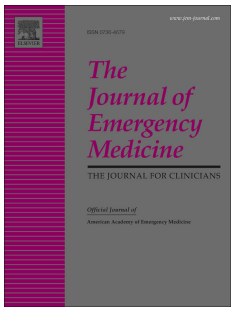
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal Pre-proof



The Ocular Manifestations and Transmission of COVID-19; Recommendations for Prevention

Dominique M. Dockery, Susannah G. Rowe, MD MPH, Marjorie A. Murphy, MD, Magdalena G. Krzystolik, MD

PII: S0736-4679(20)30398-X

DOI: https://doi.org/10.1016/j.jemermed.2020.04.060

Reference: JEM 12465

To appear in: *The Journal of Emergency Medicine*

Received Date: 22 April 2020

Revised Date: 26 April 2020

Accepted Date: 28 April 2020

Please cite this article as: Dockery DM, Rowe SG, Murphy MA, Krzystolik MG, The Ocular Manifestations and Transmission of COVID-19; Recommendations for Prevention, *The Journal of Emergency Medicine* (2020), doi: https://doi.org/10.1016/j.jemermed.2020.04.060.

The Ocular Manifestations and Transmission of COVID-19; Recommendations for Prevention

Authors: Dominique M. Dockery[1], Susannah G. Rowe, MD MPH[2], Marjorie A. Murphy, MD[1], Magdalena G. Krzystolik, MD[1,3]

Affiliations:

[1]Warren Alpert Medical School of Brown University, Providence, RI

[2]Department of Ophthalmology, Boston University School of Medicine, Boston, MA, USA

[3]Department of Ophthalmology (Retina Section), Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, MA

Running Title: Ocular Manifestations and Transmission of COVID-19; Recommendations for Prevention

Corresponding Author:

Magdalena G. Krzystolik, Massachusetts Eye and Ear Infirmary, 1 Randall Square Suite 203, Providence, RI; email: magdalena_krzystolik@meei.harvard.edu

Declarations of Interest: none

Title: The Ocular Manifestations and Transmission of COVID-19; Recommendations for Prevention

Abstract

Background: Coronavirus disease-2019 (COVID-19), caused by a novel coronavirus termed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been linked to ocular signs and symptoms in several case reports. Research has demonstrated that SARS-CoV-2 is spread primarily through close contact via respiratory droplets, but there is the possibility for ocular transmission with the conjunctiva as a conduit as well as a source of infection.

Discussion: Ocular manifestations of SARS-CoV-2 include follicular conjunctivitis and have been repeatedly noted as an initial or subsequent symptom of COVID-19 positive patients. Particularly in patients with ocular manifestations, there is evidence that the virus may present in tears based on the detection of SARS-CoV-2 in conjunctival swab samples via reverse transcription polymerase chain reaction (RT-PCR). The virus may therefore be transmittable from the ocular surface to a new host via contact with the ocular mucosa, tears, or subsequent fomites.

Conclusions: All healthcare professionals should ask patients about ocular symptoms consistent with SARS-CoV-2, use eye protection such as goggles or face shields as part of the standard personal protective equipment (PPE) for high-risk patients in addition to wearing of masks both by the patient and provider, and should consider tears to be potentially infectious.

Keywords: COVID-19, SARS-CoV-2, conjunctivitis, ocular transmission, ophthalmic precautions

Introduction

SARS-CoV-2 is an enveloped RNA virus of the betacoronavirus family of zoonotic origin, with phylogenetic similarity to other strains such as the severe acute respiratory syndrome coronavirus (SARS-CoV) responsible for the pandemic of 2003. (*1*) There are no studies to date demonstrating ocular transmission of SARS-CoV-2, despite evidence of ocular signs including follicular conjunctivitis in COVID-19 patients. Although primary transmission of COVID-19 appears to be via large respiratory droplets (*2*), the eyes may serve as a source of infection as well as an entryway for transmission.

