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EC OPHTHALMOLOGY
Mini Review

Coronavirus and Eye Involvement

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Received: March 26, 2020; **Published:** May 29, 2020

Abstract

Coronavirus disease (COVID-19) has rapidly emerge as a global health threat. The name COVID-19 which stands for coronavirus disease 2019 was proposed by the World Health Organization. The virus was officially named a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The incubation period is from 2 to 14 days but it could be up to 24 days in rare cases. Symptoms of the infection include: fever, dry cough, fatigue, myalgia, dyspnea, anosmia, dysgeusia and diarrhea. The role of the eye transmitting COVID-19 has been intensively discussed. Although the conjunctiva is directly exposed to extraocular pathogens and the mucosa of ocular surface and upper respiratory tract is connected by nasolacrimal duct and share same entry receptors for some respiratory viruses. The eye is rarely involved in human CoVs infection, conjunctivitis is quite rare in patients withs SARS-CoV and SARS-CoV-2 infection. Coronavirus gender that affect the eye are the following: NL63 (alphacoronavirus). The ocular implications of human coronavirus infections have not been widely studied, the virus can be present in the conjunctiva and in the tear but in the information available today have some limitations, like insufficient sample size, the tear and conjunctival secretions are limited so sample concentration might be insufficient for RT-PCR detection. However, pathogens exposed to the ocular surface might be transported to nasal and nasopharyngeal mucosa by constant tear rising through lacrimal duct and then cause respiratory tract infection. In this article we highlight the current available evidence for coronavirus infection of ocular tissue in humans even though further research has to be done.

Keywords: *Coronavirus Disease (COVID-19); Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)*

Introduction

In December 2019 multiple cases of pneumonia of unknown etiology were detected in Wuhan City, Hubei Province, China. The clinical picture resembled a viral pneumonia. The 2019 novel coronavirus was identified in samples of bronchoalveolar lavage fluid [2,12,14].

The SARS-CoV-2 virus is a betacoronavirus, like MERS-CoV and SARS-CoV. The coronavirus family has become the major pathogens of emerging respiratory disease outbreaks that range from common cold to severe diseases such as Severe Acute Respiratory Syndrome (SARS) and Middle east respiratory syndrome (MERS). All three of these viruses have their origins in bats [9].

On February 11, 2020, the World Health Organization announced that the disease caused by the enveloped RNA betacoronavirus SARS-CoV-2 was "COVID-19" which is the acronym of "coronavirus disease 2019".

On January 30, 2020 the rapid spread of COVID-19 to multiple countries was declared a Public Health Emergency of International Concern by the World Health Organization, and in March 11, 2020 the disease was characterized as a pandemic when more than 118,000 cases in 114 countries had been diagnosed [9].

The Human Coronavirus associated to the presence of conjunctivitis is the alphacoronavirus NL63. It is primarily associated with young children, the elderly and immunocompromised patients with respiratory illness [3]. The infection can seem like a common cold, characterized by cough, rhinorrhea, tachypnea, fever and hypoxia, and resolve on their own [3,6].

Transmission

Early on, many of the patients at the epicenter of the outbreak in Wuhan, China had some link to a large seafood and live animal market, suggesting animal-to-person spread. Subsequent cases were associated with person-to-person transmission.

Symptomatic people are the most frequent source of COVID-19 spread. The possibility of transmission before symptoms develop seems to be infrequent, although it cannot be excluded. 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 [9,11].

The median incubation period is 4 days (range 2 to 7). The transmission is believed to occur through respiratory droplets from coughing and sneezing, close contact between individuals is necessary. Aerosol transmission is also possible in case of protracted exposure to elevated aerosol concentrations in closed spaces. On average, Each infected person transmits the infection to an additional 2.2 individuals [9,13].

In the ophthalmology practice healthcare workers may be particularly susceptible to the infection because of the proximity between the patient and the ophthalmologist during examination. Currently there is not enough information to determine if SARS-CoV-2 replicates in the conjunctiva and therefore determine the risk of transmission through the ocular surface. There are isolated reports of the detection by Real Time Polymerase Chain Reaction (RT-PCR) of novel coronaviruses in tears and conjunctival secretions of SARS–CoV-2-infected patients with conjunctivitis but RNA has not been found in the absence of conjunctivitis. Controversy will continue for now as there are case reports of health care providers infected with SARS–CoV-2 wearing a mask N95 but no eye protection [8,14-16].

