REVIEW

The ocular manifestations of novel coronavirus: A literature review

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Abstract
Apart from the systemic cardinal symptoms such as fever, cough, fatigue, headache, and diarrhea, ocular symptoms have gained much importance during the peak hours of the COVID pandemic. Since an exposed ocular surface can act as a gateway for various respiratory viruses, there is an increased interest in exploring the ocular route of transmission and viral RNA detection in ocular fluids. Moreover, the ocular surface can also share some common viral binding receptors. A large number of case reports and observational studies have been published so far reporting anterior, posterior, orbital, and neurological complications of the eye and orbit. Ocular complications can range from mild self-limiting pathologies such as conjunctivitis, episcleritis, and retinal cotton wool spots to severe blinding pathologies such as mucormycosis, retinal vessel occlusions, candida retinitis, and optic neuritis. There is an increased risk of corneal graft rejection and reactivation of certain microorganisms post severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) vaccination. The present narrative review provides a brief overview of the current literature and an in-depth understanding of the ocular implications of SARS-CoV-2.

Keywords: ocular manifestations, SARS- CoV -2, ocular inflammation, coronavirus, mucormycosis, COVID 19 vaccination

Introduction

Coronaviruses are single-stranded positive-sense RNA viruses that are known to cause upper respiratory tract infections. Previously known coronaviruses like human coronavirus (HCoV) -229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1 were reported to cause only mild self-limiting symptoms and the infections were more prevalent in immune-compromised individuals with systemic morbidities.[1-3] The recently noted 3 opportunistic agents that can cause severe pneumonia are severe acute respiratory syndrome coronavirus (SARS-CoV2002), Middle Eastern respiratory syndrome coronavirus (MERS-CoV, 2012) and the severe acute respiratory syndrome coronavirus 2 (SARS,-CoV-2, 2019).[3,4] These viruses are recognized to be zoonotically transmitted and cause secondary human transmission.[5]

Similar to other respiratory viruses, the transmission of SARS-CoV-2 is believed to be through the infected person's body fluids. The respiratory droplets containing the virus are highly contagious and can eventually infect another person through inhalation, touching surfaces contaminated with the virus, and direct contact with the face, mucous membranes of the mouth, and the eyes. The mucous membranes of the mouth, nose, and eyes are common routes of microbial transmissions. The exposed ocular surface can play a significant role in transmission as well as acquiring the virus. The ocular route of coronavirus transmission and its detection in the ocular secretions is still a matter of controversy. The binding cellular receptor, angiotensin-converting enzyme 2 (ACE2) for SARS-CoV, is extensively expressed in the respiratory tract, lung alveoli, and intestinal epithelial cells. ACE2 receptors are found on the cornea, conjunctival epithelium, aqueous and vitreous humor, and retina (to a lesser extent compared to respiratory tissues).[6] Apart from the cardinal symptoms of fever, cough, fatigue, headache, and diarrhea, ocular symptoms have gained much importance.[3-6] Some of them are due to direct invasion of the virus into ocular tissues, hypersensitivity reaction to viral antigens, hypercoagulation and vascular insults, and various opportunistic infections due to compromised immunity, and nosocomial transmissions. There is an increased interest to explore the ocular manifestations of the disease, its route of transmission, and viral RNA detection in ocular fluids. In this context, the present study has attempted to review the current literature and understand the ocular implications of SARS-CoV-2.

Literature search strategy

A comprehensive literature search was performed in databases namely PubMed and Web of Science for the studies published between 20th December 2020 and 20th November 2021. The keywords used for the literature search were 'SARS-CoV-2', 'novel coronavirus', 'COVID-19', 'ophthalmic', 'ocular manifestations', 'conjunctival congestion', 'polymerase chain reaction', 'conjunctivitis', 'retina', 'orbit', 'neuro-ophthalmology', 'optic nerve', 'Vaccination', using Boolean characters 'AND, 'OR', 'NOT'. The abstracts were reviewed and full text was retrieved for those complying with the study objective. We included case reports, case series, and observational and interventional studies. We excluded studies that did not aimed or mentioned any ophthalmic manifestations.

