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Observational study post Corona virus disease-19 (COVID-19) Ocular findings.

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Short title*:* COVID-19 myopia progression

Abstract

Purpose: The present study aimed to look for visual and ocular manifestations during the recovery phase as possible sequels of COVID-19 infections for prompt diagnosis and management

Methods: This cross-sectional pilot observational study was done on eighty (80) patients who have recovered from COVID-19 infection with recent ocular findings during the outpatient clinic and routine checkup at October 6 University Hospital Outpatient clinic during the period from September 2021 to May 2022. Patients with active COVID-19 infection, severe cases with intensive care unit admission or mechanical ventilator, history of taking chemotherapy, and pregnant women were excluded from the study.

Results: Eighteen out of the eighty patients (22.5%) were found to have positive ocular findings resulting from their COVID illness. 39% of them were females while, 61% were males. As regard onset of symptoms, 12 patients showed early onset of symptoms while 5 showed late onset of symptoms. As regard ocular findings, 39% of patients suffered from diseases of external eye, 33% patients diagnosed by posterior segment affection, 17% of orbit diseases affection, and finally 11% showed anterior segment diseases.

Conclusion: COVID 19 affects ocular, extraocular and adnexal tissues especially external eye diseases and posterior segment affection. The prevalence of ophthalmic manifestations among COVID-19 patients in this study was 22.5% of the tested subjects. The highest number of patients suffered from external eye diseases (39%), followed by the posterior segment diseases (33%), subsequently orbit pathology (17%), and finally anterior segment diseases (11%). COVID 19 helps in reactivation of viral keratitis and this note can be due to affected immunity which is marked during COVID illness.

Keywords: COVID 19, pandemic, external eye disease, viral keratitis.

INTRODUCTION

In December 2019 China experienced an outbreak of a new highly infectious viral disease. It was found that the disease was caused by a new virus related to the Coronavirus family. The virus was later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease was renamed to coronavirus disease 2019 or COVID-19 for short[1,2].

On March 11, 2020 the world health organization (WHO) has declared COVID-19 as a global pandemic and reported 522,783,196 confirmed cases including 6,276,210 deaths of COVID-19 on May 23,2022.

Since COVID-19 is a disease that primarily manifests symptoms affecting the respiratory system as it is mainly transmitted through airborne large droplets, it was only logical to see most of the research efforts about COVID-19 targeted towards the respiratory complications of the disease. Ophthalmic implications were also observed in COVID-19 patients which includes the presence of the RNA of the SARS-

CoV-2 virus in the tears. The most common ocular symptom of the disease includes mild conjunctivitis while less common symptoms include minimal changes in the retina including but not limited to hyperreflective lesions in the inner layer observed through the Optical Coherence Tomography (OCT) as well as cotton-wool spots and microhemorrhages[3].

Many researchers discovered that COVID-19 patients may develop ocular surface disorders as persisting symptoms of dry eye disease (DED) in the weeks and months following recovery[4]. The ocular surface might possibly function as a route of entrance and conjunctivitis may be the only sign and symptom of COVID-19, with no fever, exhaustion, or respiratory symptoms to raise concerns[5]. The COVID-19 conjunctival symptoms seem to be self-limiting[6].

Also, reactivation of herpes simplex virus type 1 (HSV-1) can occur in severely sick individuals with compromised immune system, psychological stress, UV exposure, fever, or hormonal changes[7].

Complement-mediated thrombotic microangiopathy (TMA) is a role in the etiology of microcirculatory injury in COVID-19 patients leading to ocular vascular injuries[8].

COVID-19-associated coagulopathy may predispose to a spectrum of thromboembolic events as central retinal vein occlusion (CRVO) and central retinal artery occlusion (CRAO)[9].

Hypertension, sometimes accompanied by elevated serum concentration of cardiac troponin I (cTnI), may occur in COVID-19 patients, and become a sequela. Enhancing Ang II signaling, driven by SARS-CoV-2 infection, might play an important role in the renin-angiotensin system, and consequently lead to the development of hypertension in COVID-19[10].

Acute macular neuroretinopathy (AMN) and paracentral acute middle maculopathy (PAMM), are rare retinal disorder, in which there is ischemia to the deep retinal capillary plexus, have also been observed with COVID, marked by hyperreflective changes at the level of the outer plexiform and inner nuclear layers resulting in paracentral scotoma, usually in young female patients[9].

