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EYE AND TRANSMISSION OF HUMAN CORONAVIRUS

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ABSTRACT

Corona virus disease (COVID-19) has spread rapidly causing a threat worldwide. The term COVID-19 which stands for corona virus disease 2019 was proposed by the World Health Organization. The virus was officially named a severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Not much is known about the role of the eye in transmitting COVID-19. The conjunctiva is directly exposed to pathogens in the environment and the mucosa of ocular surface and upper respiratory tract are connected by nasolacrimal duct. Some respiratory viruses have the same entry receptors. Pathogens exposed to the ocular surface might be transported to nasal and nasopharyngeal mucosa via tears through nasolacrimal duct and then cause infection of respiratory tract. Studies suggest that the eye is not frequently involved in human Corona Virus infection. Conjunctivitis is quite rare in patients with SARS-CoV and SARS-CoV-2 infection. NL63 (alpha corona virus) is known to cause ocular manifestations in humans. The virus can be present in the conjunctiva and in the tear but the information available today have some limitations, like insufficient sample size as the tear and conjunctival secretions are very limited hence the sample concentration might be inadequate for RT-PCR detection. This article throws light on evidence for corona virus infection of ocular tissue in humans as well as the information known and unknown even though further research has to be carried out.

INTRODUCTION

A young Chinese ophthalmologist, Li Hospital in Wuhan, China, on December 30, Wenliang, working at the Wuhan Central 2019 tried to alert his colleagues, about the

outbreak of an illness that resembled severe acute respiratory syndrome (SARS). Wuhan local authorities, however, accused him of making false statements and paid no heed to him. Li returned to work, later contracted the virus from an asymptomatic, infected patient with acute angle-closure glaucoma, became symptomatic on January 10, 2020 and succumbed to the disease on February 7.

Li is considered one of the prime whistleblowers of what is now identified as COVID-19, a highly infectious disease caused by a new variant of corona virus 2019-nCoV. Unfortunately, this patient-to-ophthalmologist transmission of the new strain of corona virus is the first known case to be reported.

GENOMICS AND MORPHOLOGY

On February 11, 2020, the World Health Organization announced that the disease caused by the enveloped RNA beta corona virus SARSCoV-2 was “COVID-19” which is the acronym of “corona virus disease 2019”. CoVs have an enveloped single positive-strand RNA genome with a 5'-terminal cap structure and a poly (A) sequence at the 3' end. CoV genome is approximately 30 kb long. CoV's belong to the family Coronaviridae and the order Nidovirales [2].

SARS-CoV-2 is one of seven corona virus

species which are known to cause diseases in humans and is the largest RNA virus. Its diameter is approximately 60–140 nm [14]. The mutation rates of RNA viruses are greater than DNA mutation rates. Currently, two types of SARS-CoV-2 have been known [14]. The L form, likely more aggressive, is suspected to be a derived variant of the ancestral S type [14]. The L form was initially more prevalent in Wuhan, China, than other places [14]. SARS-CoV-2 is similar to SARS-CoV (severe acute respiratory syndrome corona virus) and MERS-CoV (Middle East respiratory syndrome corona virus), belongs to the β -CoV family and can cause fatal pneumonia. SARS-CoV-2 has a lower disease severity, but higher transmission efficiency [14].

CLINICAL MANIFESTATIONS

Symptoms of COVID-19 can appear within 2–14 days of exposure. The main symptoms of COVID-19 are fever, cough, fatigue, slight dyspnea, sore throat, headache, conjunctivitis, and gastrointestinal complaints. Complications in severe cases include pneumonia, renal failure, cardiomyopathy, encephalopathy, vasculopathy and coagulopathy [10].

The Human Coronavirus associated with causing conjunctivitis is the alphacoronavirus NL63. It primarily affects young children, the

elderly and immunocompromised patients with respiratory illness [2]. The infection can seem like a common cold, characterized by cough, rhinorrhea, tachypnea, fever and hypoxia, and may resolve on its own [2, 5].

