

Keep Eyes on COVID-19: Ophthalmic Symptoms and Potential Transmission of SARS-CoV-2 through the Oculus

Hong Li Ran^{1,2}, Xiang Tian Zhou¹, William J. Liu^{1,2}, George F. Gao^{1,2}

¹ School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou 325027, China;

² National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention (China CDC), Beijing 100052, China

Abstract

In December 2019, a new coronavirus disease 2019 (COVID-19) emerged and rapidly spread globally, posing a worldwide health emergency. The pathogen causing this pandemic was identified as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It is well known that SARS-CoV-2 transmits via respiratory droplets and close contact with infected individuals or contaminated items. In addition to these two major transmission routes, other modes of transmission have not been confirmed. Considering that some COVID-19 patients have presented with ocular discomforts and positive SARS-CoV-2 RNA in ocular surfaces, as well as the discovery of the SARS-CoV-2 receptors, angiotensin-converting enzyme 2, and transmembrane protease, serine 2, in the oculus, the ocular surface is now thought to be a possible alternative route of SARS-CoV-2 transmission and a replication site. This review summarizes the evidence connecting COVID-19 with ocular tissues, ocular symptoms during SARS-CoV-2 infection, the potential role of the conjunctiva in SARS-CoV-2 transmission, and the physiopathological mechanisms. Appropriate precautions in ophthalmology departments, including innovative complete and effective patient management plans, protective personal equipment, hand hygiene, and strict personal distance intervals, are essential to effectively minimize the spread of SARS-CoV-2 and control the pandemic.

Keywords: Conjunctivitis; COVID-19; Ocular surface; Ophthalmological infection; SARS-CoV-2

Introduction

The coronavirus disease 2019 (COVID-19) has posed a global health emergency and affected the daily lives of everyone worldwide. On January 30, 2020, the World Health Organization (WHO) declared COVID-19 to be the sixth public health emergency of international concern in history. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a new enveloped single-stranded positive-sense RNA virus that has caused the COVID-19 pandemic, is a novel coronavirus member of the *Coronaviridae* family.^[1] The main symptoms of COVID-19 are fever, cough, and fatigue.^[2] Most patients confirmed as having COVID-19 present ocular manifestations consistent with conjunctivitis, along with the typical respiratory symptoms. Notably, accumulated evidence shows that the virus can be transmitted through the oculus, especially by contacting the eyes with contaminated hands. From an anatomical point of view, the nasolacrimal system provides an anatomical bridge between ocular and respiratory tissues, potentially facilitating the

exchange of virus-containing fluid between the two sites.^[3] Thus, it is critical to increase awareness that SARS-CoV-2 can potentially be transmitted through the oculus and characterize the ophthalmic symptoms associated with COVID-19 infection. This knowledge will help to prevent virus transmission in ophthalmology departments and provide insights into the recognition of ophthalmic symptoms of COVID-19 and appropriate therapeutic approaches.

Ocular infections by respiratory viruses

It has been substantiated that some respiratory viruses can cause ocular infections, including adenovirus, influenza virus, herpesvirus, respiratory syncytial virus (RSV), as well as coronaviruses. The adenovirus infection manifests the ocular symptoms as epidemic keratoconjunctivitis, pharyngeal conjunctival fever, and non-specific conjunctivitis.^[4] The nucleic acid of the virus within conjunctival swabs from adenovirus-infected patients with ocular symptoms could be detected positive through the polymerase chain reaction (PCR) experiments, and the deep sequencing also indicated the existence of adenovirus sequence.^[5–7] The ocular symptoms of influenza A virus, especially the H7 subtype, are red eyes, teary eyes, itching, eye pain, burning eyes, eye pus, and sensitivity to light.^[8] H7N9 virus could be detected by reverse transcription-PCR (RT-PCR) from conjunctival samples of patients with conjunctivitis symptoms, and meanwhile, the influenza virus could also be successfully isolated based on the samples.^[8,9] Herpes virus-related infection also has the features of ocular symptoms, including conjunctivitis and keratitis. The presence of herpes virus in the eyes can be detected by immunofluorescence and multiplex PCR in tear samples or

Corresponding authors: George F. Gao, E-mail: gaof@im.ac.cn; William J. Liu, E-mail: liujun@ivdc.chinacdc.cn

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Table 1: Ocular symptoms, virus shedding, and corresponding ocular viral receptors for different types of viruses.