Providencia et al. discovered serpiginous choroiditis reactivation following COVID-19 infection. Unpublished cases of multifocal or serpiginous choroiditis in SARS-cov-2 infected individuals have been reported. The cause is considered to be an autoimmune response induced by SARS-cov-2[11].

Moreover, viral neurotropism is assumed to be one of the processes underlying neurological and neuro-ophthalmic symptoms [12,13].

The literature has reports of individuals who were diagnosed with COVID-19 after presenting with diplopia, ophthalmoparesis, and aberrant perineural or cranial nerve magnetic resonance imaging (MRI) findings[14].

Papillophlebitis is an uncommon condition that strikes healthy young people, although one such instance was recorded in a COVID-19 patient[15,17].

Also, bilateral optic neuritis was observed in a healthy young female one and two weeks after a moderate COVID-19 infection[12,13].

Armstrong et al. reported cases of orbital myositis following COVID-19, presenting with bulbar conjunctival hyperemia and significant restriction of different gazes. An MRI of the orbits revealed generalized fusiform enhancing enlargement of the affected muscles. The findings of laboratory testing are normal. The best therapy was nonsteroidal anti-inflammatory medications (NSAID)[16].

In addition to different orbital manifestations including dacryoadenitis, orbital cellulitis, orbital myositis and up to mucormycosis which is fatal.

PATIENTS AND METHODS

This cross-sectional pilot observational study was done on eighty (80) patients who have recovered from COVID-19 infection with recent ocular findings during the outpatient clinic and routine checkup at October 6 University Hospital Outpatient clinic during the period from September 2021 to May 2022.

Patients with active COVID-19 infection, severe cases with intensive care unit admission or mechanical ventilator, history

of taking chemotherapy, and pregnant women were excluded from the study.

While including patients who have recovered from COVID-19 infection with recent ocular findings during the outpatient clinic and routine checkup. The evidence of infection included typical COVID-19 symptoms, typical CT chest imaging and positive swab.

All selected patients received an explanation of the study design and aims. An informed consent was obtained from all patients. The study protocol was revised and approved by the Research Ethics Committee at October 6 University.

Data collected included patient's age, sex, ocular medical and surgical history, refraction with best corrected visual acuity (BCVA) using Snellen's chart, intraocular pressure, anterior segment examination using slit lamp (TOPCON slit lamp), dilated fundus examination by slit lamp biomicroscopy using +90D Volk lens and extraocular motility.

Ocular coherence tomography (OCT) using RT Vue-100 (Optovue, Fremont, CA, USA), fundus fluorescein angiography by TOPCON IMAGEnet 2000, and computed tomography (CT) scan of the orbit done in selected cases.

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data.

RESULTS

Eighty patients with post COVID 19 were enrolled in the study. 46% males while 54% females, their age is from 19 to 67 years (The mean age is 34.2). 31% of patients presented with mild COVID illness while 69% with moderate illness.

Eighteen out of the eighty patients (22.5%) were found to have positive ocular findings resulting from their COVID illness. 39% of them were females while, 61% were males, as shown in (figure 1).

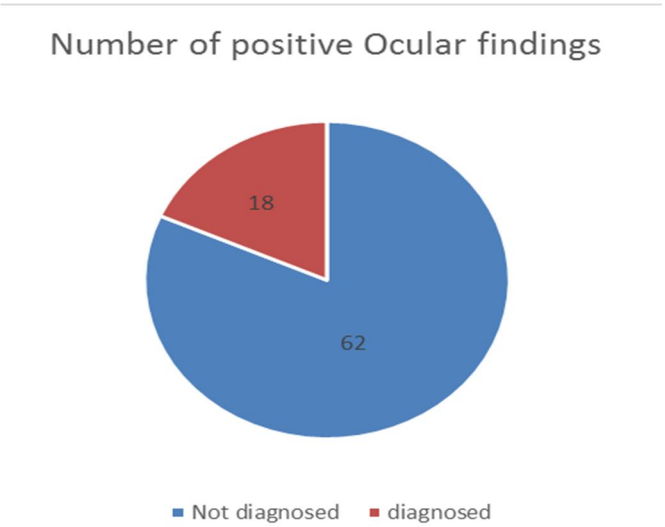

Figure 1: Ocular findings from the total samples

12 from 18 cases (66%) did not have a history of chronic disease, while 6 out of the 18 cases (34%) show that they had chronic illness in the form of diabetes mellitus, hypertension, and herpes simplex viral infection.

