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REVIEW

SARS-CoV-2 and the Eye: A Relationship for a Possible Prognostic Tool in COVID-19 Patients

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Purpose: In December 2019 there was the first report about a new viral infection in Wuhan, China. The new virus was taxonomically designed as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causing the coronavirus disease 2019 (COVID-19). SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor for cell invasion, which is expressed in different tissues including lungs, small intestine, testicles, kidneys, brain, and the eye. The purpose of this article is to review the available information on the relationship of COVID-19 with the eye, as well as evaluating the possible usefulness of ocular diagnostic tests to help in the diagnosis and/or monitoring of patients with this disease.

Methods: We performed a retrospective review of relevant articles from November 2019 to April 2020.

Results: Ocular infection by SARS-CoV-2 is still controversial; nevertheless, the possibility of being a viral reservoir has been suggested, increasing the likelihood of infection. Some reports demonstrated the presence of SARS-CoV-2 in tears, and previously published data suggest a pathological increase of cytokine concentrations in COVID-19 patients; the cytokine release syndrome or cytokine storm contributes to lung and central nervous system damage. The usefulness of tears for the measurement of inflammatory cytokines in various diseases is well known, in particular IL-6, which has been correlated to the severity of COVID-19.

Conclusion: Considering that the IL-6 signaling cascade may be activated in patients with COVID-19, makes it an excellent target for diagnostic and/or monitoring purposes.

Keywords: eye, SARS-COV-2, COVID-19, tear film, IL-6, cytokine release syndrome, tear sampling

Introduction

SARS-CoV-2 Overview

In December 2019, in Wuhan, China, the first outbreak of atypical pneumonia caused by a new beta-coronavirus was reported, which was identified by sample sequencing. Sequencing was performed using samples from airway epithelial cells of patients with pneumonia, where this new coronavirus, known at the time as 2019-nCoV, was isolated. This coronavirus is another clade within the Sarbecovirus subgenus, Orthocoronavirinae subfamily. Unlike the coronaviruses responsible for the Middle East Respiratory Syndrome and the Severe Acute Respiratory Syndrome, MERS-CoV and SARS-CoV respectively, 2019-nCoV is the seventh member of the coronavirus family known to infect humans.[1]

The World Health Organization (WHO) named the disease caused by 2019-nCoV, currently called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), as coronavirus disease 2019 (COVID-19). SARS-CoV-2 shares a 79%

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phylogenetic homology with SARS-CoV, and has a high affinity for angiotensin-converting enzyme 2 (ACE2).[1,2] The interaction of ACE2 with the spike proteins (S1), present in SARS-CoV and SARS-Cov-2, triggers the infection process in host cells. Interestingly, the affinity of SARS-Cov-2 for ACE2 is 10–20 times greater than that of SARS-CoV.[3] The angiotensin-converting enzyme 2 receptor is expressed in different tissues, including the respiratory epithelium, small intestine, testis, kidney, vascular system, and brain;[2] however, its presence has also been reported in different ocular cells.[4,5]

Symptoms of COVID-19 include fever, dry cough, myalgia, gastrointestinal symptoms and dyspnea. Although in most cases the course of the disease is mild or even asymptomatic, serious complications have been described especially in patients with pre-existing comorbidities such as obesity, diabetes, hypertension or cardiovascular diseases, and in patients with a compromised immune system such as those with human immunodeficiency virus (HIV), organ transplants or undergoing cancer treatment.[6]

Methods

Relevant studies were searched in the PubMed database from November 2019 to April 2020, using the following search strategy, considering both clinic and experimental studies: ("SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus" OR "COVID-19" OR "coronavirus disease 2019") AND ("ocular tissues" OR "humans" OR "animal models" OR "ocular manifestations" OR "presence in tears" OR "interleukins"). After removing duplicates, we obtained the full texts of eligible articles to assess their appropriateness.