Ocular surface and anterior segment manifestation of COVID-19

According to earlier literature, conjunctivitis was the initial and most prevalent ocular involvement noted in patients with SARS-CoV-2 infection. The first ocular symptom was reported by Wang Guangfa, a member of the national expert on pneumonia. He contracted the virus during his visit to Wuhan, despite wearing personal protective equipment without protective eyewear.[7] He developed conjunctivitis as a first symptom of the disease and subsequently tested positive for SARS-CoV-2. Following this incident, there was a greater awareness of ocular transmission and the World Health Organization (WHO) advocated wearing protective eyewear when inspecting SARS-CoV-2 patients, as the exposed ocular surface may serve as an alternative route for viral transmission.[8] Several observational studies and case reports have noted conjunctivitis and accompanying ocular symptoms in COVID-19 patients. The exposed ocular surface is highly amenable to various kinds of microbes, especially respiratory viruses. In a cross-sectional observational study by Chen et al. with 534 COVID-19 patients, conjunctivitis was reported in 25 patients (4.68%).[9] They also reported the occurrence of symptoms of dryness (20%), foreign body sensation (11.6%), tearing (50, 9.8%), itching (9.6%), and discharge (45, 8.8%), in patients without conjunctivitis. The various forms of conjunctivitis noted are follicular, hemorrhagic, and pseudomembranous conjunctivitis.[10-12] Kerato-conjunctivitis, first described by Cheema et al. is characterized by sub-epithelial infiltrates, corneal staining, and follicular reaction. A similar case was reported by Guo et al where a 53-year-old man developed bilateral relapsing kerato-conjunctivitis 10 days after commencement of COVID-19 symptoms.[11, 13, 14]The presentation of conjunctivitis resembles common ocular signs of viral infections namely epidemic kerato-conjunctivitis and pharyngoconjunctival fever.

Episcleritis is a rather uncommon symptom of the disease. Hernandez et al. reported two cases of episcleritis after 2-3 weeks of the onset of COVID-19 symptoms.[15] A similar case was reported by Mangana et al. in a 31-year-old woman a week after the onset of symptoms.[16] Otaif et al. identified episcleritis as an initial symptom of the disease.[17] Artificial tears and topical steroids were used to treat all cases documented in the literature, and they all resolved without any further complications.

According to different studies and case reports, the onset of conjunctivitis varies and can manifest at any point during the disease phase. The duration of systemic illness at the time of conjunctivitis varies from 3-20 days. Conjunctivitis is self-healing with a recovery time of 2 to 15 days without recurrences. Certain studies had reported the use of eye drops such as ganciclovir, ribavirin, valacyclovir, antibiotics (ofloxacin, tobramycin, moxifloxacin), and artificial tears. These medications can be used as a supportive therapy for conjunctivitis; however, the efficacy of these drugs has not been determined. To the best of our knowledge, to date, no visual impairment has been reported as a result of any of the aforementioned ocular pathologies. Table 1 provides a brief description of anterior segment manifestations.

Detection of SARS-CoV-2 RNA in the tear and conjunctival secretions

Literature studies have reported the use of reverse transcription polymerase chain reaction (RT-PCR) assay to detect viral ocular tears and conjunctival samples. Güemes et al. investigated the diagnostic utility of RT-PCR for detecting SARS-CoV-2 viral RNA in conjunctival swab specimens obtained from 36 COVID-19 patients with and without conjunctivitis.[18] They found positive SARSCoV2 RNA in two patients with one having conjunctivitis. As a result, they concluded that the detection rates in conjunctival swab were low. Another study collected conjunctival and tear samples from 27 pediatric patients with confirmed COVID-19 diagnosis. While all patients had positive nasopharyngeal swabs for SARS-CoV-2 RNA, only three patients (11%) had

Table 1: Summary of anterior segment manifestations and ocular and nasopharyngeal samples positivity rate in COVID-19 patients

