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SARS-CoV-2 and the Eyes: A Review of the Literature on Transmission, Detection, and Ocular Manifestations

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During the coronavirus disease 2019 (COVID-19) pandemic, numerous reports of ocular anomalies occurring in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have emerged. The most frequently reported pathology is conjunctivitis, which may be the first or only clinical manifestation of the disease. Involvement of SARS-CoV-2 in development of alterations in other ocular structures was suggested, including the cornea, the retina, and blood vessels. Possible mechanisms include direct activity of the viral agent, as well as systemic inflammatory response with accompanying thromboembolic complications.

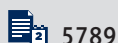
Genetic material of SARS-CoV-2 was detected in ocular secretions of infected individuals, including asymptomatic patients. Moreover, angiotensin-converting enzyme 2 (ACE2), a receptor protein used by the virus to enter the cell, has been found on the surface of various structures of the eye, which indicates a risk of transmission through ocular tissues. Therefore, it is crucial to use eye protection by medical professionals having contact with potentially infected patients.

This paper is a review of the literature regarding ocular manifestations of SARS-CoV-2 infection and a summary of the current state of knowledge about possibility of transmission from an ophthalmology point of view. For data collection, a thorough PubMed search was performed, using the key words: "COVID ocular", "COVID eye", "SARS-CoV-2 ocular", and "SARS-CoV-2 eye".

Conclusions: SARS-CoV-2 infection may manifest itself in various ocular conditions. Eye protection should not be neglected, as recent studies suggest the eye as a potential route of transmission. Further search for adequate safety measures in ophthalmology practice is required.

Keywords: **Conjunctivitis • COVID-19 • Disease Transmission, Infectious • Embolism and Thrombosis • Eye Manifestations • Severe Acute Respiratory Syndrome Coronavirus 2**

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Background

On 30 January 2020, the World Health Organization (WHO) declared a Public Health Emergency of International Concern regarding a rapidly growing outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The disease, first reported in the city of Wuhan, China, in December 2019, reached the status of a global pandemic in March 2020 [2]. SARS-CoV-2 is a positive-sense single-stranded RNA virus ((+)ssRNA) species belonging to the Betacoronavirus genus of the Coronaviridae family. Alarming information about severe acute respiratory syndrome caused by a Betacoronavirus first appeared in 2003, with an outbreak of severe acute respiratory syndrome coronavirus (SARS-CoV) infections. In 2012, another virus of this genus, Middle East respiratory syndrome coronavirus (MERS-CoV), was brought to public attention when it caused an epidemic in the Middle East [3].

During the COVID-19 pandemic, the eyes of the whole world are focused on reports regarding SARS-CoV-2, its transmission routes and prevention, symptoms and signs, early diagnosis, and treatment methods. A widely known complication, and at the same time one of the most severe ones, is interstitial pneumonia, leading to acute respiratory distress syndrome (ARDS). Therefore, special attention is being paid to symptomatology typical for a respiratory infection: cough, dyspnea, and fever. However, the infection may be signaled by other characteristic symptoms, such as smell and taste loss. They are of particular significance in early recognition of the disease, as they may be its first clinical manifestations or even the only one in mildly symptomatic patients [4].

Due to various ways of interfering, its pathogenesis involves its ability to bind to a receptor protein – angiotensin-converting enzyme 2 (ACE2) – and thus enter the cell; inhibition of heme synthesis by competing with iron for porphyrin binding; and induction of an innate inflammatory response with massive production of inflammatory mediators and dysregulation of DNA replication, which activates apoptotic pathways [5]. The main targets of the virus are epithelial cells of the upper respiratory tract and pneumocytes. Therefore, a characteristic presentation of COVID-19 is the above-mentioned bilateral interstitial pneumonia with diffuse alveolar damage and primary pulmonary hypertension. However, the presence of ACE2 protein on numerous cell types, including endothelial cells, along with the other aspects of the virus's pathophysiology, are responsible for the wide spectrum of coronavirus infection complications. Older age and comorbidities such as diabetes, hypertension, and other cardiovascular diseases, oncological conditions, and immune disorders are among the risk factors for a more severe course of infection, as well as development of systemic sequelae and multiorgan damage [6].

SARS-CoV-2 has been linked to various cardiovascular pathologies, which often are the direct cause of death in affected patients; myocarditis, acute myocardial infarction, thromboembolism, and disseminated intravascular coagulation (DIC) may occur. It is yet not clear whether cardiovascular conditions occurring in COVID-19 patients are mostly triggered by direct viral action of SARS-CoV-2 or rather result from exacerbation of pre-existing comorbidities, predisposing patients to a more severe course of the disease. Moreover, potential neurological sequelae of the coronavirus infection have been suggested [7]. Despite some unique features of SARS-CoV-2, histological pictures of pulmonary and multiorgan damage caused by this virus are similar to those produced by other viruses [5]. Further autopsy studies are needed to determine the virus's exact role in cardiovascular and neurological pathologies [6,7].

It was suggested that one of the virus's possible transmission routes is the eye surface, on which ACE2, the receptor protein for SARS-CoV-2, is present [8]. Moreover, it was proved that members of the Coronavirinae subfamily, which SARS-CoV-2 belongs to, sporadically affect ocular structures and cause uveitis, retinitis, and optic neuritis in animal models [3]. The first reports suggesting a relationship between coronaviruses and ocular pathologies in humans emerged in the early 21st century, during the SARS-CoV epidemic. The virus's RNA was then detected in tears of a small group of patients, so the eye was assumed to be a potential gateway for infection [9].

The aim of this paper is to sum up the review of the available literature regarding the possibility of transmission of SARS-CoV-2 through eye tissues and secretions, as well as ocular manifestations of the coronavirus infection and its possible clinical implications. To collect data, a thorough PubMed search was performed using the key words: "COVID ocular", "COVID eye", "SARS-CoV-2 ocular", and "SARS-CoV-2 eye".

