Strabismus

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/istr20

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To cite this article: Ilda Maria Poças, Pedro Lino, Carina Silva, Paula Mendonça, João Paulo Cunha, Olga Barroqueiro, Francisca Carvalho, Inês Nicho, Mariana Castelhano, Patrícia Condado, Rita Carmo, Júlio Almeida, Isabel Prieto & Pedro Camacho (05 Dec 2023): Ocular repercussions in COVID-19 patients: structural changes of the retina and choroid, Strabismus, DOI: 10.1080/09273972.2023.2278639

To link to this article: https://doi.org/10.1080/09273972.2023.2278639

Published online: 05 Dec 2023.

STRABISMUS
https://doi.org/10.1080/09273972.2023.2278639

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ORIGINAL ARTICLE

Ocular repercussions in COVID-19 patients: structural changes of the retina and choroid

Ilda Maria Poças, MSc[a], Pedro Lino, MSc[b], Carina Silva, PhD[c,d], Paula Mendonça, MSc[d,e], João Paulo Cunha, PhD[a,f], Olga Barroqueiro, MSc[b], Francisca Carvalho, BSc[f], Inês Nicho, BSc[b], Mariana Castelhano, BSc[f], Patrícia Condado, BSc[b], Rita Carmo, BSc[b], Júlio Almeida, MD[b], Isabel Prieto, MD[b], and Pedro Camacho, PhD[a,d]

[a]Departamento das Ciências da Terapia e Reabilitação, Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa, Lisbon, Portugal; [b]Departamento de Oftalmologia, Hospital Professor Doutor Fernando Fonseca, EPE, Amadora, Portugal; [c]Departamento das Ciências Exatas, da Vida Sociais e Humanas, Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa, Lisboa, Portugal; [d]H&TRC- Health & Technology Research Center, ESTeSL- Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa, Lisboa, Portugal; [e]Departamento das Ciências do Diagnóstico, Terapêutica e Saúde Pública, Escola Superior de Tecnologia da Saúde de Lisboa, Instituto Politécnico de Lisboa, Lisboa, Portugal; [f]Departamento de Oftalmologia, Hospital Cuf Cascais, Cascais Municipality, Portugal

ABSTRACT

Background: Neurotropic capabilities of SARS-COVs allow viruses to reach the central nervous system by hematogenous neuronal dissemination. The human retina, as an extension of the Central Nervous System, may have some neurodegenerative and/or vascular modifications related to COVID-19.

Objectives: To evaluate choroidal and inner neural layers in participants previously recovered from COVID-19 compared to the control group using optical coherence tomography.

Methods: With a cross-sectional approach, the sample ($n = 96$), constituted by patients who have recovered from COVID-19 ($n = 56$) and healthy participants control group ($n = 40$) were ophthalmologically characterized. The neurodegenerative and vascular histological assessment was performed using SD-OCT and the mean thickness was measured in Early Treatment Diabetic Retinopathy Study (ETDRS) subfields. Retinal nerve fiber layer, Ganglion cell layer and subfoveal choroidal thickness were obtained through semi-automatic measurement.

Results: A total of 40 controls (27 women [67.5%]) and 56 COVID-19 participants (34 women [60.8%]) were included in this first report. There were retinal thickness significant differences in nearly all inner ETDRS subfields: nasal 3 mm ($p = .025$), I3 ($p = .049$), and temporal 3 mm ($p = .009$). Also, a decrease in neural layers was found in the nasal 3 mm ($p = .049$) and temporal 3 mm ($p = .029$) during ganglion cell layer assessment. The peripapillary retinal nerve fiber layer thickness was thinner in the COVID-19 group in superior temporal ($p = .019$), nasal ($p = .002$), inferior temporal ($p = .046$) and global ($p = .014$). Concerning the subfoveal choroidal measurement, an increase was observed in the COVID-19 group ($p = .002$).

Conclusion: Participants who had recovered from COVID-19 showed a non-glaucomatous neuropathy trend pattern. We found differences closer to the classic description of the "bow-tie" observed in other neurological as compressive neuropathies at the chiasma location. OCT assessment also showed an increase in choroidal thickness as a result of vascular changes.

KEYWORDS
Choroid; COVID-19; ganglion cell layer; OCT; retina thickness; retinal nerve fiber layer

Introduction

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome (SARS-CoV-2) with high mortality rates affecting most frequently the airways and the lungs. Although it mainly affects the respiratory system, it can also affect cardiovascular, neurological, gastrointestinal, hepatic, renal, hematological, ocular, and cutaneous tissues.[1]

In previous situations, by other coronaviruses (CoVs), ocular involvement has been described.[2] The relationship of this virus with the ocular surface and the eventual neurotropism has also been described revealing an apparent facility of this virus to reach the Central Nervous System (CNS) by hematogenous[3] or retrograde neuronal dissemination.