Author	Study type	Sample size	Ocular manifestations	Polymerase chain reaction (PCR) results	
				Nasopharyngeal/ sputum	Ocular (%)
Chen et al.[9]	Cross-sectional prospective	534 COVID-19 cases	25 patients with conjunctivitis and other associated symptoms of itching (9.9%), tearing (10.3%), secretion (9.7%), foreign body sensation 11.8%), dry eye 103 (19.8)	371	Not done
Güemes-Villahoz et al.[18]	Cross-sectional case-series	36	Conjunctivitis in 18 patients	36	2 (5.5)
Atum et al.[20]	Prospective interventional case series	40	Conjunctivitis in 10 patients	40	3 (7.5)
Xia et al.[21]	Prospective interventional case series	30 confirmed COVID-19 patients	Conjunctivitis in 1 patient	30	1 (3.3)
Yu Jun et al.[22]	Prospective observational	17 COVID-19 patients	Conjunctivitis in 1 patient	17	None
Wu et al.[33]	Observational case-series	38 Clinically confirmed COVID-19 patients	Conjunctivitis in 10 patients. Epihora and secretion in 2 patients (total =12)	28	2 (5.2)
Xie et al.[100]	Retrospective case-series	33 COVID-19 patients	NR	33	2 (6)
Sun et al.[101]	Cross-sectional	102 COVID-19 patients	Conjunctivits in 2 patients with tearing	72	1 (1)
Zhou et al.[102]	Retrospective cohort	67 (63 laboratory confirmed and 4 suspected cases)	Conjunctivitis in 1 patient with tearing and itching	63	3 (4.5)
Liang et al.[103]	Observational	37 COVID-19 cases	Conjunctivitis in 3 patients	37	1 (2.7)
Yan et al.[104]	Cross-sectional case series	35 confirmed cases	Not reported	19	3 (8.5)
Zhou et al.[106]	Cross-sectional observational	121 confirmed COVID-19 patients	Conjunctivitis in 3 patients and 5 patients with symptoms of redness, discharge and FB sensation (total=8)	121	3 (2.5)
Karimi et al.[107]	Prospective interventional case series	43 severe COVID-19 cases	Conjunctivitis in 1 patient and 1 patient with FB sensation	30	3 (7)
Bostanci Ceran & Ozates[108]	Cross-sectional	93 confirmed COVID-19 cases	Conjunctivitis in 20 patients	93	Not done

positive conjunctival samples.[19]

Another study evaluated conjunctival swab RT-PCR results in 40 COVID-19 patients and discovered that three (7.5%) of them were positive in conjunctival samples. Despite the identification of conjunctivitis in ten (25%) patients, only one of them tested positive for viral RNA in conjunctival samples.[20] Similar findings were reported by other studies as well where the positivity rates in ocular samples were lower than in sputum and nasopharyngeal samples.[21-23]

Proposed hypothesis and possible ways of ocular surface involvement

The extension of mucous membrane from the eye into the nasolacrimal duct and the nasopharyngeal space can deliver the virus into the upper respiratory tract and the gastrointestinal tract when swallowed. Viral absorption from the ocular tissues like conjunctiva and corneal epithelial lining of the lacrimal system epithelial cells and the inner lining of the pharynx is also possible. The virus can also travel retrograde into the nasal and ocular fluids during upper respiratory tract infections. Furthermore, the similarity in the distribution of cellular receptors in the ocular surface mucosa and the respiratory tract poses a risk of viral tissue tropism adherence and transmission. As already well established, the receptors of some species of adenovirus and avian influenza (α-2-3-linked sialic acid, CD46, desmoglein-2) and the human influenza virus (α-2-6-linked sialic acid) are abundantly present in the corneal conjunctival epithelium as well as nasal and tracheal mucosal lining.[6, 24,25]

The binding cellular receptor for the SARS-CoV virus, angiotensin-converting enzyme 2 (ACE2), is extensively expressed in the lung alveoli and intestinal epithelial cells. In the eye, ACE2 expression is observed in the corneal epithelium, conjunctival epithelium, aqueous and vitreous humor, although comparatively less compared to lungs and gastrointestinal tissues.[6,25] Current evidence suggests that the binding of SARS-CoV spike protein (S240) with the ACE2 receptor is amplified by heparin sulphate and transmembrane protease, serine 2 (TMPRSS2) proteins within the host cell.[26] So far, the presence of TMPRSS2 proteins has not been reported on the ocular surfaces.[26] However, the virus may get transferred through the lacrimal passage system into the lower respiratory tissues.