Virus	Ocular symptom	Virus shedding (PCR/RT-PCR)	Ocular receptor
SARS-CoV-2	Conjunctivitis, EKC	Tears, conjunctival scrapings, and cornea RT-PCR (+)	ACE2, TMPRSS2
SARS-CoV	Conjunctivitis, EKC	Tears and conjunctival scrapings RT-PCR (+)	NA
HCoV-NL63	Conjunctivitis	NA	NA
Influenza	Conjunctivitis	Eye swab RT-PCR (+)	α -2,3 sialic acid receptor
Herpes virus	Keratitis, Conjunctivitis, EKC	Tears and corneal scrapings PCR (+)	NA
Adenovirus	Conjunctivitis, EKC	Conjunctival scrapings PCR (+)	NA
RSV	Conjunctivitis	NA	NA

SARS-CoV: Severe acute respiratory syndrome-associated coronavirus; HCoV-NL63: Human coronavirus NL63; RSV: Respiratory syncytial virus; EKC: Keratoconjunctivitis; RT-PCR: Reverse transcription-polymerase chain reaction; +: Positive result; NA: Not available; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane protease, serine 2.

corneal samples of patients with ocular discomforts.^[10,11] RSV can also cause conjunctivitis.^[12] Notably, ocular symptoms and the presence of viruses can be observed during the infection of coronaviruses. Some patients infected with the human coronavirus NL-63 (HCoV-NL63) show symptoms of conjunctivitis, and the virus shedding in the eyes can be identified by RT-PCR and/or virus isolation experiments.^[13,14] The virus RNA from tears can be detected in SARS-CoV-infected patients through RT-PCR.^[15,16] Herein, we summarize the characteristics of ocular symptoms, virus shedding during the infection with different viruses, and also the expression of corresponding viral receptors in the ocular (Table 1).

Expression of ocular surface cellular receptors that allow SARS-CoV-2 to enter cells

Coronaviruses use their spike proteins to select and enter target cells. Angiotensin-converting enzyme 2 (ACE2) has been identified as a mediator between severe acute respiratory

syndrome coronavirus (SARS-CoV) and host cells.^[17] SARS-CoV-2 has the same cellular receptor as SARS-CoV.^[18] Researchers have also demonstrated that SARS-CoV-2 also uses neuropilin-1 for cell entry.^[19,20] This is the first step in understanding the pathogenesis of the virus. Studies have reported the expressions of ACE2 and its co-factors transmembrane protease, serine 2 in different sites of the oculus, including the conjunctiva, cornea, and limbus,^[21-27] which provides evidence that the eye may be an additional entry portal for SARS-CoV-2 and may have some role in viral spread (Fig. 1).

Ocular infections by SARS-CoV-2

A report of the WHO-China Joint Mission, which summarized 55,924 cases of COVID-19^[28] and another study by Guan et al., which recruited 1099 confirmed cases^[2] reported that 0.8% of patients had signs of conjunctival congestion, and it was higher in patients with more severe COVID-19.^[29] A meta-analysis about the proportion of clinical ocular symptoms in COVID-19 patients

