PRIMARY eyecare
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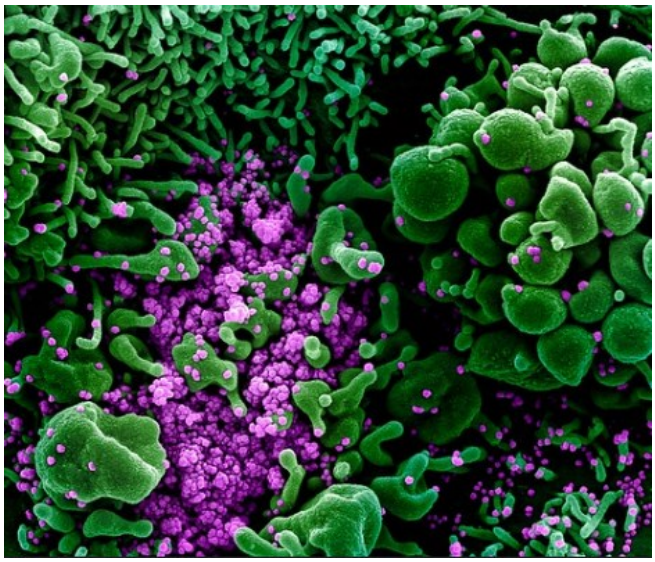
EYES AND COVID-19:
Do we yet see the complete picture?

In a commentary article in Ophthalmology, journal of the American Academy of Ophthalmology, Irene Kho, MD notes the disparate results in papers reporting on ocular involvement in COVID-19 and poses two questions : Is SARS-CoV-2 present in tears or conjunctiva of such patients? And is the virus transmissible through tears or conjunctival secretions?

Dr Kho suggests a number of possibilities for the varying of reverse-transcriptase polymerase chain reaction (RTPCR) of “tears”, “tears and conjunctival secretions,” or “conjunctival swabs.” First, she notes that the diagnostic criteria used by authors vary from article to article. There is also potential variation in the experimental setup. No guidelines exist for a test performed in a research laboratory and few publications on COVID-19 and the eye provide details on the type of laboratory performing testing, operating procedures, or positive and negative controls regarding polymerase chain reaction or viral culture. She also notes that even with proper validation and controls RT-PCR is highly specific and may lack sensitivity. Negative results may be true negatives (virus not in tears or conjunctiva) or false negatives. Dr Kho suggests false negatives could be due to transient presence of virus, inadequate sampling, or timing of sample collection (i.e. the virus is not yet in the tissue). There may be the need for sampling to be performed more than once and separated as has been true for RT-PCR analysis of respiratory samples.



Novel Coronavirus SARS-CoV-2: This scanning electron microscope image shows SARS-CoV-2 (yellow)—also known as 2019-nCoV, the virus that causes COVID-19—isolated from a patient in the U.S., emerging from the surface of cells (blue/pink) cultured in the lab. Credit: National Institute of Allergy and Infectious Diseases-Rocky Mountain Laboratories, NIH

Dr Kho notes that severe acute respiratory syndrome coronavirus, human coronavirus NL63, and other viruses (e.g., adenovirus) provide examples of ocular tropism of respiratory viruses, thus the discovery of SARS-CoV-2 tears or conjunctiva is not surprising. Experiments strongly suggest that the eye is a potential entry portal for these viruses and emphasize the importance of masking and eye protection for practitioners who examine the eye as they sit far closer to patients than the 1-2 metres for social distancing.

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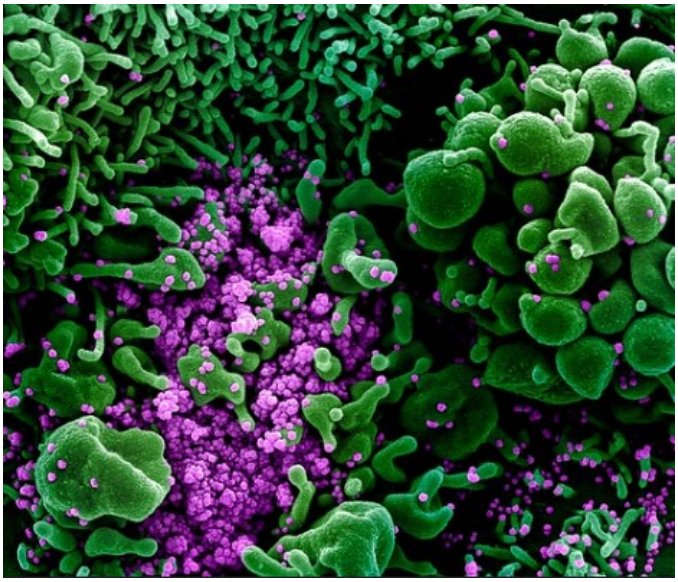
EYES AND COVID-19 – Are there eye specific manifestations of the SARS CoV-2 virus?

