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Severe SARS-CoV-2 Infection: Late Impact on the Retinal Ganglion Cell Layer Thickness

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Abstract

Purpose: The involvement of the ocular anterior segment by SARS-CoV-2 has been the subject of many studies, however, the repercussions on the posterior segment, particularly on the different layers of the retina and optic nerve, are still little known. The purpose of this study was to evaluate the impact of severe COVID-19 on the retinal ganglion cell layer (RGCL) thickness. **Methods:** This observational, prospective and analytical study was performed in the Ophthalmology Department of the FACISA University Center, Campina Grande. Three groups were included: group I (control), 29 healthy individuals who had not severe COVID-19; group II (infirmary), 24 individuals who had COVID-19 and were hospitalized in the infirmary; and group III, 25 individuals who had severe COVID-19 and required Intense Care Unit (ICU). All individuals had ophthalmologic examination and assessment of RGCL thickness using Optical Coherence Tomography (OCT). Statistical tests required $p \le 0.05$ to reject the null hypothesis. **Results:** The mean of RGCL thickness was significantly reduced in individuals from GIII (77.9 ± 8.9 μm), as compared with GII (83.9 ± 10.9 μm) and GI (82.8 ± 6.5 μm) ($p = 0.0027$). The mean measurements from the retinal neve fiber layer (RNFL) of the optic nerve head were similar. However, when evaluated sectoral, the mean of RNFL at the temporal sector of the optic disc was significantly lower in group GIII ($p < 0.001$). **Conclusion:** The RGCL thickness from patients with severe COVID-19 was significantly reduced. This finding supports that the SARS-CoV-2 has systemic action and affinity for nerve cells, including those from the retina and are related to the severity of the infection.

Keywords

COVID-19, Post-Acute COVID-19 Syndrome, Retinal Ganglion Cell

1. Introduction

The SARS-CoV-2 was first identified in humans in the Chinese city of Wuhan in late 2019 [1]. The COVID-19 disease, caused by this virus, has become a pandemic with more than six million deaths worldwide and more than 700 thousand deaths in Brazil [2].

In the Northeast region, particularly in the state of Paraiba, epidemiology recorded a higher rate of infection and mortality in the year 2021 [3].

In ocular tissue, the SARS-CoV-2 has been identified in the conjunctiva, cornea and retinal ganglion cells, causing vascular congestion and conjunctivitis [4]-[6]. The retina can be affected by direct action of the virus on neurons or affecting its microcirculation [7]-[11]. The impact of SARS-CoV-2 on the various layers of the retina can be estimated by Optical Coherence Tomography (OCT), which is a non-invasive imaging technique allowing the measurement of the thickness of the retinal layers, including the ganglion cell layer and the thickness of the nerve fiber layer of the optic disc [12].

The involvement of the anterior segment of the eye by SARS-CoV-2 has been the subject of many studies, however, the repercussions on the posterior segment, particularly on the different layers of the retina and optic nerve, are subject of investigation [5] [6] [13] [14]. This kind of approach has not been performed in Brazil.

The purpose of this study was to analyze the thickness of the retinal ganglion cell layer from patients infected with the severe form of COVID-19 admitted to Intensive Care Unit (ICU), as well as those who required only hospital ward in the city of Campina Grande, using OCT.

2. Methods

This study was performed in Campina Grande, Paraíba, Brazil, including patients who were admitted in several city hospitals. They were examined in the Ophthalmology Department from the FACISA School Clinic, where complete ophthalmological outpatient care was provided, in addition to the Optical Coherence Tomography (OCT) examination.

The study was observational, prospective and analytical. It was approved by the Human Research Ethics Committee of UNIFACISA, under number 59115722.5.0000.5175. Participants agreed and signed the Free and Informed Consent Form.

The patients were informed that they would not suffer any type of harm, and could withdraw from the study at any time, thus ensuring privacy, confidentiality and anonymity.

