COVID-19 Disease and Ophthalmology: An Update

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ABSTRACT

The worldwide outbreak of the severe and acute respiratory coronavirus disease (COVID-19) caused by the coronavirus strain SARS-CoV-2 is currently the focal point of discussion due to the suffering this syndrome is causing to humanity. However, the ophthalmological implications of this syndrome has not yet been well described. Both eyes and tears as portals of entry and sources of contagion have been the subject of debate by many authors. The purpose of this review is to summarize the evidence currently available on COVID-19 and its ocular implications and manifestations, in both animals and humans, with the aim to facilitate prevention and educate the ophthalmological community on this subject. A review of the literature revealed that the results of some studies suggest that ocular symptoms commonly appear in patients with severe COVID-19 pneumonia and that it is possible to isolate the virus from the conjunctival sac of these patients. Conjunctivitis is not a common manifestation of the disease, but contact with infected eyes could be one route of transmission. Consequently, ophthalmologists need to have correct prevention strategies in place. Some guidelines regarding the prevention and management of ophthalmology clinics are reviewed. However, well-designed trials should be conducted to rule out other ocular manifestations that may result from COVID-19 infection and to understand the transmission of the virus through the eyes.

Keywords: Conjunctivitis; Coronavirus; COVID-1; Ocular transmission; Ophthalmology; SARS-CoV-2

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Key Summary Points

The purpose of this review is to summarize the evidence currently available on COVID-19 and its ocular implications and manifestations, in both animals and humans, with the aim to facilitate prevention and educate the ophthalmological community on this subject.

Conjunctivitis is not a common manifestation of the disease, but contact with infected eyes could be one route of disease transmission.

Some guidelines regarding prevention and management of ophthalmology clinic are reviewed.

INTRODUCTION

Since December 2019, humanity has been having to deal with the emergence of a severe and acute respiratory coronavirus disease (COVID-19), caused by the strain of coronavirus referred to as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The respiratory problems caused by this pathogen is well known, but the ophthalmological implications of the syndrome have not yet been well described.

Coronavirus disease is not a new pathology. Three human coronaviruses have been known to exist since the mid-1960s: human coronavirus 229E (HCoV-229E), human coronavirus OC43 (HCoV-OC43) and severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) [1–9]. In 2004, human coronavirus NL63 (HCoV-NL63), a novel human coronavirus to date, was reported in a 7-month-old child suffering from bronchiolitis and conjunctivitis [10, 11]. The *Coronaviridae* family of viruses consist of enveloped viruses with a large plus-strand RNA genome (27–32 kb) that is capped and polyadenylated. Each serology type

is characterized by a specific host range and genome sequence.

The most pathogenic of these four types of coronaviruses is SARS-CoV, which causes a life-threatening pneumonia [12–14]. This virus is likely to reside in animals and can affect humans through zoonotic transmission [15, 16]. Coronaviruses have been identified in mice, rats, chickens, turkeys, swine, dogs, horses, rabbits, cats and humans. They can cause a variety of health problems in humans, including gastroenteritis, respiratory tract problems [17, 18] and conjunctivitis [10, 11, 19–31].

The authors of a recent study concluded that one-third of patients with COVID-19 had ocular abnormalities, a frequent manisfestation in patients with more severe disease and that although there is a low prevalence of SARS-CoV-2 in tears, it is possible to transmit the disease through ocular secretions [31]. Therefore, taking into consideration that there are more reports in the literature associating coronavirus and ophthalmic problems, the aim of this narrative review is to summarize, from an ophthalmological perspective, the pathogeny, the portal of entry and implantation of the virus at the conjunctiva, its ophthalmic implications, ocular complications, prevention in the ophthalmology context and possible treatment of the ocular disease. The relationship between COVID-19 and the ocular surface (conjunctiva, corneal epithelium and tear film) as a potencial portal of entry and as a transmission mechanism is currently under discussion due to the high transmission rate of the disease.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

