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Ocular Manifestations of COVID-19 Infection

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ABSTRACT

The eyes, which were not previously the subject of investigation, have emerged as one of the more intriguing aspect of COVID-19 infection. The probable pathways for SARS-CoV-2 infection through the eyes are either through the tear film and draining tear ducts leading to the upper respiratory tract and gastrointestinal tract, or through the conjunctiva into limbal superficial cells into the inner eye, where distribution *via* the blood or nervous system appears to be possible. Virus pathogenesis through tear and conjunctiva has been established in animal models of several coronavirus eye diseases, and preliminary research have shown that SARS-CoV-2 may do the same in humans. Given that COVID-19 cases have reached pandemic proportions and are on the rise, it is vital to recognize the illness's ocular manifestations and avert potentially vision-threatening effects. Coronaviruses may be transmitted between animals and humans through evolution, therefore investigating them in animal models could be crucial in the future to discover further elements of ocular involvement. It is recommended that health care and individual personnel take steps to avoid infection and limit viral transmission. More study is needed to understand the transmission pathways and the alternatives for COVID-19 prevention and therapy disseminated through the ocular surfaces for prompt recovery of the patients.

KEYWORDS: COVID-19, ocular associations, animal models, prevention and control

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1. INTRODUCTION

People are witnessing a global crisis in the form of the COVID-19 pandemic, which has affected both physical and mental well-being of individuals. SARS CoV-2 started raising its head by the end of 2019 and continues to be a global pandemic in the present day. As per the World Health Organization, over 318 million people worldwide have confirmed COVID-19 infection as of March 12, 2022, with over 6 million people dying from the disease and its complications (Anonymous, 2022). SARS CoV-2 and its far-reaching impacts are predicted to persist as it continues to mutate. COVID-19 is primarily characterized by fever and severe respiratory illness or pneumonia, other manifestations includes ophthalmic, neurological, cardiovascular, gastroenterological, and nephrological involvement (Leung et al. 2020, Inomata et al. 2020). SARS CoV-2 have been linked to a variety of diseases in birds and mammals. These range from common household animals like the cat (feline) and dog (canine) to large animals like beluga whales (Mihindukulasuriya et al. 2008, Tekes et al. 2016, Van Nguyen et al. 2017). The ability of coronaviruses to acquire mutations that facilitate transmission from animal to human has made it a zoonotic pathogen of concern (Woo et al. 2009). Coronaviruses can cause serious sight affecting ocular complications in wide range of animals, including anterior uveitis, retinitis, vasculitis, and optic neuritis in feline and murine species suggesting it to shed and infect ocular structures (Seah et al. 2020). Animal model research has also demonstrated association of retina with retinal vasculitis (Chin et al. 2014), retinal degeneration (Wang et al. 2000), and breakdown of the blood-retinal barrier (Vinores et al. 2001). However, ocular abnormalities associated with COVID-19 are essentially unstudied. The eye is a significant entrance point for microorganisms (Siedlecki et al. 2020). Direct transmission, such as sneezing or coughing into the eyes, or indirect transmission, such as transfer from contaminated surfaces to the eyes *via* the hands, are both possibilities. It is yet uncertain if COVID-19 may be caused just by ocular exposure, while one potential pathway could be drainage to the respiratory tract *via* the nasolacrimal duct (Qing et al. 2020). Conjunctivitis (pink eye) is linked to coronavirus in both humans and animals (Seah et al. 2020), although numerous additional ophthalmic consequences have been documented, which might result in vision loss or eye discomfort (Mirshamsi et al. 2021). According to several studies, individuals who reported conjunctivitis were later discovered to be COVID positive when tested (Ozturker, 2021, Scalinci et al. 2020). The present article focuses on the probable correlations between coronavirus and ocular issues in various animal models, directly or indirectly associated with COVID-19, during and after illness recovery. It also attempts to dwell upon the preventive techniques to reduce and prevent such occurrences to enable initiation of early treatment to avoid life and eyesight threatening sequelae.