In a later review article titled Organ-specific manifestations of COVID-19 infection Gavriatopoulou et al. note that while the SARS-CoV-2 virus presents primarily as a lower tract respiratory infection transmitted via air droplets, the multisystemic nature of the disease is becoming increasingly apparent. The authors postulate that this is related to the tropism of the virus for the ACE-2 receptors located on several different human cells.



Novel Coronavirus SARS-CoV-2
Colorized scanning electron micrograph of an apoptotic cell (green) heavily infected with SARS-COV-2 virus particles (purple), isolated from a patient sample. Image captured and colour-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland.
Credit: National Institute of Allergy and Infectious Diseases, NIH

The Gavriatopoulou et al., 2020 review is made available via the PMC Open Access Subset for unrestricted research re-use and secondary analysis in any form or by any means with acknowledgement of the original source. These permissions are granted for the duration of the World Health Organization (WHO) declaration of COVID-19 as a global pandemic. The abstract and excerpt concerning ophthalmic involvement of the SARS-CoV-2 virus from the PubMed free full text are presented below.

Abstract

Although COVID-19 presents primarily as a lower respiratory tract infection transmitted via air droplets, increasing data suggest multiorgan involvement in patients that are infected. This systemic involvement is postulated to be mainly related to the SARS-CoV-2 virus binding on angiotensin-converting enzyme 2 (ACE2) receptors located on several different human cells. Lung involvement is the most common serious manifestation of the disease, ranging from asymptomatic disease or mild pneumonia, to severe disease associated with hypoxia, critical disease associated with shock, respiratory failure and multiorgan failure or death.

Among patients with COVID-19, underlying cardiovascular comorbidities including hypertension, diabetes and especially cardiovascular disease, has been associated with adverse outcomes, whereas the emergence of cardiovascular complications, including myocardial injury, heart failure and arrhythmias, has been associated with poor survival. Gastrointestinal symptoms are also frequently encountered and may persist for several days. Haematological complications are frequent as well and have been associated with poor prognosis. Furthermore, recent studies have reported that over a third of infected patients develop a broad spectrum of neurological symptoms affecting the central nervous system, peripheral nervous system and skeletal muscles, including anosmia and ageusia. The skin, the kidneys, the liver, the endocrine organs and the eyes are also affected by the systemic COVID-19 disease. Herein, we provide a comprehensive overview of the organ-specific systemic manifestations of COVID-19.

Opthalmological complications

In animals, coronaviruses have been known to cause ocular manifestations including conjunctivitis, uveitis, retinitis and even optic neuritis [150]. In humans, the eye conjunctiva is considered to be a potential site for SARS-CoV-2 transmission [151], but currently there is no direct evidence to support that viral replication can cause injury and inflammation of the conjunctiva or other eye parts.

Among 38 COVID-19 infected patients, in the Hubei province case report series, 12 had ocular manifestations (31.6%). These were more common among patients with more severe systemic disease presentation (respiratory mostly) and blood test abnormalities. They included conjunctival congestion, chemosis or epiphora [152].

A recent protocol used optical coherence tomography to evaluate the retina of patients with COVID-19 infection in 12 adults. Hyper-reflective lesions of the inner plexiform layers and the ganglion cells were seen in all patients, and cotton wool spots and microhemorrhages in the retinal arcade of 4 patients with no effect on visual

acuity or pupillary reflexes [153]. Increasingly emerging data will allow better understanding of the nature and the mechanisms underlying the ocular manifestations associated with SARS-CoV-2.

[Organ-specific manifestations of COVID-19 infection

Maria Gavriatopoulou, Eleni Korompoki, Despina Fotiou, Ioannis Ntanasis-Stathopoulos, Theodora Psaltopoulou, Efstathios Kastritis, Evangelos Terpos, Meletios A. Dimopoulos.(2020).

Clinical and Experimental Medicine https://doi.org/10.1007/s10238-020-00648-x

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EYES AND COVID-19 – Can the cornea resist infection from novel coronavirus?

New research from a team at Washington University School of Medicine in St. Louis suggest the eye's cornea can indeed resist infection from the novel coronavirus. Although it is known that the herpes simplex virus can infect the cornea and spread to other parts of the body in patients with compromised immune systems, and Zika virus has been found in tears and corneal tissue, SARS-CoV-2, the virus that causes COVID-19, does not appear to replicate in the human cornea.