Individuals from 18 to 75 years of age were included, of both genders, without restrictions on ethnicity or socioeconomic conditions, who had recovered from COVID-19, either admitted to the ward or to the Intensive Care Unit (ICU). For the control group, healthy individuals who were not proven to be affected by COVID-19, with visual acuity of 20/20, without ophthalmological diseases and with anthropometric data equivalent to those of patients who had COVID-19.

The recruited individuals were stratified into three groups: Group I, healthy individuals who were not proven infected by COVID-19, as a control group; Group II, patients admitted for treatment of COVID-19 in a hospital ward and Group III, patients admitted to the Intensive Care Unit for treatment of severe COVID-19 infection.

Patients with previously diagnosed eye diseases (glaucoma, optic neuritis, degenerative myopia and media opacity with significant impairment of visual acuity) and significant cognitive restriction were excluded.

The patients were selected from an active search during the years 2022 and 2023, using records from some hospitals and the outpatient records of patients treated in the physiotherapy sector at FACISA University Center, Campina Grande, Paraíba. Those who met the inclusion criteria were contacted by telephone, informed about the methodological design and objectives of the study, and, after signing the free consent form, they were referred to the Ophthalmology Outpatient Department of the FACISA University Center.

The information related to COVID-19 was completed by filling out a specific form, and complemented by questions asked directly to the patient. A complete ophthalmological examination was also performed: anamnesis (age, sex, signs and symptoms present at the time of care); personal and family history; visual acuity test at distance (5 meters) and near (33 centimeters) using the Snellen and Jaeger tables, respectively, with the determination of the best correction, which was defined with the help of the Greens refractor; anterior biomicroscopy examination, using a slit lamp; tonometry examination using the Goldmann applanation tonometer; and fundoscopy, with the aid of a slit lamp associated with Volk 78 or 90 lenses. Both eyes of the individuals in the three groups were examined by the same ophthalmologist and the data were recorded in an electronic medical record and a specific form from the research, taking into accounts the evaluation of both eyes.

The HD-OCT (high-resolution optical coherence tomography) images were acquired using the Carl Cirrus 5000 Zeiss Meditec. The thickness measurements of macular ganglion cells with the internal plexiform layer were performed automatically by the device and given from the retinal ganglion cell layer (RGCL) analysis graph with macular cube protocol 512 × 128 μm. Regarding the measurement of central macular thickness, the macular thickness analysis chart: macular cube 512 × 128 and the central measurement of the macula were used. At last, the analysis chart was used: optic disc cube 200 × 200 μm, to obtain measurements of the RNFL thickness of the total optic nerve head and the four quadrants (superior, inferior, nasal and temporal) using a radial scan centered on the head of the optic nerve.

The sample was of convenience and the dates were tabulated in Excel and analyzed in SPSS, version 26.0, using descriptive and inferential analysis.

Quantitative variables were expressed as their means and standard deviations. Qualitative variables were expressed by their absolute and relative frequencies.

The Kolmogorov-Smirnov test was used to check normality. In cases where the numerical sets passed the normality test, the ANOVA pre-test was used; otherwise, Mann-Whitney test and Kruskal-Wallis were used. To evaluate differences among frequencies, the Chi-square test was used. $p \leq 0.05$ was used to reject the null hypothesis.

3. Results

Seventy-eight individuals were included, with ages from 24 to 73 years, they were stratified into three groups: group I, 29 (37.2%) individuals who were not proven to be affected by COVID-19, representing the control group; group II, 24 (30.8%) individuals who had the disease and were admitted to the ward, however and they did not require admission to the intensive care unit (ICU); and group III, consisting of 25 (32.0%) patients who were affected by a severe infection and required admission to the ICU.

The individuals were examined during the years 2022 and 2023. The mean time in months between hospital discharge and ophthalmological evaluation of the people groups GII (25.2 ± 6.5 months) and GIII (26.5 ± 7.4 months) were similar (Mann-Whitney test, $p > 0.9999$).

