Peter J. McDonnell, MD

A TIME OF CHANGE: CORONAVIRUS FORCES US TO PIVOT PAGE 4

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focal point

The eye and COVID-19: Providing facts, not fears

Details help pave way for clinicians to provide safe environments for their patients

By Lynda Charters; *Reviewed by Ella Faktorovich, MD*

A GREAT DEAL of information and misinformation has been in the news about coronavirus disease 2019 (COVID-19) since the disease began to spread rapidly in early 2020. The best way to sort out the wheat from the chaff, according to Ella Faktorovich, MD, is to rely on studies in the scientific literature to answer questions about transmission.

"Over 5 million coronavirus cases have been reported worldwide to date," Faktorovich said. "As we begin to reopen our eye care practices, key questions about the virus and the eye need to be answered. This will determine the best ways to resume patient care safely and effectively." Faktorovich is founder of Pacific Vision Institute in San Francisco, California, and the annual San Francisco Cornea, Cataract, and Refractive Surgery Symposium.

Those questions are: What is the incidence of conjunctivitis in patients with COVID-19? Can the ocular surface serve as a reservoir of virus possibly transmissible to others? Can the ocular surface serve as a portal of entry for COVID-19 virus through aerosolized droplets or hand-eye contact? Determining the answers will pave the way for clinicians to provide the safest environment for patients and staff.

To answer the above questions, Faktorovich and her research team performed PubMed, bioRxiv, and medRxiv database searches and analyzed the results of studies in peer-reviewed publications (PubMed) and in scientific preprints (bioRxiv, medRxiv) on COVID-19, coronaviruses, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

TAKE-HOME

- *During examinations, good hand hygiene and a face mask are still important for both the patient and the examiner.*

LITERATURE REVIEW

Two studies, one in the *New England Journal of Medicine* (2020;382:1708-1720) and the other in medRxiv (https://doi.org/10.1101/2020.02.11.20021956), reported that the incidence of conjunctivitis is low (respective ranges, 0.8% in a study of 1099 patients with confirmed virus examined by nonophthalmologists to 4.68% in a study of 534 symptomatic patients with confirmed virus examined by ophthalmologists).

A case report in the *British Journal of Ophthalmology* (http://dx.doi.org/10.1136/bjophthalmol-2020-316304) described a patient who presented with bilateral acute conjunctivitis 13 days after symptom onset. Polymerase chain reaction identified the presence of viral RNA isolated from conjunctival swabs.

A case report in the *Annals of Internal Medicine* (https://doi.org/10.7326/M20-1176) described a patient with viral RNA isolated from conjunctival swabs who presented with conjunctivitis 1 day after symptom onset. COVID-19 was confirmed by nasopharyngeal swab.

A study of 30 patients with confirmed COVID-19 diagnosis in the *Journal of Virology* (https://doi.org/10.1002/jmv.25725) found that only 1 patient had conjunctivitis. Viral RNA was isolated from his conjunctiva. Twenty-nine patients without conjunctivitis were negative for COVID RNA but had sputum tests positive for COVID. Two other reports on medRxiv (doi: https://doi.org/10.1101/2020.02.26.20027938 and doi:

https://doi.org/10.1101/2020.02.11.20021956) also described similar findings.

In one of the reports, 2 of 72 patients with con- firmed COVID-19 diagnosis had conjunctivitis, 1 of whom tested positive for viral RNA in their conjunctiva. Patients without conjunctivitis tested neg- ative for viral RNA in their conjunctiva. Addition- ally, conjunctivitis may be the first presenting sign of COVID-19, with the other—flulike symptoms—quickly following.

The message from this review is that the presence of conjunctivitis should be highly suspicious for the presence of the COVID-19 virus. The examiner should treat these patients as highly infectious, with very high likelihood that they are shedding virus from their ocular surface. However, patients without conjunctivitis, even if they have other COVID-19 symptoms and should also be treated as highly infectious, are unlikely to harbor viral RNA on their ocular surface.

HOW THE VIRUS WORKS

Angiotensin-converting enzyme 2 (ACE2) receptors and TMPRSS2 proteins are the portals on the surface of human cells by which the virus enters the cells. Faktorovich explained that these receptors are part of the renin-angiotensin system that is instrumental in regulating fluid and electrolyte homeostasis.

In addition to their presence in lung, intestine, kidney, blood vessels, heart, and brain tissue, they have been identified in the trabecular meshwork, ciliary body, retina, and on human corneal epithelial and conjunctival cells (Journal of Clinical Medicine https://doi.org/10.3390/jcm9051269; https://doi. org/10.1101/2020.05.09.086165; https:// doi.org/10.1101/2020.05.09.086165). However, this raises the question about the low incidence of conjunctivitis compared with respiratory tract infection. Faktorovich pointed out that the density of ACE2 receptors on the ocular surface may be at least 50% lower than in other tissues (Clinical and Experimental Optometry https://doi.org/10.1111/ cxo.13088).

"In addition to ACE2 and TMPRSS2, coronaviruses may need heparan sulfate coreceptors, such as CD209, for example, on the cell surface to facilitate viral binding, especially for highly pathogenic virus, such as SARS-CoV-2. Such receptors have been detected on the eye. They are located, however, on corneal dendritic cells and conjunctival fibroblasts, which lie beneath the ocular surface and are not immediately accessible to the virus (Current Eye Research https://doi.org/10.3109/02713683.2012.696172). There also are proteins in human tears, lactoferrin and 9-0-acetylated sialic acid, that can bind the virus, thereby potentially preventing its attachment to the ACE2 receptor (Glycobiology https://doi.org/10.1093/ glycob/cwl041)," Faktorovich said.