The Eyes as a Potential Transmission Route

It was proved that the coronavirus protein S binds to the host cell receptor ACE. Moreover, the virus employs the transmembrane serine protease TMPRSS2 for priming of the S protein, enabling virus-cell membrane fusion and invasion. Other proteins, such as alanyl aminopeptidase N (ANPEP), dipeptidyl peptidase 4 (DPP4), angiotensin II receptor type 2 (AGTR2), polymeric immunoglobulin receptor (PIGR), adhesion G protein-coupled receptor F1 (ADGFR1), and Basigin/CD147/EMMPRIN (BSG), also play an important role in SARS-CoV-2 entry into human cells. Leonardi and Rosani [8] demonstrated a low level of expression of ACE2 on both conjunctival and corneal cells, as well as TMPRSS2 on the conjunctival surface. Additionally, BSG and AGTR2 were present in both tissues, while ANPEP and PIGR were found in the conjunctiva. It is yet not clear why the

lungs, where ACE2 expression is at intermediate levels, are the most frequently and severely affected organ. The rarity of ocular lesions in the course of COVID-19 may be explained by the existence of some specific enzymes, acting as a natural antiviral protection. In the same study, high levels of deaminases ADAR-1 (double-stranded RNA-specific adenosine deaminase 1) and APOBEC3A (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A) were found in the examined conjunctival and corneal cells, suggesting that they constitute a barrier for SARS-CoV-2 transmission through ocular tissues.

The theory of SARS-CoV-2 potential entry through the conjunctiva was confirmed by Deng and Bao [10], who performed an experimental conjunctival inoculation of the virus in rhesus macaques. That suggests the existence of this transmission route in humans.

In spite of some natural mechanisms preventing the virus's entry through the conjunctivae and ocular surface, the protection is not complete. Therefore, it is crucial to implement obligatory use of personal protective equipment (PPE), such as face shields, goggles, or protective glasses, for medical professionals and each person who has contact with patients with confirmed or suspected coronavirus infection. Even though the eye is not the main gateway for the virus, this transmission route should not be ignored.

Application of Conjunctival Swabs

In a minor group of patients, SARS-CoV-2 RNA can be detected in real-time polymerase chain reaction (rt-PCR) from conjunctival swabs. A few explanations for its presence in this localization are being proposed: direct respiratory droplets or aerosol inoculation (the patient's own or of another person), hand-eye contact, migration from the nasopharynx through the nasolacrimal duct, or hematogenous spread. However, viral RNA in material obtained from conjunctival swabs is far less frequently detected than in that from nasal/nasopharyngeal swabs. According to current literature, the rate of positive results ranges between 0% and 7% [11-17].

There are numerous potential reasons for such low detectability of viral genetic material in this test [14]. Among them, the low sensitivity of rt-PCR and small numbers of cells in specimen are listed. The test is not usually performed in patients whose condition is severe, which may also affect the outcomes [12,18]. In addition, it is possible that viral RNA is detectable in ocular fluids only at early stages of infection, shorter than in case of specimens obtained from nasopharyngeal swabs [13], although Colavita and Lapa [19] described a case of a patient who had SARS-CoV-2 genetic material isolated from her conjunctival swab as late as on the 27th day since

the first symptoms, even though the nasal swabs proved negative. It is also problematic to objectively compare specimen obtained at the same time from a group of patients at different disease stages. Due to its low sensitivity, this examination does not seem to be of much significance in diagnostics. However, presence of viral RNA in ocular secretions, including those of asymptomatic patients, requires that it be regarded as a potential source of infection, even if other tests prove negative [19]. Individuals having contact with this kind of material should use proper PPE.

Difficulties in Eye Examination in Times of COVID-19 Pandemic

Due to the significant risk of contracting SARS-CoV-2 in ophthalmology practice, numerous guidelines for management of ophthalmic patients in times of COVID-19 pandemic have been developed [20-22]. Limiting procedures requiring close doctor-patient contact to the necessary minimum is suggested, as well as maintaining physical distance between patients and disinfection of hands, surfaces, and equipment. To evaluate the posterior segment, use of slit lamp with a breath shield is recommended. A major challenge is ophthalmic examination of patients in serious condition, hospitalized in intensive care units (ICUs), who cannot be seated in front of a slit lamp. Medical professionals having contact with COVID (+) patients should use PPE, such as protective suits, masks, and goggles, which make fundus examination extremely complicated and practically impossible to perform at the patient's bedside. The authors' own experience has shown that a particular difficulty for a physician is the necessity for wearing a face shield, as fogging up of its surface remarkably reduces visibility. A solution to this problem may be portable fundus cameras, which enable performing an examination from a certain distance and do not require taking off protective equipment by an examiner [23]. However, the availability of these devices is scarce compared to conventional ophthalmoscopes, especially away from specialized ophthalmology departments. Therefore, the possibility of identifying ocular pathologies, particularly affecting the posterior segment and in patients with severe disease course, is relevantly limited, and their prevalence might be significantly underestimated.

Ocular Manifestations of SARS-CoV-2 Infection

Until now, many cases of ocular manifestations of SARS-CoV-2 infection have been reported. The most commonly mentioned pathology is definitely conjunctivitis, although the virus is also suspected to be able to cause retinal lesions. In addition, single cases of some other ocular pathologies possibly related

to the virus were described. In a questionnaire survey carried out in the Netherlands among healthcare workers tested for SARS-CoV-2, individuals with positive test results significantly more often complained of ocular pain [24].

The prevalence of ocular lesions in the course of SARS-CoV-2 infection in the available literature varies greatly and ranges from 0.8 to 31.6% [13,14,17,18,25-36]; therefore, it seems that they are not a common manifestation. In a large Chinese study involving 1099 hospitalized SARS-CoV-2-positive patients, only 9 of them presented with conjunctival congestion [29]. However, according to another study, 1/3 of hospitalized patients with COVID-19 have conjunctivitis [14].

Conjunctivitis

According to the literature, conjunctivitis is the most frequent pathology of the eye co-occurring with coronavirus infection. Among the described signs are redness, hyperaemia, chemosis, epiphora, secretion and some subjective symptoms, such as irritation, foreign-body sensation, itchiness, ocular pain, photophobia, and, more rarely, blurred vision [14,18,25-27]. A very common problem among SARS-CoV-2 (+) patients is dry eye [27,30], although no more so than in the general population.

It still has not been determined whether conjunctivitis in the course of coronavirus infection is a result of a local reaction or is triggered by a systemic response [15]. Described negative conjunctival swabs in patients with ocular symptoms may indicate the second alternative. Presumably, processes such as vasculitis, endothelial dysfunction, and, subsequently, inflammatory host response to infection play a role in the pathogenesis [34].

Pathological lesions on the corneal and conjunctival surface may occur even at the initial stage of COVID-19, without producing any symptoms or signs. Bozkurt et al [37] described subclinical alterations in conjunctivae of patients with confirmed coronavirus infection. Compared to the control group, their cytology revealed decreased density and cell size of goblet cells and moderate to high enlargement, squamous changes, and increased nucleocytoplasmic ratio in non-goblet epithelial cells, as well as significantly higher presence of neutrophils.

