COVID-19 IN OPHTHALMIC PRACTICE

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The end of 2019 in China was marked by the breakout of the new Coronavirus Disease (COVID-19) caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Gradually, the infection spread around the world and in March 2020, the World Health Organization (WHO) declared Covid-19 a pandemic. The new coronavirus disease 2019 is highly contagious, causing respiratory distress syndrome and poses a huge threat to public health, especially in patients. with serious concomitant diseases such as diabetes mellitus, bronchial asthma, hypertension, etc. Many scientists have put forward the idea that COVID-19 can be transmitted through the eyes through contact and everyday life. Over the past six months, works on the ocular manifestations of coronavirus infection have begun to appear in the literature. We conducted a systematic review of scientific articles from the PubMed, e-Library, Scopus databases in order to conduct a meta-analysis of the effect of coronavirus infection on the eyes and its ophthalmological manifestations.

Keywords: coronavirus infection, COVID-19, coronavirus, coronavirus conjunctivitis

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COVID-19 В ОФТАЛЬМОЛОГИЧЕСКОЙ ПРАКТИКЕ

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Конец 2019 г. в китайском городе Ухань был отмечен вспышкой новой коронавирусной болезни (COVID-19), вызванной SARS-CoV-2. Постепенно инфекция распространилась по всему миру и уже в марте 2020 г. Всемирная организация здравоохранения объявила COVID-19 пандемией. Новая болезнь высококонтагиозна, вызывает респираторный дистресс-синдром и представляет собой огромную угрозу для здоровья населения, особенно у пациентов с серьезными сопутствующими заболеваниями, такими как сахарный диабет, бронхиальная астма, гипертоническая болезнь и др. Выдвинуты предположения, что COVID-19 может передаваться через глаза контактно-бытовым путем. За последние полгода в литературе стали появляться работы, посвященные глазным проявлениям коронавирусной инфекции. На основании обзора научных статей базы данных PubMed, e-Library, Scopus проведен метаанализ влияния коронавирусной инфекции на глаза и ее офтальмологических проявлений.

Ключевые слова: коронавирусная инфекция, COVID-19, коронавирус, коронавирусный конъюнктивит

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Coronaviruses are enveloped RNA viruses of the Coronaviridae family. They contain four main structural proteins: spike protein (S-protein), nucleocapsid, membrane and envelope proteins. There is a lipid membrane around the capsid, which contains the proteins. As seen with an electronic microscope, the structure of the virus resembles a crown, hence the name. Nucleocapsid, membrane and envelope proteins mainly contribute to formation and structuring of the virus, while spike protein enables binding to host cells [1–3]. In human beings, these viruses cause respiratory tract infections, their symptoms being nasal congestion, rhinorrhea, sore throat, fever, cough, fatigue, muscle pain. The less common symptoms are diarrhea, tachycardia, headaches, chills, anorexia. In most cases, COVID-19 takes a mild form, but with cardiovascular diseases or immunosuppressive conditions in the background, the case can become severe and aggravated with respiratory failure. There are also reports of patients that tested positive for SARS-CoV-2 and had the subsequent disease running fully asymptomatic. Such patients can also be a source of infection [2–5].

Primarily, the virus is transmitted between people via airborne and contact routes. Receptors of angiotensin-converting enzyme 2 (ACE2), to which the virus's S-protein binds, enable infection of the cells. ACE2 receptors can be found in vascular endothelium, smooth muscles of the arteries, small intestine, respiratory tract epithelium, alveolar monocytes and macrophages. The contact route lies through the MERS-CoV (Middle East COVID-19 infection) receptor — DPP4 (dipeptidyl peptidase). DPP4 receptors are found in the respiratory tract epithelium, kidneys, small intestine, liver, prostate gland, and activated leukocytes [1–4].

While COVID-19 is primarily a viral pneumonia, in some patients SARS-CoV-2 caused eye disorders [1, 2, 6, 7]. Unfortunately, there is not much data on the effects COVID-19 has on the eyes. Following the spread of the infection, only a few reviews and clinical observation reports were published that covered coronaviruses from the ophthalmological perspective [4, 6–12].

Some researchers believe that SARS-CoV-2 may spread through mucous membranes, including the conjunctiva, in addition to the airborne and contact routes [2].

There is a well-known case of SARS-CoV-2 infection that exemplifies the point: a member of the National Group of

SARS-CoV-2 Experts got infected while wearing a protective suit and a mask but no glasses to protect the eyes. A few days before his pneumonia developed, he complained of red eyes. Thus, it can be assumed that the virus got in through the unprotected eyes.

Another case report describes a 65-year-old diabetic man who initially had eye-lesion and only two days after his first complaint developed a fever. This patient tested positive for SARS-CoV-2 (nasopharyngeal swab and PCR test). The authors concluded that all cases of keratoconjunctivitis concomitant with the upper respiratory tract disorder symptoms should be considered possible cases of COVID-19. Since virus RNA was found in the conjunctiva, many researchers deduced that the disease can be transmitted through the eyes [3, 13].