2. OCULAR PATHOPHYSIOLOGY OF CORONAVIRUSES

Ophthalmic signs may be the first sign of COVID-19 infection, or they may appear several weeks later. The most commonly described symptom is conjunctivitis, which can arise at any stage of the illness. Research on the influence of animal coronaviruses on the eye suggests presence of conjunctivitis in cats (Hok et al. 1989, Stiles et al. 2014). In a study of cats infected with feline CoV (FcoV), 90% of the infected cats exhibited conjunctivitis, and the FcoV antigen was detectable in their conjunctiva (Hok et al. 1993). A study of camels infected with MERS-CoV revealed that viral RNA may be identified in high amounts in conjunctival swabs in the early stages of the disease (Chen et al. 2020a). These few studies indicate some influence of conjunctiva in animals by coronavirus infections. The findings in the eye are triggered by a direct effect of the virus, immune-mediated tissue destruction, activation of the coagulation cascade, and a prothrombotic state created by the viral infection, as well as the accompanying comorbidities and medicines used in care (Sen et al. 2021). Animal studies imply that ocular diseases may include optic neuritis, an increase in the incidence of ischemic or inflammatory optic neuropathies cases associated with COVID-19 has yet to be described in the literature (Seah et al. 2020). Furthermore, Sialodacryoadenitis virus (SDAV), the rat coronavirus has also been reported to invades acinar and epithelial cells of the lacrimal gland with a high viral load, producing degenerative and atrophic changes in the gland (Wickham et al. 1997).

SARS-CoV-2 infects mammalian cells through the transmembrane protein, angiotensin-converting enzyme 2 (ACE2), expression of which has been identified on the surface of numerous structures of the eye, including the conjunctiva and cornea provides potential for eye entry for SARS-CoV-2 (Chen et al. 2020b). Thus, the conservation and expression patterns of ACE2 may give useful insights towards tracking SARS-CoV-2 carriers. Moreover, the expression of ACE2 genes in the skin and eyes of cats and dogs showed that these animals may be involved in the transmission of SARS-CoV-2 to humans (Sun et al. 2021). The significant conservation of ACE2 genes among common mammals at both the DNA and peptide levels and their high expression in conjunctival and corneal epithelial cells suggests that SARS-CoV-2 might possibly transmit between wide range of mammalian species (Zhao et al., 2020; Deng et al., 2020).

3. ANIMALS, CORONAVIRUSES AND OCULAR MANIFESTATIONS

3.1. *Feline coronavirus*

Feline coronavirus (FCoV) has 2 pathotypes- a avirulent feline enteric coronavirus which can persist in the colon of carrier animals and virulent feline infectious peritonitis virus (FIPV) which is responsible for causing a serious systemic disease in domestic and wild Felidae (Pedersen, 2009). Feline infectious peritonitis (FIP) is a prevalent and often deadly systemic disease of cats that commonly involves ocular lesions including pyogranulomatous anterior uveitis, coroiditis with retinal detachment and vasculitis along with perivascular cuffing (Amesty et al. 2020). Fibrinous and pyogranulomatous inflammation is seen in different organ systems. The uvea, sclera, conjunctiva, retina, and optic nerve have all been shown to have pyogranulomatous inflammation and phlebitis. During systemic viremia, the blood-ocular barrier breaks down, allowing FCoV-infected macrophages to enter the eye and cause severe uveitis (Bauer et al. 2013). Bilateral panuveitis caused by FCoV has been described in lions and sphinx cats, and macrophages with FCoV were detected using immunohistochemistry. (Ziółkowska et al. 2017, Mwase et al. 2015). In natural infections, the ocular lesions are more of the dry form than the wet form of the disease and are mostly concurrent to brain lesions. An increase in the expression of Glial fibrillary acidic protein in Mueller cells is observed in FCoV induced retinitis. Also, the predominance of B cells and plasma underlines the significance of the humoral immune response in the ocular inflammation observed in cats with fatal FIP (Ziółkowska et al., 2017).

3.2. Animal models

Animal models have been used for medical knowledge and research since long back in time (Ericsson et al., 2013) and animal experiments have provided significant insights not only for development of vaccines and antibiotics but also towards understanding human disease processes (Robinson et al., 2019). The effects of coronaviruses are not fully known, although members of this family appear to be capable of infecting and disrupting many eye tissues, including the retina, conjunctiva, cornea, and uvea. The impacts of coronaviruses on the retina are restricted to animal models and have not been reported in humans (Teimouri et al., 2022). In context of coronaviruses and ocular manifestations, previous studies using animal models have highlighted probable association between the two. Furthermore, members of the Coronavirinae subfamily, to which SARS-CoV-2 belongs, have been demonstrated in animal models to sporadically affect ocular tissues and cause uveitis, retinitis, and optic neuritis (Seah et al. 2020)