The ocular immune system consisting of mucous membranes and tears plays a significant role in the ocular defense mechanisms. Therefore, it is capable of processing an inflammatory response to microorganisms and their antigens. Lactoferrin, lipocalin 2, and immunoglobulin A, which are found in saliva, gastrointestinal fluids, and mucus including tears, have been shown to block viral attachment by interfering with the ACE2 receptors. Lactoferrin levels increased 150-fold in patients with SARS-CoV-1, according to earlier literature.[27,28] The antimicrobial activity of the tears can play a protective role in the host defense mechanisms. More research is needed to gain a better understanding of these compounds. PCR of the nasopharyngeal swabs is presently the gold standard for confirmation of COVID-19.[29] The presence of viral RNA in ocular secretions and the few documented ocular signs serve as preliminary proof of the virus's presence on the ocular surface.

The aforementioned research findings can be interpreted in a variety of ways. Firstly, the sensitivity of the PCR test kits is likely to influence the results. False-negative test reports can arise when the viral load is below the detectable range and inadequate sample quantity for that kit.[30] Viral concentrations may vary for different sample collection sites, throughout the course of the disease. According to a report published, the viral load of SARS-CoV found in the nasopharyngeal swab peaked during the 10th day after the onset of symptoms. Furthermore, the study also reported that similar concentrations of viral load were detected in an asymptomatic carrier.[31] To confirm the diagnosis, multiple sample collections are frequently required. In any circumstance of repeated negative results in a suspected case, computerized tomography of the lungs serves as an alternative diagnostic tool.[32]

Furthermore, poor ACE2 expression on the ocular surface is another plausible factor contributing to the low or undetectable viral load in the PCR. Quantification of viral load over time is also an indicator of the severity and progression of the disease and is often helpful in strategizing treatment protocols. A negative PCR result may not be conclusive in determining the illness.

Posterior segment manifestations

Posterior segment manifestations of COVID-19 range from benign or self-limiting pathologies like cotton-wool spots, and dot hemorrhages to potentially blinding conditions including central retinal artery occlusion (CRAO), retinitis, acute retinal necrosis, endophthalmitis, choroiditis, optic neuritis, and optic atrophy. Certain studies have shown viral RNA in the retina of deceased COVID-19 infected patients, implying that coronavirus can cause both anterior and posterior

Table 2: Summary of posterior segment manifestations of COVID 19

Author	Type	Patients presented with ocular symptoms	Mean age ± SD (years)	Symptoms and diagnosis	Vision at the time of presentation	Vision after management
Aşikgarip et al.[82]	Case report	1	71	Acute macular neuroretinopathy	20/40	20/40
Landecho et al.[83]	Prospective study	27	56	Cotton wool pots, retinal swelling	NA	NA
Raval et al.[84]	Case report	1	39	CRVO	20/150	20/30
Finn et al.[85]	Case report	1	32	Hemi CRVO	20/20 (blurring at superior visual field)	20/20
Anuradha Raj et al.[39]	Case report	1	54	CRAO, optic neuropathy	Loss of vision in OS (VA not specified)	NA
Braceros et al.[46]	Case report	1	54	Visual snow-like symptoms, posterior uveitis	20/20	NA
Cunha et al.[52]	Case report	1	23	Unilateral multifocal choroiditis	20/800	20/60
Liu et al.[49]	Case report	1	66	Conjunctivitis, acute viral retinitis, optic neuritis, uveitis and secondary glaucoma	No PL	NA
Insausti-garcía et al.[53]	Case report	1	40	Papillophlebitis, macular edema	20/20 at presentation, which became 20/200 due to macular edema 1 week of initial examination	20/40
Azab et al.[54]	Case report	1	32	Optic neuritis	20/200	20/40
Atum et al.[57]	Case report	1	84	Ischemic stroke in the basilar artery and bilateral posterior cerebral artery region	HM+	NA