Hypotheses about how the virus lands on the ocular surface

Virus landing directly on the conjunctiva

Most researchers share the opinion that the virus infects the eyes in case infected droplets land on the conjunctiva directly. The studies of great interest are those designed to detect SARS-CoV-2 in the conjunctival secretions of the novel coronavirus pneumonia patients with the help of reverse transcription polymerase chain reaction (RT-PCR) [9]. There is a recorded case of SARS-CoV-2 RNA detection in a two-day conjunctival smear taken from a keratoconjunctivitis patient in Italy. In another case, SARS-CoV-2 was grown in an ocular smear taken from a patient that had been experiencing symptoms of the infection for three days. There are oppositely different cases described, too, when no virus RNA was detected in the lacrimal fluid of an inpatient with conjunctival infection and chemosis but, with respiratory symptoms in the background, that patient's nasopharyngeal smear returned SARS-CoV-2 positive [10, 12].

There are reported cases of detection of the virus in the lacrimal fluid. However, not all studies have confirmed presence of the virus in SARS-CoV-2 patients' tears and conjunctiva scrapings with a PCR test. The lack of such confirmation may be explained by insufficient sensitivity of the test, testing outside of the positive time window eye tissue immunity to SARS-CoV [10, 11].

Virus contraction through the nasolacrimal duct

When the patient has it in the upper respiratory tract, the virus can travel through the nasolacrimal duct and infect the eyes. This hypothesis stems from the case of an ER nurse that worked with SARS-CoV-2 patients. On the first day of the illness, her eyes were excessively red and tear shedding, so she was admitted to the ophthalmological department. No other systemic symptoms were reported except for the moderate temperature of 38.2 °C. Bacterial, hemorrhagic and allergic varieties of conjunctivitis were excluded. The nurse worked in a protective suit, glasses and a medical respirator, but she noted that the glasses did not fit tightly, constantly moved and touched the eyelids with their edges. Chest CT revealed multiple ground-glass opacities in the lungs. Conjunctival and oropharyngeal smears tested for SARS-CoV-2 returned positive results. Based on the epidemiological characteristics, clinical manifestations, chest images, the patient was diagnosed with acute viral conjunctivitis, SARS-CoV-2 infection, and pneumonia. However, there are also opposite cases. In China, conjunctiva biological material and lacrimal fluid were collected from patients having no ocular manifestations of the disease (or any such symptoms) within three weeks after infection. The subsequent examination detected no viral RNA even in samples taken from the patients showing symptoms of an upper respiratory tract infection. The authors of this study concluded that the hypothesis posing tear duct as a virus transmission channel may be questionable and requires further research [13].

Virus exudating from the vessels

There is another route the virus can take to infect the eye. Researchers have reported exudation from the vessels as a path forward for the infection, having discovered that SARS-CoV-2 invades endothelial layer of blood vessels. This, in turn, leads to disruption of blood microcirculation in organs and disruption of their functions.

Examination of the histological material of vessels revealed that COVID-19 patients have walls of their blood vessels showing signs of inflammation. It has been suggested that SARS-CoV-2 triggers a systemic inflammation of blood vessels that can affect heart, brain, lungs, kidneys, and eyes, causing severe microvascular disorders with organ dysfunction. The ACE2 receptor, to which the virus binds with the S-protein, is actively expressed in capillary pericytes. Results of the research efforts have shown that a reduced number of pericytes makes microvascular endothelial cells produce and release blood plasma glycoprotein more actively, this protein enabling platelet attachment to the damaged part of the vessel, which can explain the increased thrombosis development rate. The authors emphasize the fact that their hypothesis is a preliminary one and requires further confirmation [6–10].

Clinical manifestations of eye infection

The clinical manifestations of damage to the eye are diverse. The virus can affect both the anterior and the posterior segments of the eye. According to the published reports, the most frequent complaints are eye redness, itching, blurred vision and tear shedding. As noted above, the infection may spread via ACE2, which makes it interesting to note that epithelial cells of cornea and conjunctiva were found to express ACE2. S240, an isolated surface protein of coronaviruses, can bind to epithelial and fibroblast cells of conjunctiva and cornea epithelial cells, ACE2 enables binding on the cell surface. There is another receptor, CD209, found on the dendritic cells of human cornea and participating in transmission of the infection [3].

Frequently, the eye-related manifestations of the disease at its initial stage take form of conjunctivitis. There are many clinical cases of coronavirus-induced conjunctivitis reported in the published papers. For example, there is a coronavirus conjunctivitis case of a 65-year-old woman who returned to Italy from the city of Wuhan in China. She was admitted to the hospital one day after COVID-19 symptoms manifested. One of those symptoms was bilateral conjunctivitis, which persisted for 16 days. The conjunctival scrapings returned positive for viral RNA for 21 days after admittance.