CLINICAL EVIDENCE ON COVID-19 AND EYE DISEASE

Etiology and Pathogenesis of COVID-19

In general, coronaviruses are able to cause a wide range of upper respiratory infections (common cold: alphacoronavirus HCoV-229E,

alphacoronavirus HCoV-NL63, betacoronavirus HCoV-OC43 and HCoV-HKU1), whereas other betacoronaviruses, such as SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV), are responsible for more aggressive lower respiratory problems considered to be atypical pneumonias. The different infection sites are likely to be related to the presence of a viral surface spike composed of a dipeptidyl peptidase 4 glycoprotein that has a human receptor in the lower respiratory tract, known as angiotensin converting enzyme 2 (ACE2). Both SARS-CoV and MERS-CoV have this surface spike glycoprotein [32–34].

From the genetic point of view, SARS-CoV-2 is about 70% similar to SARS-CoV and, therefore, it is capable of using the same cell entry receptor (ACE2) to infect human cells [35, 36]. However, the SARS-CoV-2 glycoprotein spike binds to ACE2 human receptors at a 10- to 20-fold higher affinity than SARS-CoV [37].

Once SARS-CoV-2 enters the alveolar epithelial cells, its fast replication rate triggers a strong immune response causing cytokine storm syndrome (hypercytokinemia) and subsequence pulmonary tissue damage. In general, hypercytokinemias consist of a group of disorders that produce an elevation of the pro-inflammatory cytokines. These cytokines are an important cause of acute respiratory distress syndrome (ARDS) and multiple organ failure [38–40]. One analysis of the first 99 cases of SARS-CoV-2 revealed that a cytokine storm occurred in patients with severe COVID-19, of whom 17% had ARDS; among the latter patients, 11% deteriorated very rapidly and died of multiple organ failure [41]. In addition, the number of T cells (CD4 and CD8) are decreased in patients infected with SARS-CoV-2, suggesting a decreased immune function that subsequently allows a secondary infection that could worsen the respiratory failure [42].

Both viral diseases and immune problems can lead to ocular manifestations, such as conjunctivitis, uveitis, retinitis, among others. It is difficult to determine the pathogeny of the ophthalmic involvement. However, since the virus has been cultured from conjunctival secretions [43], COVID-19 ophthalmopathy is more likely to be related to the own virus infestation rather than the secondary immune reaction that the infection may cause.

Portal of Entry

It is known that SARS-CoV-2 can be transmitted through direct or indirect contact with mucous membranes in the eyes, mouth or nose [28, 44, 45] and that the respiratory tract should not be considered the only route of transmission. In fact, recent studies associate the enteric symptoms of COVID-19, such as diarrhea, nausea, vomiting [46, 47], with invaded ACE2-expressing enterocytes [48], with the oral–fecal route being another potential portal of entry.

Additional studies are required to test different portal of entries. Proposed theories include [30]:

1. Direct inoculation of the conjunctiva from infected droplets.
2. Migration of upper respiratory tract infection through the nasolacrimal duct.
3. Hematogenous infection of the lacrimal gland.

Evidence of Ocular Manifestations

Our analysis of some of the studies included in this narrative review (see Table 1) revealed that the most common ophthalmologic sign related to coronavirus infection was inflammation of the conjunctiva (conjunctivitis). Among the studies reviewed, six were performed in animals (feline, murine, canine and bird experimental models) [19–21, 24–26] and the other 11 in humans [10, 11, 22, 23, 27–31].

The first time that conjunctivitis was associated to a human coronavirus was in 2004, in a 7-month-old child [10, 11], then in 2005 [22, 23], due to the great interest in understanding the clinical manifestations of coronavirus during the first SARS-CoV crisis. However, it is not until this new 2019–2020 outbreak that conjunctivitis has once again been associated to a coronavirus outbreak and taken to be a sign of COVID-19.

