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Ocular manifestations in SARS-CoV-2 infection and pre-exposure prophylaxis of ophthalmic medical staff

Mariusz Nowak[1], **Wojciech Nowak**[2]

[1]Pathophysiology Division, Department of Pathophysiology and Endocrinology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland

[2]Science Students' Association, Pathophysiology Division, Department of Pathophysiology and Endocrinology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Poland

ABSTRACT

As the pandemic of SARS-CoV-2 develops and evolves from 2019 and new variants of the virus appear, we are obtaining more and more information on all aspects of the pathogen, including its effects on ocular tissues and the visual system.

This review summarizes the known ophthalmic signs of SARS-CoV-2 infection including anterior and posterior segments of the eye as well as the described neuroophthalmological manifestations. The recommended pre-exposure prophylaxis to reduce the risk of SARS-CoV-2 infection in ophthalmological staff is also presented in the paper.

KEY WORDS: SARS-CoV-2, ocular manifestations, conjunctivitis, keratitis, ophthalmoplegia.

INTRODUCTION

Coronaviruses (CoV) are a family of enveloped viruses with genetic material in the form of single-stranded RNA that are known to cause cold symptoms, flu-like symptoms, and severe respiratory distress. Coronaviruses are responsible for up to 10-20% of all colds in people [1].

In the year 2002, a subtype of a dangerous coronavirus causing severe acute respiratory syndrome, named SARS-CoV, was identified in the southeastern Chinese province of Guangdong [2, 3]. In one season, the virus spread to 37 countries causing 8273 infections and 775 deaths [1]. In the year 2012, another coronavirus type (named MERS-CoV) responsible for the occurrence of the so-called Middle East respiratory syndrome (MERS) was isolated [4].

A new type of the coronavirus family that causes severe pneumonia was identified in December 2019. The World Health Organization (WHO) named the disease caused by it as coronavirus disease 2019 (COVID-19) and the pathogen as SARS-CoV-2 (severe respiratory syndrome coronavirus-2) [5]. On January 30, 2020 the WHO declared a public health emergency of international concern and then on February 11, 2020 the WHO officially introduced the name coronavirus disease 2019 (COVID-19) [6].

SARS-CoV-2 has been isolated from nasopharyngeal secretions, sputum, and stool but also from the tear film of infected persons [7]. It spreads mainly by the droplet route, with the oral and nasal cavities and ocular surface tissues being the entry points for infection. It is transmitted mainly by direct contact of the virus with mucous membranes containing angiotensin II-converting enzyme (ACE2), which acts as a cellular receptor for SARS-CoV. The virus binds its spikes to ACE2 as a cellular receptor to obtain access to the cell interior. The receptor for TMPRSS2 (transmembrane serine protease 2) also plays an important role in cell infection [8]. This protein facilitates virus entry into host cells by proteolytically cleaving and activating viral envelope glycoproteins. Viruses that use these receptors to enter the cell include influenza virus and human coronaviruses HCoV-229E, MERS-CoV, SARS-CoV, and SARS-CoV-2 [8].

It has been found that virus penetration can also occur via a novel pathway using the CD147 receptor, which has been shown to be present in tears and ocular tissues such as conjunctiva, corneal epithelium and endothelium, corneal stromal keratocytes, and retinal pigment epithelium [9].

Belser *et al.* presented an anatomical theory of the transmission of respiratory diseases through the ocular pathway via the nasolacrimal system. They suggested that

CORRESPONDING AUTHOR
Prof. Mariusz Nowak, MD, PhD, Pathophysiology Division, Department of Pathophysiology and Endocrinology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, 19 Jordana St., 41-808 Zabrze, Poland, e-mail: mnowak@sum.edu

the eye's immune system, consisting of the conjunctiva, cornea, lacrimal glands, and tear drainage system, carries virus-infected fluid from the conjunctival sac, transporting it through the nasolacrimal sac under the inferior nasal auricle. Therefore, if respiratory aerosol droplets enter the ocular surface, fluid containing viruses can enter the respiratory system through the nasal cavity and further obtain entry into the lungs [10].