CONTACT Ilda Maria Poças ildampocas@gmail.com Departamento das Ciências da Terapia e Reabilitação, Instituto Politécnico de Lisboa Escola Superior de Tecnologia da Saúde de Lisboa, Av. D. João II, Lote 4.69.01, 1990-096 Lisbon, Portugal

The angiotensin converting enzyme-2 receptor (ACE-2), which has been reported to be expressed in eye tissues, may be important in understanding some COVID-19[4–6] and linked to some ocular alterations such as conjunctivitis, uveitis, vasculitis, retinitis and optic neuritis that have been initially documented in animal models.[2]

Although the first studies were focused on respiratory tract involvement and ocular surface relevance,[7] as a form of contagion and transmission,[8] precautions should be taken to assess the sequelae of COVID-19.

In early eye-related work, SARS-CoV-2 has been associated with retinal nerve fiber layers (RNFL) thinning, vascular narrowing, hyperreflective lesions, microhemorrhages and/or cotton-wool spots.[9,10] Mainly carried out in participants with severe forms of COVID-19, this initial studies, have been insufficient to clarify the impact of possible changes in the retina and choroid in patients with a history of mild/moderate COVID-19 infection.

Moreover, animal models showed that SARS-CoV and MERS-CoV can enter the brain, possibly via olfactory nerves, and rapidly spread to specific brain areas including the thalamus and brainstem. The virus neurotropism were reported with involvement such as taste and smell disorders in SARS-CoV-2 patients.[11,12] These reports prompted us to consider investigating the effects of the disease in the retinal layers.

The hyperinflammatory response is important in the development of acute respiratory distress syndrome, which plays a critical role in the prognosis of COVID-19,[13] and the choroidal thickness may reflect some systemic inflammation even without active ocular findings.[14,15] Thereby, ocular vascular structures may be affected due to vasculopathy, inflammation, and endothelial cell dysfunction due to COVID-19 pathogenesis.

The CoV neurotropism, by hematogenous dissemination[3] and/or retrograde neuronal pathway, the vascular/ischemic compromise,[16] and some hyperinflammation status[14,15] with COVID-19 brain-related sequelae[17,18] justify the use of non-invasive methodologies to characterize the retina and choroid of patients infected with COVID-19. The possible neurodegeneration associated with the coronavirus motivates the quantitative evaluation of the inner retinal layers already described in other neurodegenerative diseases.[16,19–21]

In addition, we also intended to investigate the changes in choroidal thickness due to the possible vascular and ischemic[3] impairment linked to COVID-19.[17,18] Considering the human retina an extension of the CNS,[19] with great energetic needs and an enormous vascular dependence, this study aims to (1) characterize the thickness of the ganglion cell layer (GCC), peripapillary RNFL and choroid sub-foveal thickness.

This approach with non-severe COVID-19 patients remains relevant for providing more information as there are still some remaining doubts about the impact of COVID-19 disease[22] and/or the effects of vaccination[23] in human retina.

Methods

This study aims to describe the metrics features of the retina and choroid in participants previously infected with COVID-19 and compare them with PCR-negative participants for SARS CoV2 during routine ophthalmology practice. With a cross-sectional approach, developed at the Health & Technology Research Center, ESTeSL Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa, and through noninvasive methodologies, a group of patients previously infected with COVID-19 and the control group were recruited and after a complete ophthalmic assessment the RNFL and GCL quantification in the different subfields were performed.

Participants' sampling and recruitment

For this study, only participants aged 18 years or older, with signed free and informed consent, were recruited, and all the data were confidentially maintained. The recruitment of cases and controls were carried out at the Ophthalmology services of Hospital Prof. Doutor Fernando Fonseca and at the Cuf Cascais Hospital during March 2021 and November 2021. The present study was submitted and approved by the Health Ethics Committee of the partner Hospitals and the ESTeSL with registration identification number 070/2021.

Ninety-six subjects were selected, of which 56 participants (COVID-19 study group) had been recovered from COVID-19 for at least 3 months.

The control group consisted of 40 participants with negative CRP and no history of COVID-19.