In a retrospective study, Vabret et al. investigated HCoV-NL63 infection in hospitalized

Table 1 Clinical evidence of coronavirus ophthalmic manifestions

First author [reference]	Year	Type of study	Main ocular problem	Other problems	Upper respiratory tract problems	Gastrointestinal signs
Hök K [19]	1993	Experimental	Conjunctivitis		Present	
Hök K [20]	1993	Experimental	Conjunctivitis		Present	Present
van der Hoek L [10]	2004	Clinical	Conjunctivitis		Present (bronchiolitis)	
Ahmad K [11]	2004	Clinical	Conjunctivitis		Present (bronchiolitis)	
Decaro N [24]	2004	Experimental	Conjunctivitis		Present (respiratory distress)	Present (enteritis)
Loon S-C [49]	2004	Clinical	Not specified		Present (SARS)	
Chan WM [51]	2004	Clinical	Not specified		Present (SARS)	
Fouchier RA [22]	2005	Clinical	Conjunctivitis		Present (pneumonia, SARS)	
Vabret A [23]	2005	Clinical	Conjunctivitis	Otitis, pharyngitis	Present (rhinitis, bronchiolitis)	Present
Terregino C [24]	2008	Experimental	Conjunctivitis		Present	
Ledbetter EC [25]	2009	Experimental	Conjunctivitis			
Stiles J [26]	2014	Experimental	Uveitis			
Chang LY [27]	2014	Clinical	Conjunctivitis			
Xia J [28]	2020	Clinical	Conjunctivitis			
Lai THT [29]	2020	Clinical	Not specified			
Seah I [30]	2020	Clinical	Conjunctivitis	Uveitis, retinitis, optic neuritis		
Wu P [31]	2020	Clinical	Conjunctivitis	Epiphora		
Chen L [43]	2020	Clinical	Conjunctivitis		Present (sore throat)	Present (diarrhea)
Zhang H [48]	2020		No evidence[a]			

Table 1 continued

First author [reference]	Year	Type of study	Main ocular problem	Other problems	Upper respiratory tract problems	Gastrointestinal signs
Cheema M [67]	2020	Case report	Keratoconjunctivitis		Present (rhinorrhea, cough, nasal congestion)	
Lan QQ [70]	2020	Clinical	No evidence[a]			
Hu K [71]	2020	Clinical review	Conjunctivitis		Present	
A-Yong [72]	2020	Clinical review	Conjunctivitis			

SARS Severe acute respiratory syndrome

[a] No evidence to support conjunctivitis related to coronavirus

children diagnosed with respiratory tract infection [23]. Of the 300 samples analyzed, 28 (9.3%) were positive for HCoV-NL63. The medical reports of 18 patients with HCoV-NL63–positive samples were retrospectively examined and the following symptoms noted: fever (61%, $n = 11$ patients), rhinitis (39%, $n = 7$), lower respiratory tract illness (bronchiolitis, pneumonia [39%, $n = 7$]), digestive problems (diarrhea and abdominal pain [33%, $n = 6$]), otitis (28%, $n = 5$), pharyngitis (22%, $n = 4$) and conjunctivitis (17%, $n = 3$) [23].

Xia et al. reported a prospective interventional case series involving 30 patients with confirmed novel coronavirus pneumonia [28]. Tear and conjunctival secretions were collected for reverse-transcription PCR (RT-PCR) assay. The authors demonstrated that SARS-CoV-2 were present in the tears and conjunctival secretions of coronavirus pneumonia patients with conjunctivitis; however, no virus was detected in the tears or conjunctival secretions of patients without conjunctivitis. These results could possibly indicate that tear and conjunctival secretions are not a common route of coronavirus transmission, given that the majority of COVID-19 patients do not manifest conjunctivitis. Nevertheless, this route of transmission could not be completely

eliminated in such patients [28]. As ophthalmologists, we should be aware of this finding because any sign of conjunctivitis in the clinical setting should be considered to be a possible coronavirus conjunctivitis, especially when accompanied by other respiratory tract problems or fever.

A study carried out by Loon et al. in 2004 demonstrated the presence of SARS-CoV RNA in tears [49]. Tear samples collected from 36 suspected SARS-CoV patients were sent for RT-PCR analysis for the presence of SARS-CoV; SARS-CoV RNA was identified in three of these patients [49].