Güemes-Villahoz et al [18] proposed differential diagnosis between COVID-19-related conjunctivitis and that caused by other viral infections (eg, adenoviruses), based on their observations. In both cases the onset is abrupt and may accompany upper respiratory tract symptoms. However, infections caused by coronaviruses produce ocular symptoms that are mostly unilateral, mild, and self-limited within 2-4 days without complications, unlike adenoviral conjunctivitis, which have a greater

tendency to bilateralization, vary in severity, resolve in 5-14 days, and may be followed by sequelae such as conjunctival scarring, symblepharon, subepithelial corneal infiltrates, and decreased vision. Nonetheless, these features do not seem to be sufficient to differentiate the etiology, as some cases of bilateral and more severe conjunctivitis caused by SARS-CoV-2 have been reported. Navel et al [38] described a case of a patient with severe pneumonia in the course of COVID-19, who presented with conjunctivitis with pseudomembranes and sub tarsal hemorrhages.

According to the literature, conjunctivitis may occur at any stage of SARS-CoV-2 infection. It seems that it usually starts 7 to 14 days after symptom onset [14,27]. Nayak et al [39] described a case of a patient with a severe COVID-19 course, requiring artificial ventilation, who developed conjunctivitis as late as a month after the onset of the disease.

A question of particular significance for diagnostics and epidemiology is occurrence of conjunctivitis as a first, and sometimes the only, clinical presentation of the infection. Conjunctivitis may be a reason for consulting a doctor by potentially infected, though otherwise asymptomatic patients [40-42]. It is worth mentioning that in children, whose SARS-CoV-2 infection course is often asymptomatic or oligosymptomatic, ocular manifestations may be its only demonstration. Ma et al [33] took history of 216 pediatric patients with laboratory-confirmed COVID-19, obtaining information about ocular alterations in 49 cases. Among 93 patients without any systemic manifestations, 13 had ocular symptoms. Wu et al [43] described a case of a nearly 3-year-old child with confirmed SARS-CoV-2 infection, presenting only with conjunctivitis and palpebral dermatitis. In such scenarios, new diagnostic opportunities are offered by telemedicine. Daruich et al [44] published a case report of a patient consulting an ophthalmologist online due to redness and foreign-body sensation in his eye. In 3 hours, he developed fever and headache, and soon after cough and severe dyspnea, and was diagnosed with COVID-19 afterwards.

Researchers have different opinions on whether there is a correlation between conjunctivitis and more severe course of COVID-19. Analysis of the outcomes of some studies did not reveal such a relationship [16,18,28,34], nor did a meta-analysis carried out by Liu et al [45]. Wu et al [14] described significantly higher values of inflammatory markers, including white blood cell count (WBC), neutrophil count (NEU), procalcitonin (PCT), C-reactive protein (CRP), and lactate dehydrogenase (LDH), in patients with conjunctivitis. Valente et al [13] demonstrated a positive correlation of development of conjunctivitis with older age, fever, higher values of NEU, PCT, CRP, and erythrocyte sedimentation rate (ESR). In a study carried out by Lee et al [31], conjunctivitis more frequently co-occurred with upper respiratory tract infection symptoms. It should be

noted that there is scant information on patients with severe form of the disease. Due to lack of possibility to perform ophthalmic examination on patients in serious condition staying in ICUs, they were excluded from most studies [35].

Other factors that are not directly related to the pathogen's activity may also contribute to development of conjunctivitis and associated symptoms in COVID-19 patients. Hospitalization in an ICU favors ocular infections and use of oxygen masks and intubation [25]. It has been noted that patients treated with continuous positive airway pressure (CPAP) are more likely to suffer from conjunctivitis [28]. Late onset of ocular infection in the course of COVID-19 supports its secondary nature related to the above-mentioned factors [39]. Moreover, dysfunction of the immune system triggered by a disease makes a patient more vulnerable to other pathogens, which may affect the eye. Most studies did not take into account other possible etiologies of ocular infections, such as adenoviruses or herpesviruses, and did not consider their differential diagnosis.

Non-infectious agents also seem to be of significance. Conjunctival hyperemia is typically observed in patients treated with artificial ventilation [46]. Antiplatelet drugs, used for antithrombotic prophylaxis in COVID-19 patients, predispose to subconjunctival hemorrhages, as well as cough, typically accompanying the disease, and vomiting, being a common complication of its treatment [34]. In addition, a seemingly trivial fact has been pointed out: hospitalized patients, who are not in serious condition, tend to spend more time reading and using electronic devices, which may contribute to development of symptoms such as dry eye, blurred vision, and foreign-body sensation [27].

Undoubtedly, published studies have numerous limitations, which complicate interpretation of the results. First of all, due to safety measures, in many cases it was impossible to perform a detailed ophthalmic examination with a slit lamp. Evaluation by means of portable devices does not provide accurate information about the state of the vascular layer and the retina [18,26,34,35,39]. Some studies are based only on history taking [27,28], optionally complemented with photographs [31] or questionnaires [30,33,47,48], which does not allow for patients' perceived symptoms to be compared with physical examination findings. Furthermore, data obtained from questionnaires filled in by recovered patients are not equivalent to these from history taken during the actual presence of symptoms.

Most studies have been in small groups of patients. An important problem is also absence of control groups, consisting of SARS-CoV-2 (-) patients [14,18,25,26,28,31,34,48], which remarkably affects interpretation of the outcomes. Conclusions drawn from studies including control groups differ. Gangaputra et al [47] observed that non-hospitalized SARS-CoV-2-positive

patients were not more likely to report ocular symptoms than SARS-CoV-2-negative individuals (study group: 144 patients; control group: 306 patients). Redness and epiphora were even more common in the second group. On the other hand, another study with a control group revealed significantly higher frequency of ocular symptoms (foreign-body sensation, redness, secretion) in patients with COVID-19 (35), although the small number of patients included (study group: 16 patients; control group: 32 patients) calls into question the value of data obtained.