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"The ocular surface may also be protected by the 'good' bacteria living there and comprising a unique microenvironment called the ocular microbiome," Faktorovich said, referencing a pioneering article by Anthony St. Leger, PhD (Immunity 10.1016/j.im- muni.2017.06.014). In this article, he identifies the microbiome on the ocular surface and its effects on the eye's immune homeostasis and defense against pathogens.

"The eye's microbiome may keep the number of ACE2 receptors low and the amount of lactoferrin high to protect the eye against the virus," said St. Leger, assistant professor of ophthalmology and immunology at the University of Pittsburgh School of Medicine in Pennsylvania.

THE 3 IMPORTANT QUESTIONS

Returning to the previously mentioned questions, the conjunctival incidence in published studies is low. The conjunctivitis found in these patients is a typical mild to moderate viral follicular conjunctivitis with conjunctival injection and watery discharge. Conjunctivitis can be either the first presenting sign of COVID-19 or present later in the disease course, with a duration of 4 to 7 days.

Regarding the question of the eye as a potential viral reservoir, 5 of 6 patients with conjunctivitis had conjunctival swabs positive for viral RNA. Only 1 of 161 patients with COVID-19 and no eye symptoms had a positive conjunctival swab, but that patient had other symptoms of viral infection, including fever and cough.

Regarding the question of the ocular surface being a portal of entry for COVID-19 virus, the potential exists, but that has not been proved. Although the ocular surface has receptors that the virus uses to initiate its attachment to a human cell, other components of the ocular surface may prevent viral attachment and entry.

Faktorovich pointed out that the virus may potentially travel from the ocular surface to the respiratory tract mucosa via the nasolacrimal

duct. A small animal study reported mild interstitial pneumonia after conjunctiva was inoculated with a very large inoculum (https://doi.org/10.1101/2020.03.13.990036). However, viral transmission via the eyes has not been proved in humans.

RECOMMENDATIONS

Faktorovich said she believes that questions about ocular symptoms should be added to the other questions about systemic symptoms asked of patients during screening before they enter the clinic. The ocular questions should include specific references to eye redness, tearing, discomfort, foreign body sensation, and discharge.

"Clinicians have to decide [whether] their clinic can care for patients with a high probability of shedding the virus or whether they should be triaged to a center fully prepared to safely manage such patients," Faktorovich suggested.

Faktorovich also advised physicians to assume a patient has COVID-19 if they have conjunctivitis and that they will be shedding virus from their ocular secretions and are, therefore, contagious. In this case, physicians will need more than hand sanitizer and a mask.

"Clinicians should wear gloves when examining such patients and then immediately discard the gloves using the same precautions as when discarding highly contagious waste material," Faktorovich said. "Clinicians should assume that symptomatic patients have virus in their nasopharyngeal secretions and that the virus likely will be aerosolized when they speak. Therefore, wearing an N95 mask and tight-fitting goggles is essential."

Examiners should also instruct patients to not speak when they are in close proximity to the physician or examiner.

However, if patients have neither systemic nor ocular signs and/or symptoms suggestive of COVID-19, the probability of their harboring the virus on their ocular surface is very low. During examinations of such patients, good hand hygiene and use of a face mask are still important for both the patient and the examiner, but goggles and respirator masks may not be necessary. A recent review in Frontiers of Public Health (2020 https://doi.org/10.3389/fpubh.2020.00155) recommends using chlorhexadine/alcoholic hand rub rather than alcohol alone.

"Hopefully, this fact-based information will help reduce the stress experienced by eye care providers and staff members about how to examine patients," Faktorovich concluded. ■

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ELLA FAKTOROVICH, MD
E: *ella@pacificvision.org*
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Facts vs Myths Surrounding the COVID-19 Virus

MYTH: Any ultraviolet light can kill the coronavirus disease 2019 (COVID-19) virus.

FACT: Although no published data are available yet on how ultraviolet light affects the COVID-19 virus specifically, its effect on other SARS viruses has been studied.

MYTH: Any face covering will protect against the virus.

FACT: Scarves and bandanas made of a thin fabric or a single fabric layer will not be as effective in reducing virus transmission as those that have a filter or are folded 3 to 4 times to provide a better barrier.

MYTH: Wearing gloves will provide protection from the virus.

FACT: Gloves will be effective if the wearer discards them after touching something that may be contaminated. After use, the gloves must be removed properly by peeling them from hands so they are inside out, to prevent contacting the contaminated outer surface.

MYTH: All hand sanitizers are the same, and the higher the alcohol content, the better the sanitizer will work against the virus.

FACT: The alcohol content of commercially available hand sanitizers has to be at least 60% for ethyl alcohol and 70% for isopropyl alcohol to work against the virus. Alcohol content over 80% evaporates too quickly and does not stay on the skin long enough to kill the virus. Hand sanitizers need to specify the type of alcohol they contain. A hand sanitizer showing simply alcohol does not guarantee that it will kill the virus.

MYTH: Wearing shoe covers will provide protection from the virus.

FACT: Shoe covers are effective only if an individual knows the proper way to put them on and remove them to avoid contamination. Lack of training may cause the wearer to inadvertently touch the contaminated area.