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Coronavirus infection and ophthalmology

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Abstract

This article presents a review of the ocular manifestations of coronavirus disease 2019 (COVID-19) by using materials of Russian and international researchers. After the outbreak of COVID-19 began in China in December 2019, isolated works on ocular manifestations of coronavirus infection began to appear in the literature. The review article summarizes data on the origin and species of viruses that infect humans, the structure of coronaviruses, and intermediate hosts of the virus. A separate chapter is devoted to the mode of transmission for infectious. It is shown that the main route of COVID-19 transmission from person to person is airborne. Of great interest to the ophthalmologists is the review of works devoted to the virus detection in the conjunctival sac. In particular, some studies have shown that in patients with COVID-19, the virus is present in the lacrimal fluid. According to the authors, it indicates that coronavirus might be transmitted through the conjunctiva. These statements are confirmed by clinical and experimental researches. The presence of coronavirus in tears indicates the possibility to cause disease by the ocular route. That is a potential infection source for different types of physicians during routine examinations of patients, and especially by ophthalmologists. Therefore healthcare workers should wear eye protection when dealing with patients who may have COVID-19. Ophthalmologists must take necessary safety precautions, even in conducting a routine physical examination. It is also worth noting that conjunctivitis can be the first symptom of COVID-19. It is proved that the virus in the conjunctiva was detected even in patients without symptoms of eye inflammation. Also interesting for researchers is the manifestations of coronavirus infection in animals, which, according to the authors, is essential for understanding the possible mechanisms of disease development and manifestations in humans.

Keywords: coronavirus, COVID-19, ophthalmology, conjunctiva.

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In December 2019, 41 cases of atypical pneumonia were recorded in the Chinese city of Wuhan, Hubei Province, China. Further investigation revealed that most of the patients had visited a seafood market prior to developing symptoms. On December 31, 2019, Chinese authorities informed the World Health Organization (WHO) of a viral outbreak of pneumonia. A week later, on January 7, 2020, the Chinese Center for Disease Control and Prevention confirmed that this atypical pneumonia was caused by a novel coronavirus, 2019nCoV [1]. The disease was later called COVID-19, and the pathogen was identified as SARS-CoV-2 [2,3]. The origin of the new coronavirus remains unknown; however, experts believe that its initial host is a species of bat [4].

On January 25, 2020, the WHO confirmed that SARS-CoV-2 is transmitted from person to person [5]. As early as January 31, 2020, the WHO described the COVID-19 outbreak as a public health emergency of international concern [6]. On March 11, 2020, the WHO announced a COVID-19 pandemic. As of April 8, 2020, 1,356,780 confirmed cases of infection in 212 countries have been recorded worldwide [7].

Coronaviruses are known to cause zoogenous infections characterized by mild sporadic cases of acute respiratory disease in humans [8]. However, this understanding changed after the outbreak of severe acute respiratory syndrome (SARS) caused by SARS-CoV in 2002–2003 [9]; this outbreak infected 8,098 people, 774 of whom died, in 29 countries [10, 11]. The Middle East respiratory syndrome caused by MERS-CoV in 2012–2019 resulted in 2,502 infections in 27 countries with 861

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lethal outcomes [12–14]. Among 2,223 laboratory-confirmed cases of MERS-CoV, 415 involved medical personnel [15].

Coronaviruses: structure and host

Coronaviruses are enveloped viruses containing single-stranded ribonucleic acid (RNA) and belong to the order Nidovirales, family Coronaviridae., which includes two subfamilies, Orthocoronavirinae and Letovirinae. The Orthocoronavirinae subfamily includes four genera, namely, *Alphacoronavirus*, *Betacoronavirus, Gammacoronavirus,* and *Deltacoronavirus*. As a rule, α- and β-coronaviruses infect mammals and γ- and δ-coronaviruses infect birds [16,17]. Currently, seven types of human coronavirus are known: human coronavirus 229E, human coronavirus NL63 (an α-coronavirus), betacoronavirus 1–OC43, human coronavirus HKU1, MERS-CoV (line C), SARS-CoV (line B) [17], and SARS-CoV-2 (line B; β-coronavirus).