As regard onset of symptoms, 12 patients showed early onset of symptoms ($\leq$ 30 days) while 5 showed late onset of symptoms ($\geq$ 30 days).

Five patients presented with ocular symptoms from day 1, one patient showed it after 2 days, 2 patients showed symptoms after 3 days, 4 patients showed them after 7 days, 1 patient showed it after 14 days, 4 patients showed them after 30 days, and 1 showed symptoms after 60 days.

As regard ocular findings, 39% of patients suffered from diseases of external eye, 33% patients diagnosed by posterior segment affection, 17% of orbit diseases affection, and finally 11% showed anterior segment diseases, as shown in (figure 2).

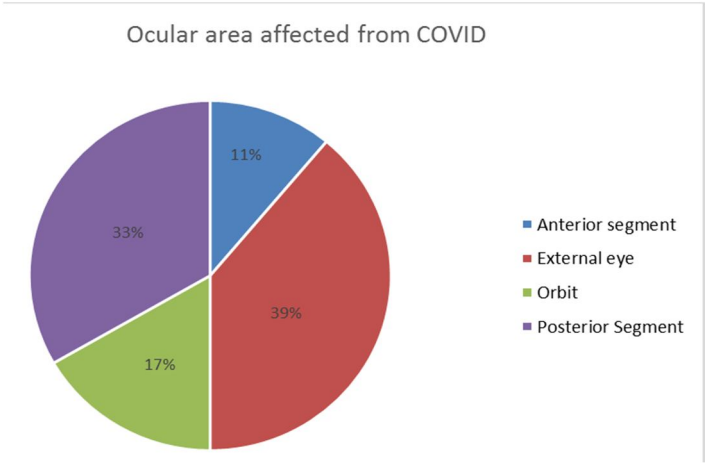

Figure 2: Specification of ocular findings.

(Table 1) shows data analysis of external eye disease patients (7 out of 18 patients) revealed that 71.4% of patient presented with mild COVID illness while 28.6% with moderate illness. Onset of symptoms was early in all cases. 5 cases presented with sever redness while, all patients presented with lacrimation and all patients revealed SPK, conjunctival injection and dryness on slit lamp examination (figure 3)

Table 1: Data analysis in patients with external eye diseases

	patient 1	patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age	19	28	41	65	27	25	27
Sex	M	F	F	F	M	M	F
Co-morbidities	N/A	N/A	N/A	Hypertension	N/A	N/A	N/A
Duration of COVID illness	10	30	30	20	7	7	10
Severity of COVID illness	Mild	Moderate	Mild	Moderate	Mild	Mild	Mild
Medications taken during COVID	N/A	Steroids	N/A	Aspirin	N/A	N/A	N/A
Onset of symptoms post COVID	Early	Early	Early	Early	Early	Early	Early
Patients' presenting complain	Severe redness and lacrimation	Severe redness and lacrimation	Severe lacrimation	Severe lacrimation	Severe redness and lacrimation	Severe redness and lacrimation	Severe redness and lacrimation
Visual acuity	6/6 6/6	6/9 6/9	6/12 6/12	6/12 6/12	6/6 6/6	6/6 6/6	6/9 6/9
Slit lamp examination	SPK, conjunctival injection, dryness	SPK, conjunctival injection, dryness	SPK, conjunctival injection, dryness	SPK, conjunctival injection, dryness	SPK, conjunctival injection, dryness	SPK, conjunctival injection, dryness	SPK, conjunctival injection, dryness

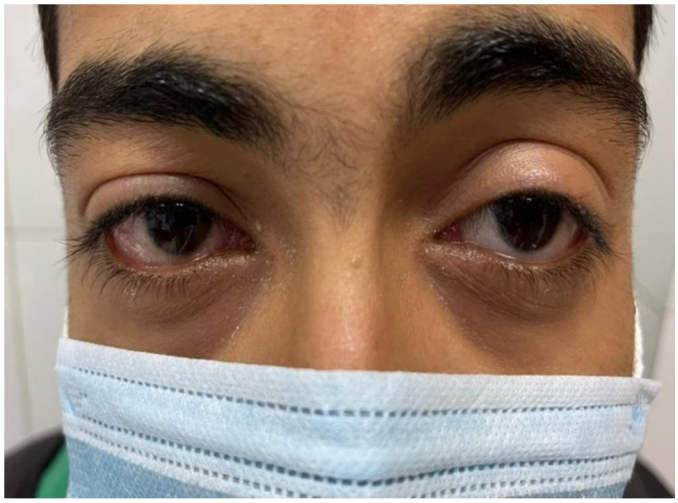

Figure 3: Viral keratoconjunctivitis in patients with COVID.

