Original Article

Ocular Manifestations of COVID-19 among Patients Admitted to the Intensive Care Unit of Khatam-Al-Anbia Tertiary Center, Tehran, Iran

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Abstract

Purpose: This study reports ocular findings in patients with COVID-19 diagnosis admitted to the intensive care unit of Khatam-Al-Anbia Tertiary Center, Tehran, Iran, from October 2020 to October 2021.

Patients and Methods: In this case series study, comprehensive ophthalmic examination of patients admitted with COVID-19 diagnosis to the intensive care unit of Khatam-Al-Anbia Tertiary Center, Tehran, Iran, was performed and data were collected during one year (October 2020 - October 2021). This included assessments of the eyelids, conjunctiva, extraocular muscle motility, anterior and posterior segments, orbit, and paraclinical imaging.

Results: The most prevalent ophthalmic findings were conjunctival problems (62.5 %), multiple manifestations (45.8 %), eyelid issues (41.6 %), and proptosis (37.5 %). Other manifestations were less common. Notably, mucormycosis involvement and its impact on the disease course were significant, regardless of its low frequency. It was observed that the female gender showed greater resistance to the infection and its complications.

Conclusion: Ophthalmic manifestations of Covid-19 are common and should be considered in patients' care. Serious ophthalmic manifestations although rare might lead to severe visual impairments. Central nervous system involvement severely decreases the chance of survival and gender plays a role, in patients' reaction to the infection.

Keywords: Ophthalmic; Manifestation; Mucormycosis; Covid-19; Neurologic.

Article Notes: Received: Dec. 14, 2022; Received in revised form: Jan. 15, 2023; Accepted: Feb. 01, 2023; Available Online: Apr. 02, 2023.

How to cite this article: Montazerin N, Rajavi Z, Ziaei Ardakani H, Haseli-Mofrad A. Ocular Manifestations of COVID-19 among Patients Admitted to the Intensive Care Unit of Khatam-Al-Anbia Tertiary Center, Tehran, Iran. Journal of Ophthalmic and Optometric Sciences . 2023;7(2): 14-24.

Introduction

In December 2019, a series of pneumonia cases were identified in Wuhan, China, presenting clinical features such as fever, dyspnea, and bilateral lung infiltrates [1]. The causative agent, determined from nucleic acid samples of infected patients, was identified as a single-stranded RNA virus from the betacoronavirus genus, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [2]. This outbreak was declared a pandemic in March 2020.

The virus is highly contagious, spreading through droplets via the oral/nasal route.

Viral RNA has been detected in 3.5 % to 5.5 % of conjunctival swabs from infected patients [3,4]. Virus particles have also been observed in tears, trabecular meshwork and iris of patients [5]. However, there is no evidence of viral replication in ocular tissues [4-6].

Ocular manifestations can occur at any stage of the illness or even post-recovery [7]. It may be primary, caused directly by the virus itself, leading to conditions like conjunctivitis (sometimes without systemic symptoms), episcleritis, optic neuritis, and various manifestations in the anterior and posterior segment and orbit due to vascular, neuronal, and inflammatory pathologies [4]. Secondary complications, such as bacterial or fungal super infections, can also occur [7, 8].

Immune dysregulation, which can be induced by the virus itself, immunosuppressive therapy, broad-spectrum antibiotic therapy [9, 10], and pre-existing morbidity [11] are factors that contribute to the likelihood of secondary infections, particularly fungal ones. These secondary infections can alter the natural course of the disease [4, 12-14].

It is also important to consider the ocular toxicities associated with certain medications used in the treatment of COVID-19. For instance, the reactivation of autoimmune conditions can be provoked by lopinavir/ritonavir [15]. Ribavirin, tocilizumab, and Interferon are also known to cause vascular and inflammatory symptoms [15]. Systemic corticosteroids, a common treatment, can lead to several ophthalmic complications like lens opacity, glaucoma, and central serous chorioretinopathy, with the most concerning being an increased susceptibility to fungal infections [15].

In dealing with COVID-19, a significant challenge arises in differentiating whether proptosis and cranial nerve palsies are consequences of primary brain involvement or secondary infections, or possibly a combination of both. Utilizing diagnostic tools such as CT scans, MRI, and MRV can be useful in clarifying this aspect [16, 17].

The primary objective of this study was to determine the ocular and orbital findings in patients affected by COVID-19 at Khatam-al-Anbia Tertiary Center, Tehran, Iran. This involved examining the extent to which the virus and its treatment can impact the eyes, considering both direct effects and secondary complications.