Epidemiology

Of the 72,314 cases reported by the Chinese Centers for Disease Control and Prevention, as of February 11, 2020, 44,672 (62%) were confirmed cases, 16,186 (22%) suspected cases, 10,567 (15%) diagnosed cases, and 889 (1%) asymptomatic cases.[7] Confirmed cases were classified by RT-PCR positive results or sequencing from nasal and throat samples; suspected cases were defined by at least three different clinical symptoms such as fever (≥38°C), dyspnea, fatigue, headache, sickness, and diarrhea. All reported cases included in the study were confirmed by RT-PCR.[8] Age distribution (n= 44,672) was of 3% (1408 cases) in ≥ 80 years, 87% (38,680 cases) from 30–79 years, 8% (3619 cases) from 20–29 years, 1% (549 cases) from 10–19 years, and 1% (416 cases) in ≤ 10 years. The spectrum of the disease (n= 44,415) was mild in 81% (36,160 cases), severe in 14% (6168 cases) and critical in 5% (2087 cases). The mortality rate was of 2.3% (1023 of 44,672 confirmed cases); however, this may vary depending on age (8% to 49%).[9] As of early April 2020, the WHO had 1,272,953 confirmed cases and 69,428 COVID-19 deaths worldwide. At the time of writing this article, on November 2020, based on the WHO Coronavirus Disease (COVID-19) Dashboard,[10] there were 53,766,728 confirmed cases and 1,308,975 deaths globally. Nevertheless, it is worth mentioning that the distribution of the disease was not (and currently is still not) uniform and homogeneous throughout the world.[11]

The Eye and SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 is transmitted by physical contact, through aerosols (drops of secretions) or contact with contaminated surfaces. The infectious process due to SARS-CoV-2 depends on the interaction of the viral S1 protein with the ACE2 receptor of the host cell. Studies have shown the presence of the renin-angiotensin system in the eye, mainly in structures that participate in aqueous humor dynamics.[4] This system includes the expression of the ACE2 receptor, which hypothetically makes ocular tissues susceptible to SARS-CoV-2 infection by offering a possible route of entry into the body. The information about the presence of the ACE2 receptor in the conjunctiva is not clear,[4,5] and although it calls into question the ocular route as a potential site of entry, it does not rule out the possibility of being a viral reservoir, increasing the possibility of infection. For example, Ma and colleagues determined the presence of the ACE2 receptor and the transmembrane protease of serine-type II or TMPRSS2, in conjunctival cells. In this same study, it was observed that mouse cornea also had ACE2 and TMPRSS2 expression similar to that observed in the intestine, suggesting susceptibility of the cornea to this viral infection, and, therefore, the possibility of infection through the ocular surface.[4] Recent reports indicate that ophthalmologists involved in the diagnosis and treatment of COVID-19 patients were infected with SARS-CoV-2, including from asymptomatic patients.[12] Napoli et al[13] discussed in detail the potential of infection derived not only from the presence of the ACE2 receptor and the TMPRSS2 protein in several ocular tissues, but also from the "dynamism" of the ocular surface system, referring to the possibility of the tear film facilitating the spread of SARS-CoV-2 from the ocular surface to the respiratory and

digestive tract in healthy subjects without dry eye or lacrimal duct obstruction. Furthermore, they discuss a very important aspect considering the current high prevalence of dry eye, which is the possibility that an altered dynamics of the tear film on the ocular surface, with a damaged ocular surface and/or a partial or total drainage impairment, causes a longer permanence of the virus on the ocular surface, promoting greater contamination derived from the presence of epiphora. Due to the potential transmission both from healthy or dry eye subjects, this article reinforces the importance of PPE and other useful strategies recommended for ophthalmologists (there are published articles on both recommendations,[13] and detailed discussions on additional safety recommendations and medical liability,[14] which are not the scope of this manuscript but are highly relevant for the ophthalmology community worldwide). Also, there are comprehensive summaries on safety recommendations for potential scenarios that ophthalmologists may face, subdividing them into confirmed/suspected cases, general, droplet and contact transmission precautions, outpatient clinics and operating room,[15] as well as guidance on risk assessment of cases.[16]

On the other hand, the infectious capacity of different coronaviruses in ocular tissues has been observed in animal models. For example, the feline CoV virus (FCoV) induces in 5% of infected cats a condition called feline infectious peritonitis (FIP),[17] highly contagious by exchange of ocular secretions, that causes eye inflammation, conjunctivitis, anterior granulomatous uveitis, choroiditis associated with retinal detachment, and retinal vasculitis.[18,19] In the case of the murine model, the JMHV strain of the CoV virus shows tropism for different tissues including the eye, with the ability to infect the posterior segment, causing an autoimmune response that leads to degeneration of the neural retina. Target cells are mainly glial cells and retinal pigment epithelium cells. This virus is used as an experimental model for retinal degeneration, called CoV retinopathy.[20,21]

In the study by Chen et al, in 534 patients with COVID-19, the reported ocular symptoms were conjunctival congestion in 3.8%, increased conjunctival secretion in 10.6%, ocular pain in 5.7%, foreign body sensation in 19% and increased tearing in 13.3%, and 31.2% of patients reported coexisting dry eye. In this same group, few patients reported a history of eye disorders (conjunctivitis 7.6%, keratitis 4.2%, and xerophthalmia 8%).[22] A summary of this representative study can be found on Table 1.