Neither COVID-19 study group nor Control Group presented a previous medication and/or condition that could have affected choroidal thickness assessment. Following the COVID-19 Treatment Guidelines Panel[24] only cases with non-severe disease were included. The exclusion criteria included previous ocular trauma, ocular surgery and any ocular disease, high myopia, and hyperopia. Were also excluded patients with any systemic diseases, such as dyslipidemia, systemic hypertension, and diabetes mellitus, as well as those using systemic or topical medication.

Ophthalmological assessment

All participants were undergoing a complete ophthalmological observation: recording of the best corrected visual acuity (BVM), slit lamp biomicroscopy and measurement of intraocular pressure (by blow tonometry) and tomographic study through optical coherence tomography – Spectral Domain (SD-OCT) CT scans were obtained using Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany®), software version 6.0, under mesopic conditions. The images were obtained by an experienced orthoptist and evaluated by an ophthalmologist, both without knowledge of the patient's diagnosis. Only scans with well-focused images, without misalignment, with a continuous pattern with no gaps or artifacts and with Q greater than 20 decibels were included. The analysis of the peripapillary RFNL was performed using the RNFL Single Exam Report OU with FoDi™ program, obtaining three high-resolution circular scans centered on the optic disc, with approximate mean diameters of 3.5 to 3.6 mm for eyes with axial length medium. The Spectralis software calculates the global mean thickness of the 360° and the four 90° sectors (Superior (S), Inferior (I), Nasal (N), and Temporal (T)), further subdividing the S and I quadrants into more four quadrants: upper Temporal (TS between 45 and 90°), Superior Nasal (NS between 90 and 135°), Inferior Nasal (NI between 225 and 270°) and Inferior Temporal (TI between 270 and 270°) if we refer to the right eye. Macular retinal analysis was performed using the fast macular thickness protocol, 25 high-resolution scans (20° × 20°, 6 × 6 mm) centered on the fovea. Spectralis automatic segmentation software was used to obtain thickness values for each retinal layer, including total retinal thickness (RT Retina Total), RNFL, GCL, IPL, Inner Nuclear Layer (INL), Outer Plexiform Layer (OPL), Outer Nuclear Layer (ONL), RPE and PR layer.

Average thickness values were calculated in the nine areas of the ETDRS grid for all the layers. The ETDRS circles consist of three concentric rings of 1, 3, 6 mm in diameter. The two outer rings were divided into quadrants by two intersecting lines and each sector will be designated C (central corresponding to the central millimeter), S3 (upper from 1 to 3 mm), S6 (upper from 3 to 6 mm), T3 (temporal from 1 to 3 mm), T6 (temporal from 3 to 6 mm), I3 (lower 1 to 3 mm), I6 (lower 3 to 6 mm), N3 (nasal 1 to 3 mm) and N6 (nasal 3 to 6 mm).

For the choroid analysis, according to a previously described method,[25] was also used the fast macular thickness protocol in the enhanced depth imaging (EDI) mode. Subfoveal Choroidal thickness (CT) was measured manually through the best horizontal scan (using the caliper function from RPE outer border to the inner scleral border).

The analysis and pre-processing of data were structured by i) Screening of data and preprocessing, using descriptive statistics to analyze the variability and the presence of missing values in the answers to the questionnaires; ii) Patient demographic and clinical categorical variables were described with frequencies (percentage) and continuous variables with mean and standard deviation (SD), or median and interquartile range (IQR: 25th percentile–75th percentile) or range (R: minimum–maximum) as appropriate. To compare the two groups, the t-student and non-parametric Mann–Whitney tests were used when the conditions were not met (after assessment with a Shapiro – Wilk's test). To study associations between categorical variables, the chi-square test was used. iii) Linear regression models were used to identify the variables that may explain the variability of peripapillary RNFL thicknesses. For the analysis and treatment of data, the IBM Statistical Package for the Social Sciences for Windows "SPSS Statistics," version 23 was used.

Table 1. Sociodemographic and ophthalmological profile of the sample.

Sample Characteristic ($n = 96$)	Control ($n = 40$)	COVID19 ($n = 56$)	*P* value
Sex, No. (%)	Male 13 (32,5) Female 27 (67,5)	Male 22 (39,2%) Female 34 (60,8%)	0,496*
Age, years	53,57 ± 14,3 (20–74)	44,89 ± 20,9 (18–77)	0,086*
Eye	right 26 (65) left 14 (35)	right 29 (51,8) left 27 (48,2)	0,197*
BCVA (Mean±SD)	0,99 ± 0,05	0,98 ± 0,06	.805*
IOP mmHg (Mean±SD)	14,25 ± 2,7	14,7 ± 3,2	0,499+
SE (Mean±SD)	−0,24	−0,91	0,944*

Legend: BCVA= Best corrected Visual Acuity; IOP= Intra ocular pressure; SE= spheric equivalent; += T-Student parametric test; *= U Mann–Whitney test (independent sample).