Patients and Methods

In this study, we included 24 individuals with COVID-19 admitted to the Khatam-al-Anbia hospital intensive care unit, during one year (October 2020 - October 2021). Two patients with multiple sclerosis and one with a history of multiple steroid injections, resulting in bilateral central serous chorioretinopathy, were not included in the study due to presenting ocular manifestations that could potentially be misinterpreted as COVID-19 symptoms. This study adheres with the Helsinki Declaration of 1975, as revised in 2008. This study received

approval from the Ethics Committee of the Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences (SBMU), with the approval number IR.SBMU.ORC.REC.1399.0. To ensure ethical compliance, we obtained informed consent from each patient or, in cases of unconsciousness, from their relatives.

The diagnosis of COVID-19 was made by pulmonary or infectious disease specialists through a variety of clinical and laboratory examinations, including swabs from the nasopharynx or oropharynx, lung CT scans, and MRI.

The treatment approach for these patients was multifaceted, involving oxygen delivery (via nasal tube, mask, or intubation as required), anticoagulants, remdesivir, broad-spectrum antibiotics, steroids, vitamins, and other supplements. Additionally, antifungal medications were prescribed based on positive laboratory results, clinical observations, or as a prophylactic measure at the discretion of the attending physician.

Our ocular examination protocol began with a basic assessment of visual acuity, conducted at the bedside. This was followed by a thorough examination of the eyelids, anterior segment, ocular motility, posterior segment, and orbit. The tools at our disposal for these examinations included direct observation, a direct ophthalmoscope, paraclinical imaging, and in one instance, a biomicroscope.

We also included neurological findings in our study, guided by neurologists' opinions and imaging results from CT scans or MRIs of the brain, orbits, and paranasal sinuses when available.

In our results, we recorded each patient's disease process, age, gender, and findings from the ophthalmic examination, along with underlying health issues.

Results

Table 1 shows a summary of patients' demographics and the disease outcomes. Notably, there was a higher incidence of severe outcomes leading to death among male patients, as detailed in table 1. A summary of each patient's most prominent findings are presented in table 2.

Table 3 highlights diabetes as the most common underlying condition, affecting 50 % of the patients. This was followed by blood hypertension and addiction, which had

Table 1: General epidemiologic characteristics of our patients

Study population		Number		Percentage	
Gender	Male	13		54.1	
	Female	11		45.8	
Age range (yrs)		31-94			
Total survival		13 Female:9	Male:4	54.1 Female:69.2 %	Male: 30.8 %
Total death		11 Female:1	Male:10	45.8 Female: 9 %	Male: 90.9 %
Total		24		100	

Table2: A summary of each patient's most prominent findings

Patients" outcome	Gender	Age (years)	Underlying disease	Ocular and orbital findings
Improved	F	35	Multiple sclerosis	Bilateral optic atrophy
Improved	F	35	Multiple sclerosis + diabetes + thyroid problems	Bilateral optic nerve temporal pallor
Improved	F	65	Lymphoma under chemotherapy + diabetes	6^{th} Cranial nerve paresis (left)
Passed away	M	60	Fatty liver + kidney problems	Right conjunctivitis and epiphora
Improved	M	40	Long term steroid misuse	Macular pigmentary changes
Improved	F	50	Diabetes + thyroid problems	Blurred vision due to induced myopia following increased blood glucose
Passed away	M	47	Diabetes + schizophrenia and probably addiction	Right severe proptosis + mature lens opacity + lid edema and conj congestion because of Staphylococcus aureus intraocular abcess
Discharged on her own will	F	92	Diabetes + high blood pressure	Unexplained decreased vision (50^{cm}) OD
Passed away	F	62	Diabetes	Right severe proptosis + lid edema + mucormycosis positive + brain involvement
Passed away	M	58	Diabetes + probably addiction	Lid edema + conjunctivitis + unexplained visual loss OS + Ophthalmoplegia + right proptosis + mucormycosis positive
Passed away	M	60	-	Bilateral lid edema + chemosis + corneal edema + proptosis + positive for mucormycosis