Ocular Tropism

Belser and colleagues previously described an anatomical theory for ocular transmission of respiratory disease via the nasolacrimal system. (*3*) They suggested that the ocular mucosal immune system, composed of the conjunctiva, cornea, lacrimal glands, and lacrimal drainage system, clears fluid from the eye and transports it to the inferior meatus of the nose. Therefore, if a respiratory droplet is deposited on the surface of the eye, the virus-containing fluid can then enter the respiratory system through the nose, gaining access to the lungs. Respiratory syncytial virus (RSV) is one respiratory illness that has been demonstrated to be primarily spread through the eyes and nose. The eyes, in addition to the nose and upper respiratory system, are home to various receptors that have been linked to viral binding in RSV infection. Therefore, the eyes are a portal of entry for RSV, and the use of eye protection has been demonstrated to reduce the nosocomial spread of RSV. (*3*)

Additional data supporting this theory includes the presence of a viral load in the tear fluid of patients with a variety of respiratory illnesses. This theory has been studied in animal models including mice, ferrets, rabbits, and cotton rats. The viruses tested in these species

included adenoviruses and influenza viruses, and the animal models used intrastromal inoculation or dropwise inoculation onto the cornea. After inoculation, viral loads were detected in tear samples from all animals. These animals were also found to have clinical signs of respiratory viral infection comparable to traditional intranasal inoculation. (*3*) Similar studies have also demonstrated ocular manifestations of feline coronaviruses. In a study of feline CoV positive cats, 90% had antigen detected in the conjunctiva after testing conjunctival swabs, suggesting ocular tissues and tears could be infectious. (*4)* Human studies assessing ocular transmission of coronaviruses are needed to confirm these theories from animal models.

Severe Acute Respiratory Syndrome 2003

Given that SARS-CoV and SARS-CoV-2 are from the same family of coronaviruses and share phylogenetic similarity, it seems likely that findings from the SARS epidemic of 2003 may be demonstrated with COVID-19. SARS-CoV was found to have a primary mode of transmission through direct or indirect contact of infectious droplets with mucous membranes including the eyes, nose, or mouth. (*5*) A study of health care workers infected by contact with intubated patients with confirmed SARS demonstrated a statistically significant relationship (p-value= 0.001) between infection and eye protection. Health care workers who did not properly wear goggles or other eye protection had higher rates of infection compared to those who did, yielding an odds ratio of 7.34. (*6*) This study provided evidence that ocular transmission of respiratory illness may occur without eye protection, particularly in healthcare settings, and highlights that the conjunctiva could have been a portal for entry for SARS-CoV.

Furthermore, a 2003 case series first reported the detection of SARS-CoV in tears after RT-PCR analysis. In this study of 36 patients with probable SARS, three patients were found to have tear samples positive for SARS-CoV via conjunctival swab. (*7*) The samples were collected

at one time point for each patient no more than nine days after onset of fever. This study highlighted the second possibility demonstrating the ocular transmission of SARS: that the tears are direct sources of infectious material. Given there is a viral load in tears, it is possible that contact with the eye and subsequent fomites can lead to inoculation of the virus in other persons much in the way demonstrated by respiratory droplets. The authors from this study recommended against the use of reusable eye equipment such as applanation tonometers and urged the use of goggles in addition to masks, gowns, and gloves for PPE.

Ocular COVID-19 Studies

There are currently few peer-reviewed studies demonstrating ocular manifestations of SARS-CoV-2; most studies published to date originate from China and consist of small case series. A study of 38 COVID-19 positive patients in Hubei Province, China demonstrated that 12 patients reported ocular symptoms and two had positive conjunctival swabs. (*8*) Signs included conjunctival hyperemia, chemosis, epiphora, or increased ocular secretions. The roughly one third of patients who were found to have ocular signs were noted to have more severe manifestations of COVID-19 in general.