OPHTHALMIC MANIFESTATIONS

There are reports on conjunctivitis being the first presenting symptom [1]. Conjunctival congestion has been documented in 9 of 1,099 patients (0.8%) with laboratory-confirmed positive results for COVID-19 from 30 hospitals across China [2]. Conjunctival swab samples from the tears of infected individuals have proved positive for SARS-CoV-2 RNA, using the reverse-transcription polymerase chain reaction (RT-PCR), whether or not there are ocular manifestations. It is interesting to note that neither conjunctival inflammation nor other ocular manifestations were reported during either the SARS-CoV or the MERS-CoV pandemics earlier. Retinal vein occlusion has been noted but it is still unclear whether it is caused by the direct infection of retina by SARS-CoV-2 virus or by thrombosis in the retinal vascular vessels as a result of raised cytokines. Chorioretinitis from fungal sepsis, acute macular neuroretinopathy, optic nerve infarction, mucormycosis of orbit and cerebral venous thrombosis have also been reported.

MECHANISM OF TRANSFER

Transmission via ocular surface is reported¹. There are also reports on transmission by aerosol contact with conjunctiva where no eye protection is worn [1]. On January 22nd, Guangfa Wang, a member of the national expert panel on pneumonia, reported that he was infected during an inspection in Wuhan. He had donned N95 mask without any eye protection. Several days before the onset of pneumonia, Wang suffered from conjunctivitis, implying that unprotected exposure of the eyes to the virus in the Wuhan Fever Clinic may have been the source of his systemic infection [1]. The virus first binds with conjunctival epithelial cells and then transmits through the conjunctiva. SARS-CoV-2 enters the host cell by reacting with two important cell surface players: the angiotensin-converting enzyme 2 receptor (ACE2) and the transmembrane protease serine 2 (TMPRSS2) [1]. The corneal epithelium and the conjunctival epithelium are both part of the conjunctival epithelium. Both ACE2 and TMRPSS2 have been found, raising the possibility of direct virus infection and transmission [5]. Expression of the ACE receptor has been found in retinal pigment epithelium (RPE), choroid and neural retina and sclera [14]. Immuno-histo-chemistry (IHC) studies have shown presence of ACE and Ang-II in the non-pigmented epithelium

of the ciliary body, corneal epithelium and endothelium, conjunctival epithelium and trabecular meshwork lining. ACE and Ang-II were detected in retinal ganglion cells, inner nuclear layer and retinal photoreceptor cells, endothelium lining of choroidal and retinal vessels [14]. ACE2 receptor were also found in the aqueous humour [14]. A recent study reported a novel route of SARS-CoV entry to human host cells – through its interactions with CD147 [14]. Certain studies have confirmed the presence of CD147 in tears, the corneal epithelium and endothelium, stromal keratocytes, conjunctiva and retinal pigment epithelium [14].

Interestingly, that is contradictory as incidence of conjunctivitis is so low (0.8%) and major transmission could have been through the conjunctival route. What could cause such a discrepancy? There is enough proof showing that the number of ACE2 receptors on the ocular surface are lower than in pulmonary tissue, and that their binding capability is likewise lower [7]. The tear film has antiviral properties which would inactivate viruses, for example, the protein lactoferrin, which likely prohibits adenovirus entry into corneal epithelial cell. As demonstrated in several animal models of corona viruses, serum IgA may play a role in virus neutralization. Other routes of

transmission includes hematogenous infection of the lacrimal gland during viremia [8].

As to why corona viruses should be found in tears, apart from direct inoculation from infected droplets reaching the eye surface (for example from a cough or sneeze of an infected person), there are other theories citing migration from the nasopharynx via the nasolacrimal duct and hematological infection of the lacrimal gland⁴. Given that SARS-CoV-2 virus has been detected in stool samples, it is possible that transmission from fecal matter to hand and then to eye also exists. Some papers even concluded that the risk of SARS-CoV-2 transmission through tears is low [12].