According to a study on cats, in addition to conjunctivitis, initial stage infection can take the form of anterior uveitis, choroiditis with retinal detachment, neuritis and retinal vasculitis [4, 14, 15].

Numerous reports indicate that vascular changes and thrombotic events, including ischemic brain damage, are among the main complications brought by COVID-19. Based on the aforesaid, there is an assumption that the retina may also be involved in the pathological process [12–15].

Effect of SARS-CoV-2 on the retina

There is little data on the effect SARS-CoV-2 has on the retina. ACE2 virus entry receptors have been found in the retina of rodents and pigs. Ocular tissue of the latter had ACE2 in the ciliary body, vitreous and retina. Rodents' retina had ACE2 expressed in the inner nuclear layer, mainly in Müller's cells [10]. In human beings, ACE2 receptors have also been found in aqueous humor [14–16]. Researchers agree that SARS-CoV-2 can also infect the retina [4].

Among the published materials, there are studies aimed at searching for the virus RNA in the human retina. For example, German scientists have found RNA of the virus in 3 retina samples out of 14 taken from confirmed COVID-19 victims. In that experiment, retinal detachment was induced in order to prevent mixing of the sampled biopsy material with choroidal structures, since blood is another source that can spread the virus [4].

Researchers from Spain reported results of a study of retinal changes in COVID-19 patients. Microangiopathy was found in 22% of patients; it took the form of clusters of velvet spots [16, 17].

Still, it is an open question whether retinal microangiopathy in COVID-19 patients is brought by the virus immediately or if it is a manifestation of other systemic vascular diseases [17, 18]. The damage mechanism requires further investigation. It is interesting to note that ACE2 is the main enzyme of the vasoprotective renin-angiotensin system, and diabetic retinopathy is associated with an imbalance between the renin and the angiotensin-aldosterone system of the retina [16]. A decrease in the ACE2 level may play an important role in triggering development of retinal ischemia and even signal of endothelial dysfunction. There are at least two types of microvascular damage to the retina of COVID-19 patients: first, due to hypercoagulability, a disseminated intravascular coagulation syndrome [19]; second, through a process similar to vasculitis, which is the result of direct viral effect on endothelial cells and diffusive endothelial inflammation. However, despite the fact that patients received heparin, 22% of them, as mentioned above, had microangiopathy. The authors suggested that ophthalmoscopic examination may help identify patients with signs of arterial microangiopathy for whom antiaggregation may be of therapeutic importance [17–19].

Similar changes in the retina, namely vasculitis, were found in children. When examining fundus, authors of one of the studies observed changes in the vessels at the equator of the left eye, as well as perivascular infiltrates and dilated retinal exudates [20].

With the help of optical coherence tomography, some researchers assessed retinal changes in COVID-19 patients and people who recovered from the disease [21]. The patients were examined 11 to 33 days after the onset of COVID-19 symptoms. Two different OCT machines were used: DRI-OCT TritonSweptSource (Topcon; Japan) and XR Avanti SD-OCT (Optovue; California, USA). Every patient examined had normal visual acuity and pupillary reflexes; there were no signs of intraocular inflammation detected. In some patients, fundus ophthalmoscopy also revealed vascular changes, such as velvet spots (infarctions of the retinal nerve fiber layer) and microhemorrhages, which could indicate that the endothelial tissue had also undergone changes. OCT angiography results were within normal limits. In three patients, OCT revealed hyperreflexive lesions at the level of retinal ganglion cells and internal plexiform layers. These OCT results are similar to the results of examination of normal retinal vessels in terms of morphology, reflectivity, location and shadow, which lead the researchers to conclude that OCT results can often be misinterpreted, and the changes found during fundus ophthalmoscopy may signal of other systemic diseases. They stated the need for further research to confirm these results [21].

Experimental CoV retinopathy (ECOR) caused by neurotropic coronavirus strains

Neurotropic strains of coronavirus are of particular importance from the point of view of ophthalmology. There are two major strains studied: the JHM strain (JHMV) and the A59 strain (MHV-A59). They were originally isolated from paralyzed mice and have been found to cause extensive demyelinization and encephalomyelitis. The virus is capable of infecting glial cells, astrocytes, oligodendrocytes and microglia. Today, the retinal degeneration pattern caused by these strains is known as Experimental CoV Retinopathy (ECOR). In mice, presence of the virus in the retina and retinal pigment epithelium leads to infiltration of immune cells and release of pro-inflammatory mediators. The virus clearance is reached in the course of the first week of infection. However, autoantibodies to the retina and pigment epithelium cells form subsequently, with the result being progressing loss of photoreceptors and ganglion cells, as well as neuroretina thinning. According to these findings, retinal damage has an autoimmune component to it [14].