Two years have passed since the WHO declared a global pandemic, and now new, more infectious variants of the virus are appearing. It seems that medical staff may now have to contend with this state of emergency for the next one or two years.

The purpose of this publication is to present the changes that the SARS-CoV-2 virus can cause in the eye and the pre-exposure prophylaxis possible when conducting an ophthalmic examination.

Severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 also cause other symptoms outside the respiratory tract, including in ocular and gastrointestinal tissues. Ocular manifestations of COVID-19 are rare, which may be due to the low amount of ACE2 in ocular surface tissues [11]. In retrospective studies, the prevalence of ocular symptoms in SARS-CoV-2 infected individuals ranged from 2 to 32% with a mean of 5.5% and symptoms were often associated with disease severity [12]. It has been shown that although the specificity of the conjunctival sac smear is high (100%, 95% CI: 0-100), its sensitivity in detecting SARS-CoV-2 infection is very low (0.6%, 95% CI: 0.1-5.1) compared with standard nasopharyngeal smears [12].

Importantly, it was shown that the presence of SARS-CoV-2 RNA in conjunctival sac secretions was detected longer than in nasopharyngeal cavity smears, indicating that viral RNA replication in the conjunctiva, compared to other mucous membranes, is longer. Thus, SARS-CoV-2 virus remains in the body longer than assessed by nasopharyngeal cavity smears [13].

ANTERIOR OCULAR SEGMENT MANIFESTATIONS OF SARS-COV-2 INFECTION

It is thought that the ocular surface may be a portal of entry and a potential route of transmission for SARS-CoV-2 and furthermore, expression of ACE2 and TMPRSS2 receptors was demonstrated in conjunctiva and cornea cells [8].

Serous conjunctivitis is relatively rare, with an incidence ranging from 0.8% [14] to as high as 64% [15] in COVID-19 patients. Most investigators indicate a prevalence of ocular manifestations between 3% and 8% and, interestingly, investigators have noted a significantly lower incidence of keratitis [16, 17]. Polish authors in a study conducted on a group of 74 patients demonstrated the presence of ocular symptoms in almost half of the examined patients (*n* = 35), but only in 7 patients was advanced conjunctivitis demonstrated [18].

Conjunctivitis in the course of SARS-CoV-2 infection may occur as a symptom in the early stage of COVID-19, or in patients already hospitalized for severe disease [19].

The pathogenesis of conjunctivitis is not well understood. It may be solely a co-morbidity unrelated to infection, or it may be closely correlated with SARS-CoV-2 infection. In the early stage of the disease, local inflammation appears and its duration does not exceed 1 week. In the late stages of the disease, the inflammation of the conjunctiva intensifies, which is associated with a sharp increase in the concentration of proinflammatory cytokines.

Conjunctivitis may be unilateral or bilateral. Badawi *et al.* found no significant association with gender or age. Moreover, they found no correlation between the severity of systemic viral infection and the severity of ocular symptoms [19]. In contrast, Wu *et al.* reported an increase in ocular symptoms by about one-third in patients with severe COVID-19 [20]. Contrary results were published by Liu *et al.*, who observed a higher frequency of ocular symptoms in patients with mild forms of COVID-19 [21].

The range of subjective and objective symptoms of acute conjunctivitis varies from mild symptoms such as foreign body sensation, conjunctival hyperemia and lacrimation to more severe symptoms such as severe photophobia, swollen eyelids, mucous secretions in the conjunctival sac, dry eye syndrome, conjunctival chemosis (swelling) and nodular reaction in the conjunctival sac [19, 22, 23].

Almost all cases of conjunctivitis associated with COVID-19 were self-limiting and resolved with topical treatment without further ocular complications [24, 25].

Other investigators have reported the occurrence of pseudomembranes composed of fibroblasts and inflammatory cells located on the tarsal conjunctiva and nodular reactions with small petechiae or hemorrhages under the tarsal conjunctiva along with chemosis and mucous filaments [26].

In COVID-19 patients with more severe disease requiring intensive medical care, ocular surface abnormalities are more common, the mechanism of which is due to lagophthalmos and an impaired blink reflex as well as a drying effect with the use of an oxygen supply "mustache" or oxygen masks when using high-flow oxygen therapy [27].