Table 1 Summary of COVID-19-Related Ocular Findings in a Cross-Sectional Study

Characteristics	All Patients with COVID-19 (N=534)
Conjunctival congestion	3.8%
Conjunctival secretion increase	10.6%
Ocular pain	5.7%
Foreign body sensation	19%
Increased tearing	13.3%
Dry eye	31.2%
Conjunctivitis	7.6%
Keratitis	4.2%
Xerophthalmia	8%

Note: Data from (Chen L, et al).[22]

Wu P, et al (2020)[9] analyzed 38 patients with COVID-19, of whom 25 (65.8%) were male, with a mean age of 65.8 years. From these patients, 28 (73.7%) were positive for SARS-CoV-2 in RT-PCR of samples taken with nasopharyngeal swabs, and of these, 2 patients (5.2%) showed positive results for SARS-CoV-2 both in conjunctival and nasopharyngeal samples. Of the 38 patients, only 12 presented ocular manifestations such as epiphora, conjunctival congestion, or chemosis, besides the more severe systemic manifestations. Using univariate analysis, it was observed that patients with ocular symptoms were 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. However, this is a small sample that precludes drawing definitive conclusions.[23]

A meta-analysis performed by Sarma et al (2020) in COVID-19 patients,[24] showed that 3.17% of COVID-19 patients had conjunctivitis/red eye (95% CI 1.165 to 6.127); however, only 0.70% of patients (95% CI 0.0358–-3.269) had conjunctivitis as the first symptom of the disease, and only 1.94% patients (95% CI 0.743–4.113) were positive for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR) in tear or conjunctival samples. Despite the presence of the virus in the tear film, only 33.3% showed signs of conjunctivitis/conjunctival chemosis or red eye. Therefore, the absence of ocular symptoms does not mean that the virus is not present in the tear film and, conversely, the appearance of ocular symptoms is not an indication of the presence of the virus in tears. However, a study by Cheema et al[25] reported keratoconjunctivitis as the primary symptom in a COVID-19 patient. In this case, the patient showed red eye with constant tearing prior to respiratory symptoms, accompanied by fever. In addition, conjunctival samples

showed the presence of SARS-CoV-2. Regardless of these discrepancies, health personnel should take all the necessary precautionary measures whether or not patients have ocular symptoms, since negativity rates may not reflect a true absence of the virus due to the extensive use of different topical eye medications. Several eyedrops used for a wide variety of disorders have an antiviral effect, especially preservatives used in the vast majority of eye medications and several ingredients used for dry eye treatment, to name a few. For this reason, studies need to recruit patients who do not use eye drops, or who are using eyedrops that lack antiviral activity, to exclude potential bias that may conduct to false negatives.[26]

Tear Samples for the Diagnosis and Management of COVID-19

Although the transmission of the virus through tears is controversial, the presence of viral RNA in the tears of patients with severe acute respiratory syndrome has been determined by quantitative reverse transcription-polymerase chain reaction (RT-qPCR), so there is a possibility of viral detection in tears in the early phase of the disease, which could be a vital tool to identify potential cases of COVID-19.[27] This observation becomes relevant considering the report by Cheema et al[25] that determined the viral load in the tears of a COVID-19 patient. On the other hand, Seah et al[28] observed that from a total of 17 COVID-19 patients analyzed from day 3 to 20 after diagnosis, there were no ocular symptoms or viral load detection in tears, suggesting a low risk of ocular transmission. Nevertheless, it is necessary and imperative to perform more tests with a larger number of patients, to clarify the presence of SARS-CoV-2 in tears.