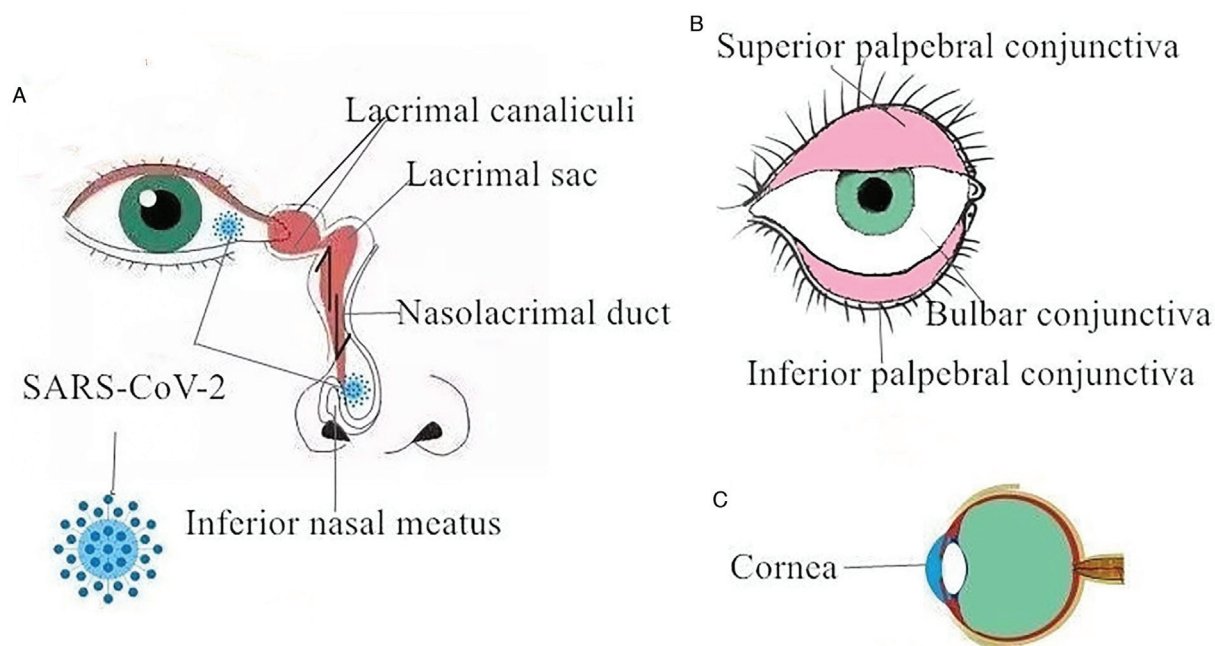


Figure 1: The anatomical structure of the human eye and the potential circulating way of SARS-CoV-2 on the ocular surface and respiratory tract. (A) The anatomy structure of the nasolacrimal duct may facilitate the exchange of virus-containing fluid between the ocular surface and respiratory tract. (B) and (C) Show the approximate anatomical positions of the conjunctiva and cornea which are the main distribution sites of ACE2 and TMPRSS2 in the oculus that mediate the entry of SARS-CoV-2. SARS-CoV: Severe acute respiratory syndrome-associated coronavirus; ACE2: Angiotensin-converting enzyme 2; TMPRSS2: Transmembrane protease, serine 2.

reported an incidence of 11.2%.^[30] The main ocular manifestations are consistent with conjunctivitis^[29,31,32] including conjunctival hyperemia, chemosis, epiphora, increased secretions, foreign body sensation, blurred vision, dry eye, and itching. Furthermore, it has been reported that a few confirmed cases manifested keratoconjunctivitis^[33,34] and keratouveitis,^[35] even retinal change.^[36,37] Therefore, there is speculation that this virus may infect the ocular surface first, spread, and then cause pneumonia through the nasolacrimal tube.