Data analysis of patients with anterior segment affection (2 out of 18 patients) revealed that 50% of patient presented with mild COVID illness while 50% with moderate illness. Onset of symptoms was early in one case and late in the 2nd case. One of the two patients presented with redness and visual disturbance with AC flare on slit lamp examination and diagnosed as anterior uveitis while, the 2nd patient presented with sever lacrimation with corneal ulcer on slit lamp examination and diagnosed as dendritic ulcer (Table 2).

(Table 3) shows data analysis of patients with posterior segment affection (6 out of 18 patients) revealed that 50% of patient presented with mild COVID illness while 50% with moderate illness. Onset of symptoms was early in 33.3% of cases and late in 66.7% of cases. All patients presented with diminution of vision with variable fundus examination and diagnosis (circinate maculopathy, central retinal vein occlusion (CRVO), hypertensive retinopathy& combined CRVO with cilio-retinal artery occlusion as shown in (figure 4 and 5)).

Table 2: Data analysis in patients with anterior segment affection

	Patient 1	**Patient 2**
Age	65	41
Sex	F	M
Co-morbidities	N/A	Herpes Simplex Virus
Duration of COVID illness	20	7
Severity of COVID illness	Moderate	Mild
Medications taken during COVID	Oxygen & Steroids	N/A
Onset of symptoms post COVID	Late	Early
Patients' presenting complain	Visual disturbance and red eye	Severe lacrimation
Visual acuity	6/12 6/12	6/6 6/18
Slit lamp examination	AC flare	Corneal ulcer
Diagnosis	Active uveitis	Dendritic ulcer

Table 3: Data analysis in patients with posterior segment affection

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	64	37	36	40	27	65
Sex	F	F	F	M	M	M
Co-morbidities	Diabetes Mellitus & Hypertension	Diabetes Mellitus	N/A	N/A	N/A	Diabetes Mellitus
Duration of COVID illness	30	15	20	30	15	30
Severity of COVID illness	Moderate	Mild	Mild	Moderate	Mild	Moderate
Medications taken during COVID	IV steroids			Steroids		Steroids
Onset of symptoms post COVID	Late	Late	Early	Late	Early	Late
Patients' presenting complain	Diminution of vision	Diminution of vision	Diminution of vision	Diminution of vision	Diminution of vision	Diminution of vision
Visual acuity	6/60 HM	6/36 6/24	3/60 3/60	6/9 CF	6/60 6/6	6/60 6/12
Fundus examination	Circle of white spots around the macular area	Bilateral CRV tortuosity, flame shaped hemorrhages	Bilateral ill-defined disc margin with obliterated cup, attenuated bl.vs, flame shaped hemorrhages	Left CRV tortuosity	Right CRV tortuosity, flame shaped hemorrhages	Bilateral PDR, RT CRV tortuosity & flame shaped hemorrhages
Diagnosis	Circinate maculopathy bilaterally	Bilateral CRVO	Hypertensive Retinopathy	Left CRVO & Cilio-retinal artery occlusion	Impending CRVO	Right CRVO