In contrast, there have been studies which have assessed both tears and conjunctival scrapes from 17 patients with confirmed SARS-CoV infection, with no positive results from the RT-PCR analysis [50, 51]. The authors propose three explanations of these results: (1) low sensitivity of RT-PCR on ocular surface secretions; (2) if there is viral shedding in ocular tissue, the window period may only last a short period of time; (2) the possibility that SARS-CoV does not exist in ocular tissues.

Regarding the severity of the COVID-19 disease, patients with ocular symptoms are more likely to have higher white blood cell and neutrophil counts and higher levels of

procalcitonin, C-reactive protein, and lactate dehydrogenase than patients without ocular symptoms [31].

Another interesting detail regarding the ocular implication of this infection is that the human eye actually has its own intraocular renin–angiotensin system, and ACE2 receptors have been found in the aqueous humor [52]. As previously explained, the main receptor for SARS-CoV-2 is the ACE2 receptor, which indicates that aqueous humor could be a target in COVID-19 infection. More studies exploring the hypothesis of SARS-CoV-2 ocular manifestation through the ACE2 receptor need to be performed.

The study of ocular manifestations in animals could improve our current understanding of eye disease in humans. Therefore, in the following section, ocular manifestations associated with coronavirus infections in animals are discussed.

Association of Other Coronaviruses with Ocular Manifestations in Animals

Earlier studies have reported an association between coronaviruses and ocular problems in animal models. For example, feline infectious peritonitis (FIP) is caused by a feline coronavirus (FCoV). Vasculitis is a common feature in FIP, and ocular manifestations include pyogranulomatous anterior uveitis, coroiditis with retinal detachment and retina vasculitis, with perivascular cuffing by inflammatory cells [53–56]. These manifestations are more common in the non-effusive (dry) form than in the effusive (wet) form of the disease. Also, it can be present without other systemic signs of FIP [26]. The treatment of uveitis associated with FIP has been described: large fibrin clots in the anterior chamber were treated with intracameral injections of 25 μg tissue plasminogen activator. However, cats with mild uveitis responded only to topical therapy [26].

A murine coronavirus, the mouse hepatitis virus (MHV), has shown involvement of the posterior pole of the eye. The MHV neurotropic strains are of particular importance in animal model studies in the ophthalmology field. The

two main strains are JHM (JHMV) and A59 (MHV-A59), both of which were isolated from a paralyzed mouse as a result of extensive demyelination and encephalomyelitis [57]. JHMV-infected mice were subsequently utilized for intravitreal inoculation to study the mechanisms of virus-induced retinal degeneration [58]. This model is known as the experimental CoV retinopathy (ECOR) model, and it is used to examine genetic and host immune responses that may contribute to retinal disease [30].

In the ECOR model, the infection has two phases, namely, inflammation in the early phase and retinal degeneration in the late phase. Following inoculation, the presence of the virus in the retina and retina pigment epithelium will result in the infiltration of immune cells and release of proinflammatory mediators. After the first week of infection, viral clearance is achieved. However, retinal and retinal pigment epithelial cell autoantibodies are subsequently produced, resulting in progressive loss of photoreceptors and ganglion cells as well as thinning of the neuroretina [59]. In this case, the autoimmune process is the cause of the majority of the retinal damage.

MHV-A59 models, on the other hand, have been used to create viral-induced optic neuritis. This line of research is based on the increasingly popular hypothesis that viral-induced inflammation is the likely etiology of multiple sclerosis. Shindler et al. inoculated MHV-A59 intracranially into mice, inducing meningitis, focal acute encephalitis and, most importantly, optic neuritis [60]. Inflammation of the optic nerve was detected as early as 3 days after inoculation, with the peak incidence at 5 days. Axonal loss was highlighted by the significant decrease in axonal staining compared to control optic nerves 30 days after inoculation [60].