With a view to the considerable proportion of SARS-CoV-2-related conjunctivitis cases, appropriate medical treatment is of particular importance. Generally, although viral conjunctivitis tends to self-heal, antibiotics, steroids, and artificial tears can also be used clinically to relieve the signs and symptoms of inflammation. Most drugs currently available for the treatment of viral conjunctivitis mainly target herpes virus and adenovirus infections.^[38] Although some clinicians have used eye drops/ophthalmic ointment locally in the eyes of COVID-19 patients to relieve ocular symptoms, there is currently no specific antiviral drug for SARS-CoV-2-related conjunctivitis.^[39] Studies have shown that theoretically, the topical use of 1% povidone-iodine (eye drops) in the eye potentially can have an effect on SARS-CoV-2-related conjunctivitis.^[40] In addition, researchers have found ingredients with potential antiviral activity (including anti-coronavirus) in various commonly used eye drops and ointments, indicating that ophthalmic preparations can be used as potential drug candidates for antiviral therapy.^[39]

Transmission evidence of SARS-CoV-2 via eyes and corresponding ophthalmic precautions

A national expert on infectious diseases was infected with COVID-19 in Wuhan and stated that the most likely route of exposure was through his unprotected eyes.^[41] Another case involved a nurse who was fully protected but occasionally worked with dislocated eye goggles that means her eyes may be at risk of exposure.^[42] Researchers initiated an interesting animal study to investigate whether SARS-CoV-2 can cause systemic disease through the conjunctiva.^[43] They inoculated two rhesus macaques with SARS-CoV-2 via conjunctiva and the other one inoculated via intratracheal route as a comparison and then detected virus load in the respiratory tract and systemic tissues including lungs and digestive tract of conjunctiva-inoculated rhesus macaques. This finding indicated that SARS-CoV-2 can cause systemic disease through the conjunctiva. Another study used SARS-CoV-2 to infect *ex vivo* cultures of human conjunctiva tissues and the viral titers of the culture supernatants continued to increase 24 to 48 hours after inoculation. At the same time, the virus-inoculated conjunctiva tissues were subjected to immunohistochemical staining with monoclonal antibodies against SARS-CoV-2 nucleoprotein, the results showed the presence of virus particles in the conjunctiva tissues. It indicates that the eyes may be the additional way for SARS-CoV-2 to infect the human body.^[44]

One previous study reported that hand-eye contact (such as eye rubbing) was a risk factor of epidemic keratoconjunctivitis^[45] and that a total of 332 (62%) out of 534 COVID-19 patients had a history of hand-eye contact,^[46] indicating that transmission by hand-eye contact should not be ignored.^[47]

Other researchers have speculated that ophthalmologists are susceptible to SARS-CoV-2 infection.^[48,49] The conjunctival mucosa is directly exposed to infectious droplets and fomites during close contact.^[50] It is probable that ophthalmologists are

extremely reliant on physical examination during patient consultation, and there is generally almost no distance between ophthalmologists and patients during these exams.^[51] Thus, contagious droplets from patients probably are transmitted to the nose, mouth, and ocular surfaces of health care workers, which leads to infection. Thus, it is recommended that a full set of personal protective equipment be used by ophthalmologists, non-urgent ophthalmic operations should be delayed during the pandemic,^[52] if possible, and telemedical consultation is considered as another good option.^[53,54] Strict hand hygiene, handwashing with soap and water carefully and regularly, avoiding touching the eyes, nose, and mouth, especially in vulnerable areas, is recommended. Moreover, various types of slit-lamp covers, face covers, indirect ophthalmoscope covers, and shielded slit-lamp cabinets to prevent the spread of the virus have been rapidly developed for use along with a strict and complete disinfection program.^[52,55] Additionally, a set of targeted patient management plans, including the establishment of triage stations, risk assessment of patients, and strict safety intervals in the waiting area of the clinic have been developed.^[54]