Results

Table 1 shows the sociodemographic and ophthalmological profile of the sample. The COVID-19 participants (group 1 – PCR positive) consist of 56 participants (34 females and 22 males) with the ages range between 18 and 77 years of age (44.89 ± 20.9 years). The control group (Group 2 – PCR negative) consists of 40 participants (27 females and 13 males) with the ages range between 20 and 74 years of age (53.57 ± 14,3 years).

With similar features, there are no statistically significant differences in the best corrected visual acuity ($p = .825$), Intraocular pressure (0.499), spherical equivalent (0.944), between the two groups.

1) SD-OCT assessment:

Regarding the global retina thickness assessment through SD-OCT (Table 2 and Figure 1) a retinal decrease is observed within inner ring (3 mm). Statistical significance difference is evident in Nasal ($p = .029$), Inferior ($p = .038$) and Temporal ($p = .010$).

The ganglion cell layer evaluation by SD-OCT (Table 3 and Figure 2) shows a significant GCC decrease S3 ring ($p = .020$), N3 ring ($p = .032$) and T3 ring ($p = .034$).

In the peripapillary nerve fiber layer assessment (Table 4 and Figure 3) there is a significant decrease in Superior Temporal ($p = .019$), Inferior nasal ($p = .002$), Inferior temporal ($p = .046$), and the global value ($p = .014$).

Opposite to the RNFL and GCC decrease pattern of thickness, in the sub-foveal choroidal analysis (Table 5) our data revealed a thickening ($p = .002$) in COVID-19 group (278 ± 64 μm) compared to Control Group (230.9 ± 76 μm).

Table 2. Distribution of total retinal thickness (μm) by control and COVID-19 participants.

ETDRS location	Control Mean±SD	COVID-19 Mean±SD	*P* value
Central fóvea	229.4 ± 21.4 (185–267)	232.7 ± 21 (201–304)	.465+
Min Fovea	226.7 ± 21.2 (184–265)	228.6 ± 22.4 (193–298)	.676^{+}
1 mm fovea	278.3 ± 21 (235–309)	270 ± 23.8 (221–345)	.054*
Superior 3 mm ring	344.6 ± 19 (262–375)	339.2.1 ± 18 (286–376)	.069*
Nasal 3 mm Ring	348 ± 15 (321–374)	339 ± 20.1 (270–381)	**.029**$^{+}$
Inferior 3 mm ring	343 ± 14 (317–370)	335.6 ± 18 (274–372)	**.038**$^{+}$
Temporal 3 mm Ring	333.1 ± 13 (311–355)	324.4 ± 17 (286–366)	**.010**$^{+}$
Superior 6 mm ring	302.8 ± 14 (277–337)	297.9 ± 18.6 (207–322)	.169^{+}
Nasal 6 mm ring	317.4 ± 13 (290–343)	312.1 ± 17.2 (250–340)	.109^{+}
Inferior 6 mm ring	290.5 ± 12 (258–313)	288.7 ± 16.6 (220–316)	.561^{+}
Temporal 6 mm ring	287.1 ± 13 (265–315)	283 ± 18 (190–308)	.253^{+}

Legend: SD = standard deviation; $^{+}$T-Student parametric test; *Mann–Whitney test (independent sample).