Keratitis and Episcleritis

Guo et al [49] described a case of recurrent viral keratoconjunctivitis in a patient with COVID-19. A 53-year-old man, approximately 3 weeks after the onset of systemic symptoms, developed unilateral conjunctivitis, which subsided after topical treatment. Within 5 days the condition recurred, that time bilaterally and with peripheral cornea involvement. The patient tested positive for SARS-CoV-2 based on a conjunctival swab taken during the first episode, while the second swab, taken during the relapse, was negative. Based on that, the authors conclude that keratitis was, unlike conjunctivitis itself, caused by immune response and inflammatory cytokine surge and not by direct pathogen action. This theory may be supported by the fact that the patient admitted to neglecting hand hygiene and frequently rubbing his eyes before the illness, as well as by unilateral conjunctival manifestations of the first episode, contrary to bilateral corneal affection of the relapse. However, a patient described by Cheema et al [50], who had right keratoconjunctivitis, had SARS-CoV-2 genetic material detected in her conjunctival swab; ocular symptoms were the first clinical manifestation of the infection.

Bostanci et al [26] identified episcleritis in 2 out of 93 patients with COVID-19. Apart from that, only 2 such cases have been described. Méndez et al [51] reported episcleritis in a 31-year-old woman who consulted the ophthalmology department due to red eye, foreign-body sensation, epiphora, and photophobia 7 days after the onset of systemic symptoms of a confirmed SARS-CoV-2 infection. Meanwhile, Otaif et al [52] reported a case of episcleritis in a 29-year-old man who was diagnosed 3 days before the onset of full-blown COVID-19.

Most cases of episcleritis are of idiopathic nature, although in nearly 1/3 of patients, this condition coexists with systemic diseases [53]. Occurrence of this pathology is also reported in the course of viral infections, caused by agents such as Ebola, Herpes zoster, or hepatitis C virus (HCV) [54-56]. Taking into account immunovascular alterations present in COVID-19 patients, which also play a part in pathogenesis of episcleritis, it may be presumed that their coexistence is more than a coincidence.

Retinal Pathologies

An association between SARS-CoV-2 and pathological alterations of the retina has not yet been clearly defined, although presence of ACE2 receptor on retinal cells suggests a probability of such complications [57]. Moreover, in a study carried out by Casagrande et al [58] SARS-CoV-2 was detected in retinal biopsy material obtained from patients who had died due to COVID-19. There are at least 2 mechanisms known for viral agents to cause retinal pathologies. The first, which can be observed in infections caused by cytomegalovirus (CMV), consists of a direct cytopathic effect on neurons. The second involves damage secondary to microangiopathy resulting from endothelial cells being affected, such as in retinopathy associated with human immunodeficiency (HIV). Seah et al [3] described retinitis caused by coronaviruses in feline and murine models.

Retinal blood reflects the systemic vasculature state, being affected by the same pathological processes. Therefore, it is likely that vascular alterations triggered by SARS-CoV-2 can manifest themselves in the retina as well. Of special interest are thromboembolic complications often occurring in COVID-19 patients, especially those with severe form of the disease. Their pathogenesis may involve a hypercoagulable state with diffuse intravascular coagulation (DIC) [59] and vasculitis induced by direct infection of endothelial cells [60]. Diffuse damage to the endothelium and thromboembolic events affects not only pulmonary vasculature, but also other localizations, particularly the central nervous system [61], and thus they may be expected in retinal vessels as well.

Dumitrascu et al [62] presented a case of a sudden right eye vision loss as a result of acute ophthalmic artery occlusion in a 48-year-old man who was on therapeutic anticoagulation with apixaban for 1 day due to deep vein thrombosis (DVT) as a complication of severe COVID-19. Sheth et al [63] described retinal vein occlusion in a patient diagnosed with coronavirus infection 10 days before, and Gaba et al [64] reported a similar case of bilateral central retinal vein occlusion in a 40-year-old patient with COVID-19 pneumonia and right leg DVT. Insausti-García et al [65] reported a case of a 40-year-old man with a history of infection symptoms 6 weeks before, who was then diagnosed with papillophlebitis. Laboratory tests revealed the presence of IgM and IgG anti-SARS-Cov-2 antibodies. This condition, affecting mostly young, healthy patients, is associated with inflammatory and hypercoagulable states, so it can be assumed that coronavirus infection did play a part in its pathogenesis in that case. Another possible sequelae of vascular COVID-19 vascular complications are acute macular neuroretinopathy (AMN) and paracentral acute middle maculopathy (PAMM), found by Virgo et al [66] in recovered patients. The above-mentioned examples emphasize the importance of antithrombotic prophylaxis in patients diagnosed with coronavirus infection.

Invernizzi et al [67] discovered that in retinal imaging of COVID-19 patients, the median artery diameter (MAD) and median vein diameter (MVD) observed were significantly larger than in the control group. In addition, MVD was positively correlated with disease severity and negatively correlated with the time from symptoms onset, which suggests that the alterations are reversible and resolve over time. Retinal veins passively enlarge due to impaired drainage, while arteries actively dilate in response to O₂ decrease or CO₂ increase. In addition, dilation of both vessel types can be promoted by inflammatory mediators. Data obtained should be compared with the same measurements in a group of patients with other inflammatory diseases to determine if the above-mentioned phenomena are specific for COVID-19, and if the viral agent contributes directly to their development, or whether they are rather a consequence of systemic inflammation.

The literature mentions hyperreflective lesions at the level of ganglion cell and inner plexiform layers, microhaemorrhages, and cotton wool spots (CWS) visible on optical coherence tomography (OCT) scans of COVID-19 patients [68,69]. It is, however, hard to establish whether these abnormalities, similar to those occurring in diabetic or hypertensive retinopathy, are indeed an effect of SARS-CoV-2 infection, or rather are incidental findings. To answer this question, patients with chronic diseases associated with retinopathy should be excluded from the study group, and (although very difficult) retinal imaging of infected patients should be compared with corresponding pictures from the period prior to the disease [70]. A theory of coronavirus involvement in pathogenesis of CWS is supported by the fact that their presence has been linked to other viral agents, including HIV [71]. Moreover, the aforementioned destructive effect of the pathogen on blood vessels predisposes to focal ischemia, which is at the root of this phenomenon. In addition, it should be noted that many patients with a severe course of disease have diabetes and/or hypertension, being risk factors for more aggressive disease and serious cardiovascular complications [72]. Individuals with underlying conditions of retinal microcirculation due to chronic diseases are more vulnerable to potential damage caused by direct activity of the virus, immune response, and toxic systemic treatment.

