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INVITED REVIEW



Can the Coronavirus Disease 2019 (COVID-19) Affect the Eyes? A Review of Coronaviruses and Ocular Implications in Humans and Animals

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ABSTRACT

In December 2019, a novel coronavirus (CoV) epidemic, caused by the severe acute respiratory syndrome coronavirus – 2 (SARS-CoV-2) emerged from China. This virus causes the coronavirus disease 2019 (COVID-19). Since then, there have been anecdotal reports of ocular infection. The ocular implications of human CoV infections have not been widely studied. However, CoVs have been known to cause various ocular infections in animals. Clinical entities such as conjunctivitis, anterior uveitis, retinitis, and optic neuritis have been documented in feline and murine models. In this article, the current evidence suggesting possible human CoV infection of ocular tissue is reviewed. The review article will also highlight animal CoVs and their associated ocular infections. We hope that this article will serve as a start for further research into the ocular implications of human CoV infections.

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Coronaviruses (CoVs) are viruses that have been known to affect birds and mammals.¹ CoVs rose to public prominence after the outbreak of the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003.² The SARS-CoV outbreak was reported to have infected more than 8000 people and resulted in 774 deaths globally.³ Since then, the Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) has also been in the public spotlight.⁴ In December 2019, a new CoV epidemic, caused by the Severe Acute Respiratory Syndrome Coronavirus – 2 (SARS-CoV-2) started in the city of Wuhan, China. This new epidemic has spread across the globe rapidly, affecting 76 769 people in 27 countries as of the 21st of February, 2020.⁵

On the 30th of January, the World Health Organization (WHO) has declared a public health emergency of international concern (PHEIC).⁶ A set of recommendations for personal protective equipment (PPE) based on the experience of MERS-CoV and SARS-CoV have been released.⁷ This set of recommendation includes wearing goggles or faceshield 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.

The Coronavirus Structure and Host

CoVs belong to the subfamily Coronavirinae, in the family Coronaviridae of the order Nidovirales. CoVs have four known genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. The CoV name is a derivative from the Latin word *corona* which means crown. This is due to the characteristic structure of the virus whereby surface projections on the viral envelope gives it an appearance similar to a crown. The virus is a single-stranded positive-sense RNA virus with a genome of around 30 kb in length. This makes them the largest known RNA viruses.⁸ The RNA genome codes for both structural proteins (SPs) and non-structural proteins (NSPs). All known CoVs share a similar structure made of four main structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Some CoVs also encode special structural and accessory proteins.⁹ While the exact functions of most accessory proteins are still currently being researched on, it is recognized that the structural proteins aid the viral infection of host cells and subsequent replication. The S-protein is responsible for attachment to host receptors, M protein helps shape the virion particles and binding to nucleocapsid, E-protein plays a role in the assembly and release of particles while N-protein aids with the binding of the genome to a replication-

transcription complex which is required for the replication of genomic material.

CoVs are known to affect a wide range of birds and mammals. These include everyday household animals such as the cat (feline) and dog (canine) to large animals such as beluga whales.^{10–12} The ability of CoVs to obtain mutations which facilitate the transmission between animal to humans has made it a zoonotic pathogen of concern.¹³ In fact, the recent emergence of human CoVs capable of causing respiratory failure, such as SARS-CoV and MERS-CoV has had the origins traced back to animals such as bats.¹⁴ This review will cover CoVs in cats and mice as they have been published to develop ocular infections involving CoVs.

Human Coronaviruses and the Evidence for Ocular Manifestations

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 runny nose, sore throat, fever, and cough.¹⁵ However, in instances of immunocompromise or underlying cardiopulmonary disease, they can cause pneumonia or bronchitis.¹⁶ On the other spectrum, the SARS-CoV, MERS-CoV, and SARS-CoV-2 have been known to causing life-threatening respiratory failure.¹⁷

CoVs have also been known to manifest in other regions apart from the respiratory tract, including the gastrointestinal tract and ocular tissues.^{18,19} However, most CoV research is focused on the respiratory tract due to its life-threatening nature. Despite this, the manifestations of CoVs in other organ systems should not be ignored as they can represent an alternative mode of transmission. For instance, during the SARS-CoV outbreak in 2003, it was reported that a severe outbreak of SARS-CoV occurring at a housing estate in Hong Kong was likely transmitted through the sewage system.²⁰ It was later discovered that SARS-CoV RNA can be detected from stools of infected patients and may even survive through the sewage that has not undergone adequate disinfection.²¹ Such examples highlight the need for more research into the non-respiratory clinical manifestations of the disease. In fact, it has already been established that the SARS-CoV-2 can be shed through the oral–fecal route as well.²²

From the ocular perspective, there have been reports suggesting CoVs affecting the eye. 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 had symptoms and physical examination findings of bronchiolitis and conjunctivitis.²³ Together with the SARS-CoV crisis that was happening during that period of time, it triggered greater

interest in understanding the spectrum of clinical manifestations associated with the new HCoV-NL63. In 2005, a retrospective study that analyzed the nasal swabs of children with respiratory illnesses from 2000 to 2003 for HCoV-NL63 was conducted in France. In this study, they found that 17% (n = 3) of HCoV-NL63 patients (n = 18) had developed conjunctivitis.²⁴ However, to date, there has not been any further studies detailing the pathogenic mechanisms of HCoV-NL63 in the infection of ocular tissues.