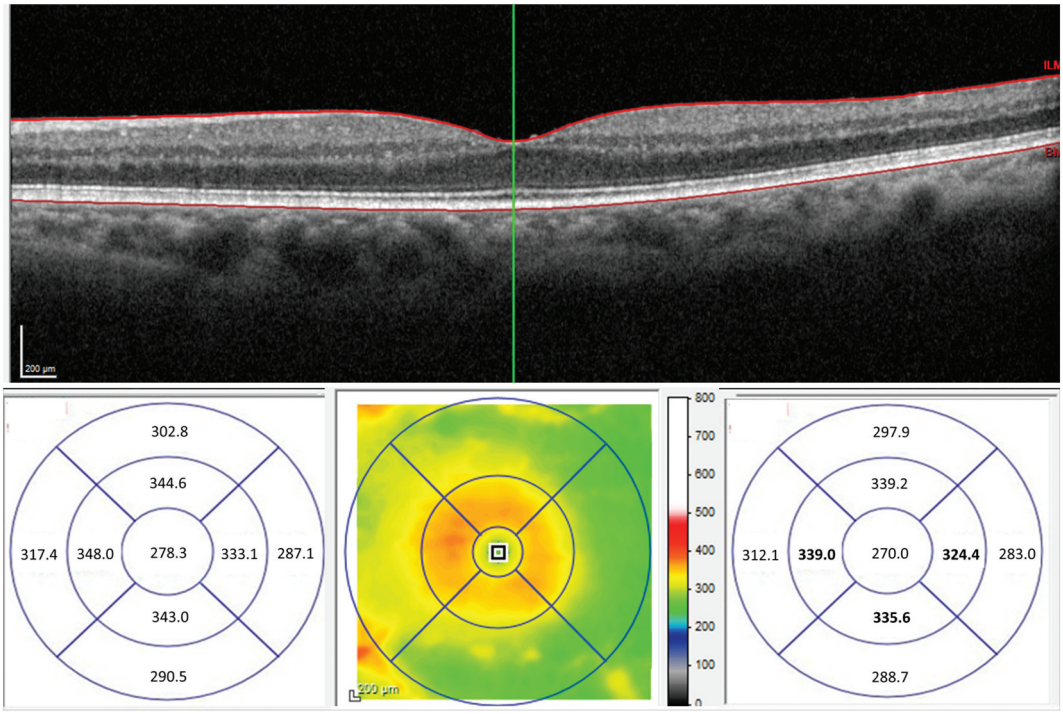

Figure 1. Macular thickness (µm) of the total retina (RT) comparison between the control group (CG) and the study group in the nine sectors; control group on the left, study group on the right. Results are expressed as mean and standard deviation (SD); *p* values obtained by univariate linear regression models.

Table 3. Distribution of ganglion cell layer thickness (µm) by control and COVID-19 participants.

ETDRS location	Control Mean±SD	COVID-19 Mean±SD	*P* value
1 mm fovea	15 ± 3.6 (9–25)	14.3 ± 4.4 (6–28)	.343^{+}
Superior 3 mm ring	52.9 ± 4.2 (24–60)	50 ± 7.9 (23–60)	**.020+**
Nasal 3 mm Ring	52.1 ± 4.5 (44–61)	49.4 ± 6.9 (26–63)	**.032**$^{+}$
Inferior 3 mm ring	52.3 ± 5.7 (32–61)	49.7 ± 7.2 (24–61)	.083*
Temporal 3 mm Ring	47.6 ± 4.8 (35–56)	44.9 ± 6.7 (30–60)	**.034**$^{+}$
Superior 6 mm ring	35.3 ± 3.8 (25–42)	34.4 ± 5.3 (12–41)	.391^{+}
Nasal 6 mm ring	38.9 ± 4.9 (26–51)	37.8 ± 4.2 (26–47)	.254^{+}
Inferior 6 mm ring	34 ± 3.6 (25–41)	33.3 ± 5.6 (10–42)	.467^{+}
Temporal 6 mm ring	36.1±/4.5 (25–46)	35.9 ± 5.6 (13–45)	.816^{+}

Legend: SD = standard deviation; $^{+}$T-Student parametric test; *Mann–Whitney test (independent sample).

Discussion

Coronaviruses are known to involve organs and systems other than the respiratory tract, including the digestive system, nervous system, and ocular tissues. Previous reports suggest ocular infection in the recent SARS-CoV-2 epidemic, and ocular transmission might be a potential route of SARS-CoV-2 infection tissues.[1–3]

Although several months have gone by since the epidemic, not much has been published about the mechanisms of pathogenicity of SARS-CoV-2, especially with respect to the ocular tissues. Additionally, because some questions remain about the impact of COVID-19 disease[22] and/or vaccination[23] effects on the human retina, this approach may provide important insights into non-severe and non-