Transmission of corona virus infection from the conjunctival surface of one individual to another, during the course of a clinical examination, has not been documented so far. The ocular surface is an open microenvironment, conjunctiva can be infected directly by an aerosol droplet from an infected patient or secondary to viral spread from the upper respiratory tract through nasolacrimal duct or via hematogenous spread [14].

CONTROL OF INFECTION

One should have a high index of COVID-19 suspicion in all patients with conjunctivitis

and need a thorough ocular examination to rule out other causes of conjunctivitis such as bacterial, chlamydial, adenoviral, or microsporidial disease. Extreme precautions must be practiced to minimize the risk of contracting the infection. A careful history and symptoms pertaining to covid -19 should be enquired and if there is evidence of conjunctivitis with any of the COVID-19 symptoms they should undergo COVID-19 testing. Travel history to containment areas should not be omitted. Virus detection in tears and on the ocular surface is dependent on a number of factors, including viral shedding, viral load, sample methodologies, disease-related sampling time, investigative mode and the host immune response.

PROTECTION

According to current information, there is only a low risk of transmission through conjunctival surfaces and tears, hence eye protection and scrupulous disinfection are recommended. Washing of hands with soap and water quite often for at least 20 seconds [7]. Nose and mouth should be covered while coughing or sneezing and then the cloth should be thrown away [7]. Avoid touching your eyes, mouth or nose if you have not washed your hand properly. Avoid close contact with people that may be sick with the fear of contracting or transmitting the

infection [7]. Clean and disinfect surfaces and objects touched frequently [3]. Stay at home or a confined space if sick [3]. Use a N95 respirator as it prevents 95% of small particles from entering nose and mouth [3]. Use gloves, gowns and goggles as precautionary measures [2].

WHAT WE KNOW

SARS-Cov-2 has been linked to ocular involvement in two recent studies [3, 4]. Guan W presented data from 1,099 patients treated in 552 hospitals across 30 Chinese regions. There were 926 non-severe cases and 173 severe cases, with conjunctival congestion seen in 9 (0.8%) patients, out of it 5 was in non-severe cases (0.5%), and 4 in severe cases (2.3%) [4]. Wu Ping *et al.* evaluated 38 patients in Hubei province and discovered ocular manifestations in 12 (31.6%) of them, which consisted of conjunctivitis, conjunctival hyperemia, chemosis, epiphora, or excessive secretions [4]. There were four non-severe instances and eight severe or critical cases among the 12 patients [4]. In both conjunctival and nasopharyngeal samples, only two patients tested positive for SARS-CoV-2 [4]. Patients with ocular symptoms had increased white blood cell counts and neutrophils, as well as procalcitonin, C-reactive protein, and lactate dehydrogenase, according to the univariate

analysis [4]. Both these investigations demonstrate that severe pneumonia is associated with eye symptoms. Conjunctivitis as the first symptom of SARS-CoV-2 has been reported in only a few cases.

It's not surprising that the viral load in conjunctival samples is substantially lower than in nasopharyngeal samples [9]. RT-PCR is a standard method for detecting viruses, and the ocular results should be seen in the perspective of its high specificity but low sensitivity (about 50–60 percent) [9]. In the presence of conjunctival symptoms, the lack of a virus on RT-PCR does not necessarily suggest the virus is absent in tears or on the conjunctival surface [9]. Conjunctivitis is not always caused by the presence of the virus on the ocular surface or in tears [9]. There is no obvious proof of virus replication on the surface of the eye [9]. It would be unfair to bring up the topic of nasolacrimal duct obstruction when viruses are transmitted through the nasolacrimal duct in both directions, that is, between the ocular surface and the respiratory system (NLDO). The assumption that NLDO can worsen ocular retention and periocular contamination is inconceivable [9]. Summarizing these aspects, there is no evidence to show that SARS-CoV-2 appears to prefer the conjunctiva as a route of entry or a preferred

tissue. Three requirements must be met to prove conjunctival transmission. One, the virus in the epithelial cells of the conjunctiva. Two, it causes cytopathic alterations that may be seen and three, it is isolated from epithelial cells. It's safe to assume that SARS-CoV-2 transmission through the conjunctiva is impossible in the absence of these visible alterations. It can cause conjunctivitis, possibly transmitted by aerosol contact with conjunctiva.