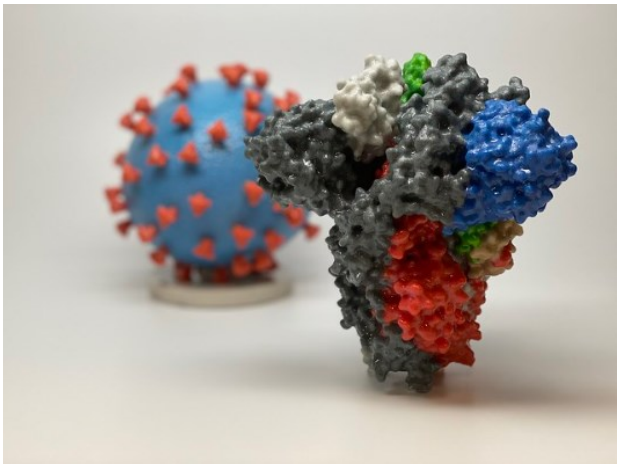
In a news release on the university's website [https://medicine.wustl.edu/news/cornea-appears-to-resist-infection-from-novel-coronavirus/] Jim Dryden reports on the new findings which are published Nov. 3 in the journal Cell Reports.

The researchers have yet to determine, however, whether other tissue in and around the cornea, such as the tear ducts and the conjunctiva, are vulnerable to the virus.

"Our findings do not prove that all corneas are resistant," said first author Jonathan J. Miner, MD, PhD. "But every donor cornea we tested was resistant to the novel coronavirus. It's still possible a subset of people may have corneas that support growth of the virus, but none of the corneas we studied supported growth of SARS-CoV-2."

Miner, an assistant professor of medicine, of molecular microbiology and of pathology and immunology, teamed up with ophthalmologist Rajendra S. Apte, MD, PhD, to study mouse and human corneas exposed to the herpes simplex, Zika and SARS-CoV-2 viruses.

"Some COVID-19 patients get eye symptoms, such as conjunctivitis, but it's not clear that the viral infection itself causes that; it could be related to secondary inflammation," said Apte, the Paul A. Cibis Distinguished Professor in the John F. Hardesty Department of Ophthalmology & Visual Sciences. "The cornea and conjunctiva are known to have receptors for the novel coronavirus, but in our studies, we found that the virus did not replicate in the cornea."



Novel Coronavirus SARS-CoV-2 Spike Protein

3D print of a spike protein of SARS-CoV-2—also known as 2019-nCoV, the virus that causes COVID-19—in front of a 3D print of a SARS-CoV-2 virus particle. The spike protein (foreground) enables the virus to enter and infect human cells. On the virus model, the virus surface (blue) is covered with spike proteins (red) that enable the virus to enter and infect human cells. Credit: US National Institutes of Health

Prior research in human and mouse corneal tissue had demonstrated that Zika virus could be shed in tears, and the researchers wanted to learn whether the cornea might serve as an entry point for SARS-CoV-2. Apte, Miner and their colleagues tested that by exposing the eye tissue to the different viruses and observing whether the viruses could grow and replicate. The scientists also identified key substances in corneal tissue that can promote or inhibit viral growth.

One inhibitor they identified is called interferon lambda. They found that interferon lambda prevented efficient growth of Zika virus and herpes simplex virus in the cornea. But with SARS-CoV-2, levels of the substance had no effect on whether the virus could replicate. It simply could not gain a foothold whether interferon lambda was present or not.

That's reassuring to Apte, also a professor of developmental biology and of medicine, who said it suggests COVID-19 probably cannot be transmitted through a cornea transplant or similar procedures in the eye.

"Our data suggest that the novel coronavirus does not seem to be able to penetrate the cornea," Apte said.

Miner added, however, that because of unknowns involving the tear ducts and the conjunctiva, it's too soon to dismiss the importance of eye protection.

"It's important to respect what this virus is capable of and take appropriate precautions," he said. "We may learn that eye coverings are not necessary to protect against infection in the general community, but our studies really are just the beginning. We need larger clinical studies to help us better understand all the potential routes of SARS-CoV-2 transmission, including the eye."

[*Miner JJ, Platt DJ, Ghaznavi CM, Chandra P, Santeford A, Menos AM, Dong Z, Wang ER, Qian W, Karozichian ES, Phillips JA, Apte RS. HSV-1 and Zika virus but not SARS-CoV-2 replicate in the human cornea and are restricted by corneal type III interferon. Cell Reports, Nov. 3, 2020.* ***DOI****: 10.1016/j.celrep.2020.108339]*

Season's Greetings from the NZAO team