal thickness are thinner as a result of nervous damage.[22–25] Hence, the increases observed in our series could be due to acute damage, which could turn into atrophy in the long-term. Moreover, multiple sclerosis might be triggered by an infectious agent, a virus being the most likely cause. Animal models describe that the best method to induce neuroinflammation is intracranial inoculation, leading to optic nerve inflammation.[26] Optic neuritis secondary to multiple sclerosis are commonly posterior, but anterior optic neuritis in other diseases typically cause increases in peripapillary RNFLT and clinically significant oedema.

As with other neurotropic viruses, SARS-COV-2 may invade the CNS through various routes, including the hematogenous or retrograde neuronal route. Neurological manifestations may be due to the CNS invasion of the virus, similar to other CoV.[27,28] On the other hand, smell impairment is a typical feature of SARS-CoV-2 and a possible neural pathway given by the olfactory nerve has been found in models.[29] Recent reports have demonstrated virus RNA in the human retina, the optic nerve could thus be affected through a transynaptic retrograde pathway from the olfactory bulb.[30,31] Through its binding to angiotensin-converting enzyme 2 (ACE2) receptors, the virus may access the PNS and travel transneuronally to the CNS, similar to other neurotropic viruses.[17] In this sense, anosmia due to virus damage to the olfactory pathways could be justified by this mechanism. The brain also has a high expression of ACE2 receptors, which supports the high penetration of the virus into the CNS.[32]

The changes observed when post-COVID-19 patients are stratified by anosmia or ageusia presentation support the idea that these symptoms are very characteristic in COVID-19 patients and a key in viral neurotropism. Hence, headache and dizziness might not be due to CNS viral invasion, and instead anosmia and ageusia are. Nevertheless, it must be kept in mind that neurological manifestations

observed in COVID-19 do not always imply CNS viral invasion and these are just possible hypothesis to justify our results.

In the current study, the differences observed could be the sequelae of much larger changes during the acute period of the disease, similarly to what occurs in neurologic symptoms in COVID-19. In this regard, recent reports have noted a high recovery rate of olfactory function 1–2 weeks after the onset of the symptoms.[33] However, on objective tests in a study, 80% of the patients who reported spontaneous regression of anosmia and ageusia still presented a certain degree of residual dysfunction.[12] This suggests that although neural damage may improve substantially after COVID-19 symptoms have ceased, subtle changes may still remain.

Several limitations of our study must be addressed. Firstly, this is a cross-sectional study and there is no ophthalmological evaluation at earlier stages of the disease due to the emergency situation, risk of contagion, poor general health condition in some cases, and exploration of contagious patients in the Ophthalmology clinic was avoided to reduce the risk of cross-infection. Therefore, the ophthalmological examination was performed 4 weeks after COVID-19 diagnosis because the patients had to comply with the 14-day period of mandatory isolation. A within-patient-comparison during and after COVID infection would be of great value, but great limitations apply. In addition, only refractive error was considered to exclude those with refractive error greater than 6 diopters, but axial length was not measured. The patient group was heterogeneous regarding the patients' general history and disease severity, which could explain the difficulties in identifying associations with the clinical variables.

Consequences of SARS-CoV-2 neurologic invasion and the effect of this neurotropic virus on the optic nerve and the retina are still unknown. This is the most complete study to date assessing structural changes in the retina and optic nerve of recovered COVID-19 patients using OCT technology. In the current study we prove optic nerve involvement in SARS-CoV-2 infection, although we cannot prove the exact mechanism of these changes. Hence, the inflammation caused by the virus would account for the thickening of some layers and the atrophy of other layers could be a result of transinaptic damage.

In conclusion, we found features related to optic nerve involvement in recovered COVID-19 patients. SARS-CoV-2 may be a neurotropic virus and affect the optic nerve, the olfatory bulb being the main entry pathway of the virus to the CNS. These alterations in the retinal layers may represent residual inflammation of the acute illness, transient changes, or long-term sequelae and the clinical significance of these findings is unknown. Therefore, larger and long-term follow-up studies including subgroups would make valuable contributions.