The coronavirus genome, which includes 26,000–32,000 nucleotides, is approximately two or more times larger than any of the other viral RNA genomes [17,18]. The virion of representatives of the Orthocoronavirinae subfamily has a spheroidal shape with a diameter of 120–160 nm. The virions of all coronaviruses have a lipid membrane with club-shaped peplomers measuring 5–10 nm long formed by protein S trimers. The presence of these peplomers, which resemble corona teeth, are the basis of the names of members of the entire Coronaviridae family [17,19]. Besides protein S, the viral genome encodes the main structural proteins, namely E (small envelope protein), M (membrane glycoprotein), and N (nucleocapsid protein).

The genes of non-structural proteins of the replicative complex occupy two-thirds of the genome and are translated into a large polyprotein consisting of 16 proteins. These genes are conserved for all coronaviruses [17,20]. S-protein is responsible for binding to the receptor and subsequent penetration into the host cell; therefore, it is considered a main target for therapy [17,21–24]. M-protein has three transmembrane domains and gives the virion its shape; this protein allows the membrane to bend and forms the virion particles [17,25,26]. E-protein is necessary for viral assembly and departure from a cell; it plays a significant role in the disease pathogenesis [17,27,28]. A nucleocapsid has helical symmetry and is formed by phosphorylated protein N containing two domains in complex with the virion RNA [17,19,29–31]. N-protein is also an interferon antagonist and suppressor of RNA interference; thus, it facilitates viral replication [17,32].

Coronaviruses are known to affect a wide range of birds and mammals, including domestic animals, such as cats and dogs, and large animals, such as beluga whales [33–35]. The ability of coronaviruses to mutate is of great concern because this ability contributes to the transmission of the virus from animals to humans [36]. The origin of MERS-CoV and SARS-CoV is associated with animals such as bats [37].

Epidemiological and biological characteristics of coronaviruses

Bats are the main natural reservoir of the three species of coronaviruses causing outbreaks of SARS-CoV, MERS-CoV, and SARS-CoV-2 infections. Transmission of the virus from bats to humans presumably occurred through an intermediate host, such as civets (SARS-CoV) [17], one-humped camels (MERS-CoV), or other unconfirmed animal species (SARS-CoV-2), including bats, civets, pangolins [17,38–40].

SARS-CoV, MERS-CoV, SARS-CoV-2 are transmitted from animals to humans and from humans to humans. The main transmission routes from person to person include the air and direct contact for SARS-CoV and SARS-CoV-2 and direct contact for MERS-CoV. The predominant transmembrane receptor for SARS-CoV and SARS-CoV-2 is angiotensin-converting enzyme (ACE2), while that for MERS-CoV is a dipeptidyl peptidase (DPP4). ACE2 is distributed in the body through the vascular endothelium, smooth muscle of arteries, small intestine, respiratory tract epithelium, alveolar monocytes, and macrophages; DPP4 is distributed through the epithelium of the respiratory tract, kidneys, small intestine, liver, prostate gland, and activated leukocytes [37,38].

Fecal–oral transmission. During the SARS-CoV outbreak in a residential complex in Hong Kong in 2003, the virus was most likely transmitted through sanitation [41]. Later reports revealed that SARS-CoV RNA could be detected in the feces of infected patients and even in wastewater that had not been disinfected adequately [42]. Today, SARS-CoV-2 is known to be transmitted through the fecal–oral route [43].

Optic transmission. Studies on the tears of patients with severe acute respiratory syndrome revealed the presence of SARS-CoV nucleic acids [44]. Examination of the chromosomes of SARS-CoV and SARS-CoV-2 revealed an 82% match [45]. A number of authors have suggested that SARS-CoV-2 is transmitted through the mucous membranes, including the conjunctiva [46].

The case of Guangfa Wang, a member of the SARS-CoV-2 National Expert Group, is widely known. Dr. Wang was infected with SARS-CoV-2 in January 2020 during an inspection in Wuhan.