Systemic and eye presentation

The illness can present with different symptoms . Fever, cough , shortness of breath and fatigue are the most common symptoms associated to the infection, Gastrointestinal symptoms including nausea, vomiting and diarrhea have been seen in patients suffering from COVID-19 but are not the norm. Other described symptoms include conjunctival injection, nasal congestion, sore throat, headache. Anosmia and dysgeusia have been associated to COVID-19 and some societies have recommended to include these symptoms as part of the screening tools for the illness [5,12,13,17].

There is now growing evidence that human to human transmission is occurring Among close contacts and there are reports of more than 1700 healthcare professionals having been infected with 6 deaths including one ophthalmologist. Of the affected health workers, one was part of the experts task force who visited Wuhan , and he has reported that despite being fully gowned with protective suit and N95 respirator he was still infected by the virus with the first symptom being unilateral conjunctivitis, followed by the development of fever a few hours later. Since his report, healthcare professionals in China have been urged to use eye protection when they are in close contact with patients [18].

Consequences in the eyes

There are 4 -7 type of CoVs known to infect humans , but only the NL63 (alphacoronavirus) can affect the eyes: NL63 (alphacoronavirus). In 2004 toward the end of the SARS-CoV crisis, a new human coronavirus was identified. This was the HCov-NL63. The virus was first isolated from a 7 month old child before being identified in seven additional individuals. During the infection the child has symptoms and physical examination findings of bronchiolitis and conjunctivitis [10].

In 2004, tear samples collected from 36 suspected SARS-Cov patients were sent for RT-PCR for the SARS-CoV, the findings of this study suggested that SARS-CoV can be present in tears and emphasized the need for appropriate precautions to prevent transmission through ocular tissues and secretions. However, up till today, it is unclear how SARS-CoV can end up in tears. Proposed theories include the conjunctiva being the direct inoculation site of SARS-CoV from infected droplets, the migration of upper respiratory tract infection through the nasolacrimal duct or even hematogenous infection to the lacrimal gland [10].

However, from genomic and structural analyses it has been reported that the SARS-CoV-2 has a similar receptor binding-motif as SARS-CoV, which allows it to infect host cells via the angiotensin-converting enzyme 2 (ACE-2). Interestingly, the renin-angiotensin system (RAS), apart from its well-known endocrine role in blood pressure regulation, also has complicated autocrine function within specific tissues. The human eye has its own intraocular RAS, a system that has been the interest of many projects focusing on developing anti-glaucomatous drugs. ACE-2 has been found in the aqueous humor. However, the expression of ACE2 has to be conducted [10].

THE SARS-CoV-2:

- It can cause conjunctivitis: possibly transmitted by aerosol contact with conjunctiva.
- It can star with an inflammation of the eye followed by a fever and a buildup of mucus in the nose and throat [4].
- Photophobia, irritation and watery discharge [7].
- Ocular discharge and tear are a potential source of contamination [7].

Currently there is no evidence that it causes adverse outcomes in neonates or that it can pass to the child while in the womb. [2]

Considering that the virus is present in the body fluid, tear fluid is a type of body fluid, and SARS -CoV-2 is similar to SARS-CoV, it is speculated that there may be a risk of tear and conjunctival transmission [18].

However, the eye is rarely involved in human CoVs infection. Until now, conjunctivitis has been reported only in five cases with COVID-19 infection and in four cases with HCoV-NL63 infection, whereas no conjunctivitis or other ocular complications was confirmed in patients with SARS-CoV and MERS-CoV infection. Recently human COVs RNA in tears and conjunctival secretions were tested by RT-PCR assay in patients with SARS-CoV and COVID-19. Zhou and colleges in their preprint posted at medRxiv, reported that conjunctivitis was identified in only one patient out of 63 COVID-19 cases and 4 COVID-19 suspects. Conjunctivitis was also the first symptom of COVID-19 in this patient [20].

SARS-CoV-2 was not detected in conjunctival swab samples from the COVID-19 patient complicated by conjunctivitis, whom was anesthesiologist. Her ocular symptoms occurred soon after performing tracheal intubation for a patient who was confirmed as COVID-19 later, followed by fever and cough. Unfortunately, personal protections used by the anesthesiologist were only surgical mask, cap and gloves without gown, face shield or goggles during the tracheal intubation procedures. Sun and colleagues in their preprint posted at me-

dRxiv, reported conjunctivitis in two patients out of 72 laboratory confirmed COVID-19 cases in one patient who was a nurse working in Emergency Department. This patient presented with excessive tearing and redness in both eyes which were typical ocular manifestation of viral conjunctivitis, followed by a moderate fever of 38.2ºC one day later. COVID RT-PCR test for conjunctival and oropharyngeal swabs sampled 6 days after the onset of conjunctivitis was positive, but for those sampled 10, 19, 21 days after onset of conjunctivitis was all negative [20].

