International Journal of Medical Ophthalmology

E-ISSN: 2663-8274
P-ISSN: 2663-8266
www.ophthalmoljournal.com
IJMO 2023; 5(1): 54-58
Received: 10-02-2023
Accepted: 21-04-2023

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A cross sectional study to clinically evaluate the retina of COVID-19 patients in a tertiary care Government designated COVID hospital

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DOI: https://doi.org/10.33545/26638266.2023.v5.i1a.140

Abstract
Importance: Retinal vacuities can cause visual disturbances if not treated on time. Past researchers have shown an association of COVID19 with retinal vacuities.
Objective: To evaluate the retina of patients who tested RTPCR or Rapid Antigen test positive for COVID-19.
Design: Cross-sectional study
Setting: COVID-designated Government tertiary healthcare institution. Clinical evaluation of the retina of the patients who suffered COVID-19, either hospitalized or home isolated and/ or who come for follow up in the medicine outdoor patient department was done from September 2020 to January 2022.
Participants: 18 years of age and above were included in the study (by convenience sampling). Patients in the acute phase were evaluated cot side in COVID wards while the patients in the convalescent phase were those who were screened at least 15 days after hospital discharge and after 2 weeks of symptom onset or COVID testing in OPDs. Since the possibility of COVID-19 occurrence is high in diabetes and hypertension such patients were included in study to assess whether it can increase the frequency of retinal vasculitis
Main Outcomes and Measures: Proportion of retinal vasculitis in patients of COVID-19.
Results: Of the 274 study participants having COVID-19 who were evaluated for retinal changes, 187 were males and 87 were females; age group 40-60 years mainly: The patients of three different COVID-19 waves, having mild to severe disease and from acute or convalescent phase of disease were observed (including diabetic and hypertensive patients). None of the patients had significant retinal vasculitis changes in absence of systemic comorbidities. We observed one case of venous fullness, a case with superficial hemorrhage, and one having hard exudates where such retinal lesions were found without any systemic comorbidities.

Keywords: Retinal vasculitis, COVID-19

Introduction

COVID-19 is a disease caused by a virus called SARS-CoV-2. It infects the host using the angiotensin-converting enzyme (ACE 2) receptor, which is expressed in several organs including retinal endothelial cells [1, 2]. Endothelial cell involvement with COVID-19 has been shown in the lung, heart, kidney, intestine, and brain and histopathological studies have demonstrated direct viral infection of endothelial cells, endothelitis and vasculitis in both arterial and venous circulations [3, 4]

Furthermore, viral RNA of COVID-19 has been detected in the retina of affected patients [5]. This finding raises the hypothesis that COVID-19 may cause retinal vasculitis and ischemia. This possibility is particularly important in patients at high risk for retinopathy, such as diabetes and hypertension. Whether COVID-19 retinal microangiopathy is a direct viral effect or shares the diabetic mechanism of damage requires further investigation. It is remarkable that ACE2 is the primary enzyme of the vaso protective axis of the renin–angiotensin system, and diabetic retinopathy is associated with impaired balance of the retinal renin– angiotensin–aldosterone axis. ACE2 down regulation might play a major role in inducing the development of retinal ischemia. [6, 7, 8] It is noteworthy that SARS-CoV and likely SARS-CoV-2 lead to down regulation of the ACE2 receptor [9]. Hence it would be inaccurate to exclude diabetic and hypertensive patients having CoV infection. We evaluated the retina of COVID-19 patients admitted to our institute to examine changes in retina based on the severity of COVID-19, retinal changes in the different phase of the disease (Acute or convalescent) and COVID-19 patients of different waves having different strains of virus.

Materials and Methods

The study protocol of this cross sectional study was submitted to the institutional Human Research ethical committee and got approved. It was conducted during the period of September 2020 to January 2022 at our multispecialty government hospital. It was an observational study to clinically evaluate the retina of the COVID patients who were admitted in wards (acute phase) and those visiting the Outdoor Patient department(OPD) for follow up within 2 weeks discharge from the hospital or after home isolation (Convalescent phase).

When the study protocol was being prepared, in the hospital records, 806 COVID-19 patients were treated in the hospital for period of last two months. Amongst them, 50% could not to be included in the study due to loss to death, migration and non-responsiveness. Hence the sample size was estimated to be 403. However, due to further 20% attrition (Exclusion criteria, recent migration etc.), the final sample size calculated was 323. Though the number of COVID-19 patients increased further in wave 2 of the disease, more than 50% could not be included due to lack of ocular complaints resulting in less consenting patients for a detailed ophthalmic examination; we could include a total of 274 patients (548 eyes) in the study.