He was wearing a protective overalls and an N95 mask but had no eye protection. Several days prior to the development of pneumonia, the doctor complained of eye redness. Subsequent investigations suggested that infection occurred through the doctor's unprotected eyes [47].

Cases of SARS-CoV-2 infection of ophthalmologists during routine examinations of patients have been reported [46].

Studies on the presence of SARS-CoV-2 in the conjunctival secretions of patients with COVID-19 confirmed by reverse-transcription polymerase chain reaction (RT-PCR) are of great interest for ophthalmologists. Several works reporting the detection of the virus in the tear fluids of SARS-CoV-2 patients have been published [48–50].

Wei Deng et al. [51] proved the possibility of SARS-CoV-2 infection through the conjunctiva via an experiment involving three male Rhesus macaques. Two of the animals underwent conjunctival grafting with tissue culture of SARS-CoV-2. On the third animal, grafting was performed intratracheally to compare the transmission routes of the virus. For the conjunctival route, the maximum viral load was determined in the lacrimal gland, optic nerve, and conjunctiva. The authors thus concluded that Rhesus macaques can be infected with SARS-CoV-2 through the conjunctival route.

The current situation is aggravated by the fact that the virus can be transmitted during the incubation period, as well as by patients with an atypical or mild course of infection or those in the convalescence period; these routes have been established in both the clinical and laboratory settings [52, 53].

Ocular manifestations of coronavirus infection in animals

Feline coronaviruses are α-coronaviruses that infect wild and domestic cats. In animal shelters, up to 90% of the animals are seropositive; in domestic cats, this indicator is 20%–60% [54]. Two biotypes of coronavirus have been observed in felines, namely, the intestinal biotype and infectious peritonitis virus. In most cases, the disease process is benign and proceeds in the form of diarrhea [55]. In approximately 5% of all cases, peritonitis develops [56, 57]. When monocytes and macrophages are affected, vasculitis, which causes granulomatous and exudative reactions, occurs in infected cats [58]. The manifestations of vasculitis are multisystemic and often include recurrent conjunctivitis. In 90% of cats, coronavirus is found in the conjunctival cavity [59]. Specifically, granulomatous uveitis, retinal detachment, and retinal vasculitis may be observed [60].

Murine coronaviruses are divided into two biotypes. One biotype mainly affects the gastrointestinal tract, while the other affects many organs, such as the central nervous system, liver, and lungs. In medicine, these viruses are used to create experimental models of pneumonia, multiple sclerosis, and hepatitis [61–63]. Coronaviruses in mice can affect glial cells, astrocytes, oligodendrocytes, and retinal microglia [64]. Neurotropic strains of murine coronaviruses are essential in experimental ophthalmology. Two strains of murine coronavirus are used to create experimental models of virus-induced retinal degeneration and optic neuritis [65–67].

General and ocular manifestations of coronavirus infection in humans

General manifestations. Human coronaviruses are widely known to cause respiratory infections. Strains 229E, NL63, OC43, and HKU1 mainly cause upper respiratory tract infections accompanied by symptoms such as rhinorrhea, pharyngalgia, fever, and cough [68]. However, if the infection develops in the presence of cardiovascular diseases or immunosuppressive conditions, they can cause pneumonia or bronchitis [69].

SARS-CoV, MERS-CoV, and SARS-CoV-2 cause respiratory failure in the severe course of the disease. An atypical course featuring asymptomatic infection, i.e., the result of laboratory tests for SARS-CoV-2 is positive but no clinical symptoms are observed, has been reported. Unfortunately, patients who are asymptomatic or have mild forms of the disease, as well as patients in the convalescence period, have been proven to be sources of infection in the clinical and laboratory settings [52].