In addition to conjunctivitis, ocular surface manifestations of COVID-19 described in the literature also include keratitis [22, 28, 29] and scleritis [30, 31].

Corneal manifestations in SARS-CoV-2 infections are rare. They are mainly cases of superficial punctate keratitis [28, 29]. Subepithelial inflammatory tree-like keratitis similar to that seen in herpetic keratitis has also been described [22].

A case of episcleritis as a possible ocular complication of COVID-19 has also been published. The pathogenesis may be related to immune-mediated episcleral vasculitis and/or vascular thrombotic complications that occur in COVID-19 patients [30, 31].

It is important that because infection of the ocular surface with SARS-CoV-2 induces immune and inflammatory dysregulation and can potentially impair the ocular immune system, cases of acute corneal graft rejection in patients with COVID-19 have also been described [32, 33].

POSTERIOR OCULAR SEGMENT MANIFESTATIONS OF SARS-COV-2 INFECTION

There are few studies describing posterior ocular segment manifestations of SARS-CoV-2 infection in humans, although animal studies have shown signs of inflammation in the posterior segment of the eye as well. Benito-Pascual *et al.* presented a case of development, after an initial episode of conjunctivitis, of uveitis with reduced visual acuity, opalescence of fluid in the anterior chamber, posterior synechiae, vitreous inflammation, and optic nerve edema with subretinal fluid and choroidal folds in a patient subsequently diagnosed with COVID-19 [34]. Marinho *et al.* demonstrated the presence of hyperreflective lesions in the ganglion cell layer and the inner plexiform layer of the retina, especially in the area of the papillomacular bundle with signs of retinal microangiopathy in the form of cotton wool spots and microhemorrhages along the retinal arcade [35].

Sight-threatening acute retinal necrosis due to Varicella-Zoster virus occurring simultaneously in COVID-19 patients receiving immunosuppressive treatment has been reported [36].

SARS-CoV-2 infection is associated with activation of the coagulation system.

Various authors have described the occurrence of acute deterioration or even loss of vision in patients with COVID-19, which they linked to systemic vascular complications of disease. These may manifest as occlusion of a branch or central retinal artery/vein and ischemic optic neuropathy [37-39]. A case of unilateral papillophlebitis (a condition in which there are clinical signs of central retinal vein occlusion [CRVO] but no history of vascular disease) has also been presented as a possible ocular complication of COVID-19 [40]. Three pathogenetic components of papillophlebitis have been suggested: endothelial inflammation that leads to mechanical vasoconstriction, high levels of cytokines that activate clotting factors, and finally venous stasis and hypoxia that also stimulate clotting mechanisms [40].

There have also been reports of diplopia and ophthalmoplegia in COVID-19 patients involving unilateral or bilateral palsy of the oculomotor, abducens or trochlear nerve [41-47].

Falcone *et al.* reported a case of unilateral abducens nerve palsy with atrophy of the lateral rectus muscle found on MRI 5 weeks after the development of COVID-19 [47]. Dinkin *et al.* described a case of unilateral oculomotor nerve palsy with its enlargement on MRI following the development of COVID-19 [41]. Cases of ophthalmoplegia due to cranial nerve palsy have been described in other studies [43-46].

CONTACT LENS WEAR AND SARS COV-2 INFECTION

Reports to date provide no evidence for the possibility of SARS-CoV-2 infection through contact lenses. Contact lens use does not appear to correlate with an increased risk of SARS-CoV-2 infection, although silicone lenses have been shown to be more susceptible to viral deposition on their surface than hydrogel lenses [48]. Patients should be reminded of the importance of strict hygiene when handling contact lenses, washing hands with soap, drying with a disposable paper towel before and after handling lenses, and proper disinfection, storage and replacement of lenses and cases. Patients should not wear lenses when they feel ill and should consciously avoid touching their face to avoid infection. During the pandemic period, particularly intensive exposure prophylaxis is recommended for medical staff involved in contact lens fitting [49].