- It can start with an inflammation of the eye followed by a fever and a buildup of mucus in the nose and throat [11].
- Photophobia, irritation and watery discharge [12].
- Ocular discharge and tear are a potential source of contamination [12].

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 patient's 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. Xia., *et al.* mentioned that transmission of SARS-CoV-2 through conjunctiva is uncommon, but also stated that the risk of

transmission could not be completely eliminated [13]. The positivity of SARS-CoV-2 RNA, in tears and conjunctival secretions of the patient with conjunctivitis does not mean that SARSCoV 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.

WHAT WE DO NOT KNOW

Virus with a spike glycoprotein, also interacts with angiotensin-converting enzyme 2 (ACE-2) which is a receptor-binding domain [7]. ACE-2 is expressed in the membranes of respiratory, renal and intestinal tracts. In the eye, this receptor is expressed in conjunctival epithelium, choroid, retina as well as vascularised retinal pigment epithelium. So, the discovery of SARS-CoV-2 in the tears or conjunctiva is not surprising. This raises a few questions like how does it appear into the conjunctival sac? Is it actively secreted by the lacrimal gland? Or is it possible that the obstruction of lacrimal drainage pathway plays a role in retaining the coronavirus on the ocular surface regardless of its presence in the nasal cavity? [7]. Could the virus be pushed upwards along the nasolacrimal passage due to positive pressure of ventilators? Although, there is a low risk of this virus spreading

through ocular discharge, in patients with conjunctivitis, it may survive or replicate in the conjunctiva for up to 21 days, even after signs of conjunctivitis resolve [1]. Since the virus may not appear in the conjunctiva initially, conjunctival sampling as a screening tool is not of much benefit. Although ocular complications are infrequently encountered in corona virus infected individuals, the presence of both SARS-CoV and 2019-nCoV RNA in tears was confirmed, indicating that ocular exposure may represent a route of entry for the virus [2, 11].

The detection window for the virus in the conjunctival cul-de-sac is likewise debatable. Some believe there is a three-day window in which a positive patient can be detected, while others say it can take up to two weeks⁹. The cytopathic effects on the nasolacrimal duct are not known. The after effects of this infection in the eye and complications involving other ocular structures are yet to be known.

CONCLUSION

Mild conjunctivitis manifesting as conjunctival congestion is common and is one of the major ocular manifestations in COVID-19 positive patients even with milder disease [10]. It is postulated that the eye may play three roles in humans. Firstly, as a target organ, secondly the conjunctiva may be portal of entry or transport of 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, as eyes and nose are 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 human COV RNA test by RT-PCR in tears and conjunctival secretions from patients has an exceedingly low positive rate, may be related to the relatively low sensitivity of current RT-PCR technique, the delay in sample collection, the activation of host immune system and significant increase in lactoferrin and secretory IgA levels in tears and increase in circulating IgM and IgG levels in plasma. Hence, current negative RT-PCR results cannot exclude the possibility of presence of SARS-CoV and 2019-nCoV in tears and conjunctival secretions.

Given the evidence regarding SARS-CoV-2 transmission through ocular tissue, more research has to be done to confirm its ability to infect ocular tissue, its pathogenic mechanisms and to confirm the presence of ACE2 on corneal and conjunctival

cells. Summarizing, a need for well-designed trials have to be conducted in order to rule out other ocular manifestations, besides conjunctivitis, that may result from COVID-19 infection and make known the mechanisms of transmission through the eyes.

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