A study made by Xia., *et al.* showed that virus existed in one patient, tears and conjunctival secretions with conjunctivitis were positive on 3 and 5 days after the onset of COVID -19, and there was no virus in the patients conjunctival sac without conjunctivitis. But the study had limitations: the sample size was small, the tear and conjunctival secretions were limited so sample concentration might be insufficient for RT-PCR detection of the virus. In this study of 30 patients, 60 samples, two samples of tear and conjunctival secretions yielded positive RT-PCR results, 58 samples from other patients were all negative [19].

With this information Xia., *et al.* mentioned that transmission of SARS-CoV-2 through conjunctiva is not common, but also stated that the risk of transmission could not be completely eliminated [19].

Indeed ophthalmologists are easily infected with SARS-CoV-2 but this does not mean that SARS-CoV-2 is transmitted through the conjunctiva. Xia., *et al.* reasonably explained this issue: close contact with the patients during ophthalmic examination [19].

The positivity of SARS -CoV-2 RNA, in tears and conjunctival secretions of the patient with conjunctivitis does not mean that SARS-CoV can replicate in the conjunctiva. Since COVID-19 patients have viremia during the acute phase, the positivity of SARS-Cov-2 is likely resulted from the virus in the exudation of conjunctivitis. Despite being a small sample size, undectable of SARS-CoV-2 in 29 patients without conjunctivitis support this explanation. Nevertheless, sufficient sample size and well characterized studies are required to obtain more evidence [19].

Based on the Report of the WHO - China Joint Mission of Coronavirus Disease 2019, summarized from 55924 laboratory confirmed cases the typical signs and symptoms, and the conjunctival congestion is present in 0.8% [13].

Overall, only a very small proportion of the patients had conjunctival presentation, which is unknown whether the conjunctival congestion was initial or coexisted symptom [18].

The extremely low positive rate of human COV RNA test by RT-PCR in tears and conjunctival secretions from patients with SARS and COVID-19 may have several interpretations. Previous reports about the sensitivity for RT-PCR in excretions ranged from 50% to 60% [20].

The contribution of antimicrobial agents in tears including lactoferrin and secretory IgA and constant tear rising which continuously eliminating the virus on ocular surface into nasal cavity through nasolacrimal duct [20]. Lactoferrin can inhibit the binding of SARS-CoV to its entry receptor angiotensin-converting enzyme 2 (ACE2), by preventing the attachment of SARS CoV to heparin sulfate proteoglycans. Secretory IgA is another important antimicrobial agent in tears which help to kill both bacteria and viruses. Host immune system can be activated and result in an evident increase in lactoferrin and secretory IgA levels in tears and circulating IgM level in plasm on the 3rd to 5th day, and circulating IgG level in plasm on the 10th to 15th day after COVID-19 which may explain why RNA-CoV presents only in the early phase of the disease [20].

Prevention for ocular care providers:

- For suspect and probable cases regardless of SARS appointments were recommended to be deferred [8].
- Wash your hands often with soap and water for at least 20 seconds [8].

- Cover your nose and mouth when you cough or sneeze and then throw it away [8].
- Avoid touching your eyes, mouth or nose if you have not washed your hand properly.
- Avoid close contact with people that may be sick [8].
- Clean and disinfect frequently touched surfaces and objects [4].
- Stay home if you are sick [4].
- Use a N95 respirator: it prevents 95% of small particles from entering nose and mouth [4].
- Use gloves, gowns and goggles [8].
- Optometrists and Ophthalmologists can use well-fitting P2/N-95 masks for themselves and their staff [7].
- Decontamination and sterilization protocols of clinical rooms and equipment should be improved, as coronaviruses have been found to survive in environments outside the body for a long time [8].
- Sterilize Goldman tonometer, B-scan probes, contact lenses for photocoagulation [8].
- Reduction of non urgent ophthalmic surgeries and for emergency operations full personal protective equipment can be considered to reduce the probability of healthcare transmission [8].