Passed away	M	94	Blood hypertension + addiction	Lid edema + chemosis + proptosis + mydriasis OD + high intraocular pressure by finger exam
Passed away	M	68	-	Conjunctivitis + lid margin necrosis OS
Passed away	M	76	Diabetes	Bilateral lid edema and chemosis and proptosis with lagophthalmus
Improved	F	65	Blood hypertension	Conjunctivitis with bilateral pus discharge
Improved	F	55	Diabetes	Conjunctivitis
Improved	F	52	Asthma	Conjunctival congestion + Chemosis + miosis + Iris neovascularization + Lens opacity and 360° post synechia following uveitis resulting in phthisis OD + Ptosis probably due to brain involvement
Improved	M	40	-	History of diplopia + Central serous retinopathy OS
Improved	M	35	-	Hx of diplopia + blurred vision both had improved at exam time papilledema OD + cavernous sinus thrombosis proved by magnetic resonance venography + intracranial hypertension under treatment
Improved	M	68	-	Conjunctivitis + epiphora + end gaze nystagmus + one and half syndrome (medical longitudinal fasciculus involvement)

Passed away	M	89	Diabetes	Lid edema + Ophthalmoplegia + ptosis + proptosis + mid dilated pupil OS + retinal detachment + mucormycosis positive in biopsy
Passed away	M	32	Diabetes	Lid edema + chemosis + proptosis + Ophthalmoplegia + mid dilated pupil + retinal detachment OS + left 7th nerve. palsy + mucormycosis (proved in pathology) + exenteration OS
Passed away	M	32	Leukemia under chemotherapy	Dry eye
Improved	F	79	Diabetes + blood hypertension	Right lid edema + proptosis + chemosis + positive for mucormycosis + drained orbital abcess

significantly lower prevalence rates.

In terms of ocular symptoms, table 4 reveals that conjunctival manifestations and multiple ophthalmic manifestations were the most prevalent signs, observed in 62.5 % and 45.8 % of patients, respectively. Lid edema was present in 41.6 % of the cases, and proptosis in 37.5 %. Ophthalmoplegia, visual impairment, and suspected mucormycosis each accounted for 29.1 % of cases. It is worth mentioning that only 7 out of the 24 patients were able to report on their visual impairment; the others were either unconscious or did not experience any issues, which applied to 70 % of the participants.

Table 3: Prevalence of underlying disease among patients entering the study

Underlying disease	Number	Percentage
Diabetes	12	50
Multiple Sclerosis	2	8
High blood pressure	3	12
Addiction	3	12
Thyroid disease	2	8
Hematologic factors	2	8
Kidney problems	2	8
Long term steroid intake	1	4
Gastrointestinal problems	1	4
Asthma	1	4

Table 4: Ocular and orbital manifestations among patients entering the study

Ocular Manifestation	Number	Percentage
Visual impairment complains	7	29.1
Lid edema / margin necrosis	10	41.6
ptosis	2	8
Dry eye	1	4
Conjunctivitis + chemosis + conjunctival congestion	15	62.5
Corneal edema	1	4
Mid dilated or miotic pupil	3	12.5
Iris rubeosis	1	4
Uveitis	1	4
Lens opacity	2	8
Optic nerve atrophy / edema	3	12.5
Macular pigmentation and CSR	3	12.5
Retinal detachment in context of mucormycosis	2	8
Ophthalmoplegia	7	29.1
Proptosis	9	37.5
Mucormycosis suspect	7	29.1
Biopsy proven Mucormycosis	6	25
Multiple ophthalmic manifestations	11	45.8

Discussion

There is a broad spectrum of reported ophthalmic manifestations in COVID-19, observed in 2 % to 32 % of patients [3,4, 18]. Determining the true prevalence is challenging and controversial due to the lack of uniformity in examinations and data collection methods [19]. Adding to the ambiguity is the fact that about 60 % of severely ill patients admitted to intensive care units suffer from renal and cardiopulmonary failure, electrolyte imbalance, and carbon dioxide retention. These conditions can present symptoms such as dry eye, chemosis, conjunctival redness, and even proptosis and ophthalmoplegia, making it difficult to ascertain whether these symptoms are directly related to COVID-19 infection [20, 21].

Öncül et al.,[17] conducted a study to explore the relationship between ocular, systemic, and laboratory findings in COVID-19 patients. They concluded that although uncommon, ocular findings might occur at any time during the disease and may sometimes be the only sign, a finding comparable to our results [17].

