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LETTER TO THE EDITOR

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Receptors modulation on the ocular surface: A novel insight into the ocular infection and disease transmission of SARS-COV-2

To the Editor,

First reported in Wuhan City, Hubei Province, China, in December 2019, coronavirus disease 2019 (COVID-19) has taken a massive toll across the world and has been declared as a global pandemic by WHO on March 11, 2020.[1,2]

The most common ocular manifestation in COVID-19-positive patients is conjunctivitis with a reported prevalence of 0.9%–31.6% in hospitalized COVID-19 patients.[1,2] Keratoconjunctivitis has also been reported as the presenting symptom in a young patient.[3] Reports have shown that the hospitalized patient showed SARS-CoV-2-positive conjunctival swabs up to 21 days from symptom onset, suggesting the ongoing process of replication of the virus in conjunctiva.[4] Variable yields of the organism from conjunctival swabs of COVID-19 cases have been noted in various preliminary studies conducted worldwide. In the study conducted by Wu et al.,[2] out of 38 COVID-19-positive patients, 12 had conjunctivitis, of which 2 conjunctival swabs tested positive for the organism. Conversely, in the study conducted by Liang et al.[5], the virus was isolated from the conjunctival swabs of a minor number of patients, all of whom did not have any ocular manifestations at the time of swab collection. Thus, the ocular secretions and tissue may harbor the organism without necessarily manifesting any ocular symptoms. Also, it is possible that the virus is present in ocular secretions only during very early phase of infection when systemic spread hasn't developed , as lactoferrin, present in tears, may prevent binding of COVID virus to ubiquitous viral receptor heparan sulfate.[5]

Like other betacoronaviruses, SARS-CoV-2 enters into the target cells with the aid of angiotensin-converting enzyme 2 (ACE2) receptor by binding the viral spike protein, followed by its priming by host cell transmembrane protease, serine 2 (TMPRSS2).[6] Studies have revealed abundant gene expression of ACE2 receptor in the human conjunctiva and cornea, together with TMPRSS2 protein.[7] Interestingly, the researchers have found that IL6, a pro-inflammatory cytokine that is high in COVID-19 patients with severe infection, is stimulated by endothelial cells that have receptors for interferons released by infected corneal and conjunctival cells. IL-6 activates other cellular interferon pathways associated with inflammation, whereas ACE2 suppresses them, providing a tight balance between them.[8] As the human eye has its indigenous renin–angiotensin system (RAAS), widely present on the ocular surface formed by conjunctiva and cornea, as well as trabecular meshwork, aqueous humor, iris, ciliary body, retina, it should be thoroughly explored whether the SARS-CoV-2 virus causes anterior or posterior uveitis, iridocyclitis, vitritis, or retinal vasculitis, as anecdotal reports and animal studies seem to suggest.[9] These receptors substantiate the affinity of the virus to the ocular surface that may be directly exposed to the infectious droplets while in close contact with an asymptomatic carrier.

A recent meta-analysis has shown that higher levels of inflammatory markers such as WBC, CRP, PCT, ESR, and IL-6 are associated with the severity of COVID-19.[10] Also, it has been seen that patients with ocular symptoms are more likely to have higher white blood cell and neutrophil counts and higher levels of procalcitonin, C-reactive protein, and lactate dehydrogenase than patients without ocular symptoms.[10] This correlation may justify, to some extent, the finding that conjunctivitis is more common in patients with severe COVID-19 as compared with those with less severe illness.[11,12]

Tear film physiology is an important factor facilitating the transmission of SARS-CoV-2, from the infected ocular surface to the respiratory tract via the lacrimal canaliculi, regardless of the expression of ACE2 receptors on the ocular surface. The expression and distribution of the ACE2 receptors and TMPRSS2 protein on the corneal limbal stem cells may facilitate the dissemination of SARS-CoV-2 from the ocular surface to the other body part via the hematogenous route or through the ophthalmic branch of trigeminal nerve.[13] In ocular surface disorders or in lacrimal drainage obstruction, these viruses can be easily retained in the eyes, triggering an inflammatory response in the form of conjunctivitis or reactive keratoconjunctivitis.[8] Hence, it can be postulated that the eye may play a role in the interpersonal transmission of SARS-CoV-2.

Scientific studies on human ocular SARS-CoV-2 infection need to be further elaborated to identify the specific mediators and receptors of ocular route of transmission of novel coronavirus. Considering the fact that the conjunctiva and cornea of the eye are directly exposed to the infectious droplets and fomites during close contact with infected individuals and while rubbing the eyes with contaminated hands, the potential risk of infection should be taken seriously. Ophthalmologists, due to the nature of their job and close proximity to the patients, are vulnerable to the risk of acquiring the infections. Hence, safety measures in the form of face shields, slit lamp shields, hand gloves, and protective eye goggles should be frequently encouraged in routine practice. It is, thus, recommended that eye protection should be used not only by the healthcare providers but also by those who are susceptible to infection, like immunocompromised patients, geriatric age group, and patients with ocular surface disorders.

AUTHOR CONTRIBUTIONS

Jaya Kaushik: Conceptualization; review and editing (equal); project administration (equal). **Ankita Singh**: Original draft (equal); data curation; review and editing (equal). **Divya Kochhar**: Original draft (equal); data curation; review and editing (equal). **T. Murari**: Review and editing (equal). **Rakesh Shetty**: Original draft (equal); data curation; review and editing (equal). **J. K. S. Parihar**: Supervision; project administration (equal).

CONFLICT OF INTEREST

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