CRVO: central retinal vein occlusion, CRAO: central retinal artery occlusion, PL: perception of light, HM: hand movement, NA not available

Table 3: Ocular manifestations post COVID-19 vaccination

Author	Vaccine type	Ocular manifestations	Duration of manifestation post vaccination
Rehman et al.[86]	Covishield	Herpes zoster opthalmicus	3 days and 28 days post vaccination
Pawar & Ravindran[87]	Covishield	Acute abducens nerve palsy	Post 1 week of first dosage
Kakarla et al.[88]	COVAXIN	Bilateral multifocal choroiditis	5 days after first dosage
Sanjay Gopi et al.[89]	Covishield	Acute macular neuroretinopathy	3 days after first dosage
Reddy et al.[90]	Covishield	Harada-like symptoms	7 days after first dose
Roy et al.[91]	Covishield	Unilateral optic neuritis	9 days post first dose
Parmar et al.[92]	Covishield	Post penetrating graft rejection	4 days post first dose
Somya Ish[93]	COVAXIN	Facial palsy	3 weeks post second dose
Sonawane et al.[94]	Covishield	Central vein occlusion	4 days post second dosage
Fowler et al.[95]	Pfizer-BioNTech	Central serous retinopathy	69 hours post first dose
Mudie et al.[96]	Pfizer-BioNTech	Panuveitis	3 days after second dose
Koong et al.[97]	Pfizer-BioNTech	Vogt-Koyanagi-Harada syndrome	1-day post first dosage
Goyal et al.[98]	Sputnik V	Unilateral retinal vein occlusion	11 days after second dose
Tagliaferri et al.[99]	Moderna	Myasthenia gravis	1 week after second dosage

ocular diseases.[33, 34] A brief review of posterior segment manifestations is provided in table 2.

Retinovascular occlusions

COVID-19 has been linked to coagulopathy.[35] Autopsies on patients with severe COVID-19 infection revealed diffuse small vessel thrombosis, which was earlier thought to be caused by complement-mediated microvascular injury with platelet-fibrin microthrombi.[36] In addition, SARS-CoV-2 has an affinity for vascular endothelial cell ACE2 receptors, which activates apoptotic pathway signaling and prothrombotic cascade process.[37] In healthy patients hypercoagulability is the main risk factor for retinal vessel occlusion. In the literature, there have been a few examples of central retinal vein occlusion (CRVO).[38] Patients were treated with oral corticosteroids and intravitreal anti-vascular endothelial growth factor (ranibizumab). Within two weeks, all of the patients regained their vision. In patients with COVID-19, the appearance of central retinal artery occlusion (CRAO) has also been reported. Raj et al. reported CRAO in a 37-year-old patient who was recovering from COVID-19.[39] He presented with sudden onset vision loss with ptosis and internal ophthalmoplegia in the left eye. MRI of brain and orbit showed cavernous sinus thrombosis with left diffuse pre-septal and retro-orbital edema with swollen optic nerve sheath. However, his ocular condition did not improve after treatment and at 1 month he presented with optic disc atrophy. The patient had a poor prognosis.

Candida retinitis

Immune suppression and the use of aggressive immunosuppressives have raised the risk of opportunistic infections in COVID-19 patients. *Candida albicans* is one of the common causes of opportunistic infection in immunocompromised patients.[40] Candida retinitis is commonly reported post-influenza infections. Its diagnosis can be challenging in the early stage with only chorioretinal involvement. Bhagali et al. reported the case of a 42-year-old male who presented with visual impairment in both eyes 2 months post recovery from COVID-19 infection. [41] His history was positive for *Candida albicans* during the COVID-19 phase, for which he has been treated with antifungals and other supportive medications. On presentation, his bilateral visual acuity was finger counting close to his face. Fundus examination revealed multiple yellowish-white fluffy lesions and retinitis in both eyes. Based on the clinical findings and previous blood investigation, he was diagnosed with Candida retinitis and treated with oral and intravitreal anti-fungal agents. At the last 1 month follow-up, the patient responded slowly to treatment and gained 3/60 bilateral visual acuity. Another case of Candida retinitis was reported by Goyal et al. in a 57-year-old male who was hospitalized for severe candida septicemia during COVID-19.[42] He presented with panuveitis and retinitis in both the eyes. The patient was aggressively managed with intravenous, intravitreal, and systemic antifungals, and showed marked improvement in ocular condition.