3.3. Retinal degeneration mouse model

This animal model also known as Experimental coronavirus retinopathy (ECOR) was established using a murine coronavirus namely mouse hepatitis virus (MHV) a betacoronavirus, to examine the genetic and host immune responses contributing to retinal disease (Robbins et al., 1990). When the JHM strain of mouse hepatitis virus is injected intravitreally into BALB/c mice it results in a biphasic disease. Development of acute virus induced retinitis in susceptible BALB/c mice is observed from 3rd to 7th day post inoculation which progresses to chronic retinal degeneration from the 20th to 100th day. However, when MHV is injected into resistant CD-1 mice, only the acute infection is observed and the late retinal degenerative phase of the disease is absent (Wang et al., 1996). In the acute phase, infectious virus could be detected within the retina and the retinal pigment epithelium (RPE) (Wang et al. 1993) followed by infiltration of immune cells like macrophages, CD4 T cells and CD8 T cells in the retina is evident (Hooks et al., 2003). In the chronic degenerative disease, a progressive loss of photoreceptors, ganglion cells and RPE cells occurs. The degenerative phase may be attributed to host responses to the infection (Detrick et al., 2008). In an earlier study, it was reported that the retinal degeneration was associated with increased release of TNF-a/TNF receptors along with a down-regulation of Nitrous Oxide. They further suggested that these alterations led to autoimmune reactivity (Hooper et al., 2005). Infection with induced MHV originates in the RPE and ganglion cells and progresses to photoreceptors, Müller cells, and the inner retinal layers' optic nerve (Robbins et al. 1990). There are various methods for inoculating mice with MHV. Primarily pathological alterations in the retina have been detected following injections into the eye's anterior chamber (AC) and cerebral hemisphere. Long-term retinopathy is also caused by viral inoculation in AC. MHV possesses tropism in contrast to several retinal cells, including neural retina and RPE, due to presence of particular MHV receptors found on the surface of these cells (Rasoulinejad et al., 2015a, Rasoulinejad et al. 2015b, Chen et al. 2020a). Significantly, when mice with different genetic origins were inoculated with the virus, the retinal degeneration process was only initiated in genetically vulnerable hosts. It is uncertain if COVID-19 individuals will experience uveitis, retinal vasculitis, or retinal degeneration throughout their convalescence. However, animal model systems of RNA viruses in the area of emerging infectious diseases (e.g. Ebola, Marburg) have mimicked human clinical results (Larsen et al., 2007, Cooper et al., 2018).

3.2.2. Experimental infection of non-human primates

In earlier studies while trying to unravel the mechanisms of SARS-CoV and MERS-CoV infections, Nonhuman primates were infected with SARS-CoV *via* the conjunctival route. Viral replication was evident along with the development of neutralizing antibodies 8-weeks post infection. The conjunctival route was found to be more efficient in comparison to intravenous injection (Lawler et al., 2006). Similarly, in Rhesus macaques infected with MERS-CoV *via* intratracheal, intranasal, oral, and ocular surface routes, virus could be detected in conjunctival swabs by 3 days post infection. However, the virus was no longer present by the 6th day suggesting that conjunctival testing would be useful during the early stages of the disease (Armstrong et al., 2021).

Similar studies for understanding probable extra respiratory routes for SARS-CoV-2 showed that nasal and throat swabs collected from conjunctively inoculated cynomolgus macaques had detectable viral RNA 1st –7th day post-inoculation. A higher viral load was observed in the nasolacrimal system in the conjunctively infected animal than the intratracheally infected one. Moreover, presence of mild interstitial pneumonia indicated distinct virus distributions. The researchers opined that the lacrimal duct could function as a channel draining the virus from the ocular tissues to respiratory tract tissues (Deng et al., 2020).

4. COVID-19 AND OPHTHALMIC RELATEDNESS IN HUMANS

The eyes, which have not been initially the focus of attention, have become one of the more interesting organs affected by COVID-19 for three reasons. First, the lacrimal duct has been used to describe transmission from the eyes into the nose and upper airways (Qing et al., 2020). Second, some COVID-19 patients have ocular symptoms such as kerato-conjunctivitis, epiphora, and chemosis during the acute stage (Wu et al. 2020, Xia et al., 2020). Third, the viral Spike protein binds to the ACE2 receptor and the transmembrane protease serine 2 (TMPRSS2), allowing SARS-CoV-2 to enter the host body (Zhou et al., 2020, Hoffmann et al. 2020) found both in tissue of the eye. SARS-CoV-2 infection *via* the eyes appears to have two possible routes. Either through the tear film and draining tear ducts into the upper respiratory tract and gastrointestinal tract, or potentially through the conjunctiva into limbal superficial cells into the inner eye, where distribution *via* the blood or nervous system appears to be conceivable (Napoli et al., 2020).