Detection of viral RNA in ocular surfaces of COVID-19 patients

Previous studies have shown that SARS-CoV RNA can be detected in tears via RT-PCR.^[15,16] Continuous studies have reported positive detection of SARS-CoV-2 RNA in the tears and conjunctival secretions of COVID-19 patients.^[29,31] One meta-analysis reported that 16.7% (10/60 cases) of conjunctival samples were SARS-CoV-2-positive by RT-PCR.^[30] In one case report, SARS-CoV-2 RNA was tested in the cornea.^[35] Nonetheless, positive detection by RT-PCR does not reliably indicate the emergence of conjunctivitis^[56] because some COVID-19 confirmed patients presenting with conjunctivitis have tested negatively for SARS-CoV-2 RNA in tears and conjunctival secretions while some cases without ocular symptoms detected positively.^[57] Many factors account for this result, and overall, the positive rate of SARS-CoV-2 in tears and conjunctival secretions from patients with COVID-19 via RT-PCR is low. Possible reasons include 1) the viral load in conjunctival secretions is too low to be detected; 2) the positive results of conjunctival swabs occur during the early onset of the infection in conjunction with delayed sample collecting; 3) irregular test procedures that lead to genetic material damage or sample contamination and result in false negatives and false positives, respectively,^[58] and inappropriate collection techniques (including the sample container and the sample volume collected); and 4) antimicrobial agents of the host immune system and constant tear rinsing from the ocular to the nasal cavity through the nasolacrimal duct may facilitate the elimination of the virus from the eyes.^[50,59] It should be noted that positive detection of SARS-CoV-2 RNA in post-mortem cornea and sclera of COVID-19 patients via RT-PCR.^[60] In another study of five fatal COVID-19 cases, virus RNA and intraocular vascular damage were found.^[61] Overall, the evidence indicates that virus shedding can occur in the oculus of COVID-19 patients and the eye may have some role in the transmission of SARS-CoV-2.

Conclusions and perspectives

In this review, we showed that the ocular surface may be an additional entry portal and infection for SARS-CoV-2, supported by anatomical and clinical observations and evidence from

animal studies. We emphasized the importance of protecting eyes during close contact with confirmed patients. In consideration of the continuing COVID-19 pandemic, a comprehensive understanding of how the virus spreads is vital for the prevention and control of viral propagation to decrease the risk to public health.

In addition to respiratory droplets and close contact with infected patients or contaminated items, alternative routes of SARS-CoV-2 transmission have been a concern. Considering the ocular manifestations observed in COVID-19 patients and the SARS-CoV-2-positive RT-PCR results from conjunctiva and tear specimens as well as cornea, increased attention has been given to determine if ocular tissues are a SARS-CoV-2-transmission route. We presented evidence to support that the ocular surface is an additional entry portal for SARS-CoV-2 and possibly has a role in viral transmission. However, additional details of the pathogenic mechanism and immune reaction of ocular infection in COVID-19 remain unclear. Further clinical observations and detailed animal studies would be important to investigate the ability of SARS-CoV-2 to infect ocular tissues and transmit via eyes. Protecting our eyes, especially those of health care workers, is essential during this pandemic. The one common deficiency of these studies is that the sample sizes were small; thus, sufficient sample size and well-characterized studies are required to obtain more evidence. Although COVID-19 can cause ocular symptoms, solid evidence is still needed to confirm that SARS-CoV-2 is the cause of ocular manifestations in these cases. Differential diagnosis is necessary to distinguish symptoms related to the virus from symptoms related to the patients' own underlying eye disease or other systematic diseases. Given that COVID-19 can cause fatal viral pneumonia, most studies have focused on respiratory tract disease, and only a small number of researchers have investigated the role of the eye in the disease process. Studying the connection of SARS-CoV-2 with the ocular surface is important to understand the comprehensive transmission routes of this virus, not only to help control viral spread during the pandemic but also to provide better infection preventive measures.

Author Contributions

George F. Gao, William J. Liu and Xiang Tian Zhou conceived the manuscript. Hong Li Ran prepared the manuscript. All authors read, edited, and approved the manuscript.

Conflicts of Interest

None.

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