Uveal manifestations

COVID-19 has been reported as a precursor of various autoimmune and autoinflammatory diseases, including pediatric inflammatory syndrome (PIMS) and Guillain-Barre syndrome.[43,44] This can be correlated with autoimmune and autoinflammatory sequelae. Singh et al. have reported a case of bilateral recurrent idiopathic anterior uveitis in a 35-year-old female who had recovered from COVID-19.[45] A similar case report by Braceros et al. has discussed the case of a 54-year-old patient diagnosed with visual snow-like symptoms and posterior uveitis.[46] Visual snow is a neurologic condition where a patient presents with constant positive visual disturbance as 'static' or innumerable small dots throughout the visual field, which are associated with other visual symptoms such as palinopsia, entoptic phenomena, photophobia, and nyctalopia.[47,48] Both the cases had negative serologies for ACE, HLA-B27, ANA, lysozyme, CRP, RA, HIV 1 and 2, ESR, syphilis Ab IgG, QuantiFERON Gold, mitogen, TB1 Ag, TB2 Ag, and CBC. They concluded that COVID-19 can trigger autoimmune and autoinflammatory responses, mainly via molecular mimicry, and can play a primary role in the development of ocular inflammation. Liu et al. reported the case of severe panuveitis associated with monocular blindness in a recovered 61-year-old COVID-19 patient who presented with no light perception in the left eye.[49]

Several studies have reported the reactivation of serpiginous choroiditis and multifocal choroiditis in COVID-19 patients.[50, 51] Cunha et al. reported an atypical appearance of chorioretinal lesions in a patient who tested positive for COVID-19 and complained of progressive painless loss of vision.[52] A diagnosis of atypical unilateral multifocal choroiditis was made based on history and ocular investigations.

Neuro-ophthalmic manifestations

Papillophlebitis

Papillophlebitis is an idiopathic rare disease entity and considered as a clinical variant of CRVO. It is thought to be due to inflammation of retinal vessels and capillaries at the optic disc. Insausti et al. have reported the case of a 40-year-old male who complained of sudden painless vision loss post 6 weeks of recovery from COVID-19 infection and was diagnosed with papillophlebitis.[53] All serological investigations comprising of complete blood count, glycemia, lipid profile, homocysteinemia, anti-cardiolipin IgM and IgG antibodies, and screening for genetic thrombophilia were normal. However, the patient was positive for serum IgM and IgG for SARS-CoV-2 qualitative enzyme-linked immunoassay, and parameters of the coagulation system. D-dimers, fibrinogen, and the c-reactive protein (CRP) were found to be altered. The patient was treated with a dexamethasone implant, which significantly decreased the macular edema, and a significant improvement in visual acuity was observed.

Optic neuritis

Optic neuritis is an autoimmune inflammatory condition where patients developed a sudden drop of vision accompanied by pain during ocular movement. Certain literature studies have reported optic neuritis as one of the possible presentations post recovery from COVID-19 infection.[54] Azab et al. presented the case of a 32-year-old male patient with the sudden drop of vision in his left eye, throbbing headaches, and central dark areas in the visual field after 2 weeks of COVID-19 infection.[54] Mild disc swelling noted on fundus examination also correlated with OCT findings and axial T2 MRI showed left optic nerve swelling of the retro-bulbar intra-orbital segment. The treatment regimen was similar to normal cases with 1 gm intravenous methylprednisolone for 3 days followed by 60 mg oral prednisone with tapper dosage. The visual acuity improved to 20/40 from 20/200 in the subsequent follow-up visits.