Effect of anti-coronavirus drugs on eye and vision

There have been suggested multiple SARS-CoV-2 treatment options. In addition to antiviral drugs, chloroquine (CQ), hydroxychloroquine (HCQ) and the like drugs are used widely. They are believed to reduce viral replication [22, 23]. Since therapeutic doses of these drugs are rather high compared to the maximum safe daily doses, taking them brings numerous toxic side effects, including those affecting the retina. According to the American Academy of Ophthalmology, the most significant toxicity-related risk factors the retina is exposed to in connection with these drugs are high doses and long duration of use [1, 2, 22, 23].

Researchers at the Royal College of Ophthalmologists in the UK tried to determine a safe dose and duration of CQ and HCQ therapy that would leave the retina unharmed. They recommend to not take more than 5 mg/kg/day of HCQ and keep the course shorter than 5 years. The researchers failed to determine a safe dose of CQ, but made a conclusion that those who received CQ for more than a year ran the risk retina damage [24].

It has been noted that in COVID-19 patients treated with high doses of hydroxychloroquine macular abnormalities have no visual symptoms [24-26].

The mechanism behind the toxic effect hydroxychloroquine has on the retina is unclear. Chloroquine and hydroxychloroquine were shown to strongly inhibit absorption capacity of the organic anion-transporting polypeptide 1A2 (OATP1A2), which is expressed by the human retinal pigment epithelium cells and participates in the complete recirculation of trans-retinol. The authors write about the possible effect of hydroxychloroquine on the visual cycle [25].

Both drugs are reported to damage the photoreceptor layer and the outer nuclear layer of the retina. Chloroquine can also damage inner nuclear layer of the retina. Light absorption and cone cell metabolism may also play a role in the damage. These mechanisms lead to such a characteristic maculopathy

as "bovine eye", which may develop after chronic exposure to both agents, even the safe doses thereof [22, 23]. It is important to note that both drugs are known for their binding affinity for melanin in the retinal pigment epithelium. This ability can contribute to the mechanism of manifestation of toxic effects [22].

Given the long half-life of these drugs, systemic clearance is delayed for several months after discontinuation. It is assumed that during this period the toxicity persists and may affect the severity of toxic maculopathy at the time of discontinuation. One study assessed visual acuity, SD-OCT and electroretinogram (ERG) data in patients that received HCQ. Six months after discontinuation, the patients had their visual acuity and ERG response improved, but no positive trends in the OCT-registered parameters. A further study was designed to examine 11 HCQ-induced retinopathy patients within 4 years after discontinuation. This work revealed that if a patient stops taking the drug before there is damage to the pigment epithelium, the retinopathy, as registered with SD-OCT, is limited to the first year only and does not affect the parafoveal region [26]. The researchers believe that preservation of the external limiting membrane is a favorable prognostic sign of hydroxychloroquine-induced retinopathy [26–27].

According to the analysis of the recommendations, doctors agree that when prescribing these drugs, all possible toxic effects should be taken into account and discussed with the patient. Those whose COVID-19 treatment plan included CQ or HCQ should visit ophthalmologists in case of any eye-related complaints [23]. The American Academy of Ophthalmology, the UK Royal College of Ophthalmologists and many other organizations recommend annual screenings for HCQ/CQ-induced retinopathy after 5 years of drug therapy. Patients who are exposed to risk factors should be screened before expiration of the said 5 years. Diagnostics should include computed perimetry, OCT and angiography. There is no screening duration figure mentioned in most recommendations, but it is likely the observation period should span several years, as the newly published statistical data show that toxic effects are manifested in 20–50% of people with more than 20 years of treatment [22, 27].

CONCLUSION

Coronaviruses can infect the eyes, causing a wide range of manifestations from anterior segment abnormalities such as conjunctivitis and anterior uveitis to vision-threatening conditions such as retinitis and optic neuritis. It is important to recognize that periodic mutations of the virus can dramatically change manifestations of the viral infection. Literature analysis shows that the data on SARS-CoV-2 transmission through the ocular tissue and eye damage are scarce, so there is a standing need for further research.

Despite the fact that the frequency of SARS-CoV-2 contraction through the surface of the eye is extremely low in the general population, it is important to remember that this is a route medical personnel and other categories may contract the infection. Accordingly, both ophthalmologists and patients should take precautions to minimize human-to-human contact transmission during the COVID-19 pandemic.

Further investigation of the mechanisms of action of the virus, as well as understanding of its connection to the symptoms in the visual domain, will help reinforce infection control measures, as well as allow understanding if eye tissue or even tear fluid may be used for diagnostic purposes. It is also important to identify new therapeutic approaches that minimize the use of toxic drugs in order to avoid the associated side effects on the eyes.

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