It is important to note that in animal models, coronaviruses affect not only the anterior surface of the eye; thus, we should be careful as ophthalmologists and prevent any possible ocular transmission of the disease. It is important to learn more about the transmission mechanism to the eye and try to understand the pathogeny of the virus in the ocular tissues. We have clear knowledge of retinal and optic nerve problems related to coronavirus in animals, and

the implications thereof; consequently, we should be meticulous when examining patients who have tested positive for COVID-19. Nevertheless, to the best of our knowledge, there is no evidence of human coronaviruses causing intraocular ophthalmic problems, such as uveitis, retinitis and optic neuritis, as observed in animals.

Ophthalmological Prevention

According to a number of authors, ophthalmologists could have a higher risk of contracting SARS-CoV-2 infection due to face-to-face communication with patients, frequent exposure to tears and ocular discharge and the unavoidable use of equipment, such as slit lamp, tonometer, laser, etc. [29, 61]. Ssome guidelines have been recently published to minimize the risk of infection.

Before the patient's visit
The number of patients visiting the clinic should be strictly limited, and there should be a strict timetable of appointments to prevent any agglomeration of patients in the clinic waiting room [29, 61]. Online platforms, such as the hospital's official website, should be used. Telephone assistance could be useful in helping the patient distinguish between urgent and not-urgent ocular problems, recommending treatments for non-urgent diseases, reminding patients of the use of personal protection equipment (PPE) before coming to the clinic and answering questions on possible symptoms relative to COVID-19 [61]. A triage system is also important to identify patients with fever, respiratory symptoms and/or acute conjunctivitis or who have recently traveled to outbreak areas. Online ordering and delivery of prescribed medication, especially for chronic medication for chronic eye diseases, such as glaucoma, is also recommended [61].

During the patient's visit
The number of accessible entry points to the hospital/clinic should be reduced and checkpoints set up at the hospital entrance. The temperature of patients should be controlled and patients should be screening for COVID-19 symptoms and contact history with confirmed or suspected COVID-19 patients within the past 14 days. Patients should be provided with a mask if they do not bring one from home and social distancing in the registration and waiting area should be practiced. Patients with conjunctivitis or other similar infections should be seen in a separate clinic, and there should be a separate waiting area. Patients should be tested more than two times for SARS-CoV-2 RNA in the conjunctival sac and tears. Inside the clinical examination room, the number of people should be limited (1 doctor and 1 patient per room), with the exception of visually impaired patients, patients with communication/mobility difficulties or small children. The room should be well ventilated, and the instruments used should be disinfected immediately after each patient visit. Infection control training should be provided to all clinical staff. Installation of protective shields on slit lamps, frequent disinfection of equipment and provision of eye protection for staff should be implemented in all clinics. Universal masking, hand hygiene and the correct use of PPE should be promoted [29]. Direct ophthalmoscope examination is not recommended and could be replaced by slit light lenses, optical coherence tomography (OCT) or fundus photography [61].

Inpatient management and surgeries
Preoperative infection screening of the inpatients is recommended, especially before any surgical procedure. General anesthesia should be avoided, and local anesthesia is preferable to avoid contamination. Any emergency operation of a COVID-19–positive patient should be performed in a negative pressure operating room. If such a surgical area is not available, the patient should be referred to another qualified hospital equipped with such an operating room. Operations on healthy patients can be performed in a space with a positive pressure laminar flow, as is standard practice [61].

Staff management
Infection control training for all staff is necessary. The taking of temperature and the query-

and-questionnaire procedure before entering the hospital also applies to the staff. Strict hand hygiene is required, and gloves should be changed regularly; one pair of latex gloves should not be used for long periods of time [61].

According to current evidence, human coronavirus can remain infectious on inanimate surfaces for up to 9 days [62]. Therefore, reducing the viral load on surfaces by disinfection is very important. The World Health Organization recommends cleaning environmental surfaces with water and detergent and applying commonly used disinfectants, such as sodium hypochlorite [63]. Bleach is typically used at a dilution of 1:100 of 5% sodium hypochlorite, resulting in a final concentration of 0.05% [64]. It has also been suggested that a concentration of 0.1% is effective in 1 min. It therefore seems appropriate to recommend a dilution 1:50 of standard bleach in the coronavirus setting. In case of small surface desinfection, ethanol (62–71%) has shown an efficacy against coronavirus [62, 64]. Other biocidal agents, such as 0.05–0.2% benzalkonium chloride or 0.02% chlorhexidine digluconate are less effective [65]. Duan et al. found that irradiation with ultraviolet light for 60 min on several coronaviruses in culture medium resulted in undetectable levels of viral infectivity.