Other smaller studies have confirmed that SARS-CoV-2 is shed in tears, albeit with a low incidence. A study at Wuhan University identified 67 laboratory-confirmed or suspected COVID-19 positive patients. Of these patients, three had positive RT-PCR results from conjunctival swab but no ocular symptoms. (*9*) One patient reported conjunctivitis as his first symptom but had a subsequent negative conjunctival swab. Another single-center cross-sectional study at Tongji Hospital in Shanghai, China demonstrated similar results. Of 72 patients with laboratory confirmed COVID-19, two patients reported conjunctivitis and of the two, only one tested positive via RT-PCR from conjunctival swab. (*10*) A prospective interventional study was

also performed at Zhejiang University. The protocol called for two tear and conjunctival collections per patient at intervals of two to three days which were tested via RT-PCR. Of 30 patients enrolled, only one patient had conjunctivitis and he was the sole patient with positive conjunctival swab. (*11*)

A case report from Shenzhen, China highlighted a patient presenting with bilateral ocular redness, foreign body sensation, and tearing without blurred vision on day 13 after developing systemic COVID-19 symptoms. (*12)* The patient then had a slit lamp examination that showed bilateral moderate conjunctival injection, watery discharge, inferior palpebral conjunctival follicles, and tender palpable preauricular lymph nodes consistent with acute viral conjunctivitis. RT-PCR results from conjunctival swab on days 13, 14, and 17 were positive for SARS-CoV-2 but were found to be in lower concentration than respiratory specimens. The patient was treated with ribavirin eye drops and had resolution of ocular symptoms by day 19 of illness.

Similarly, a case report from the National Institute for Infectious Diseases in Rome, Italy confirmed ocular symptoms and SARS-CoV-2 positive RT-PCR conjunctival samples in a COVID-19 positive patient. (*13*) This patient had bilateral conjunctivitis as part of her initial presentation in addition to cough, sore throat, and coryza. Ocular swabs were collected starting on day three of hospital admission and were continued with almost daily frequency until day 27. The conjunctivitis was noted to resolve at day 20 and the patient continued to have daily viral SARS-CoV-2 RNA detection in ocular samples until day 21. Furthermore, this patient had a subsequent positive ocular swab on day 27, which was days after SARS-CoV-2 was undetectable by a nasopharyngeal swab. This suggests that tears can be a potential source of infection early on in the disease course and that the conjunctiva may sustain viral replication for an extended period of time.

Discussion

Although the reported incidence of both ocular symptoms and positive conjunctival swabs for SARS-CoV-2 has been fairly low to date, it is important to note that conjunctival swabs from these small case series may have had insufficient tear material to detect the virus in the samples, thus accounting for the low incidence of positive swabs. However, a paucity of evidence is not enough to rule out the possibility of ocular transmission. Suspected COVID-19 patients could also have experienced ocular symptoms that are being underreported. In order to increase the accuracy of ocular data collection in patients presenting with COVID-19 symptoms, we recommend including questions for the eye portion of the review of systems. Suspected COVID-19 patients should be asked about eye redness, itching, and discharge when a full review of systems is sought by the emergency physician. Emergency physicians should also include COVID-19 in their differential diagnosis for patients presenting with conjunctivitis or isolated ocular signs given the various aforementioned case reports demonstrating conjunctivitis as a first symptom of the disease.

In addition, we recommend informing patients of the possibility of ocular transmission of SARS-CoV-2. This includes informing patients that there has been anecdotal demonstration of COVID-19 seropositivity with isolated ocular symptoms and signs. Regardless of whether they have ocular signs, patients should be instructed to avoid touching the eyes, nose, and mouth to prevent viral spread. They should be advised to discontinue contact lens use if conjunctivitis is diagnosed. In addition, the American Academy of Ophthalmology (AAO) has recently published an article asking all contact lens wearers to consider switching to glasses during this outbreak. (*14)* They urge that reducing contact lens use will reduce the amount of times the patient touches

the eye and can provide a physical barrier between respiratory droplets and ocular mucosa in order to limit ocular transmission of SARS-CoV-2.