Bilateral visual loss due to ischemic stroke

Previous literature studies have reported the incidence of ischemic stroke in COVID-19 patients as 5% and it may develop within the first 10 days after the diagnosis of the disease.[55] The responsible mechanisms for the development of stroke in SARS CoV 2 infection are hypercoagulation, intracranial cytokine storm-induced vasculitis, and atrial fibrillation.[56] Atum et al. described the case of an 84-year-old male who presented with sudden bilateral loss of vision and hand movements.[57] He did not have any history of stroke, diabetes, hypertension, or any other systemic disorders. The ophthalmic evaluation was unremarkable. However, acute ischemia in the bilateral posterior occipital lobe and bilateral cerebellar hemispheres was noted in the MRI scan. Additionally, elevated serum D dimer, c-reactive protein, lactate dehydrogenase, and neutrophil count levels were noted. Based on the above findings, the diagnosis of ischemic stroke in the basilar artery and bilateral posterior cerebral artery region was made. The patient was treated in the intensive care unit. However, the author has not reported any follow-up visit findings and management options.

Orbital manifestations

Mucormycosis

The most common and fatal orbital manifestation of COVID-19 is rhino-orbital mucormycosis. Mucormycosis is an uncommon angioinvasive disease caused by mold fungi, which is most commonly seen in immunocompromised individuals. The mode of infection is mostly through the inhalation of fungal spores. It mainly affects individuals with moderate to severe COVID-19 infection with reduced CD4+ and CD8+ counts.[58] Infection with mucormycosis can be life-threatening in individuals with systemic comorbidities such as diabetes, hypertension, underlying autoimmune conditions, and individuals on systemic steroids and immunosuppressives. According to Smith and Krichner, the clinical diagnosis of mucormycosis is based on signs such as black, necrotic turbinate's blood-tinged nasal discharge and facial pain, soft peri-orbital or peri-nasal swelling with discoloration, presence of ptosis of the eyelid, proptosis of the eyeball, and complete ophthalmoplegia.[59]

The estimated global prevalence of mucormycosis between 2019-2020 ranged from 0.005 to 1.7 per million population, and the prevalence in India was 0.14 per 1000 population, nearly 80 times higher than compared to developed countries.[60-62] Uncontrolled diabetes is one of the major risk factors for ocular mucormycosis. Development of mucormycosis after recovery was reported by the majority of the studies.

Out of the 101 cases of mucormycosis reported by Singh et al. 82 were from India, 9 from the USA, 3 from Iran, and one each from the UK, France, Italy, Brazil, Turkey, Austria, and Mexico.[63] In their study, 78.9% were males and 83.3% of patients were hyperglycemic at the time of presentation. The locations of mucormycosis noted were nasal sinus (88.9%), rhino-orbital (56.7%), rhino-orbito-cerebral (22.2%), bone involvement (14.9%), pulmonary (7.9%), gastrointestinal (1%) and cutaneous (1%).

Management of mucormycosis is challenging and often requires aggressive antifungal and antibiotic treatment. The Centre for Disease Control and Prevention (CDC) has recommended some important protocols for prevention of mucormycosis such as control of blood sugar level and diabetic ketoacidosis, steroid monitoring and dosage variance based on the severity of COVID-19 infection, antifungal prophylaxis, radio-imaging and clinical monitoring of progression of the fungal infection.[64] Surgical removal of necrotic tissue and enucleation of the eye can be performed in severe life-threatening cases.

Orbital myositis

Orbital myositis is a rare idiopathic orbital inflammatory syndrome, which involves one or multiple extraocular muscles. It usually presents with acute onset of pain, and diplopia, and responds well to oral corticosteroids.[65] Though very rarely reported in COVID-19 patients, Armstrong et al. have reported a case of orbital myositis in a 44-year-old man with COVID-19.[66] He presented with worsening of unilateral eyelid swelling, proptosis, and periocular erythema. An orbital CT scan showed opacification of the superior rectus and levator complex, which extended into the eyelid. Blood investigation showed decreased leucocytes count and MRI revealed no para sinus involvement. Since all possible etiological factors were excluded, the diagnosis was concluded as orbital myositis. His condition resolved following a course of oral prednisone and antibiotics. A similar case of orbital myositis was reported by Eleiwa et al. in a 10-year-old boy who presented with orbital pain, diplopia, and occasional vomiting.[67] He was started on oral steroids along with antibiotics and dramatic improvement in his ocular condition was observed.