Ortiz-Seller et al [73] described a case of inflammatory chorioretinopathy with coexisting Adie syndrome occurring in a 51-year-old patient diagnosed with COVID-19 who reported retroocular pain and reading impairment 2 days after the onset of disease symptoms. A fundus examination revealed numerous yellowish, creamy, deep peripheral chorioretinal lesions, and OCT demonstrated bilateral areas of impaired capillary perfusion, inner retinal thinning, and focal disruptions of the outer retinal layers. A lack of any coexisting chronic diseases in the patient's medical history calls for looking for a relationship between abnormalities observed and SARS-CoV-2 infection.

Regression of the lesions after treatment with corticosteroids suggests an underlying immune factor, consistent with the hypothesis of involvement of the virus in the pathogenesis.

Pirraglia et al [9] evaluated 46 patients hospitalized due to SARS-CoV-2 pneumonia, without finding any related alterations in the posterior segment. However, a bedside ophthalmic exam does not provide complete information about retinal condition, and a small study group does not allow for ruling out development of pathologies of the retina and its vessels in the active stage of COVID-19.

Immune system dysfunction occurring in patients with a severe course of the disease, along with prolonged stay in an ICU, predisposes to opportunistic infections, such as *C. albicans*, with possible ocular manifestations. Ophthalmic examination in COVID-19 patients may be thus useful in detecting conditions of other etiology indirectly related to the disease [9].

Considering all the above-mentioned reports, it appears reasonable to include fundus examination in the diagnostic test panel performed in SARS-CoV-2-positive patients as a quick, available, and non-invasive procedure providing valuable information about the condition of the retina. It should be pointed out that the observed retinal anomalies were not associated with any symptoms of an anterior segment disease, which would suggest performing a funduscopy in all patients, regardless of symptoms reported. Unfortunately, difficulties in preventing transmission of the virus during a procedure requiring close doctor-patient contact, as discussed above, stand in the way of introducing it into routine practice.

Uveitis and Other Inflammatory Pathologies

Systemic inflammatory response with accompanying cytokine storm, which deregulates the immune system, along with direct endothelial damage in the course of COVID-19, may predispose to developing inflammatory pathologies of the eye, including uveitis. Until now there have been only a few such cases reported.

Collange et al [74] described a 56-year-old patient with numerous systemic sequelae of COVID-19, who was diagnosed with posterior uveitis, including hyalitis, and vasculitis. Meanwhile, Mazzotta et al [75] presented a case of acute anterior uveitis and bilateral conjunctivitis in a 30-year old woman, who at the moment of coming to the eye emergency room, besides bilateral eye redness lasting 2 weeks, unilateral photophobia and blurred vision in her right eye, presented symptoms of coronavirus infection, laboratory-confirmed afterwards. Benito-Pascual et al [76] described a 68-year-old patient suffering from panuveitis with associated optic neuritis, who developed

full-blown COVID-19 10 days after an ophthalmology consultation. What is more, she had a history of conjunctivitis, having appeared 2 weeks before along with upper respiratory tract infection. It is hard to determine whether in this case optic neuritis was a result of the virus directly damaging neural tissue or rather a condition secondary to uveitis, although the presence of ACE2 receptors on the neuronal surface suggest the first possibility [77].

Speaking of inflammatory anomalies of the eye in COVID-19 patients, one should not omit Kawasaki-like syndrome, mainly affecting children [78]. One of its diagnostic criteria, as in Kawasaki disease associated with other viral infections, is bilateral nonsuppurative conjunctivitis [79,80]. Lidder et al [81] published a case report of an adult COVID-19-positive patient with a similar constellation of symptoms. A 45-year-old man, in addition to fever, sore throat, diarrhea, reduced ejection fraction of 40%, unilateral cervical lymphadenopathy, and remarkably elevated inflammatory, presented with bilateral eye redness, photophobia, eyelid swelling, a diffuse rash including bilateral upper and lower eyelids, and perioral mucosal changes. An eye examination showed symptoms of conjunctivitis (hyperaemia, swelling), bilateral superficial punctate keratitis, and symmetric anterior chamber inflammation. A punch biopsy of the palpebral rash showed sparse superficial perivascular infiltrate. This example perfectly depicts the diversity of clinical manifestations of systemic inflammation in the course of COVID-19, which can also affect structures of the eye.

Ocular Manifestations of Neurological Complications

Reports of neurological complications of COVID-19 producing ocular manifestations are important to consider. Although they are rather a preserve of neurology, they can be of interest from an ophthalmology point of view.

There has already been mentioned a case of a COVID-19 patient diagnosed with inflammatory chorioretinopathy and accompanying Adie's tonic pupil [73]. She presented with slow pupillary reaction to light and hypersensitive response to cholinergic agonists, as are typical for this syndrome. The mechanism of this pathology consists in damage to postganglionic nerve fibers innervating the pupillary sphincter and the ciliary muscle, caused, for instance, by a viral agent. Taking into account the probable neurotropism of SARS-CoV-2, it can be assumed that the virus might have been the direct cause of this phenomenon.

Sriwastava et al [82] documented the only reported case to date of ocular myasthenia gravis (MG) associated with COVID-19. A 65-year-old woman with a 2-week history of signs of infection

(cough, fever, myalgia, fatigue, diarrhea) developed left eye ptosis that was fatigable, diplopia with vertical up-gaze, and mild eye closure weakness, that improved with pyridostigmine. Bacterial and viral infections are a well-known trigger for myasthenic crises in patients with confirmed MG, although their role as an etiological factor in previously healthy patients has not yet been determined. Among infectious agents supposedly able to cause such complications are varicella zoster virus, West Nile virus, and Zika virus [83-85]. The literature contains a few cases of exacerbation of previously diagnosed MG and 1 case of newly recognized disease in patients with COVID-19, all of which refer to its generalized form [82]. Antibodies produced in response to a pathogen, such as a virus, can cross-react with acetylcholine receptors as a result of molecular mimicry. SARS-CoV-2 induces an inflammatory cascade with accompanying cytokine storm, leading to damage in an immunological mechanism; therefore, it is entirely reasonable to think there may be a non-random coexistence of MG and COVID-19 [86].

Méndez-Guerrero et al [87] presented a case of a 58-year-old patient with acute hypokinetic-rigid syndrome associated with vertical opsoclonus that followed a severe SARS-CoV-2 infection. The clinical picture suggested involvement of basal brain structures, and diagnostic imaging revealed loss of integrity in the terminal fields of the nigrostriatal neurons without showing any potential cause. There have also been a few case reports published on oculomotor nerve palsy with impairment of motor activity of the eyeballs and diplopia in the course of COVID-19 [88-90]. Coronavirus infection can produce complications from the nervous system, suggesting the possibility of ocular manifestations of neurological anomalies as a result of SARS-CoV-2 infection. Due to the presence of ACE2 receptors on their surface, neurons are considered a direct gateway for the virus [77]. Other proposed mechanisms of neurological alterations comprise neuronal dysfunction as an effect of inflammation and immune response leading to damage of neurons themselves, as well as myelin sheaths [90].