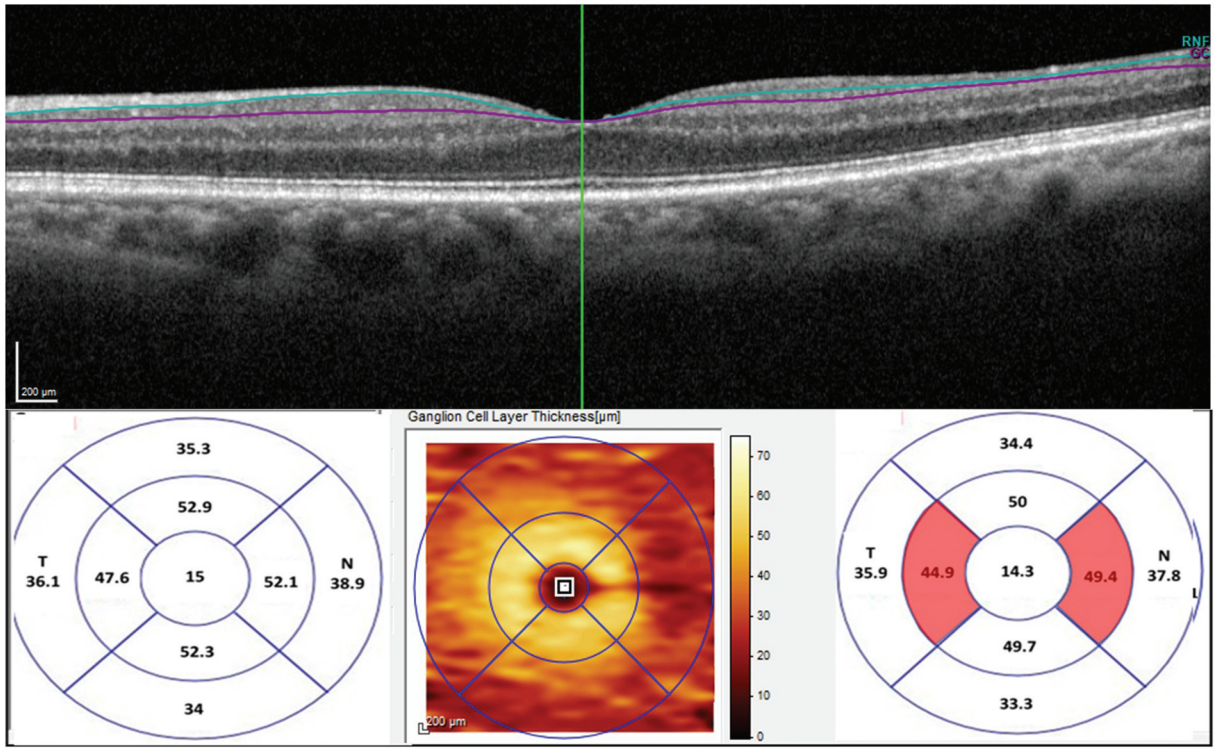

Figure 2. Thickness of the peripapillary retinal nerve fiber layer obtained by the fast macular program (Spectralis Heidelberg®) with mean values, per group: On the left, values obtained in the control group; right study group.

Table 4. Distribution of retinal nerve fiber layer thickness (µm) by control and COVID-19 participants.

Characteristic	Control Mean±SD	COVID-19 Mean±SD	*P* value[+]
Superior temporal	147.2 ± 29.3 (97–198)	133.1 ± 19.9 (78–175)	**.019**
Superior nasal	119 ± 43.1 (78–165)	111.3 ± 25.5 (50–161)	.532
Nasal	85.2 ± 44.5 (49–143)	76.7 ± 16.6 (33–110)	.642
Inferior nasal	132.9 ± 53.3 (64–176)	111 ± 21.1 (73–155)	**.002**
Inferior temporal	152.6 ± 24.6 (115–200)	141.2 ± 20.6 (81–179)	**.046**
Temporal	73.4 ± 24.4 (52–92)	69.5 ± 13 (23–92)	.908
Global	108.9 ± 32.7 (82–126)	98.5 ± 10.6 (73–119)	**.014**

Legend: SD = standard deviation; [+]T-test (independent sample).

vaccinated patients. For this reason, we evaluated the retinal findings from recovered COVID-19 patients (for at least 3 months), during routine clinical practice, and SD-OCT imaging, which were compared with a normal match control.

The retina by its embryological origin is considered an extension of the CNS. Thus, not only for a merely ophthalmological purpose but also with neurological interest for its easy access by noninvasive methodologies such as OCT, its evaluation becomes eminent.

Despite a few contradictory studies,[26] our results point to a neural retinal thickness in patients previously infected with COVID-19 when compared to the control group. This is in agreement with a recent study published by Zapata et al., in which patients with SARS- Moderate and severe CoV-2 showed a decrease in central retinal thickness compared to that of asymptomatic cases or control subjects.[27,28] Similarly, the most robust changes were obtained in the inner rings.

