Review Article

"Covid – 19 Revisited" With Ocular Manifestations

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Abstract

In December 2019, a novel corona virus (CoV) pandemic, caused by the severe acute respiratory syndrome corona virus – 2 (SARS-CoV-2) emerged from China. This virus causes the corona virus disease 2019 (COVID-19). The ocular implications of human CoV infections have not been widely studied. There are few reports on the association of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) with ocular abnormalities. Understanding ocular manifestations of patients with COVID-19 by ophthalmologists and others may facilitate the diagnosis and prevention of transmission of the disease. The review article will also highlight CoVs and their associated ocular infections. We hope that this article will serve as further research into the ocular implications of human CoV infections. As the current pandemic continues, a better understanding of the virus will emerge, hopefully with more emphasis on research into the relationship between human CoVs and the eye. This understanding will not only help us to guide infection control measures but can also provide insights on the feasibility of using ocular tissue or even tears as a medium of diagnosis. Meanwhile, ophthalmologists and other health-care workers should continue to work on the side of caution and continue to prevent the possible transmission of CoVs through ocular tissue.

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Introduction

Since December 2019, coronavirus disease 2019 (COVID-19) has been reported among patients in China. Currently, the disease is quickly spreading worldwide. The pathogen of COVID-19 is a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), identified as a member of the coronaviridae family. Another coronavirus, named SARS-CoV-1, was responsible for severe acute respiratory syndrome. Compared with SARS-CoV-1, SARS-CoV-2 has a similar binding receptor and similar pathologic features.[1,2] Although there is no direct evidence that SARS-CoV-1 replication results in conjunctivitis and other ocular diseases, reports have emphasized the eye as a potential site for virus transmission.[3]

Similarly, SARS-CoV-2 transmission through the eye has been suspected. Nevertheless, there are no reports in the medical literature at this time, to our knowledge, that identifies a direct relationship between SARS-CoV-2 and the eye. Researchers have not reported ocular abnormalities nor have they stated in the medical literature if there was conjunctivitis or viral presence detected in the tears of patients with COVID-19. The objective of this study was to evaluate ocular involvement systematically in patients highly suspected of having or confirmed to have COVID-19.

Coronaviruses (CoVs) are viruses that have been known to affect birds and mammals.[4] CoVs rose to public prominence after the outbreak of the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003.[5] The SARS-CoV outbreak was reported to have infected more than 8000 people and resulted in 774 deaths globally.[6] Since then, the Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) has also been in the public spotlight.[7] In December 2019, a new CoV pandemic, caused by the Severe Acute Respiratory Syndrome Coronavirus – 2 (SARS-CoV-2) started in the city of Wuhan, China. This new pandemic has spread across the globe rapidly, affecting 11,598,155 people in 215 countries or territories or areas as of the 6th of July 2020. On the 30th of January, the World Health Organization (WHO) has declared a public health emergency of international concern (PHEIC).[8,9] A set of recommendations for personal protective equipment (PPE) based on the experience of MERS-CoV and SARS-CoV have been released.[10] This set of recommendation includes wearing goggles or face shield for protection against ocular transmission of the CoV. Interestingly, the evidence of ocular transmission has not been well studied. However, CoV ocular infection has been well established in various animals. In some cases, such as CoVs which affect the murine and feline orders, they can cause sight-threatening ocular complications. Such evidence suggests that CoVs can shed and even infect ocular issues. More research has to be done to understand the ocular manifestation of human CoVs. This review article will first introduce the structure of the CoV and the various hosts that they have been discovered in. The article will then highlight the currently available evidence for CoV infection of ocular tissue in humans. Finally, it will attempt to bridge the knowledge gap by featuring known ocular infections by various CoVs in animals such as mice (murines) and cats (felines). We hope that this article will serve as a starting platform for research into human CoV infections and its ocular implications.

Etiology

CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (corona is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily Orthocoronavirinae of the Coronaviridae family (order Nidovirales) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the

betaCoV genus divides into five sub-genera or lineages.[11] Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs.

Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. To date, seven human CoVs (HCoVs) capable of infecting humans have been identified. In general, estimates suggest that 2% of the populations are healthy carriers of a CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections.[12]

This, SARS-CoV-2 belongs to the betaCoVs category. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat. Furthermore, these viruses can be effectively inactivated by lipid solvents including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid and chloroform except for chlorhexidine.

Epidemiology

Data provided by the WHO Health Emergency Dashboard (July 6, 11.00 pm CET) reported 11,598,155 confirmed cases worldwide since the beginning of the epidemic. 58,735 (1%) cases have been fatal.[13]

In USA, 2,985,897 cases confirmed clinically and in the laboratory, and 132,610 deaths are reported. In addition to USA, there are 8,612,258 confirmed cases in 214 other countries or territories or areas. The countries with most cases are Brazil (1,604,585) and India (704,607). The most up-to-date source for the epidemiology of this emerging pandemic can be found at the following sources:

- The WHO Novel Coronavirus (COVID-19) Situation Board
- The Johns Hopkins Center for Systems Science and Engineering site for Coronavirus Global Cases COVID-19, which uses openly public sources to track the spread of the epidemic.

Transmission

Because the first cases of the COVID-19 disease were linked to direct exposure to the Huanan Seafood Wholesale Market of Wuhan, the animal-to-human transmission was presumed as the main mechanism. Nevertheless, subsequent cases were not associated with this exposure mechanism. Therefore, it was concluded that the virus could also be transmitted from human-to-human, and symptomatic people are the most frequent source of COVID-19 spread. Moreover, there are suggestions that individuals who remain asymptomatic could transmit the virus. This data suggests that the use of isolation is the best way to contain this epidemic.

As with other respiratory pathogens, including influenza and rhinovirus, the transmission is believed to occur through respiratory droplets from coughing and sneezing. Aerosol transmission is also possible in case of protracted exposure to elevated aerosol concentrations in closed spaces. Analysis of data related to the spread of SARS-CoV-2 in China seems to indicate that close contact between individuals is necessary. The spread, in fact, is primarily limited to family members, healthcare professionals, and other close contacts.

Based on data from the first cases in Wuhan and investigations conducted by the China CDC and local CDCs, the incubation time could be generally within 3 to 7 days and up to 2 weeks as the longest time from infection to symptoms was 12.5 days (95% CI, 9.2 to 18).[14] This data also showed that this novel epidemic doubled about every seven days, whereas the basic reproduction number (R0 - R naught) is 2.2. In other words, on average, each patient transmits the infection to an additional 2.2 individuals. Of note, estimations of the R0 of the SARS-CoV epidemic in 2002-2003 were approximately 3.[15]

It must be emphasized that this information is the result of the first reports. Thus, further studies are needed to understand the mechanisms of transmission, the incubation times and the clinical course, and the duration of infectivity.

Pathogenesis

The virus enters the body through mucous membranes like oral cavity, nasal mucosa, conjunctiva and replicates inside the host cells. Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings and increased level of plasma pro-inflammatory cytokines.
The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, combined with the incidence of ground-glass opacities, and acute cardiac injury. Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection. Cytokines exert their effects in tissues locally or circulate in the blood and lymph. Cytokine storms occur in viral infections when large amount of cytokines are produced. This can worsen a patient's condition and cause multi-organ failure, which is frequently fatal. Cardinal features of a cytokine storm include unremitting fever, cytopenia, massive increases in ferritin, high erythrocyte sedimentation rate (ESR) and Adult Respiratory Distress Syndrome (ARDS).During infection from SARS-CoV-2, which causes COVID-19, this cytokine storm is associated with increased levels of interleukins IL-2, IL-7 and other cytokines. Thrombocytopenia is also a marker of a fatal outcome.Cytokine storms can be severe in young patients who have more efficient immune systems and responses than older patients.

Differential Diagnosis

The symptoms of the early stages of the disease are nonspecific. Differential diagnosis should include the possibility of a wide range of infectious and non-infectious (e.g., vasculitis, dermatomyositis) common respiratory disorders.