The duration of the study was spread over three waves of COVID-19, first wave in September 2020 when the study began, second wave in April 2021, and third wave in January 2022. All participants were 18 years and above and tested positive for COVID-19 by either RTPCR or Rapid Antigen test. Both gender adult patients who gave consent for complete ophthalmic evaluation after reading Participation Information Sheet were included. Patients with diabetes and hypertension who could have preexisting retinopathies, were still included as COVID occurrence was found more in them [10]

Exclusion criteria were 1. Known case of Ischemic heart disease or history of angiography/ angioplasty 2. History of any ocular trauma causing retinal lesions. 3. Patients having history of glaucoma. 4. Patient having Tuberculosis, toxoplasmosis like illnesses which can cause vasculitis 5. ARMD, Optic nerve drusen, macular lesions etc. having gross dimness of vision

A thorough history was conducted noting chief eye complaints if any with their onset, duration, and characteristics. Complete COVID-19 medical diagnosis, clinical parameters, lab parameters and treatment given in medical wards were noted from case sheets (indoor patients) or the discharge sheets of patients (follow-up patients) to categories severity of disease. The disease was classified into mild, moderate, and severe disease by treating physicians as per the guidelines of AIIMS/ ICMR-COVID-19 National Task Force/Joint Monitoring Group (Dte. GHS), Ministry of Health & Family Welfare, Government of India [11].

The Ophthalmology Resident Doctors were given duties in various COVID-19 wards as the entire Government hospital was converted into COVID-19 hospital. 'Acute phase' participants were examined by the researcher and the same cadre of ophthalmology residents who were on duty in wards after taking his/her consent. The anterior segment was examined on torch light in Indoor patients. Indirect ophthalmoscopy was performed to examine retina thoroughly after dilating the pupils. Those patients who came after discharge for follow up (referred from medical OPD to Eye OPD) were put in the category of 'convalescent phase'. The researcher explained the importance of a complete ophthalmological check-up and took their consent in eye OPD). The Visual acuity of these patients was taken on an illuminated Snelling's chart. Refractive errors were corrected if any to exclude diminution of vision because of refraction. The Anterior segment assessment was done on the slit lamp bio microscope. A thorough evaluation of fundus was done in eye OPD after dilating pupils with 0.5% Tropic amide+ 1% phenylephrine drops. Heine's indirect Ophthalmoscope was used with a 20 Diopter Volk lens to examine the retina.

Age, gender, and presence of systemic comorbidities of patients were documented from case records in an excel sheet and their retinal changes in relation to phase, wave and severity of the disease were mentioned in corresponding columns of the data sheet. Data was analyzed using SPSS software.

Results

Of the total 274 study participants having COVID who consented for retinal evaluation, 187 were males and 87 were females. Maximum number of patients belonged to the Age group 40-59 years. The Median age of the sample population was 49.1 years. Only16 (5.8%) out of 274 patients had ocular signs in form of Redness of eyes, having no symptoms and it disappeared on follow-up in all patients. 72 (27.2% of the total) COVID patients in the study had associated systemic comorbidities (Table 1), Hypertension being the commonest (46 patients). None of these participants had retinal vasculitis. However 21 (29.1% of comorbid participants), had retinal changes which could be traced to their systemic associations (Table 2). We observed a case of diabetes with no other sign of diabetic retinopathy but few cotton wool spots (CWS). From the remaining 202 cases which were without any co morbidities, none had retinal vasculitis. One case with venous fullness, another with unexplained hyperemic disc and third case having hard exudates were the only three cases where retinal signs observed in absence of systemic comorbidities.

194 patients were evaluated in the acute phase of the disease and 80 in convalescent phase of disease. On Indirect Ophthalmic examination we observed that the retinal changes had no difference in presentation with the phase of COVID-19. Infect Retinal Vasculitis was not found in any of them. Distribution of the retinal changes in both acute and convalescent phase (with and without comorbidities is shown in (Table 3).

As per the severity of COVID classification, 132 patients had mild disease, 97 had moderate and 45 suffered severe disease in the present study. We observed that majority of the retinal changes were related to their associated comorbidity and not due to difference in severity of disease (Figure 1). Retinal vasculitis was not observed in any of these category also.

In COVID-19, Wave 1 we could evaluate 177 cases in wave, 50 cases n Wave 2 and 47 in Wave 3. The table taken from our hospital data showing the virus strain in different waves (Table 4) No signs of retinal vacuities in any of the waves of COVID was documented. We also noted that in all the three waves of the disease whatever retinal changes that were noticed were only from the group of patients with systemic comorbidities as (Table 5) and were not related to any of the viral strains of COVID-19.

