

COVID-19: ocular manifestations, ocular secretions, and ocular portal of entry

Abstract

SARS-Cov-2 is a Coronavirus in the subfamily Coronavirinae, in the family Coronaviridae and in the order of *Nidovirales* and is responsible for COVID-19 disease. General characteristics of the virus are discussed with an emphasis on ocular manifestations of infection. In addition, the potential of ocular secretions including tears are reviewed as a potential for human to human spread of the virus. Finally, a discussion is made of the latest information on the eye as a portal for exposure and development of COVID-19 infection.

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Introduction

Nidovirales, derived from the Latin nidus (nest) is an order of single stranded RNA genome viruses with both human and animal hosts and includes the family *Coronaviridae*, *Roniviridae*, *Arteriviridae*, and *Mesoniviridae*. All viruses in this order produce a 3' co-terminal nested set of subgenomic mRNA's during infection. With a genome of approximately 30 kb in length, they are among the largest known RNA viruses.^{1,2} Coronavirus (derived from ancient Greek, korone, meaning crown or halo) is the common name for *Coronaviridae* and *Orthocoronavirinae*, also called *Coronavirinae*.³ Typical of the virus is petal shaped projections of approximately 20 nm, which by electron microscopy create an image similar to the solar corona or crown. Coronaviruses can cause disease in mammals and birds. In humans, Coronaviruses may lead to respiratory infections including the common cold. MERS, Sars-Cov-1, and Sars-Cov-2 are coronaviruses which have been associated with more severe human infections and a higher incidence of mortality. Middle East Respiratory Syndrome (MERS) was first reported in Saudi Arabia in 2012. SARS-CoV-1 was responsible for severe acute respiratory syndrome outbreak in 2003 in Asia with secondary cases around the world. SARS-CoV-2, another strain of severe acute respiratory syndrome-related coronavirus, is responsible for the 2019-2020 COVID-19 disease pandemic. This paper will discuss the ocular manifestations of COVID-19, whether ocular secretions may lead to human to human spread of the virus, and how the eye's mucosal surfaces may represent a means of human exposure and eventual infection.

Ocular manifestations

Coronavirinae can cause ocular infections in animals including conjunctivitis, subconjunctival hemorrhage, uveitis, retinitis, and optic neuritis. Vision threatening ocular complications have been well documented by Coronavirus in murine and feline orders.⁴ In a study of 1099 COVID-19 patients, only 0.8% developed conjunctival congestion (9 of 1099 patients in 30 hospitals across China),⁵ however, conjunctivitis has been demonstrated as the initial presenting symptom of Sars-Cov-2 infection.⁶ Typically the conjunctivitis has been described as mild follicular conjunctivitis otherwise indistinguishable from other viral causes. The nurses at the Life Care Center Nursing Home in Kirkland, Washington noted that the single most important sign of infected patients was eye redness.⁷ A report by Wu et al

described the findings of 38 patients with COVID-19 and severe pneumonia in Hubei Province, China. They found 31.6% of patients demonstrated ocular manifestations consistent with conjunctival hyperemia, chemosis, epiphora, or increased secretions.⁸ Only one patient presented with conjunctivitis as the first symptom.⁸ Of the 17 patients recruited, none presented with ocular symptoms and only 1 patient developed conjunctival injection and chemosis during the stay in the hospital.

Ocular secretions as a potential of human to human spread

Ocular transmission via infected ocular tissue or tears COVID-19 is uncertain.^{4,9} In 2004, 36 tear samples from suspected SARS-CoV-1 patients were sent for RT-PCR and the SARS-CoV RNA was identified in three patients, suggesting that SARS-CoV-1 can be present in tears.⁹ A second study by Loon et al in the British Journal of Ophthalmology detected SARS-CoV-1 in tears early in the course of infection.¹⁰ A more recent study evaluating SAR-CoV-2 (COVID-19) showed a positive reverse-transcription polymerase chain reaction assay in tears and conjunctival secretions in patients with conjunctivitis and pneumonia, but for patients with pneumonia and no conjunctivitis, there was no virus detected in tears or conjunctival secretions.¹¹ In a study by Ivan Seah Yu Jun et al out of Singapore in 2019,¹² 64 tear samples were collected via Schirmer's strip tear collection from 17 COVID-19 patients between Day 3 to Day 20 from initial symptoms. Neither viral culture nor 36 reverse transcription polymerase chain reaction (RT-PCR) detected the virus. A study from Yichang Central People's Hospital in Hubei Province by Wu et al in February 2020, found that of 38 patients with clinically confirmed COVID-19, two patients yielded positive findings for SARS-CoV-2 in their conjunctival as well as nasopharyngeal specimens.⁸ It appears that the presence of virus in tears may be low, but none the less, virus can be present and can serve as a source of transmission of the virus.

The eye as a portal for exposure and human infection

Even if COVID 19 positive patients have no virus shedding through tears, the eye remains a potential portal of entry for ocular and systemic disease from the virus. Both avian and human influenza A viruses have shown a capacity to cause disease via entry from ocular tissues.¹³ The conjunctival and corneal epithelium represents a mucosal surface

that, similar to the respiratory tract, bears receptors for influenza virus¹⁴ and avian influenza virus.¹⁵ SARS-CoV-2 has been known to infect cells via ACE-2 receptors.¹⁶ Ace-2 is a type I transmembrane metalloprotease enzyme part of the Renin-Angiotensin system and a target for the treatment of hypertension.¹⁷ It is mainly expressed in vascular endothelial cells, the renal tubular epithelium, and in Leydig cells in the testes.^{18,19} SARS-CoV-2 may utilize ACE-2 as a cellular entry receptor to gain entry into ACE-2-expressing HeLa cells.²⁰ The presence of ACE2 has been found in the aqueous humor,²¹ however the human eye has its own intraocular renin-angiotensin system, a system that has been the interest of many projects focusing on developing anti-glaucomatous drugs.⁴ More studies are required to definitely prove the presence of ACE2 on corneal and conjunctival cells. Regardless of which receptor COVID-19 utilizes, many respiratory viruses have been shown to cause ocular complications which then leads to respiratory infection.²² Studies have demonstrated that in individuals wearing both ocular and respiratory protection exposed to live attenuated influenza have lower viral loads than individuals wearing respiratory protection alone.²³ Li Wenliang, MD, the whistleblower ophthalmologist from Wuhan, Hubei Province, China believed he was infected by an asymptomatic glaucoma patient. A clinician inspecting in Wuhan (Guangfa Wang) was infected while working with a N95 mask but no eye protection.²⁴ He first developed conjunctivitis and then later pneumonia. Transmission of COVID-19 through the ocular surface must not be ignored as it well could be an alternative route of transmission.^{8,25}

In summary, COVID-19 does affect the eye and may be the presenting sign of infection. Ocular transmission by exposure to tears may be low, but has not been ruled out. Finally, the eye may serve as a portal of entry for the COVID-19 virus leading to human infection. Ophthalmologists may be the first providers to evaluate patients possibly infected with COVID-19 as patients may present with conjunctivitis. Eye protection (including goggles or face shields) is warranted to reduce viral infection especially in health care providers exposed to known positive viral patients. In addition, all people should avoid touching or rubbing their eyes to avoid potential inoculation of virus into the eye.

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Conflicts of interest

Author declares that there is no conflict of interest.

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