For the ophthalmic examination in particular, universal precautions should be followed including standard infection prevention strategies as well as new approaches geared toward COVID-19, as outlined by AAO. (*15*) Disposable equipment such as tonometer tips should be used wherever possible and ophthalmic examination should be performed in a limited number of rooms by a limited number of people. Equipment including slit lamps should be thoroughly wiped down with disinfectant wipes, as should all other surfaces in the patient room. Extra caution should be taken during ophthalmic examinations due to the close proximity of the provider's and patient's face. AAO has recommended the use of N95 masks for ophthalmologists or other physicians providing ophthalmic care to patients potentially infected with SARS-CoV-2 for this reason. (*15*) Given the shortage of PPE, if N95 is not available, a surgical face mask should still be worn by both parties. If the patient's presentation constitutes a slit lamp examination, breath shields should be installed on all slit lamps, and the patient should be instructed to refrain from speaking during the exam. The use of a direct ophthalmoscope should also be limited in the emergency department setting.

Conclusion

SARS-CoV-2 is primarily spread through respiratory droplets, though aerosolized transmission is important as well. The eye may represent a source of transmission through infected tears as well as a window for infection via respiratory droplets or aerosolized particles contacting the conjunctiva. Moving forward, all emergency departments, hospitals, and physician offices should follow precautions to limit potential ocular transmission of COVID-19. (*16*) This is especially important as the number of patients presenting to the emergency department with

ocular complaints is likely to rise given the temporary closure of comprehensive ophthalmologists' and optometrists' offices due to the pandemic. The mitigation strategies outlined above for preventing ocular transmission of COVID-19 go beyond the standard infection prevention protocols currently used in ophthalmology practices and would be recommended for emergency physicians taking care of any eye patients.

References

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020; 283:727-33.
2. Li Q, Med. M, Guan X, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020; 382(13):1199-1207.
3. Belser JA, Rota PA & Tumpey TM. Ocular Tropism of Respiratory Viruses. *Microbiology and Molecular Biology Reviews*. 2013; 77(1):144-156.
4. Seah I & Agrawal R. Can the Coronavirus Disease 2019 (COVID-19) Affect the Eyes? A Review of Coronaviruses and Ocular Implications in Humans and Animals. *Ocular Immunology and Inflammation*. 2020.
5. Peiris JSM, Phil D, Yuen K, et a. The Severe Acute Respiratory Syndrome. *N Engl J Med*. 2003; 349:2431-2441.
6. Raboud J, Shigayeva A, McGeer A, et al. Risk Factors for SARS Transmission from Patients Requiring Intubation: A Multicentre Investigation in Toronto, Canada. *PLoS One*. 2010; 5(5).
7. Loon SC, Teoh SCB, Oon LLE, et al. The severe acute respiratory syndrome coronavirus in tears. *Br J Ophthalmol*. 2004; 88:861-863.

8. Wu P, Duan, F, Luo C, et al. Characteristics of Ocular Findings of Patients with Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol*. 2020.
9. Zhou Y, Zeng Y, Tong Y & Chen C. Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva. *MedRxiv*. 2020.
10. Zhang Z, Chen X, Chen L, et al. The infection evidence of SARS-CoV-2 in ocular surface: a single-center cross-sectional study. *MedRxiv*. 2020.
11. Xia J, Tong J, Liu M, et al. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. *J Med Virol*. 2020;1-6.
12. Chen L, Liu M, Zhang Z, et al. Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. *Br J Ophthalmol*. 2020; 0: 1-4.
13. Colavita F, Lapa D, Carletti F, et al. SARS-CoV-2 Isolation From Ocular Secretions of a Patient With COVID-19 in Italy with Prolonged Viral RNA Detection. *Ann Intern Med*. 2020.
14. Mukamal R, Tuli SS. Coronavirus Eye Safety. *AAO*. 2020.
15. Chodosh J, Holland GN, & Yeh S. Important coronavirus updates for ophthalmologist. *AAO.org*. American Academy of Ophthalmology. 25 April 2020.
16. Mermel LA. Eye protection for preventing transmission of respiratory viral infections to healthcare workers. *Infection Control & Hospital Epidemiology*. 2018; 39:1387.