Cross-antigenicity can arise when a new virus or bacterium infects a body. This implies that certain viral antigens mirror those found in the body, eliciting an immunological response throughout the body, including the eyes (Ahmed, 2021). COVID-19 deprives the entire body, particularly the brain of oxygen, which can result in eye and vision problems. Coronaviruses can cause eye problems and are a common entrance route for viruses in people. A 2021 study (Coroneo et al., 2021) highlights that the eyes may be an underappreciated but possible route for SARS-CoV-2 transmission. The most likely method of transmission, according to researchers, is direct contact with the mucous membranes of the eye (Hu et al., 2020). As a result, if a person comes into contact with a contaminated surface and then touches their eye, they may become infected with SARS-CoV-2. It can potentially enter the eye *via* aerosol droplets if a person bearing the virus coughs or sneezes. Thus, regular evaluation of a COVID-19 patient hospitalised with moderate to severe infection should include clinical examinations such as visual acuity charting, pupillary examination for light reflexes, extra ocular movements assessment, and eliciting sinus discomfort to rule out any eye disorder.

5. OCULAR COMPLICATION POST RECOVERY

Recently, the post-COVID syndrome or post-COVID condition (Anonymous, 2021) has been proposed, taking into consideration the high frequency (from 10% to 35% of SARS-CoV-2 patients) who continue to have symptoms after the disease's acute phase (Nalbandian et al., 2021). According to a Times of India report, among recovered COVID patients, there has been a rise in the detection of ocular surface inflammation in eye and retinal vasculitis (clotting in the eye), which was mistaken for the frightful mucormycosis (Ahmed, 2021). A study (Benz-Yakov et al., 2021), where a previously healthy individual, 20 days after recovering from a COVID- 19 was diagnosed as Multi system inflammatory syndrome in adults which is a post infectious inflammatory syndrome that tends to present several weeks after recovering from COVID-19 infection (Tenforde et al., 2021, Hekimian et al., 2021, Morris et al., 2020). Another study found that long-term COVID can cause nerve fibre loss and an increase in dendritic or key immune cells in the cornea, which can assist diagnose long COVID (Bitirgen et al., 2021). Corneal confocal microscopy (a real-time, noninvasive, high-resolution imaging laser technology) identifies corneal small nerve fibre loss and increased dendritic or key immune cells in patients with long-term COVID, especially those with neurological symptoms (Bitirgen et al., 2021). Such approaches might be utilised to identify patients with long COVID objectively. The ability of clinicians to objectively identify individuals with long COVID will allow them to identify those with a specific condition and also open the way for evaluating the efficacy of medicines that may aid in nerve restoration. Data on the long-term effect of COVID-19 on visual function and ocular architecture following infection are currently inadequate; the long-term hazards are still being investigated, and hence further studies are required to identify the long-term concerns.

6. TACKLING EYE HEALTH RELATED

ISSUES: PREVENTION AND CONTROL STRATEGIES

COVID-19 ocular involvements can be broad and non-specific, and might emerge as the first symptoms, ophthalmologists must be alert in recognizing possible COVID-19 patients (Zhong et al., 2021). The ocular surface is a putative route of such transmission by the deposition of respiratory droplets on a surface followed by hand eye contact, or aerosolized droplets. SARS-CoV-2 in conjunctival tissues might be a source of infection, especially in severely ill individuals with significant viremia. Irrespective of whether patients with SARS-CoV-2 have a symptomatic or asymptomatic ocular presentation, healthcare professionals must exercise extreme caution during patient examination to minimise cross-infection. Further, the American Optometric Association (Amesty et al., 2020) recommends the following precautions to protect the eyes: guarding the eyes and wearing safety goggles, avoiding touching the eyes, washing hands frequently and avoiding touching the eyes with unwashed hands, keeping at least 6 feet away from people who are coughing or sneezing, cleaning and disinfecting areas that people share, such as light switches, doorknobs, and phones, avoiding using contact lenses when sick, and disinfecting lenses according to the manufacturer's instructions for those who do not use disposable lenses. Ophthalmologists should notify instances associated with COVID-19 to add to the worldwide reservoir of information in order for researchers to get new insights for improved prevention and treatment. More study is needed to understand the mechanisms of transmission as well as the possibilities for prevention and treatment of SARS-CoV-2 *via* the ocular surfaces.

7. CONCLUSION

In light of that COVID-19 reaching pandemic proportions, identifying its ophthalmic manifestations is critical in order to avoid potentially vision-threatening consequences. Coronaviruses may transmit between animals and people through mutations, therefore exploring them on animal models may be useful in the future to investigate additional aspects of ocular involvement. Further studies are needed to understand the processes of transmission and the possibilities for COVID-19 prevention and treatment *via* the ocular surfaces in order for the patient to recover quickly.

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