Conclusion

Recently COVID-19 infection has become a world-wide threat. Although respiratory droplets and direct contact have been identified as the main routes of transmission SARS-CoV-2 and is less likely transmitted through the conjunctiva, it does not mean that protective goggles are not required in managing COVID-19 patients. As it is postulated that the eye may play three roles in humans. First as a target organ, secondly the conjunctiva may be portal of entry for or transporter for human SARS CoV-2 and thirdly tears and conjunctiva secretions may be a medium to spread human Coronavirus. Because of this is, it is recommended to use eye protection like goggles all the time, as eyes and nose are very closely, located the upper edge of a mask is just about one centimeter below the eyes. There is usually a narrow gap underneath the upper edge of a mask because of the uneven surface at nose root, leaving the chance of pathogen exposure. A pair of protective goggles can overcome this problem. Moreover, the extremely low positive rate of human COV RNA test by RT-PCR in tears and conjunctival secretions from patients with SARS and COVID-19, may be related to the relatively low sensitivity of current RT-PCR technique, the later time for sample collecting, and the activation of host immune system and significant increase in lactoferrin and secretory IgA levels in tears and in circulating IgM and IgG levels in plasm. Hence, current negative RT-PCR results cannot exclude the possibility of presence of SARS-CoV and 2019-nCoV in tears and conjunctival secretions. Considering close doctor-patient contact is quite common in ophthalmic practice which are apt to transmit human COVs by droplets and fomites, strict hand hygiene and proper personal protection are still highly recommended for health care workers to avoid hospital-related viral transmission during ophthalmic practice.

Given the actual 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 epidemic continues. A better understanding of the virus will emerge, hopefully with more emphasis on research into the relationship between human CoVs and the eye. There is no complete and fully understand evidence so further research has to be done.

Bibliography

1. Chodosh J., *et al.* "Alert: Important coronavirus context for ophthalmologists". *American Academy of Ophthalmology* (2020).
2. Chen H., *et al.* "Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records". *The Lancet* (2020).
3. Shuo Su., *et al.* "Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses". *Science Direct* 24.6 (2016): 490-502.
4. Egan John. Coronavirus: How eyes may play a role in its spread (2020).
5. CDC. Coronavirus Disease (2019).
6. Vabret A., *et al.* "Human coronavirus NL63, France". *Emerging Infectious Diseases* 11 (2005): 1225-1229.
7. Carter H. "Coronavirus may cause ocular signs and symptoms; anecdotally linked to and transmitted by conjunctivitis". *Optometry Australia* (2020).
8. Seah I., *et al.* "Revisiting the dangers of the coronavirus in the ophthalmology practice". *The Royal College of Ophthalmologists* (2020).
9. Cascella M., *et al.* "Features, Evaluation and Treatment Coronavirus (COVID-19)". Statpearls Pubmed (2020).
10. Seah I and Agrawal R. "Can the Coronavirus Disease 2019 (COVID-19) Affect eyes? A review of coronaviruses and Ocular implications in humans and animals". *Ocular Immunology and Inflammation* 28.3 (2020): 391-395.
11. Chan JF., *et al.* "A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster". *The Lancet* 395 (2020): 514-523.
12. Huang C., *et al.* "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *The Lancet* 395 (2020): 497-506.
13. Guan W., *et al.* "Clinical characteristics of coronavirus disease 2019 in China". *The New England Journal of Medicine* (2020).
14. Xia J., *et al.* "Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection". *Journal of Medical Virology* (2020): 25725.
15. Yuzhu P and Yi-Hua Z. "Is novel coronavirus disease (COVID-19) transmitted through conjunctiva?" *Journal of Medical Virology* (2020).
16. Lu CW., *et al.* "2019-nCoV transmission through the ocular surface must not be ignored". *The Lancet* 395.10224 (2020): e39.
17. American Academy of Otolaryngology-Head and Neck Surgery. Coronavirus Disease 2019: resources (2019).
18. LiJ-PO., *et al.* "Novel coronavirus disease 2019. Recognising possible early ocular Manifestation". *British Journal of Ophthalmology* 104 (2020): 297-229.
19. Jianhua Xia., *et al.* "Evaluation of coronavirus in tears and conjunctival secretions of patients withs SARS-CoV-2 infection". *Journal of Medical Virology* (2020).
20. Chuan-bin Sun., *et al.* "Role of the eye in transmitting human coronavirus : what we know and what we do not know (2020).

Volume 11 Issue 6 June 2020