Conclusions

The most frequently reported ocular symptoms in the course of COVID-19 are consistent with conjunctivitis. Most are mild, but they should not be ignored, and in more severe cases (patients treated with artificial ventilation, staying in ICUs) doctors need to watch for possible sequelae; they may be of clinical significance in early diagnosis if they are a first manifestation of the disease, and may help identify patients who are otherwise asymptomatic. Further research is needed to determine the exact pathogenesis of ocular alterations and their correlation with disease severity.

Involvement of SARS-CoV-2 in the origin of retinal abnormalities has not yet been fully explained. Thromboembolic events in the course of COVID-19 can affect the retina just like other localizations. Underlying pathologies of the retinal microcirculation, commonly present in high-risk patients, such as those with diabetes and/or hypertension, may predispose to exacerbation of previously existing damage or development of new damage.

The recent literature contains reports of single cases of other ocular pathologies observed in SARS-CoV-2-positive patients. The direct effect of the virus on their evolution is hard to prove, and underlying chronic diseases common in patients at particular risk of developing COVID-19 should be kept in mind. However, systemic immune response and its sequelae, especially those resulting from vascular dysfunction and hypercoagulable states, as well as damage to the nervous system, undoubtedly can have consequences for the eyes.

The potential role of the eye in coronavirus transmission must not be neglected; both the possible entry of the pathogen through the ocular and conjunctival surface and its presence in ocular secretions should be taken into account. In case of contact with a potentially infected patient, safety measures and effective eye protection are needed.

An important problem is to perform ophthalmic examination while maintaining safety precautions and preventing transmission of SARS-CoV-2. Particular difficulties come from the necessity to use personal protective equipment by a physician (eg, fogging up of the face shield) and keeping a safe doctor-patient distance. Carrying out a detailed diagnostic process in COVID-19 patients is therefore complicated, and in patients in a serious condition it seems practically impossible. This issue is a major challenge during the current pandemic and requires a search for new solutions in ophthalmology practice.

Limitations of This Review

The authors are aware of certain limitations of the presented review. Firstly, PubMed was the only search engine used for the literature search. The MEDLINE database, although vast, does not provide access to all published scientific papers. Secondly, the search was conducted in English, which may have led to omitting papers written in other languages and thus studies carried out in some geographic regions. The literature search was finalized in November 2020, so studies and reports published afterwards were not included. Moreover, the review lacks the specificity and sensitivity of a meta-analysis. However, we believe our study provides a valuable review of the main issues raised in the recent literature and hope it will serve the readers as a useful introduction to the topic.

Conflict of Interests

None declared.

References:

1. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). WHO, 30 January 2020
2. WHO Director-General's opening remarks at the media briefing on COVID-19 – 11 March 2020
3. Seah I, Agrawal R. Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. *Ocul Immunol Inflamm.* 2020;28(3):391-95
4. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. *Nat Med.* 2020;26(7):1017-32
5. Mansueto G. COVID-19: Brief check through the pathologist's eye (autopsy archive). *Pathol Res Pract.* 2020;216(11):153195
6. Mansueto G, Niola M, Napoli C. Can COVID 2019 induce a specific cardiovascular damage or it exacerbates pre-existing cardiovascular diseases? *Pathol Res Pract.* 2020;216(9):153086
7. Fisicaro F, Di Napoli M, Liberto A, et al. Neurological sequelae in patients with COVID-19: A histopathological perspective. *Int J Environ Res Public Health.* 2021;18(4):1415
8. Leonardi A, Rosani U, Brun P. Ocular surface expression of SARS-CoV-2 receptors. *Ocul Immunol Inflamm.* 2020;28(5):735-38
9. Pirraglia MP, Ceccarelli G, Cerini A, et al. Retinal involvement and ocular findings in COVID-19 pneumonia patients. *Sci Rep.* 2020;10(1):17419
10. Deng W, Bao L, Gao H, et al. Ocular conjunctival inoculation of SARS-CoV-2 can cause mild COVID-19 in rhesus macaques. *Nat Commun.* 2020;11(1):4400
11. Karimi S, Arabi A, Shahraki T, Safi S. Detection of severe acute respiratory syndrome Coronavirus-2 in the tears of patients with Coronavirus disease 2019. *Eye (Lond).* 2020;34(7):1220-23
12. Kumar K, Prakash AA, Gangasagara SB, et al. Presence of viral RNA of SARS-CoV-2 in conjunctival swab specimens of COVID-19 patients. *Indian J Ophthalmol.* 2020;68(6):1015-17
13. Valente P, Iarossi G, Federici M, et al. Ocular manifestations and viral shedding in tears of pediatric patients with coronavirus disease 2019: A preliminary report. *J AAPOS.* 2020;24(4):212-15
14. Wu P, Duan F, Luo C, et al. Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol.* 2020;138(5):575-78
15. Xie HT, Jiang SY, Xu KK, et al. SARS-CoV-2 in the ocular surface of COVID-19 patients. *Eye Vis (Lond).* 2020;7:23
16. Xia J, Tong J, Liu M, et al. Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. *J Med Virol.* 2020;92(6):589-94
17. Zhou Y, Duan C, Zeng Y, et al. Ocular findings and proportion with conjunctival SARS-COV-2 in COVID-19 patients. *Ophthalmology.* 2020;127(7):982-83
18. Güemes-Villahoz N, Burgos-Blasco B, García-Feijóo J, et al. Conjunctivitis in COVID-19 patients: Frequency and clinical presentation. *Graefes Arch Clin Exp Ophthalmol.* 2020;258(11):2501-7
19. Colavita F, Lapa D, Carletti F, et al. SARS-CoV-2 isolation from ocular secretions of a patient with COVID-19 in Italy with prolonged viral RNA detection. *Ann Intern Med.* 2020;173(3):242-43
20. <https://www.aaao.org/headline/alert-important-coronavirus-context>
21. Hua L, Zhu H, Liu H. Self-protection of medical workers in ophthalmology clinic during COVID-19 epidemic. *Eur Rev Med Pharmacol Sci.* 2020;24(9):5155-61
22. Szaflik JP, Stopa M, Horban A, et al. Guidelines of the Polish Ophthalmological Society on how to deal with ophthalmic patients during the COVID-19 epidemic. *Klin Oczna.* 2020;122(1):11-13
23. Shih KC, Chau CYC, Chan JCH, et al. Does the COVID-19 pandemic spell the end for the direct ophthalmoscope? *Ophthalmol Ther.* 2020;9(4):689-92
24. Tostmann A, Bradley J, Bousema T, et al. Strong associations and moderate predictive value of early symptoms for SARS-CoV-2 test positivity among healthcare workers, the Netherlands, March 2020. *Euro Surveill.* 2020;25(16):2000508
25. Abrishami M, Tohidinezhad F, Daneshvar R, et al. Ocular manifestations of hospitalized patients with COVID-19 in northeast of Iran. *Ocul Immunol Inflamm.* 2020;28(5):739-44
26. Bostanci Ceran B, Ozates S. Ocular manifestations of coronavirus disease 2019. *Graefes Arch Clin Exp Ophthalmol.* 2020;258(9):1959-63
27. Chen L, Deng C, Chen X, et al. Ocular manifestations and clinical characteristics of 535 cases of COVID-19 in Wuhan, China: A cross-sectional study. *Acta Ophthalmol.* 2020;98(8):e951-59
28. Cavalleri M, Brambati M, Starace V, et al. Ocular features and associated systemic findings in SARS-CoV-2 infection. *Ocul Immunol Inflamm.* 2020;28(6):916-21
29. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-20
30. Hong N, Yu W, Xia J, et al. Evaluation of ocular symptoms and tropism of SARS-CoV-2 in patients confirmed with COVID-19. *Acta Ophthalmol.* 2020 [Online ahead of print]
31. Lee YH, Kim YC, Shin JP. Characteristics of ocular manifestations of patients with coronavirus disease 2019 in Daegu Province, Korea. *J Korean Med Sci.* 2020;35(35):e322
32. Liu WR, Zuo GJ, Qin Y. Clinical characteristics and outcomes of 2019-nCoV-infected patients admitted at different time periods. *Eur Rev Med Pharmacol Sci.* 2020;24(14):7826-33
33. Ma N, Li P, Wang X, et al. Ocular manifestations and clinical characteristics of children with laboratory-confirmed COVID-19 in Wuhan, China. *JAMA Ophthalmol.* 2020;138(10):1079-86
34. Öncül H, Öncül FY, Alakus MF, et al. Ocular findings in patients with coronavirus disease 2019 (COVID-19) in an outbreak hospital. *J Med Virol.* 2020;93(2):1126-32
35. Shemer A, Einan-Lifshitz A, Itah A, et al. Ocular involvement in coronavirus disease 2019 (COVID-19): a clinical and molecular analysis. *Int Ophthalmol.* 2020;41(2):433-40
36. Sindhuja K, Lomi N, Asif MI, Tandon R. Clinical profile and prevalence of conjunctivitis in mild COVID-19 patients in a tertiary care COVID-19 hospital: A retrospective cross-sectional study. *Indian J Ophthalmol.* 2020;68(8):1546-50
37. Bozkurt E, Özates S, Muhafiz E, et al. Ocular surface and conjunctival cytology findings in patients with confirmed COVID-19. *Eye Contact Lens.* 2020;47(4):168-73
38. Navel V, Chiambaretta F, Duthel F. Haemorrhagic conjunctivitis with pseudomembranous related to SARS-CoV-2. *Am J Ophthalmol Case Rep.* 2020;19:100735
39. Nayak B, Poddar C, Panigrahi MK, et al. Late manifestation of follicular conjunctivitis in ventilated patient following COVID-19 positive severe pneumonia. *Indian J Ophthalmol.* 2020;68(8):1675-77
40. Ozturker ZK. Conjunctivitis as sole symptom of COVID-19: A case report and review of literature. *Eur J Ophthalmol.* 2021;31(2):NP161-66
41. Salducci M, La Torre G. COVID-19 emergency in the cruise's ship: A case report of conjunctivitis. *Clin Ter.* 2020;171(3):e189-91
42. Scalinci SZ, Trovato Battagliola E. Conjunctivitis can be the only presenting sign and symptom of COVID-19. *IDCases.* 2020;20:e00774
43. Wu P, Liang L, Chen C, Nie S. A child confirmed COVID-19 with only symptoms of conjunctivitis and eyelid dermatitis. *Graefes Arch Clin Exp Ophthalmol.* 2020;258(7):1565-66
44. Daruich A, Martin D, Bremond-Gignac D. Ocular manifestation as first sign of Coronavirus Disease 2019 (COVID-19): Interest of telemedicine during the pandemic context. *J Fr Ophtalmol.* 2020;43(5):389-91
45. Liu M, Dai C, Lv X, Li B. Letter to the Editor: Are severe COVID-19 patients more susceptible to conjunctivitis? *J Med Virol.* 2020;92(11):2394-95
46. Spapen HD, D'Haese J, Diltoer M, Huyghens LP. Bedside evaluation of intraocular pressure in critically ill patients, ventilated at different levels of positive end-expiratory pressure. *Acta Anaesthesiol Belg.* 1993;44(2):39-43
47. Gangaputra SS, Patel SN. Ocular symptoms among nonhospitalized patients who underwent COVID-19 testing. *Ophthalmology.* 2020;127(10):1425-27