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References

1. Ren L-L, Wang Y-M, Wu Z-Q, et al. Identification of a novel coronavirus causing severe pneumonia in human. *Chin Med J (Engl)* 2020; 133(9): 1015–1024.
2. Larici AR, Cicchetti G, Marano R, et al. Multimodality imaging of COVID-19 pneumonia: from diagnosis to follow-up. A comprehensive review. *Eur J Radiol* 2020; 131: 109217.
3. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 382: 1708–1720.
4. Vabret N, Britton GJ, Gruber C, et al. Immunology of COVID-19: current state of the science. *Immunity* 2020; 52(6): 910–941.
5. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; 77: 683–690.
6. Ahmad I and Rathore FA. Neurological manifestations and complications of COVID-19: a literature review. *J Clin Neurosci* 2020; 77: 8–12.
7. 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: 2501–2507.

8. Seah I and Agrawal R. Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. *Ocul Immunol Inflamm* 2020; 28(3): 391–395.
9. Burgos-Blasco B, Guemes-Villahoz N, Donate-Lopez J, et al. Optic nerve analysis in COVID-19 patients. *J Med Virol*. 2021; 93(1): 190–191.
10. 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.
11. Lamirel C, Newman NJ and Biousse V. Optical coherence tomography (OCT) in optic neuritis and multiple sclerosis. *Rev Neurol (Paris)* 2010; 166(12): 978–986.
12. Vaira LA, Deiana G, Fois AG, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases. *Head Neck* 2020; 42: 1252–1258.
13. Tong JY, Wong A, Zhu D, et al. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg* 2020; 163(1): 3–11.
14. Gómez-Iglesias P, Porta-Etessam J, Montalvo T, et al. An online observational study of patients with olfactory and gustory alterations secondary to SARS-CoV-2 infection. *Front Public Health* 2020; 8: 243.
15. Invernizzi A, Torre A, Parrulli S, et al. Retinal findings in patients with COVID-19: results from the SERPICO-19 study. *EClinicalMedicine* 2020; 27: 100550.
16. Savastano A, Crincoli E, Savastano M, et al. Peripapillary retinal vascular involvement in early post-COVID-19 patients. *J Clin Med* 2020; 9(9): 2895.
17. McGavern DB and Kang SS. Illuminating viral infections in the nervous system. *Nat Rev Immunol* 2011; 11(5): 318–329.
18. Bernard-Valnet R, Pizzarotti B, Anichini A, et al. Two patients with acute meningo-encephalitis concomitant to SARS-CoV-2 infection. *medRxiv*. DOI: 10.1101/2020.04.17.20060251.
19. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis* 2020; 94: 55–58.
20. Pereira A. Long-term neurological threats of COVID-19: a call to update the thinking about the outcomes of the coronavirus pandemic. *Front Neurol* 2020; 11: 2019–2021.
21. Santos SF, de Oliveira HL, Yamada ES, et al. The gut and Parkinson's Disease: a bidirectional pathway. *Front Neurol* 2019; 10: 574.
22. 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.
23. 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.
24. Garcia-Martin E, Larrosa JM, Polo V, et al. Distribution of retinal layer atrophy in patients with Parkinson disease and association with disease severity and duration. *Am J Ophthalmol* 2014; 157(2): 470–478.e2.
25. Hasanov S, Demirkilinc Biler E, Acarer A, et al. Functional and morphological assessment of ocular structures and follow-up of patients with early-stage Parkinson's disease. *Int Ophthalmol* 2019; 39(6): 1255–1262.
26. 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.
27. Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med* 2005; 202(3): 415–424.
28. Zhou L, Zhang M, Wang J, et al. Sars-Cov-2: underestimated damage to nervous system. *Travel Med Infect Dis* 2020; 36: 101642.
29. Perlman S, Evans G and Afifi A. Effect of olfactory bulb ablation on spread of a neurotropic coronavirus into the mouse brain. *J Exp Med* 1990; 172(4): 1127–1132.
30. Pouga L. Encephalitic syndrome and anosmia in COVID-19: do these clinical presentations really reflect SARS-CoV-2 neurotropism? A theory based on the review of 25 COVID-19 cases. *J Med Virol*. Epub ahead of print 16 July 2020. DOI: 10.1002/jmv.26309.
31. Casagrande M, Fitzek A, Püschel K, et al. Detection of SARS-CoV-2 in human retinal biopsies of deceased COVID-19 patients. *Ocul Immunol Inflamm* 2020; 28(5): 721–725.
32. Li M-Y, Li L, Zhang Y, et al. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. *Infect Dis Poverty* 2020; 9(1): 45.
33. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Oto-Rhino-Laryngology* 2020; 277: 2251–2261.