Some rare orbital complications reported were orbital cellulitis and sinusitis, dacryoadenitis, and retro-orbital pain. However, all these conditions had a favorable outcome with good visual recovery, except for some cases of mucormycosis.

Ocular complications post COVID-19 vaccination

The vaccines that are approved for use against COVID-19 are the modified nucleoside RNA vaccine (Pfizer-BioNTech), recombinant adenoviral vector encoding SARS-CoV-2 spikes glycoprotein (COVISHIELD) by Serum Institute of India, inactivated SARS-CoV-2 vaccine (Sinopharm), Sputnik V(Russia), mRNA-1273 Moderna, Janssen COVID-19 vaccine (Johnson and Johnson), COVAXIN (Bharat Biotech, India), and CoronaVac (Sinovac Biotech).[68] The Indian government has adopted a flag-waving vaccination drive throughout the country. Commonly reported side effects of the vaccine were fever, myalgia, and tenderness at the site of injection. Ophthalmic manifestations reported in literature post-vaccinations were erythematous edema, scleritis, varicella zoster virus reactivation, optic neuritis, acute macular neuroretinopathy, Vogt-Koyanagi-Harada like syndrome, uveitis, choroiditis, central serous chorioretinopathy, retinal vascular occlusions, optic neuritis, and abducens nerve palsy (Table 3).

One of the most debated topics on ocular manifestation post-COVID-19 vaccination is corneal graft rejection. Various recent studies have investigated this concern.[69,70] Vaccination may enhance the immune response that can induce class II MHC antigens and CD4+ Th1 cells in all grafted layers of the cornea and may trigger allograft rejection like the influenza vaccine.[71] In practice, an increase in the dose of corticosteroids 1 week before and after each vaccine dose has been preferred by many cornea surgeons. Reactivation of tubercular choroiditis and uveitis were most commonly reported manifestations post COVID-19 vaccination.[72,73] In addition, there are isolated reports of reactivation of varicella zoster ophthalmicus in patients who received Moderna and Pfizer vaccines. This reactivation may be due to an immune reaction process to mRNA vaccines in general. Although the exact mechanism is still unknown.[74]

Conclusion

The current review has provided a brief overview of the current literature evidence on various ocular manifestations that occurred due to COVID-19 and post-vaccination. Ophthalmic manifestations vary in terms of presentation, severity, and timing. Routes of transmission of the virus to the ocular structure include direct inoculation of conjunctiva by droplets, migration of upper respiratory tract infection through the nasolacrimal duct, and lacrimal gland involvement by the hematogenous route. Cultured conjunctival swabs have detected the viral RNA in a few COVID-19 patients. The low yield of RT-PCR is due to the significantly lower viral load in conjunctival samples as compared to nasopharynx, and variation in sampling timings and methods. However negative RT-PCR does not necessarily indicate the absence of virus in the tears or ocular surface. Previous literature studies have found a very low risk of SARS CoV-2 transmission through the ocular surface. Ocular complications can range from mild self-limiting pathologies such as conjunctivitis, episcleritis, and retinal cotton wool spots to severe blinding pathologies such as mucormycosis, retinal vessel occlusions, candida retinitis, and optic neuritis. Eye care professionals should be aware of the potential blinding conditions and their treatment.

Competing interests
The authors declare that they have no competing interests.

Contribution
All the authors have contributed equally to the conceptualization, data capturing and developing the content.

Citation
Dutta R, Sadhu S, Biswas J. The ocular manifestations of novel coronavirus: A literature review. IJIR. 2022;(6)1:R2.

Submitted: 20 April 2022, **Accepted:** 30 June 2022, **Published:** 28 October 2022

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