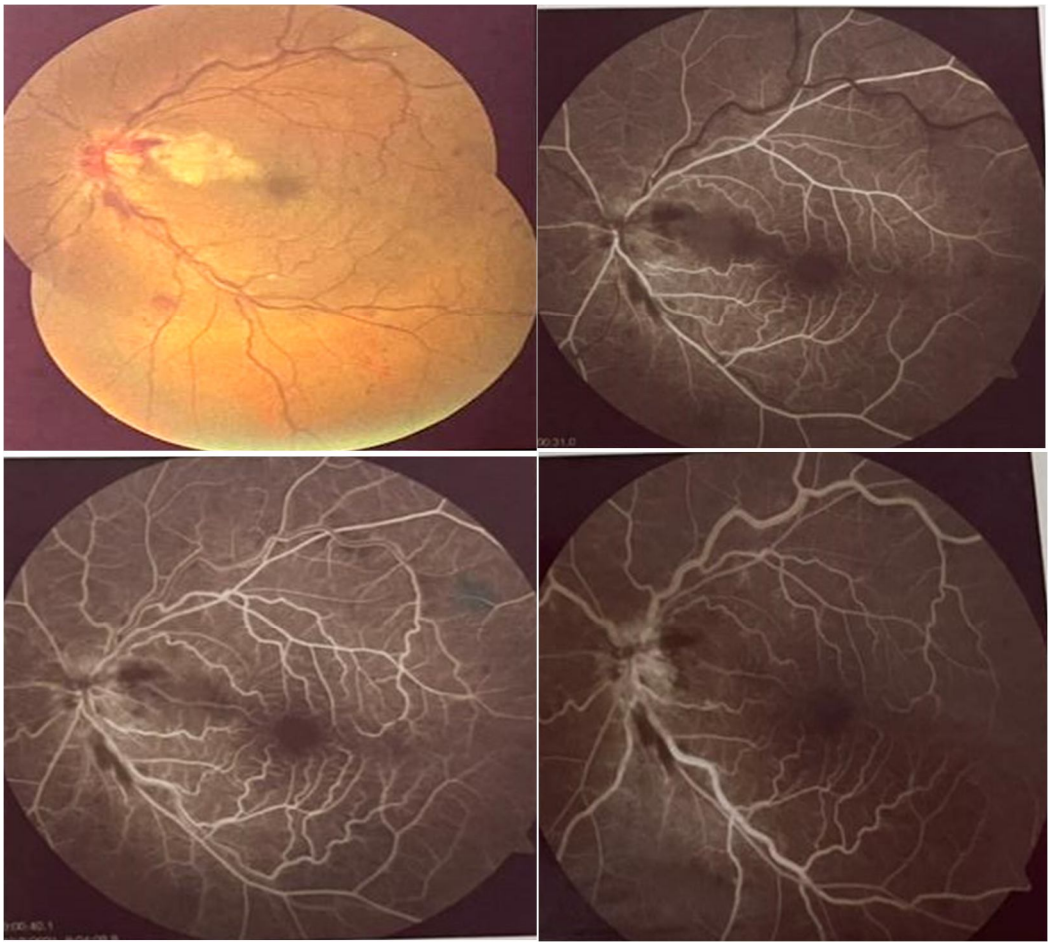

Figure 4: FFA of Left eye that shows cilio-retinal artery occlusion and non-ischemic CRVO with macular edema.