Regardless of the presence of the virus on the ocular surface, the usefulness of tears for the measurement of inflammatory cytokines in various diseases is well known, in particular IL-6, due to the role it plays in the severity of COVID-19. Therefore, it is relevant to study the behavior of this easily accessible biomarker in patients with COVID-19. The presence of serum IL-6 has been correlated with respiratory failure, severe respiratory syndrome, and subsequent clinical sequelae. The binding of IL-6 to the soluble form of its receptor, sIL-6R, activates the JAK-STAT3 pathway in cells that do not express IL-6R, such as endothelial cells. Activation of this pathway exacerbates cytokine release syndrome (CRS), due to the release of proteins such as vascular endothelial growth factor (VEGF), monocyte-attracting chemo protein-1 (MCP-1), IL-8 and even IL-6, and reduces the expression of E-cadherin in endothelial cells. Both the release of VEGF and the decrease of E-cadherin increase vascular permeability, inducing the hypotension and pulmonary dysfunction observed in SARS.[29–32]

It is important to note that the tendency towards thrombosis in COVID-19 patients precludes venous blood sampling by puncture, and catheter blood sampling may not be adequate for several reasons. For example, it is associated with hemolysis (especially in acute care settings such as intensive care units), and there are some tests that require larger amounts of blood or where accuracy is decreased if catheter-drawn blood is used.[33] In these cases, capillary collection may be an option. Nevertheless, poor circulation, the small volumes involved and the variability in sample quality, among others, make capillary sampling deficient in some instances.[34]

Thus, given the severity of COVID-19 and the relevance of biomarkers evaluation for disease monitoring and prognosis, tear sampling may be a non-invasive, easily accessible, and appropriate technique for widespread use. The collection of tears may be complicated due to difficulty in tear film sampling, but several authors have shown consistent and reproducible results,[35,36] even in children.[37] There are multiple examples of successful tear testing for diseases like systemic sclerosis, cancer, and rosacea, among others.[38–41] Tear sampling may be direct or indirect; each method has advantages and disadvantages and the selection depends on the subsequent analysis (for an exhaustive review, see Rentka A, 2017).[42]

There are several methods to evaluate cytokines in the tear film. Bead-based multiplex assays have been successfully applied to tear samples to analyze cytokines in different diseases,[35,43] with the availability of commercial kits.[44] Tear sampling techniques using a Schirmer strip, help to achieve standardized and reliable results with an improved signal-to-noise ratio for microwell plate assays.[45] Even more, there is a publication that reported standard operating procedures to provide reliable information on tear cytokines that allows to interpret and compare clinical trial outcomes in dry eye disease (DED),[46] that can be used as a reference to develop widespread testing for COVID-19. Interestingly, IL-6 is one of the main cytokines that participate in dry eye,[46] and it also plays a key prognostic role in COVID-19.

Perspectives

The possibility of measuring different biomarkers in easily accessible secretions without the need for invasive maneuvers allows the detection of proteins that may serve as prognosis markers in patients with COVID-19. Therefore, tear samples (accessible with a small swab, Schirmer strip, or capillary tubes) are a potential tool for the detection of IL-6 in COVID-19 patients.[28,46] It is known that different types of cytokines are released during the CRS, so the measurement of other cytokines such as IL-2, IL-7, IL-1B, GCSF, IFN-α, TNF-α, and TGF-β could provide information on the progress and response to treatment, allowing a better management strategy for patients in a timely manner.[29]

Finally, information about CRS, especially regarding IL-6 and activation of its signaling cascade in patients with COVID-19, makes this cytokine an excellent pharmacological target for its treatment.[32] As previously stated, the presence of this cytokine in tears makes it a potential diagnostic, prognostic, and monitoring marker.[46]

Conclusions

Considering the studies related to the presence of SARS-CoV-2 in ocular tissues, only few reports (around 5%) have determined the presence of viral RNA. The scarce information about the infective capacity of SARS-CoV-2 in the ocular tissue does not rule out the possibility of the ocular surface being a reservoir for the virus, with a high infective capacity. It also does not exclude the possibility that SARS-CoV-2 uses the ocular surface as a route of infection, so it is imperative to conduct more studies to clarify this possibility.

The fact that different studies have shown efficiency in the treatment of patients with COVID-19 using different cytokine blockers or modulators, suggests the importance of these proteins in the treatment of the disease. However, these cytokines, mainly IL-6, could also represent a potential tool both for monitoring and prognosis of the clinical status.

Disclosure

Dr Rosario Gulias-Cañizo is an employee at Alcon Laboratories, outside the submitted work. The authors report no other conflicts of interest in this work.

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