Of greater concern to health-care professionals is a case series published which highlighted the presence of SARS-CoV RNA in tears. In 2004, tear samples collected from 36 suspected SARS-CoV patients were sent for RT-PCR for the SARS-CoV. The SARS-CoV RNA was identified in three of these patients. Out of the three, one patient had the RNA identified in all three stool, respiratory swab, and tear samples. One patient had RNA identified in stool and tear samples but the respiratory swab was not sent. The last patient had RNA identified in tear samples only while stool samples were negative and the respiratory swab was not sent. 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.¹⁸ However, up till today, it is still 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 haematogenous infection of the lacrimal gland. Furthermore, the results were inconsistent across studies. Another study that assessed both tears and conjunctival scrapings from 17 patients with confirmed SARS-CoV infection did not yield any positive result from RT-PCR. The authors attributed the findings to three possibilities. Firstly, the RT-PCR was not sensitive enough to pick up small quantities of SARS-CoV RNA. Secondly, the sample collection was a one time process, which may have missed the window if viral shedding in ocular tissue only lasted for a short period of time. Finally, there is also the possibility that the SARS-CoV did not exist in ocular tissue. However, as the SARS-CoV epidemic died down, these crucial questions were left unanswered.^{25,26}

There have been anecdotal reports of ocular infection in the recent SARS-CoV-2 epidemic as well. On the 22nd of January 2020, Guangfa Wang, a member of the national expert on pneumonia had developed conjunctivitis during an inspection of Wuhan, the epicenter of the outbreak. He was subsequently tested positive for the SARS-CoV-2 but recovered from the infection eventually.²⁷ This has resulted in a call for research into ocular infection as a possible alternative route of SARS-CoV-2 transmission.^{28,29} As the epidemic is still in its early stages, not much has been published with regards to the SARS-CoV-2 pathogenic mechanisms, especially with respect to ocular tissues. 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 (ACE2).³⁰ Interestingly, the renin-angiotensin system (RAS), apart from its well-known endocrine role in blood pressure regulation, also has

complicated autocrine functions 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. ACE2 has been found in the aqueous humor.³¹ However, the expression of ACE2 in more anterior tissues such as the conjunctiva or cornea has yet to be established. Hence, more research exploring the hypothesis of SARS-CoV-2 ocular infection through ACE2 has to be conducted.

As the literature on human ocular CoV infection is still sparse, there is value in studying ocular manifestations of CoVs in various animals. It was also suggested that the SARS-CoV-2 virus may recognize ACE2 from a diversity of animal species including cats and non-human primates.³⁰ Hence, understanding the ocular manifestations of animal CoV infections may provide insights into the spectrum of ocular diseases that CoVs can cause. This will be covered in the subsequent segments of this review article.

Feline Coronaviruses and Ocular Manifestations

The feline CoV (FCoV) is an *Alphacoronavirus* that affects both domestic and wild cats. Approximately 20–60% of domestic cats are seropositive, while in animal shelters, the seropositive rates can approach almost 90%.³² FCoVs can be further classified into two biotypes which reflect very varied clinical presentations. These are the feline enteric CoV (FECV) and the feline infectious peritonitis virus (FIPV). In majority of these seropositive cases, the FCoVs exist as FECV. For most of the FECV cases, the infection is usually benign or associated with a self-limiting diarrhea.³³ This is because FECV has been shown to demonstrate tropism to the apical epithelium of the intestinal villi from the small intestine to the cecum.³⁴ As such, FECV shedding in feline feces is responsible for the fecal–oral spread and maintenance of FECV infection in feline populations, explaining the high seropositive rates of the infection.

Interestingly, 5% of cats affected by FECV will develop feline infectious peritonitis (FIP).³⁵ Apart from the tropism toward epithelial cells in the gut, a small proportion of FECV can affect monocytes as well. It has been suggested that within the monocytes, the FECV acquires mutations in the genome which result in the transformation to FIPV.³⁶ The FIPV then display an altered cell tropism, infecting monocytes and macrophages more efficiently as compared to FECV. These cells play a pivotal role in the drastically different clinical manifestation of the disease. The FIP disease is characterized by fibrinous and granulomatous serositis, protein-rich serous effusion in body cavities and granulomatous lesions. It has been suggested that the underlying pathogenic mechanism is a vasculitis triggered by the infected monocytes and macrophages leading to endothelial barrier dysfunction and extravasation of these immune cells into the tissue.³⁷ These lesions are multi-systemic and lead to an extremely poor prognosis of the infected felines. Those affected had fever, loss of appetite, and weight loss. The majority of felines who have been experimentally infected with FIPV died within 4–5 weeks.³⁸