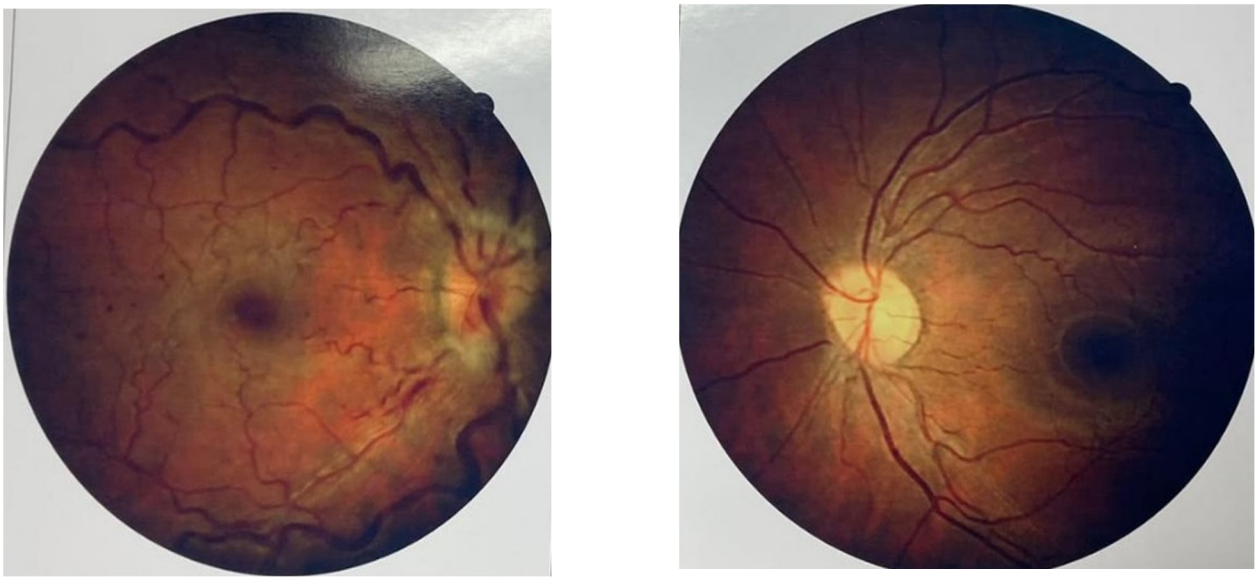

Figure 5: right Papillophlebitis with parafoveal diffuse macular edema showing impending CRVO.

Data analysis of patients with orbital affection (3 out of 18 patients) revealed that 33.3% of patient presented with mild COVID illness while 66.7% with moderate illness. Onset of symptoms was early in two cases and late in one case. One of the patients presented with severe headache and marked diminution of vision with proptosis, unreactive pupil and total ophthalmoplegia on examination and diagnosed as left mucormycosis, the second patient presented with severe

headache with restricted ocular motility on examination and diagnosed as orbital myositis, while the 3rd patient presented with headache and left peri-orbital swelling with left lateral gaze restricted ocular motility on examination and diagnosed as orbital myositis (Table 4).

Table 4: Data analysis in patients with orbital affection

	Patient 1	Patient 2	Patient 3
Age	51	46	19
Sex	F	F	F
Co-morbidities	Diabetes Mellitus & Hypertension	N/A	N/A
Duration of COVID illness	10	12	10
Severity of COVID illness	Moderate	Moderate	Mild
Medications taken during COVID	Steroids	Aspirin	N/A
Onset of symptoms post COVID	Early	Early	Late
Patients' presenting complain	Marked diminution of vision and severe headache	Severe headache	Headache, left peri orbital swelling
Visual acuity	6/6 no PL	6/6 6/6	6/6 6/6
Slit lamp examination	Unreactive pupil, total ophthalmoplegia, proptosis	Restricted ocular motility with normal color vision	Left lateral gaze restricted ocular motility with normal color vision
Diagnosis	Left mucormycosis	Orbital myositis	Left orbital myositis

DISCUSSION

We noticed with great interest the wide spectrum of COVID-19 manifestations on various body systems, so we thought about detecting the possible ocular findings that may arise post COVID-19 illness.

A retrospective study conducted by Tohamy et al. (2021) reviewed that post-acute COVID-19 syndrome could affect the eyes in the form of coagulation problems, neurological morbidities, and other manifestations. Study sample included 100 patients who had recovered from COVID-19. Mean SD of age was 55.5 ± 6.2 in COVID group. 57 patients (57%) were males, the other compared parameters including history and risk factors showed non-significant difference except for ESR and D-dimer which were elevated in COVID group. In COVID group, 5 patients (5%) were having retinal vascular occlusion, 2 patients (2%) were having anterior ischemic optic neuropathy AION, 3 patients (3%) were having uveitis and 2 patients (2%) were having central serous chorioretinopathy CSCR[18].

Sen et al. (2021) reported 120 patients with ocular surface and corneal symptoms and signs. The mean age was 45 ± 15.3 (range 24-72, median 46.9) years. The median gap between COVID-19 symptom/diagnosis and ophthalmic findings was 8.5 (mean 11.1 ± 8.8, 2-32) days. But it was the initial or concurrent presentation in 12/26 published articles.

While posterior segment involvement has varied manifestation and are vascular, inflammatory, and neuronal changes triggered by the viral infection. The literature review showed that the mean age of the patients was 47.4 ± 14.8

(median 50, 17-75) years. The median duration between appearance of ophthalmic symptoms and the COVID-19 symptoms /diagnosis was 12 (17.6 ±13.1, 4-55) days. About 50% (14/23) were male and eight had no associated systemic comorbidity.

Orbital manifestations incidence will rise considering the interplay of comorbidities and treatment along with the infection itself. The case reports and series published show patients with a mean age of 50.2 ± 43 (median 60, 12-76) years. 12/14 patients were males with nine being diabetic and six hypertensive patients. Asthma was notably present in eight patients. Five of these patients presented either with ophthalmic symptoms and were tested for COVID-19 on screening or presented concurrently with systemic symptoms of viral infection. The median time of presentation from the development of COVID-19 symptoms was 12 (mean 15.8 ± 13.8, 2-42) days. 10/14 patients had moderate to severe disease[19].