General manifestations of SARS-CoV-2 infection. In most cases, the infection is mild [70–73]. The main symptoms of the disease include fever, fatigue, muscle pain, and cough [70, 72, 74, 75]. Symptoms such as diarrhea, tachycardia, headaches, chills, pharyngalgia, and anorexia are relatively less common [72, 74, 76, 77]. SARS-CoV-2 patients have been reported to exhibit neurological symptoms, likely due to the neurotrophy of the virus. SARS-CoV-2 and SARS-CoV, which has been demonstrated to induce nerve cell damage, are highly similar [78]. Symptoms such as anosphresia and ageusia, which have been observed in some patients at the incubation phase of the disease, can confirm the occurrence of neurotrophy [79–81].

After the emergence of SARS-CoV-2, isolated reviews on the role of coronaviruses in ophthalmology appeared in the literature [82, 83].

Ocular manifestations. The first reports of the ocular manifestation of coronavirus diseases appeared after the outbreak in 2004. Coronavirus NL63 was isolated in a 7-month-old child with SARS. Besides lung damage, the patient had con-

junctivitis [84]. This finding aroused great interest. Later, in France, a retrospective study of smears from the nasal mucosa of children who had acute respiratory infections from 2000 to 2003 was conducted to detect coronavirus NL63; in this work, 17% of the cases (3 out of 18 pediatric patients) had conjunctivitis symptoms [85].

The emergence of studies on the detection of SARS-CoV in patients' tears has caused great concern among medical professionals. Lacrimal fluid samples were studied in 36 patients with SARS-CoV-induced pneumonia, and three cases were found to have viral RNA. In one case, RNA was detected in fecal, tear, and respiratory tract samples; in another case, viral RNA was observed in fecal and tear samples (a respiratory swab was not presented). Finally, in the third case, only tear samples were presented. The results of this work led to the conclusion that coronavirus infection could be transmitted through the eyes; thus, the need for eye protection is imperative when in contact with patients infected with SARS-CoV [44].

In one study, conjunctival scrapings and tears from 17 patients with confirmed SARS-CoV-induced pneumonia were examined for viral RNA; however, no sample revealed viral RNA. The authors offered several reasons for this finding. First, the amount of virus in the sample may have been too low for detection by PCR. Second, material sampling was performed only once and the viral load at the time the samples were collected may have been low. Third, SARS-CoV may not actually affect the eyes [86].

Results such as those obtained from the study above reflect contradictions in terms of the eye damage caused by SARS-CoV infection. The researchers were unable to come to a definitive conclusion because the epidemic was quickly controlled. The route of viral entry through the conjunctival cavity remains unclear. One hypothesis states that such entry occurs via the hematogenous route into the lacrimal gland; according to another hypothesis, the virus enters the eyes through the nasolacrimal canal and the mucous membranes of the respiratory tract through the aerosol route [87].

Ocular manifestations of SARS-CoV-2. The pneumonia specialist Guangfa Wang developed conjunctivitis while working with patients at the epicenter of the SARS-CoV-2 disease outbreak and subsequently tested positive for SARS-CoV-2. At work, the doctor used protective overalls and an N95 mask but had no eye protection. He eventually recovered [47]. This case sparked appeals to study the possibility of infection transmission through alternative routes, specifically, through the mucous membrane of the eyes.

After this incident, the WHO published a set of measures to protect personnel from infection during contact with SARS-CoV-2 patients; these new measures included wearing safety glasses to protect against transmission through the eyes [88].

In the literature, research providing data on attempts to detect SARS-CoV-2 in the conjunctival cavity. Liang Liang and Ping Wu, ophthalmologists at the multidisciplinary Central People's Hospital of Yichang City, Hubei Province, China, examined 37 patients with SARS-CoV-2-induced pneumonia to detect the virus in the conjunctival cavity. In this work, 12 patients had a severe course of the disease and the remaining patients had moderate pneumonia. Three patients had conjunctivitis symptoms. In one patient with severe pneumonia, the virus was found in the conjunctival cavity. No signs of inflammation of the conjunctiva were observed. In the remaining 36 patients, conjunctival secretion tests for coronavirus were negative [49].

A prospective study on the presence of SARS-CoV-2 confirmed by RT-PCR in the conjunctival secretion of patients with atypical pneumonia is of great interest. The virus was detected in a patient at an early stage of the disease (i.e., day 3), at which point no severe fever or respiratory symptoms had yet manifested [48].