The ocular manifestation of FIP is likely due to underlying vasculitis, resulting in inflammation of varying ocular

segments. In a study that observed FIPV-infected felines and their offspring, 90% of the infected cats had FCoV antigen detected in the conjunctiva. Viral isolates from conjunctival swabs also contained live FCoV which suggest that ocular tissues and secretions were potentially infectious as well. Furthermore, the initially healthy offspring, after being kept with the infected parents for 100 days, developed recurrent bouts of conjunctivitis.³⁹ Apart from conjunctivitis, ocular manifestations include pyogranulomatous anterior uveitis, choroiditis with retinal detachment and retinal vasculitis.⁴⁰ In general, ocular manifestations of FIPV infection have poor prognosis both visually and systemically.

Mouse Coronaviruses and Ocular Implications

The murine CoV mouse hepatitis virus (MHV) is a collection of strains that demonstrate very different organ tropisms. MHV can be divided into two main biotypes: the first biotype affects mainly the gastrointestinal tract and is usually responsible for the MHV outbreaks in house rodent colonies such as those within the lab. The biotype includes strains such as the MHV-D, MHV-Y, MHV-RI, MHV-S/CDC, LIVIM, and DVIM.⁴¹ The other biotype contains strains that can affect multiple organs including the central nervous, hepatic, and pulmonary systems. MHV has been extensively utilized to create models of human disease including multiple sclerosis, viral hepatitis, and pneumonitis.^{42–44}

The rationale for the varying tropism among different strains of MHV is still not well understood. It was initially widely believed that all MHVs utilize the same cellular-receptor for entry, the carcinoembryonic antigen molecule 1 (CEACAM1), which suggests that the tropism is likely due to post-viral entry events.⁴⁵ However, further studies suggested that cellular infection can also occur independently of the CEACAM1 receptor.⁴⁶ Thus, the exact mechanism responsible for tissue tropism still remains to be investigated.

Of particular significance in the ophthalmology field are the neurotropic strains of MHV. The two main viruses which are studied are the JHM strain (JHMOV) and the A59 strain (MHV-A59). This viral was originally isolated from a paralyzed mouse and found to be capable of producing extensive demyelination and encephalomyelitis.⁴² The virus is capable of infecting glial cells, astrocytes, oligodendrocytes, and microglia. Over time, the virus was passaged multiple times through mice brains leading to varying clones with differing pathogenic phenotypes. The MHV-A59 was isolated from a leukemic mouse in 1961 and is less neurovirulent as compared to JHMOV.⁴⁷

As the initial studies of JHMOV also showed involvement of the posterior pole in the eye, JHMOV-infected mice were subsequently utilized for intravitreal inoculation to study the mechanisms of virus-induced retinal degeneration.⁴⁸ Today, this model of retinal degeneration, known as the experimental CoV retinopathy (ECOR) is used to examine genetic and host immune responses that may contribute to retinal disease. In the model, the disease is biphasic, characterized by inflammation in the early phase and retinal degeneration in the late phase. After inoculation, the presence of the virus in the retina and retina pigment epithelium will result in the infiltration of

immune cells and release of pro-inflammatory mediators. After the first week of infection, viral clearance is achieved. However, subsequently retinal and RPE cell autoantibodies are produced, resulting in progressive loss of photoreceptors and ganglion cells as well as thinning of the neuroretina.⁴⁹ This suggests an autoimmune process causing majority of the retinal damage.

MHV-A59, on the other hand, has been utilized for the creation of viral-induced optic neuritis models. This is due to the increasingly popular hypothesis that viral-induced inflammation is the likely etiology for multiple sclerosis. When inoculated intracranially in mice, MHV-A59 induced meningitis, focal acute encephalitis, and most importantly optic neuritis. Inflammation of the optic nerve was detected as early as 3 days after inoculation with the peak incidence at 5 days. Axonal loss was highlighted by the significant decrease in axonal staining compared to control optic nerves 30 days after inoculation.⁵⁰

Conclusion

As CoVs can cause ocular infection across different animals, the possibility of SARS-CoV-2 having ocular implications cannot be ignored. However, the examples in animals also highlight that CoVs are a heterogeneous group of viruses that can cause ocular implications through a wide variety of mechanisms. Some of these mechanisms are extremely different from those adopted by human CoVs. Nevertheless, there are lessons to be learned by understanding these infections. Firstly, CoVs are capable of producing a wide spectrum of ocular manifestations from anterior segment pathologies like conjunctivitis and anterior uveitis to sight-threatening conditions like retinitis and optic neuritis. Secondly, it may also be prudent to recognize that CoVs can also develop in-vivo mutations which drastically alter the manifestations of the disease.

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 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. This understanding will not only help 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 err on the side of caution and continue to prevent the possible transmission of CoVs through ocular tissue.

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