48. Rokohl AC, Loreck N, Wawer Matos PA, et al. More than loss of taste and smell: burning watering eyes in coronavirus disease 2019. *Clin Microbiol Infect.* 2020;26(11):1560.e5-e8
49. Guo D, Xia J, Wang Y, et al. Relapsing viral keratoconjunctivitis in COVID-19: A case report. *Virology.* 2020;17(1):97
50. Cheema M, Aghazadeh H, Nazarali S, et al. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19). *Can J Ophthalmol.* 2020;55(4):e125-29
51. Méndez Mangana C, Barraquer Kargacin A, Barraquer RI. Episcleritis as an ocular manifestation in a patient with COVID-19. *Acta Ophthalmol.* 2020;98(8):e1056-57
52. Otaif W, Al Somali AI, Al Habash A. Episcleritis as a possible presenting sign of the novel coronavirus disease: A case report. *Am J Ophthalmol Case Rep.* 2020;20:100917
53. Tappeiner C, Walscheid K, Heiligenhaus A. [Diagnosis and treatment of episcleritis and scleritis]. *Ophthalmologe.* 2016;113(9):797-810 [in German]
54. Hereth-Hebert E, Bah MO, Etard JF, et al. Ocular complications in survivors of the Ebola outbreak in Guinea. *Am J Ophthalmol.* 2017;175:114-21
55. Yawn BP, Wollan PC, St Sauver JL, Butterfield LC. Herpes zoster eye complications: Rates and trends. *Mayo Clin Proc.* 2013;88(6):562-70
56. Gill K, Ghazianin H, Manch R, Gish R. Hepatitis C virus as a systemic disease: Reaching beyond the liver. *Hepatology.* 2016;10(3):415-23
57. Duan Y, Beli E, Li Calzi S, et al. Loss of angiotensin-converting enzyme 2 exacerbates diabetic retinopathy by promoting bone marrow dysfunction. *Stem Cells.* 2018;36(9):1430-40
58. Casagrande M, Fitzek A, Püschel K, et al. Detection of SARS-CoV-2 in human retinal biopsies of deceased COVID-19 patients. *Ocul Immunol Inflamm.* 2020;28(5):721-25
59. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020;18(4):844-47
60. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet.* 2020;395(10234):1417-18
61. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. *Intensive Care Med.* 2020;46(6):1089-98
62. Dumitrascu OM, Volod O, Bose S, et al. Acute ophthalmic artery occlusion in a COVID-19 patient on apixaban. *J Stroke Cerebrovasc Dis.* 2020;29(8):104982
63. Sheth JU, Narayanan R, Goyal J, Goyal V. Retinal vein occlusion in COVID-19: A novel entity. *Indian J Ophthalmol.* 2020;68(10):2291-93
64. Gaba WH, Ahmed D, Al Nuaimi RK, et al. Bilateral central retinal vein occlusion in a 40-year-old man with severe coronavirus disease 2019 (COVID-19) pneumonia. *Am J Case Rep.* 2020;21:e927691
65. Insausti-García A, Reche-Sainz JA, Ruiz-Arranz C, et al. Papillophlebitis in a COVID-19 patient: Inflammation and hypercoagulable state. *Eur J Ophthalmol.* 2020 [Online ahead of print]
66. Virgo J, Mohamed M. Paracentral acute middle maculopathy and acute macular neuroretinopathy following SARS-CoV-2 infection. *Eye (Lond).* 2020;34(12):2352-53
67. Invernizzi A, Torre A, Parrulli S, et al. Retinal findings in patients with COVID-19: Results from the SERPICO-19 study. *EClinicalMedicine.* 2020;27:100550
68. Landecho MF, Yuste JR, Gándara E, et al. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease? *J Intern Med.* 2020;289(1):116-20
69. Marinho PM, Marcos AAA, Romano AC, et al. Retinal findings in patients with COVID-19. *Lancet.* 2020;395(10237):1610
70. Vavvas DG, Sarraf D, Sadda SR, et al. Concerns about the interpretation of OCT and fundus findings in COVID-19 patients in recent Lancet publication. *Eye (Lond).* 2020;34(12):2153-54
71. Jaworski C. Morphology of the HIV versus the diabetic cotton wool spot. *Optom Vis Sci.* 2000;77(11):600-4
72. Tascioglu D, Yalta K, Yetkin E. Hypertension and diabetes mellitus in patients with COVID 19: A viewpoint on mortality. *Cardiovasc Endocrinol Metab.* 2020;9(3):108-9
73. Ortiz-Seller A, Martínez Costa L, Hernández-Pons A, et al. Ophthalmic and neuro-ophthalmic manifestations of coronavirus disease 2019 (COVID-19). *Ocul Immunol Inflamm.* 2020;28(8):1285-89
74. Collange O, Tacquard C, Delabranche X, et al. Coronavirus disease 2019: Associated multiple organ damage. *Open Forum Infect Dis.* 2020;7(7):ofaa249
75. Mazzotta C, Giancipoli E. Anterior acute uveitis report in a SARS-CoV-2 patient managed with adjunctive topical antiseptic prophylaxis preventing 2019-nCoV spread through the ocular surface route. *Int Med Case Rep J.* 2020;13:513-20
76. Benito-Pascual B, Gegúndez JA, Díaz-Valle D, et al. Panuveitis and optic neuritis as a possible initial presentation of the novel coronavirus disease 2019 (COVID-19). *Ocul Immunol Inflamm.* 2020;28(6):922-25
77. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* 2020;92(6):552-55
78. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. *Lancet Infect Dis.* 2020;20(11):e276-88
79. World Health Organization (WHO). Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. 2020
80. Stankovic K, Mialhes P, Bessis D, et al. Kawasaki-like syndromes in HIV-infected adults. *J Infect.* 2007;55(6):488-94
81. Lidder AK, Pandit SA, Lazzaro DR. An adult with COVID-19 kawasakilike syndrome and ocular manifestations. *Am J Ophthalmol Case Rep.* 2020;20:100875
82. Sriwastava S, Tandon M, Kataria S, et al. New onset of ocular myasthenia gravis in a patient with COVID-19: A novel case report and literature review. *J Neurol.* 2020 [Online ahead of print]
83. Felice KJ, DiMario FJ, Conway SR. Postinfectious myasthenia gravis: Report of two children. *J Child Neurol.* 2005;20(5):441-44
84. Hawkes MA, Hocker SE, Leis AA. West Nile virus induces a post-infectious pro-inflammatory state that explains transformation of stable ocular myasthenia gravis to myasthenic crises. *J Neurol Sci.* 2018;395:1-3
85. Molko N, Simon O, Guyon D, et al. Zika virus infection and myasthenia gravis: Report of 2 cases. *Neurology.* 2017;88(11):1097-98
86. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: Tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem Neurosci.* 2020;11(7):995-98
87. Méndez-Guerrero A, Laespada-García MI, Gómez-Grande A, et al. Acute hypokinetic-rigid syndrome following SARS-CoV-2 infection. *Neurology.* 2020;95(15):e2109-18
88. Belghamidi S, Nassih H, Boutgayout S, et al. Third cranial nerve palsy presenting with unilateral diplopia and strabismus in a 24-year-old woman with COVID-19. *Am J Case Rep.* 2020;21:e925897
89. Dinkin M, Gao V, Kahan J, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology.* 2020;95(5):221-23
90. Wei H, Yin H, Huang M, Guo Z. The 2019 novel coronavirus pneumonia with onset of oculomotor nerve palsy: A case study. *J Neurol.* 2020;267(5):1550-53