Data regarding sex, age, weight and BMI are homogeneous, Table 1.

Table 1. Sex, age, weight and BMI distribution among study participants.

Variables	Control Group (GI)		Infirmary Group (GII)		ICU Group (GIII)		p
	n	%	n	%	n	%	
Sex							
Male	15	51.7	12	50.0	16	64.0	0.4625*
Female	14	48.3	12	50.0	9	36.0	
	$\bar{X} \pm SD$		$\bar{X} \pm SD$		$\bar{X} \pm SD$		p
Age (year)	46.1 ± 11.9		51.5 ± 10.7		47.8 ± 12.2		0.2435**
Weight (kg)	82.4 ± 14.2		86.5 ± 18.1		90.6 ± 15.5		0.1399***
BMI (kg/m²)	29.8 ± 4.9		31.7 ± 6.6		31.9 ± 5.44		0.3212***

*Chi-square test; **ANOVA test; ***Kruskal-Wallis test; ICU: Intense Care Unit; BMI: Body Mass Index $\bar{X}$: Mean; SD: Standard deviation.

The best corrected visual acuity (BCVA) of participants was 20/20 in the control group. In the ward group, two patients had BCVA equal to 20/40 in the right eye and one had BCVA equal to 20/30 the right eye. Regarding the left eye, two patients had BCVA, one had 20/30 and two had BCVA equal to 20/25, the others had 20/20. In relation to the ICU group, in both eyes, one patient had BCVA equal to 20/25 and the others had 20/20.

Incipient cataracts were observed in two eyes in the control group, 11 eyes in the ward group and four eyes in the ICU group. Pterygium was observed in three eyes in the ward group and two eyes in the ICU group.

The measurement data from the optic disc excavations of the study participants are shown in **Table 2**. The inferential analysis of the frequencies of this parameter reveals a homogeneous distribution (Chi-square 5.421, p= 0.0665).

Table 2. Optic disc excavation data distribution among participants.

Variable Optic disc excavation	Control Group (GI)		Infirmary Group (GII)		ICU Group (GIII)	
	n	%	n	%	n	%
Right eye						
- Up to 0.4	18	62.1	12	50.0	11	44.0
- Equal or greater than 0.5	11	37.9	12	50.0	14	56.0
Left eye						
- Até 0.4	17	58.6	13	54.2	8	32
- Maior ou = a 0.5	12	41.4	11	45.8	17	68

Chi-square test: p > 0.05.

The mean intraocular pressures (IOP) of the participants were: group I, 14.0 ± 2.8 mmHg, group II, 15.3 ± 3.1 mmHg, group III, 13.7 ± 3.6 mmHg (Kruskal-Wallis, p = 0.0104). The mean IOP of the ICU group (GIII) was significantly lower than the means of the ward groups (GII) and the control group (GI) (Kruskal-Wallis, p < 0.01).

The means of total optical disc retinal nerve fiber layer (RNFL) thicknesses were similar. However, the mean temporal RNFL thickness of the optic disc was significantly smaller in the GIII group (ANOVA test, p < 0.001), **Table 3**.

Table 3. Comparison of mean RNFL thickness of the optic disc.

Variable	Control Group (GI) $\overline{X} \pm SD$	Infirmary Group (GII) $\overline{X} \pm SD$	ICU Group (GIII) $\overline{X} \pm SD$	p
RNFL thickness of the optic disc	96.7 ± 8.3 µm	96.7 ± 12.1 µm	94.0 ± 10.3 µm	0.2024*
Upper optic disc RNFL thickness	121.6 ± 10.3 µm	118.9 ±18.9 µm	117.3 ± 16.8 µm	0.347**
Inferior optic disc RNFL thickness	124.1 ± 15.8 µm	128.9 ± 18.3 µm	124.3 ± 17.9 µm	0.305**
Nasal optic disc RNFL thickness	71.9 ± 11.4 µm	74.8 ± 15.1 µm	75.9 ± 10.3 µm	0.224**
Temporal optic disc RNFL thickness	66.8 ± 10.0 µm	64.5 ± 10.6 µm	58.5 ± 9.2 µm	**<0.001****

*Kruskal-Wallis test; **ANOVA test; ICU: Intense Care Unit; $\overline{X}$: Mean; SD: Standard Deviation.