Figures

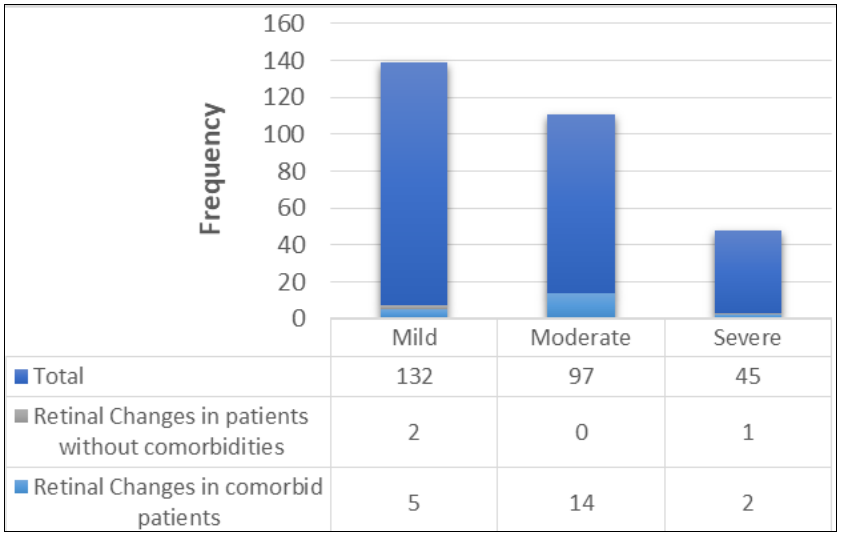

Fig 1: (Distribution of retinal changes found in patients with different severity of COVID-19)

Tables

Table 1: (Frequency of patients and Systemic comorbidities)

	Patients with comorbidity n=72	**Patients without comorbidity n=202**
Frequency (n=274)	(26.2%)	(73.8%)

Table 2: Retinal changes found in patients with systemic comorbidities (n=72)

Retinal changes (N=21) 29.1%	**Hypertension (n=35)** 48.6%	**Diabetes (n=26)** 36.1%	**Both Hypertension and Diabetes (n=11)** 15.3%
Arteriosclerosis	3	0	1
Non-proliferative Diabetic Retinopathy	0	2	1
Venous Fullness	1	1	1
Diabetic Maculopathy	0	0	1
Hyperemic disc	2	0	0
Hypertensive Retinopathy	2	0	0
Hard Exudates	3	0	1
Cotton wool spots	1	1	0

Table 3: Distribution of patients in Acute and Convalescent phase of COVID-19

	Acute (n=194)	**Convalescent (n=80)**
Retinal vascular changes in COVID patients WITH systemic comorbidity (n=72)	15	6
Retinal vascular changes in COVID patients WITHOUT comorbidity (n=202)	2	1

Table 4: In COVID-19, Wave 1 we could evaluate 177 cases in wave, 50 cases n Wave 2 and 47 in Wave 3

n = n1+n2+n3 = 274	**Wave 1**	**Wave 2**	**Wave 3**
Retinal vascular changes in COVID patients WITH systemic comorbidity **(21)**	17	2	2
Retinal vascular changes in COVID patients WITHOUT comorbidity **(3)**	2	0	1

Discussion

Retinal vasculitis can be an isolated idiopathic condition; as of infectious diseases such as tuberculosis, Lyme disease, syphilis, toxoplasmosis, or acute retinal necrosis; as part of neurologic disorders such as multiple sclerosis; or in association with a systemic immune-mediated disease [12].

Active vascular disease is characterized by exudates around retinal vessels resulting in white sheathing or cuffing of the affected vessels, which may be segmental (skip lesions) or confluent. Retinal vasculitis results in leakage leading to retinal swelling, exudation, and macular edema. Cystoid macular edema is a significant contributing factor for poor vision in retinal vasculitis. Occlusive retinal vasculitis affecting the retinal arterioles may cause cotton-wool spots representing micro infarcts of the retina. Central retinal artery and branch retinal artery occlusions are also reported in patients with retinal vasculitis [13]

Support for the hypothesis of the occurrence of retinal vasculitis has been shown in some case reports and series in the literature. However, there are also studies that contradict the hypothesis. The inconsistencies in various studies can be explained by exploring more variables and conducting more research in the same area

Present study was designed to find if retinal vasculitis occurred in COVID-19 (In different phases of illness, waves and disease severity) and whether association of systemic comorbidities played a key role in the causation of its occurrence. Not one retinal change could be traced back specifically to COVID-19.

In a retrospective, multicenter case series and PubMed

review of cases [14] reported from March 2020 to September 2021 the clinical and ophthalmologic features and outcomes of patients with COVID-19 with retinal vascular occlusions was done. Among the 24 cases from this literature review, retinal vein occlusion was the predominant lesion and had favorable outcomes.

Virgo and Mohamed [15] reported two patients with par central acute middle maculopathy (PAMM) and acute macular neuroretinopathy following SARS-CoV-2 infection which can be incidental.