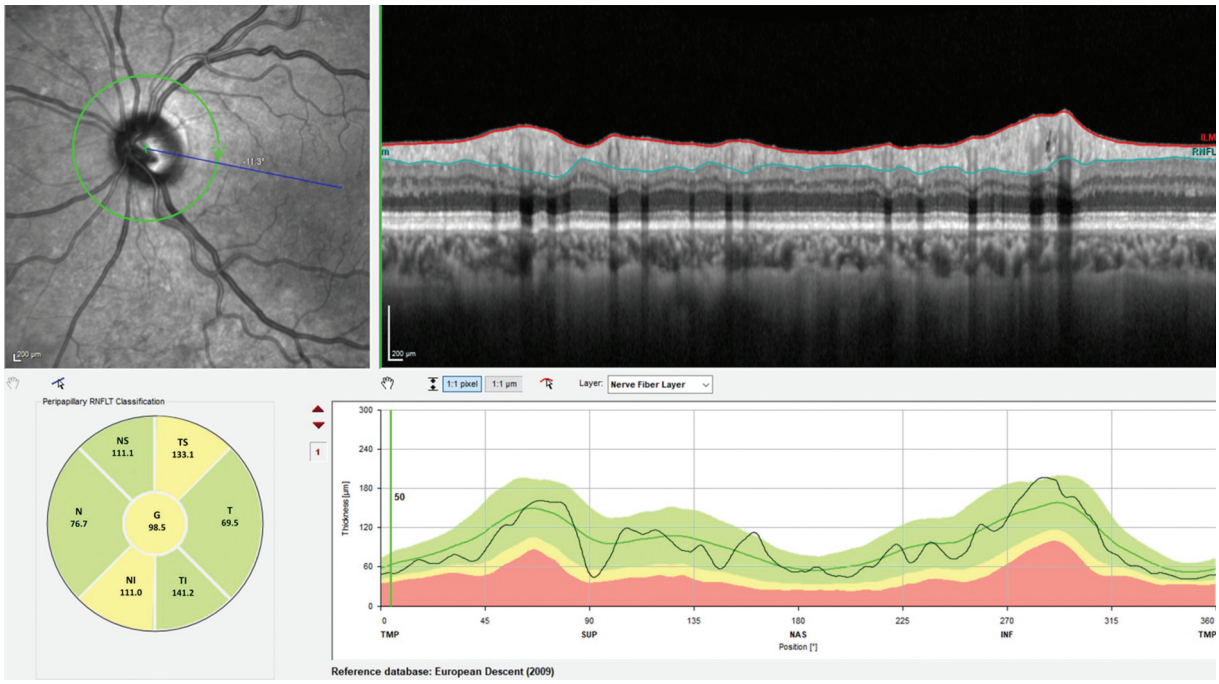

Figure 3. Thickness of the ganglion cell layer (GCL) – eccentricity 3 mm (micrometers): Left – control group (COVID-19 neg.); right – infected group (COVID-19 pos.).

Table 5. Distribution of sub-fovel choroidal thickness (µm) by control and COVID-19 participants.

Characteristic	Control Mean±SD	COVID-19 Mean±SD	*P* value[+]
Sub-foveal thickness	230.9 ± 76 (117–484)	278 ± 64 (131–485)	**.002**

Legend: SD = standard deviation; [+]T-test (independent sample).

Regarding the ganglion cell complex and peripapillary RNFL, there is a reduction in thickness with typical characteristics of non-glaucomatous optic neuropathies with a pattern already described of a "bow-tie" that differs from essentially vertical losses in glaucoma.[19,20] Our results regarding the ganglion cell complex are in agreement with other studies such as the one by González-Zamora et al., which describes that patients previously infected with COVID-19 have a significantly thinner ganglion cell complex.[28] On the other hand, our results regarding the peripapillary RNFL contradict the results published by Beni et al, in which they obtained an increase in the thickness of the peripapillary nerve fiber layer compatible with optic disc edema.[29] also typical of some cases of ocular inflammation in the active phase.