The mean thickness measurements of the ganglion cell layer with the inner plexiform layer are described in Table 4 and Table 5.

The mean thickness of the ganglion cell layer with the internal plexiform layer from the patients admitted to the ICU, who underwent mechanical ventilation, as compared with the mean thickness of those who did not receive mechanical ventilation, were similar: patients without mechanical ventilation = 78.3 ± 9.9 μm; patients with mechanical ventilation = 77.5 ± 8.1 μm (Mann Whitney, p = 0.8918).

The means central macular retinal thicknesses were similar: group I, 258.2 ± 20.0 μm; group II, 264.6 ± 30.0 μm; and group III, 247.9 ± 27.5 μm (Kruskal-Wallis, p = 0.0645) (Table 4).

Table 4. The mean thickness of the ganglion cell layer with internal plexiform layer and the central macular thickness among the groups.

Variable	Control Group (GI) $\overline{X} \pm SD$	Infirmary Group (GII) $\overline{X} \pm SD$	ICU Group (GIII) $\overline{X} \pm SD$	p
Ganglion cell layer and the inner plexiform layer thickness	82.8 ± 6.5 μm	83.9 ± 10.9 μm	77.9 ± 8.9 μm	**0.0027***
Central macular retinal thickness	258.2 ± 20.0 μm	264.6 ± 30.0 μm	247.9 ± 27.5 μm	0.0645*

*Kruskal-Wallis test; ICU: Intense Care Unit; $\overline{X}$: Mean; SD: Standard deviation.

Table 5. Mean measurements of the ganglion cell layer among the groups.

Comparison	p
Control × Infirmary	p >0.05*
Control × ICU	p < 0.05*
Infirmary × ICU	p < 0.01*

Note: *Kruskal-Wallis test; ICU: Intense Care Unit.

From the 25 patients admitted to the ICU (GIII), 12 used non-invasive ventilation (NIV) with positive pressure, 13 were intubated, six underwent tacheostomy, one required hemodialysis and one required tracheoplasty after hospital discharge.

4. Discussion

The signs and symptoms most frequently related to SARS-CoV-2 infection involve several systems, including: the respiratory; the gastrointestinal; the cardiovascular; the immune; the kidney; the liver; the endocrinological; the reproductive and the neurological [15].

Neuroinflammation in SARS-CoV-2 infection affects the Central Nervous System and, consequently, the optic nerve, and may have an impact on the retinal ganglion cell layers [16] [17]. This is the basis that supports this investigation, which until proven otherwise is being conducted as original and pioneering in Brazil. In the present study it was used a non-invasive tool that faithfully represents the measurement of this layer of cells. The results support involvement of retinal glanglion cells in severe cases of COVID-19 and emphasize the need to monitor retinal pathologies potential sequelae of "long COVID" [16].

The stratification of patients into three groups is justified by the presence of a first group (GI) serving as a reference for comparison. A second group (GII) of patients who were admitted to the ward, however, did not present a serious infection to require intensive therapy. The third group (GIII), made up of critically ill patients who showed signs and symptoms sufficient to be admitted to Intensive Care Unit (ICU). In this context, the stratification of groups seems appropriate, particularly when considering that homogeneity was observed in terms of age, gender and anthropometric data.

The most relevant finding of the current study relating the hypothesis that the SARS-CoV-2 virus simultaneously affects the Central Nervous System (CNS) and the retina is concretely manifested in the significant reduction in the thickness of the ganglion cell layer plus internal plexiform layer, in the group III which had the most important clinical manifestation of the disease, requiring patients to be admitted to an Intensive Care Unit (ICU). This information was shown in previous international studies [10] [13], but it was not reported in Brazil.