However, the American Academy of Ophthalmology (AAO) has made a recommendation that when possible, contact lens users should consider temporarily switching to glasses. They encourage limiting contact lens use, which will reduce the number of patient touches to the eye, reducing possible contact between respiratory droplets and the ocular mucosa, which in turn may reduce SARS-CoV-2 transmission through the conjunctival-lacrimal-nasal pathway [50].

PRE-EXPOSURE RECOMMENDATIONS FOR OPHTHALMIC CARE STAFF

SARS-CoV-2 has been detected in the tears and conjunctival sac secretions of patients with COVID-19 conjunctivitis. Transmission of infection by contact with aerosol generated from conjunctival secretions cannot be excluded [51]. Even if the possibility of infection through ocular secretions is low, ophthalmologists should use especially intensive personal protective equipment. Any patient in addition to basic questions about cough or fever should be asked about subjective symptoms of conjunctivitis (burning, itching, or photophobia), which is important for the protection of medical staff but also for pandemic control.

Universal exposure prophylaxis agents, including recommended infection prevention strategies, should be followed at the time of ophthalmic examination, and new COVID-19-targeted policies should be followed, consistent with guidelines from the AAO, Polish Ophthalmological Society (PTO), and other national scientific societies [52, 53].

Special care should be taken during the ophthalmic examination because of the close distance between the examining physician and the patient's face. For this reason, the Societies recommend the use of N95 or better protective masks by ophthalmologists and physicians providing ophthalmic care for all patients, not only those potentially infected with SARS-CoV-2 [52, 53]. In 2020, a meta-analysis was published on the optimal distance to protect against SARS-CoV-2 transmission and the effectiveness of using masks and eye protection in preventing coronavirus infection [54, 55].

If both people (patient and doctor) have well-fitting surgical masks, within 20 minutes the virus can be transmitted with a maximum probability of 10%. If both people wear well-fitting FFP2 (NN 95) or better masks, the maximum risk of infection after 20 minutes is less than one in a thousand.

The examination room should have good external ventilation. However, it should be noted that the study was conducted before the appearance of the Omicron variant of the SARS-CoV-2 virus.

If the patient requires slit-lamp examination, appropriately large mechanical shields (screens) should be installed on the slit lamp and the patient should be instructed to refrain from speaking during the examination. The use of direct ophthalmoscopes should be limited to emergency departments only [52, 56].

Researchers tested the effectiveness of applied shields (screens) installed on a slit lamp using a spray gun that simulated a sneeze. They found that the least effective shield blocked 46% of the spray from the simulated sneeze, while the best shield stopped as much as 97% of the spray. Larger shields were more effective than smaller ones. Shields of comparable size were more effective when attached to the lens arm rather than hanging by the eyepiece. Despite the use of screens attached to the slit lamp, it is recommended that each specialist be provided with a mask, gloves, and goggles and the patient should wear a mask [57].

The safest option is to use non-contact testing methods. Non-contact "air puff" tonometry, on the other hand, can create aerosols through a strong puff of air, increasing the risk of transmission of infection. Where possible, disposable equipment such as disposable Goldman tonometer tips (prisms) should be used. Eye examination should be performed in a limited number of rooms and by a limited number of staff.

It is recommended to disinfect medical devices between the subjects with chemicals that do not interact with the materials they are made from. The most common disinfectants for use on optical surfaces are sodium hypochlorite and 70% alcohol or isopropyl alcohol (IPA), which is characterized by excellent evaporation as well as excellent cleaning and degreasing properties on a variety of surfaces [52, 53].

CONCLUSIONS

SARS-CoV-2 is spread primarily by the droplet route. The visual organ may be a source of transmission through infected tears, as well as a "window" for aerosol particles coming into contact with the conjunctiva.

The most common ocular manifestations in COVID-19 are serous conjunctivitis or conjunctivitis with superficial punctate keratitis. However, the occurrence of other ocular manifestations such as retinal lesions or ophthalmoplegia should call attention to SARS-CoV-2 infection even in patients with mild signs of infection. Despite even a triple dose of vaccination, we should remain vigilant, as we can still get infected and either be a source of transmission or suffer from COVID-19, the course of which is unpredictable.

DISCLOSURE

The authors declare no conflict of interest.

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