The choroid consists of a vascular network that acts as a blood supply for the outer retina, optic nerve, and avascular fovea. Choroid tissue can rapidly change its thickness in response to a variety of stimuli. Changes in choroidal circulation, autonomic nervous system, or inflammation can cause changes in choroidal thickness. Using a sample without severe symptoms, this study seems to document some changes that may reflect a slight pattern of inflammation (one of the important pathophysiological mechanisms of COVID-19).[30] We observed an increase in its thickness when compared to the control group, possibly secondary to systemic inflammation/infection as in other systemic inflammatory diseases.[1,16,31] SARS-CoV-2 infection activates a systemic inflammatory response that leads to the release of inflammatory mediators. There is increasing evidence that COVID-19 predisposes to thrombosis in both arterial and venous circulation. Reported findings showed that organ dysfunction in patients with COVID-19 can be caused by immunosuppression, endothelial activation, or direct viral-mediated

tissue damage.[8] The presence of ACE-2 receptors in the choroid is well known. Cat CoV and murine CoV mouse hepatitis virus can cause retinal detachment, vasculitis, retinitis, retinal atrophy, optic neuritis, uveitis, and choroiditis.[11] In pathogenesis, pulmonary endothelial inflammation possibly mediated by endothelial ACE-2 after SARS-CoV-2 infection increases the inflammatory response in vascular lesions and may cause endothelial dysfunction and vascular dilatation.[11]

There were certain limitations to this study. Despite the use of a control group, this study design makes it difficult to have a clear notion of the cause–effect relationship of COVID-19 on retinal and choroidal thickness. In this sense, prospective studies continue to be the most adequate. Next, we cannot forget some fragility in the recruitment of control participants. Even without a history of COVID-19 and negative PCD there is always the possibility of a history of undetected disease. In this sense, it would have been important to have some serological test to confirm the control group was free of previous COVID-19 infections. Another important aspect is related to the evaluation of the choroid. In this evaluation, it would have been important to be able to characterize the axial length of the participants. Also, we cannot forget that the thickness of the choroid is influenced by multiple drugs used in the control of diabetes mellitus and arterial hypertension, so our results may be biased because we do not know the usual medication of the patients, which is assumed as a limitation of this study, so that Examining patients with the additional diseases or requiring intensive care hospitalization may have prevented objective results being obtained in the previous studies. Therefore, no patients with additional disease or using anticoagulants that might have affected choroidal thickness were included in this study. This made it possible to reveal the effects of COVID-19 in the fovea and choroid more clearly. In addition, evaluating a period reporting after 14 days after the onset of first symptoms enabled the exclusion of temporary changes that might occur due to acute inflammation.

Conclusions

No changes were found in the structure of the macula and choroid on SD-OCT compatible with chorioretinopathy. Our results show a tendency toward a non-glaucomatous neuropathy – our results differ from the preferentially vertical locations (typical of glaucoma), being closer to the classic description of the "bow-tie" observed in other neurological as compressive neuropathies at the chiasma location.

Our exploratory results allow us to describe and alert clinicians to possible changes in the retina, choroid, and optic nerves in patients previously infected with COVID-19. They also allow to reflect and guide/raise new questions that will give rise to new studies, namely of longitudinal design, to find out if the alterations found are only acute and of short duration or if they tend to take on some chronicity that may affect the visual function of individuals. In future investigations, in addition to the assessment of structural damage at the nervous level, it may still be relevant to study vascular alterations using OCT-A; as well as the assessment of functional damage through microperimetry, contrast sensitivity and color vision.

Acknowledgements

Authors acknowledge the support of H&TRC- Health & Technology Research Center, ESTeSL Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa. This project was partially supported by an IDI&CA grant IPL/2020/OCLOVI-19_ESTeSL.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This project was partially supported by an IDI&CA grant [IPL/2020/OCLOVID-19_ESTeSL] by H&TRC- Health & Technology Research Center, ESTeSL- Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa.

ORCID

Ilda Maria Poças, MSc http://orcid.org/0000-0002-1695-3231
Pedro Lino, MSc http://orcid.org/0000-0002-8237-5521
Carina Silva, PhD http://orcid.org/0000-0003-1021-7935
Paula Mendonça, MSc http://orcid.org/0000-0003-3648-525X

João Paulo Cunha, PhD http://orcid.org/0000-0002-3162-0531
Olga Barroqueiro, MSc http://orcid.org/0009-0005-6586-7152
Francisca Carvalho, BSc http://orcid.org/0009-0005-5609-4557
Inês Nicho, BSc http://orcid.org/0009-0005-4891-0278
Mariana Castelhano, BSc http://orcid.org/0009-0009-2705-3106
Patrícia Condado, BSc http://orcid.org/0009-0005-6580-8515
Rita Carmo, BSc http://orcid.org/0009-0004-2833-1239
Júlio Almeida, MD http://orcid.org/0000-0002-4651-8812
Isabel Prieto, MD http://orcid.org/0000-0001-7094-817X
Pedro Camacho, PhD http://orcid.org/0000-0002-2986-5652

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