We speculate that some ocular spray disinfectants that contain hypochlorous acid, usually applied to treat blefaritis in order to reduce bacterial and viral load on the skin and eyelashes, could be used as a measurement of prevention for the facial area where many other chemical agents cannot be applied.

Treatment of Ocular Problems in Patients with COVID-19

Little evidence exists on the treatment of the viral conjunctivitis associated with COVID-19. Some antiviral systemic drugs have been used during this outbreak, such as umefenovir, lopinavir, ritonavir [43], but not specifically for the ocular problem. Chen et al. reported the possibility that ribavirin eye-drops could help the ocular symptom treatment [43]. Cheema et al. recently treated one patient who presented with

pseudodendritic keratoconjunctivitis with oral valacyclovir 500 mg orally three times per day and moxifloxacin 1 drop once daily to the right eye, based on a presumed diagnosis of herpetic keratoconjunctivitis; this patient, however, turned out to have a positive SARS-CoV-2 conjunctival swab result [67].

The most common cause of infectious conjunctivitis is human adenovirus (HAdV), accounting for up to 75% of all conjunctivitis cases and affecting people of all ages and demographics. As a coronavirus, it can also cause systemic infections in the form of gastroenteritis and respiratory disease. HAdV causes lytic infection of the mucoepithelial cells of the conjunctiva and cornea, as well as latent infection of lymphoid and adenoid cells. Despite it being the most common ophthalmological viral infection, there is no U.S. Food and Drug Administration-approved antiviral for treating HAdV keratoconjunctivitis. Therefore, managing viral persistence and dissemination constitute a challenge. Some treatment modalities have been investigated, such as systemic and topical antivirals, in-office povidone-iodine irrigation, immunoglobulin-based therapy, anti-inflammatory therapy and immunotherapy. Other posible therapeutic options are sialic acid analogs, cold atmospheric plasma, N-chlorotaurine and benzalkonium chloride [68].

Although viral conjunctivitis can cause discomfort to patients, it is not a life-threatening condition. Therefore, all the treatment efforts in patients testing positive for SARS-CoV-2 are destined to be vital problems rather than serious threats to the eye itself. Treatment for viral conjunctivitis is mostly supportive, and the majority of cases are self-limited. Nonetheless, it is important that ophthalmologists to decrease the possible viral load on the conjunctiva and decrease the potential of transmission through tear and eye secretions. Some of the general ophthalmic recommendations for viral conjunctivitis could apply to COVID-19 patients in terms of reducing both the transmission rate and possible complications; these include hygienic measures (frequent hand washing, especially when eye drops need to be applied or contact lens are worn; avoiding touching or rubbing the eyes; changing pillowcases, sheets,

towels, regularly; not sharing personal items, etc.).

More studies should be conducted to establish a specific antiviral ocular treatment aimed at reducing the viral load, if present, on the conjunctiva of patients and reducing the transmission rate from the ophthalmological perspective. However, it is very difficult to determine a treatment when so many doubts still remain regarding the ophthalmic implications of SARS-CoV-2 infection [69, 70].

CONCLUSION

Our review of the literature reveal that some studies suggest that ocular symptoms commonly appear in patients with severe COVID pneumonia and that it is possible to detect viral RNA from the conjunctival sac of these patients. Apparently, conjunctivitis is not a frequent manifestation of the coronavirus disease in patients with non-severe COVID-19. Despite conjunctivitis generally being a self-limited and benign condition, it is an important route of viral transmission and, therefore, prevention is the most important aspect to remember as ophthalmologists to protect our patients and ourselves.

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