On March 31, 2020, the work of a group of researchers from the People's Republic of China was published; this work aimed to study the ophthalmic symptoms of COVID-19 in hospitalized patients. The study included 38 patients with a confirmed diagnosis of COVID-19. General symptoms and ocular manifestations were evaluated, computed tomography of the chest and blood tests were performed, and RT-PCR of smears from the nasopharynx and conjunctiva for the presence of SARS-CoV-2 was carried out. In 2 (5.2%, 95% confidence interval 0.6–17.8) of 38 patients, SARS-CoV-2 was detected in the conjunctiva by RT-PCR. Moreover, 12 (31.6%, 95% confidence interval 17.5–48.7) out of 38 patients had ocular manifestations in the form of conjunctivitis, especially conjunctival injection, chemosis, lacrimation, or increased secretion. The general condition of these 12 patients was estimated as moderate in four cases, severe in four cases, and critical in six cases according to the classification of the PC-NCP manual [89]. These findings suggest that ocular symptoms usually appear in patients with severe pneumonia.

Analysis revealed that patients with ocular symptoms have higher leukocyte and neutrophil counts and higher levels of procalcitonin, C-reactive protein, and lactate dehydrogenase compared with patients without ocular symptoms. In addition, 11 out of 12 patients had ocular abnormalities. Two

(16.7%) out of 12 patients tested positive for SARS-CoV-2 using swabs obtained from the conjunctiva and nasopharynx. In one patient, conjunctivitis was the first symptom of SARS-CoV-2 [50].

Conclusion

Besides the airborne route, coronavirus infections may spread through alternative routes. Infection through the mucous membrane of the eyes, for example, which has been clearly demonstrated by cases of viral detection in conjunctival secretions, is possible. The conjunctiva may simultaneously represent an entrance gate for infection and a source of infection. While this route of infection is not the main one, understanding that it is possible can help prevent new infections from developing.

Our findings highlight the need to observe special safety measures when working with patients confirmed with COVID-19, as well as those patients with suspected coronavirus infection. Besides common precautionary measures, the use of protective spectacles appears to be necessary. In ophthalmology clinics, the use of special protective screens during routine ophthalmological examinations, such as biomicroscopy, ophthalmoscopy, and tonometry, is mandatory because nearly all eye examinations are conducted with very close contact between doctor and patient. The literature confirms that conjunctival damage is the first symptom of SARS-CoV-2 infection. Indeed, that the virus was present in the conjunctival cavity of patients without symptoms of conjunctivitis is an alarming finding.

Whether the virus can enter the human body through the eyes must be examined. The prevailing transmembrane receptor that allows the penetration of SARS-CoV and SARS-CoV-2 is ACE2. These receptors are not found in the conjunctiva or cornea but are present in the nasolacrimal canal and nasal cavity. The epithelium of the respiratory tract is damaged there.

Lesions may develop in the posterior segment of the eyeball. ACE2 appears to be present in the retina and aqueous humor [90,91]. Viral neurotrophy is evidenced by the emergence of neurological symptoms in SARS-CoV-2 patients, anosphresia, and ageusia. Damage to the vascular tract of the eye, retina, and optic nerve in animals with coronavirus infection suggests potential areas of eye damage in humans. The possibility of genome mutation is an alarming issue because mutations could lead to viral transformation *in vivo*. While these suppositions require further study, the likelihood of uveitis and lesions of the retina and optic nerve in patients with coronaviruses cannot be ignored. Thus, screening for coronavirus infection in patients with inflammatory diseases of the posterior segment of the eye of unknown etiology may be a reasonable undertaking.

CONCLUSIONS

1. The virus can be contained in the conjunctival cavity of SARS-CoV-2 patients, and an inflammatory reaction may not occur in all cases.
2. Conjunctivitis may be the first symptom of SARS-CoV-2 infection.
3. Healthcare workers should understand that the ocular surface represents a potential hazard in all patients.
4. Healthcare workers must wear safety glasses.

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