Insausti-Garcı´a *et al*. [16] reported a case of papillophlebitis associated with COVID19. Most of these cases of Retinal vasculitis or Retinal Ischemia in literature were either a case report or small sample studies.

Mojtaba Abrishami [17] *et al*. in February 2021 worked on quantifying the microvasculature density of the optic nerve head (ONH) using optical coherence tomography angiography (OCTA) analysis in patients recovered from Coronavirus Disease 2019. The PRNFL thicknesses in all sectors was higher in patients with a history of COVID-19; however, this did not reach statistical significance.

In the present study 16 out of 274 patients had non-significant ocular complaints. Redness was the most common. None had the picture of viral conjunctivitis, redness was temporary and was absent on follow up examinations. A meta-analysis published in April 2021 by Lorenzo Loffredo *et al*. [18] described that conjunctivitis could be associated with a severe COVID disease. Six out of 17 patients presented ocular manifestations, such as conjunctivitis in children with PIMS (Pediatric inflammatory multisystem syndrome), episcleritis and isolated cases of retinal vasculitis and retro bulbar optic neuritis was noted by Celia Fernández Alcalde *et al*. [19] COVID-19 PCR was negative in all of them, while SARS-CoV-2 IgG antibodies were positive.

72 (About 26%) of the COVID patients taken in our study had associated systemic comorbidities, 21 patients out of these had retinal changes which could be linked to their systemic associations as per Table 2.

As far as the phase of the disease was concerned, there was retinal vasculitis in the current study. 2 cases in acute phase and 1 case in convalescent had a retinal lesion but wasn't significant to label vasculitis as shown in results. Publication in June 2021 volume 8 of Frontiers in medicine [19] screened 142 patients' retina in the acute phase and 93 in the convalescent phase. None in their patients in acute phase show retinal lesion that could be attributed exclusively to COVID-19 and 5 of their patients in the convalescent phase had cotton wool spots with/without retinal hemorrhage, with no other retinal finding and no visual symptoms 20.

When we looked for any difference in retinal involvement as per the severity of COVID, retinal vasculitis was not observed in either mild, moderate or severe COVID patients in this study. A 2020 study done by Ravi Bypareddy *et al* [21] on fundus evaluation in COVID-19 patients with non-severe disease described that COVID-19 was not a threat to retina in mild to moderate cases (non-severe disease).

In the present study, other than the three retinal signs mentioned in results, one case of Diabetes, we observed few cotton wool spots (CWS). The fundus picture of the same case did not show any other signs of diabetic retinopathy but just CWS. Cotton-wool spots representing micro infarcts of the retina due to precapillary retinal arteriolar occlusion are often seen in Retinal Vasculitis. So this patient though we have reported in category COVID patients with systemic comorbidities brought a suspicion of ischemic retina.

The SERPICO-19 study [21] Retinal findings in COVID-19 reported hemorrhages (9·25%), cotton wools spots (7·4%), dilated veins (27·7%), tortuous vessels (12·9%). Mean arteries diameter (MAD) and mean veins diameter (MVD) were compared between patients and unexposed subjects in this study.

Landecho *et al*. [22] Evaluated 27 asymptomatic subjects with previous COVID-19 infection and found that six of them had cotton wool spots. The study had small sample size, may/may not carry its significance.

This study was, to our knowledge one of the first to compare if the virulence of COV affected the retinal changes. The patients were taken from all three waves of COVID-19 that hit the city. Retina vasculitis was not observed in any of the patients from three waves having different virus strain.

Large epidemiologic studies in India are warranted to better define the association between a retinal vascular event and COVID-19 infection. Also, longitudinal studies to establish the role of systemic co-morbidities causing predisposition to the vascular event need to be conducted.

Conclusion

Retinal vasculitis was not seen in any of the COVID-19 study patients, whether acute /convalescent or related to severity of disease or having a different virus strain. Whatever retinal elisions found in the patients were comorbidity associated retinopathies. Large epidemiologic studies in India are warranted to better define the association between a retinal vascular event and COVID-19 infection. Also, longitudinal studies to establish the role of systemic co-morbidities causing predisposition to the vascular event need to be conducted.

Acknowledgments

The COVID designated institute gave us a great opportunity to cater to and examine many COVID-19 patients. Dr. Priti Kapadia Gupta for the idea behind the study and the constant support to write an article for a publication. Dr Hiteshri of Community Medicine department for her inputs on the statistical and analytical aspects

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How to Cite This Article
G Rashi, KG Priti. A cross sectional study to clinically evaluate the retina of COVID-19 patients in a tertiary care Government designated COVID hospital. International Journal of Medical Ophthalmology. 2023;5(1):54-58.