- Adenovirus
- Influenza
- Human metapneumovirus (HmPV)
- Parainfluenza
- Respiratory syncytial virus (RSV)
- Rhinovirus (common cold)

For suspected cases, rapid antigen detection, and other investigations should be adopted for evaluating common respiratory pathogens and non-infectious conditions.

Human Coronaviruses and The Evidence for Ocular Manifestation

There are seven types of CoVs known to infect humans: 229E (alphacoronavirus), NL63 (alphacoronavirus), OC43 (betacoronavirus), HKU1 (betacoronavirus), MERS-CoV (betacoronavirus),SARS-CoV (betacoronavirus), and the most recent SARS-CoV-2. It is widely agreed that these CoVs cause respiratory tract infections and patients can present with a large spectrum of clinical manifestations. 229E, NL63,OC43, and HKU1 have been known to cause mainly self-limiting upper respiratory tract infections which present with symptoms such as running nose, sore throat, fever, and cough.[16] However, in immunocompromised states or underlying cardiopulmonary disease, they can cause pneumonia or bronchitis.[17] On the other spectrum, the SARS-CoV,MERS-CoV, and SARS-CoV-2 have been known to cause life-threatening respiratory failure.[18]

Ocular manifestations of COVID-19 are overall rare in the published literature. Only 9 (0.8%) out of 1,099 patients from 552 hospitals across 30 provinces in China were reported to have "conjunctival congestion."[19]

A recent case series reported ocular symptoms in 12 (31.6%) of 38 hospitalized patients with COVID- 19 in Hubei province, China. These 12 of 38 patients had conjunctival hyperemia (3 patients), chemosis (7 patients), epiphora (7 patients), or increased secretions (7 patients). Of note is that one patient who had epiphora presented with epiphora as the first symptom of COVID-19. Of those with ocular manifestations, 2 (16.7%) patients had positive results of SARS-CoV-2 on reverse-transcriptase polymerase chain reaction (RT-PCR) by a conjunctival swab as well as by nasopharyngeal swabs. Only one patient in this study presented with conjunctivitis as the first symptom.[20] The authors noted that patients with ocular symptoms had higher white blood cell and neutrophil counts, C-reactive protein, and higher levels of procalcitonin and lactate dehydrogenase compared to patients without ocular abnormalities.

Out of 30 hospitalized patients with COVID-19 tested by Xia et al., one patient had conjunctivitis and was also the sole patient in the study to test positive for SARS-CoV-2 in ocular secretions by a conjunctival swab. This patient did not have a severe fever or respiratory symptoms at the time of testing.[21] There have been no reports of COVID- 19 patients experiencing blurred vision, subconjunctival hemorrhage, eyelid ecchymoses, conjunctival scarring, keratitis, or pseudomembrane formation.

The potential of infection through ocular secretions is currently unknown, and it remains unclear how SARS-CoV-2 accumulates in ocular secretions. Possible theories include direct inoculation of the ocular tissues from respiratory droplets or aerosolized viral particles, migration from the nasopharynx via the nasolacrimal duct, or even hematogenous spread through the lacrimal gland.[22]

In a study done on 30 COVID positive patients in Zhejiang[23] one patient was noted to have conjunctival involvement and conjunctival swabs taken early in the course of the disease were positive for SARSCoV2 by RT-PCR. Wu P et al. from Guangzhou[24] reported conjunctival congestion in 12 out of 38 patients, with conjunctival swabs of 2 patients showing positivity for SARSCoV2 by RT-PCR. This study showed conjunctival involvement in more severely ill patients with COVID-19, unlike the previous study 23 which showed involvement in non-severe COVID-19 patients.

While the above two studies raised possibility of transmission of virus through the tears of these patients, another study done on serial tear samples of 17 patients in Singapore,[25] could not demonstrate RT-PCR positivity of tear samples at any time point, though one patient had conjunctival redness during the course of the illness.

Treatment / Management

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock.

Treatment to combat cytokine storms requires support including management of the ARDS. As during previous pandemics (Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome), corticosteroids are not routinely recommended and might exacerbate COVID-19-associated lung injury. However, in hyperinflammation, immunosuppression is likely to be beneficial. Tocilizumab (IL-6 receptor blockade, licensed for cytokine release syndrome), has been approved in patients with COVID-19 pneumonia and elevated IL-6 in China. Role of plasma therapy as the new emerging treatment modality has shown promising results.