Another important manifestation of SARS-Cov-2 infection is lung involvement, particularly manifested in GIII patients who required mechanical ventilation due to the fact that lung involvement led to significant hypoxia [18], which could also manifest itself through the reduction of the ganglion cell layer of the retina.

Although optic disc excavations, expressed as qualitative variables, present different frequencies in the recruited groups for the study, the inferential analysis revealed homogeneity. Therefore, this variable did not result in a confounding parameter regarding the studied phenomenon. This information is important given the possibility of possible undiagnosed glaucoma acting as a confounding variable [19]. Furthermore, other diseases that could interfere with optic disc excavation were excluded from the study.

The finding of lower mean IOP in individuals admitted to the ICU (GIII) may be considered irrelevant, as all IOP assessed were within the normal range. Another plausible explanation would be that the minimal differences in the measured IOPs were taken within the context of the operator dependent measurement error. Furthermore, the use of various means of ventilatory assistance and anesthetic drugs or medications used in the post-COVID period could have interfered with the measurement of IOP [20].

The reduction in the temporal quadrant of the RNFL thickness mean was observed, which could represent a manifestation of the retinal ganglion cells involvement of the severe COVID-19 disease or it could simply be the result of statistical inference. Otherwise, it could mean that the SARS-Cov-2 may have a tropism for the nerve fibers of the temporal sector of the optic nerve, equivalent to what occurs in neoroinflammation caused in congenital ocular toxoplasmosis, in which the parasite responsible for this disease, appears to have tropism for the posterior ocular pole [21] [22].

Although a significant reduction in the thickness of the ganglion cell layer was observed, there was no statistically significant reduction in the thickness of the retina as a whole in the central macular region, as such a reduction appears not to have been sufficient to trigger a decrease in this area, as it happens in glaucoma disease [23]. Another possible justification for a certain fact would be that the number of patients examined was not sufficient to reach a sample number with a greater capacity to prove this significance.

Another hypothesis raised would be the influence of the use of mechanical ventilation, done in half of the patients from GIII, resulting in reduction of the ganglion cell layer [24], however, a certain statement did not have statistical support, because when evaluated within the group of ICU patients (GIII), comparing those who underwent mechanical ventilation with those who did not undergo, no significant decrease in this layer was observed among those who specifically underwent invasive therapy.

It has been reported that barotrauma is associated with mechanical ventilation in patients with severe COVID-19 [25]. The use of mechanical ventilation did not affect the thickness of the retinal ganglion cell layer according to the current study. However, the severity of the clinical condition appears to be an important factor in the occurrence of a decrease in this cell layer, as the lowest mean was identified in the group with the most severe clinical condition [11] [18].

One of the limitations of the current study is the fact that it was recruited patients that represents a small convenience sample. This, theoretically, could have contributed to some type 1 error. Perhaps, the assessment of change in central macular thickness did not reach significance was due to this likely study flaw.

Although individuals who had reports of eye diseases, such as glaucoma, which could act as a confounding variable, were excluded, full propedeutic investigation it was not used to prove this disease. Similarly, two cases of patients from the ward group (GII) who had suspected diabetic retinopathy and were referred to the specialized sector, but the condition was not conclusively proved.

5. Conclusions

The Retinal Ganglion Cell Layer (RGCL) thickness from patients with severe COVID-19 was significantly reduced. This finding supports that the SARS-CoV-2 has systemic action and affinity for nerve cells, including those from the retina and are related to the severity of the infection.

The means of retinal nerve fiber layer thickness from the optic disc were similar among the groups, as well as the superior, inferior and nasal portions. However, the temporal portion of the optic nerve head showed a significant reduction in group III of patients (ICU).

The use of modern equipment, which provides accurate and quality data with a minimally invasive performance, such as Optical Coherence Tomography (OCT), can help in these cases. Furthermore, it is also possible to have a reliable assessment of a probable central nervous injury, which these patients may suffer.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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