Many studies focused on the external eye affection.

To start with, a prospective interventional case series study was performed by Xia et al. (2020) on 30 confirmed COVID patients. At an interval of 2 to 3 days, tear and conjunctival secretions were collected twice with disposable sampling swabs for reverse-transcription polymerase chain reaction (RT-PCR) assay. Two samples of tear and conjunctival secretions were obtained from the only one patient with conjunctivitis yielded positive RT-PCR results[20].

Also, Chen et al. (2020) recruited 535 post COVID patients, 27 patients (5.0%) presented with conjunctival congestion and 4 patients had conjunctival congestion as the initial symptom. The average duration of conjunctival congestion was 5.9 ± 4.5 days (mean [SD]). The other ocular symptoms, including increased conjunctival secretion, ocular pain, photophobia, dry eye and tearing, were also found in patients with conjunctival congestion. Notably, hand-eye contact was independently correlated with conjunctival congestion in COVID-19 patients. They also found that some COVID-19 patients had chronic eye diseases, including conjunctivitis (33, 6.2%), xerophthalmia (24, 4.5%) and keratitis (14, 2.6%)[21].

Furthermore, Wu et al. (2020) recorded 38 patients with clinically confirmed COVID-19, 25 (65.8%) were male, and the mean (SD) age was 65.8 (16.6) years. A total of 12 of 38 patients (31.6%; 95% CI, 17.5-48.7) had ocular manifestations consistent with conjunctivitis, including conjunctival hyperemia, chemosis, epiphora, or increased secretions[22].

Majtanova et al. (2021) reported five cases of herpes simplex keratitis in COVID-19 patients. They also noted a sharply increase of 2.5- and 2-fold higher incidence of herpes keratitis during this pandemic wave in COVID-19 positive patients. The prevalence of herpes keratitis was higher in male patients.

Therefore, SARS-CoV-2 infection may be a risk factor for developing HSV-1 keratitis, or it may act as a potential activator of this ocular disease[23].

Wasfy et al. (2021) carried a retrospective study included 425 records of patients with confirmed COVID-19 infection. Their mean age was 41.73 ± 13.59 years (ranging from 19 to 85 years), 50.8% were males. About 30.8% (131 patients) had ophthalmological manifestations. Among the entire group of patients, conjunctivitis was presented in 111 (26.1%) patients, keratitis in two (0.5%), episcleritis in three (0.7%), neuro-retinal affection in nine (2.1%), and secondary fungal orbital cellulitis in six (1.4%) patients[24].

These different studies shows that COVID-19 had a clear role in the manifestation of ocular conditions but unfortunately due to several factors, the results shown in this study can hardly be comparable to the results of the afore mentioned studies. These factors include the numerous episodic waves of COVID-19, many in which the virus being mutated into different forms. The different mutations of COVID-19 usually expressed itself with different systemic complications, leading to a diverse suit of ocular manifestations i.e., broad spectrum of manifestations.

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hardly be comparable to the results of the afore mentioned studies. These factors include the numerous episodic waves of COVID-19, many in which the virus being mutated into different forms.

CONCLUSION

COVID 19 affects ocular, extraocular and adnexal tissues especially external eye diseases and posterior segment affection. COVID 19 helps in reactivation of viral keratitis and this note can be due to dropped immunity which is marked during COVID illness.

The prevalence of ophthalmic manifestations among COVID-19 patients in this study was 18 out of 80 patients, counting for 22.5% of the tested subjects. The highest number of patients suffered from external eye diseases (39%), followed by the posterior segment diseases (33%), subsequently orbit pathology (17%), and finally anterior segment diseases (11%). This study alongside other studies mentioned earlier, show that COVID-19 has influence on the eye.

Declarations

Funding: No sources of funding were used to conduct this review.

Availability of materials and data: Data supporting results in this article are available if requested.

Ethics approval: The research approval of the study was obtained by the Research Ethics Committee at October 6 University.

Authors Contribution: All authors read and approved the final manuscript.

Consent for publication: Not applicable.

Conflict of interests: No financial affiliations or financial involvement with any organization or entity with a financial competing with the subject matter or materials discussed in the review.

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