In our study, starting with visual acuity, two patients had decreased vision due to optic atrophy, one caused by very high blood glucose, one cased by macular pigmentary change, and one due to central serous retinopathy (CSR). Two cases (involving three eyes) had severe decreased vision with normal fundoscopy, potentially attributable to acute macular neuroretinopathy (AMN), a rare condition sometimes associated with influenza-like and respiratory diseases, possibly due to ischemia in the deep capillary plexus [22, 23]. Loss of vision, color vision disturbance, and visual field defects can be induced by the viral infection itself, ischemia, thrombotic events, underlying disease, and medications. Dumitrascu et al.,[24] and Gascon et al.,[22] each reported a case of

acute loss of vision due to ophthalmic artery occlusion and acute macular retinopathy, respectively. Invernizzi et al.,[25] and Walinjkar et al.,[26] noted that venous thromboembolism is reported in 19 % -25 % of infected patients in the ICU, even while receiving anticoagulants, and this event occurred in patients with mild or moderate disease. Fernández Alcalde et al.,[7] reported one case of optic neuritis and one of retinal vasculitis, each accounting for 6 % of blurred vision etiologies in their study of seventeen COVID-19 patients under 17 years of age [7].

In our study, eyelid edema was never the only sign; all 9 patients (37.5 %) with eyelid edema had other inflammatory signs as well. One patient had eyelid margin necrosis (4 %), accompanied by conjunctivitis. Six of our cases (25 %) had conjunctivitis, and 15 (62.5 %) had conjunctivitis combined with chemosis and conjunctival congestion. In the patient with eyelid necrosis, we believe both direct viral invasion and secondary ischemia played a role.

In the present study conjunctival manifestations were observed in 62.5 % of patients and were the most common ophthalmic manifestation of the disease. Conjunctivitis, mostly follicular, has been reported as the most common ocular manifestation of the COVID-19 and may be seen at any stage, even weeks after the acute phase [4]. The prevalence of conjunctivitis in the literature varies from 5 % to 31.6 %, with differences possibly due to varying definitions of conjunctivitis or the severity of infection and time of onset [9, 21, 27].

Regarding neurologic manifestations, we observed 7 cases of cranial nerve involvement (29.1 %). Including optic nerve atrophy and edema cases, central nervous system (CNS) involvement was observed in 10 patients (41 %). The more severe the infection, the more common CNS manifestations become, occurring through direct viral infection causing vascular problems or demyelination, mucormycosis spread, or both [28,29]. However, the early occurrence of neurologic manifestations suggests a direct infection [16]. Olfactory bulb involvement is a known route of virus entry to the CNS, often accompanied by hypogeusia and anosmia, and may lead to encephalitis and acute necrotizing encephalopathy [16,30]. Our study's findings align with the results reported by Ling Mao et al., [28] who found that 36.4 % of their COVID-19 infected patients had neurologic disorders [28].

Regarding the secondary infections, particularly mucormycosis, in our study, out of 9 patients with severe proptosis (unilateral or bilateral), 7 were suspected of mucormycosis, with 6 confirmed by pathology. All received amphotericin B and sinus debridement, and two underwent orbital exenteration. Among biopsy-proven cases, only one patient with very mild nasal mucosal mucor involvement survived despite having a bacterial orbital abscess, which was drained. One patient had a spontaneously draining bacterial ocular abscess. Another was diagnosed with multiple abscess formations throughout the body, including the brain, with negative biopsy and laboratory results for the causative agent. By the time she was examined, her right eye was lost (iris rubeosis + 360° posterior synechia formation + lens opacity + phthisis). Considering endophthalmitis responsible for the lost eye, there would be three bacterial infections (12.5 %) in this study.

Sen et al.,[4] reported 6 male cases of mucormycosis, all diabetics, who received systemic steroids and underwent mucosal debridement and orbital exenteration in two cases. Hargrove et al., [31] conducted a large survey and literature review, including 292

orbital mucormycosis cases, and found no standard care to guide physicians on when exenteration should be done for a mucormycosis patient. In COVID-19 patients, the decision may differ due to the complex interplay of factors compromising the patients' immunity. Orbital/intracranial extension of mucormycosis should be considered a medical as well as surgical emergency. However, our study suggests that in COVID-19 patients, such extension often means little can be done.

Conclusion

Ophthalmic manifestations of Covid-19 are common and should be considered in patients' care. Serious ophthalmic manifestations although rare might lead to severe visual impairments. Central nervous system involvement severely decreases the chance of survival and gender plays a role, in patients' reaction to the infection.

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Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present manuscript.