Treatment Of Conjunctivitis during Covid-19 Pandemic

As with other viral infections, ocular manifestations of COVID-19 are presumed to be self-limited and can be managed with symptomatic care.

As of March 18, 2020, the American Academy of Ophthalmology has urged all ophthalmologists to provide only urgent or emergent care to reduce the risk of SARS-CoV-2 transmission and to conserve disposable medical supplies. In the absence of significant eye pain, decreased vision, or light sensitivity, many patients can be managed

remotely with a trial of frequent preservative-free artificial tears, cold compresses, and lubricating ophthalmic ointment. A short course of topical antibiotics can be added to prevent or treat bacterial superinfection based on the patient's symptoms and risk factors (e.g. contact lens wear).[26] For analgesia, non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen are better avoided as they have been shown to worsen the systemic effects of COVID infection, oral Paracetamol may be added instead.

Although preliminary studies suggest that the risk of viral transmission through ocular secretions is low, large-scale research has not yet been done, and new data is emerging daily. Healthcare providers are, therefore, still urged to wear proper protection of the eyes, nose, and mouth when examining patients (see below). It has been suggested that ocular transmission of the COVID-19 virus may occur.[27]

Eye care providers and technicians may be more susceptible to infection due to the nature and proximity of the ophthalmic examination.[28] Eye care providers are encouraged to use slit lamp breath shields and should counsel patients to speak as little as possible when sitting at the slit lamp to reduce the risk of virus transmission. Disinfection and sterilization practices should be employed for shared clinic equipment such as tonometers, trial frames, pinhole occluders, B-scan probes, and contact lenses for laser procedures.[29]

Sterilization of Equipment

- The slit-lamp shields are disinfected with 70% ethyl alcohol after each patient. 70% ethyl alcohol has been shown to reduce coronavirus infectivity.[30]
- Slitlamps, B-scan probes, and any other tools are similarly cleaned with 70% ethyl alcohol.
- Goldman tonometers are sterilized with a 10% diluted sodium hypochlorite solution, which inactivates coronaviruses.[31]

Prevention

Preventive measures are the current strategy to limit the spread of cases. Because this pandemic will increase as long as R0 is greater than 1 (COVID-19 is 2.2), control measures must focus on reducing the value to less than 1.

Preventive strategies are focused on the isolation of patients and careful infection control, including appropriate measures to be adopted during the diagnosis and the provision of clinical care to an infected patient. For instance, droplet, contact, and airborne precautions should be adopted during specimen collection, and sputum induction should be avoided.

The WHO and other organizations have issued the following general recommendations:

- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash your hands frequently, especially after contact with infected people or their environment.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.
- Strengthen, in particular, in emergency medicine departments, the application of strict hygiene measures for the prevention and control of infections.
- Individuals who are immunocompromised should avoid public gatherings.

The most important strategy for the population is to frequently wash their hands and use portable hand sanitizer and avoid contact with their face and mouth after interacting with a possibly contaminated environment.

Healthcare workers caring for infected individuals should utilize contact and airborne precautions to include PPE such as N95 or FFP3 masks, eye protection, gowns, and gloves to prevent transmission of the pathogen.

Conclusion

As CoVs can cause ocular infection across different animals, the possibility of SARS CoV-2 having ocular implications cannot be ignored. Given the anecdotal nature of evidence regarding SARS CoV- 2 transmission through ocular tissue, more research has to be done to confirm its ability to infect ocular tissue and its pathogenic mechanisms. As the current pandemic continues, a better understanding of the virus will emerge, hopefully with more emphasis on research into the relationship between human CoVs and the eye. This understanding will not only help us to guide infection control measures but can also provide insights on the feasibility of using ocular tissue or even tears as a medium of diagnosis. Meanwhile, ophthalmologists and other health-care workers should continue to work on the side of caution and continue to prevent the possible transmission of CoVs through ocular tissue.

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