

Review

Ocular Manifestations of COVID-19 (SARS-CoV-2): A Critical Review of Current Literature

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Abstract. *The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in China in the city of Wuhan in December of 2019 and since then more than 5,000,000 people have been infected, with approximately 338,000 deaths worldwide. The virus causes the coronavirus disease 2019 (COVID-19), which is characterized by fever, myalgia and cough, with severe acute respiratory syndrome being the most fearsome complication. Nevertheless, the vast majority of cases present mild symptoms or none. Central nervous system and cardiovascular manifestations have been reported. The range of ocular manifestations, either as a result of the infection or as a result of the treatment, has not yet been discussed. In this study, a systematic review of current literature relevant to COVID-19 was performed with focus on modes of transmission, ocular manifestations related to infection and medications, as well as the control of infection in ophthalmic practice.*

In December 2019, a novel coronavirus (CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in China in the city of Wuhan. On March 11, 2020 the World Health Organization formally declared the COVID-19 outbreak a pandemic. The number of cases has been dramatically increasing and in the light of high contagiousness and lack of effective treatments, it is still impossible to predict how close we are or not to the end of this pandemic. As of

May 23, 2020, a total of 5,209,266 cases have been confirmed in more than 187 countries of which 2,056,506 have recovered while 338,121 have died (1).

SARS-CoV-2 belongs to the family of *Coronaviridae*, which is a large family of enveloped, positive-sense, single-stranded RNA, and to the *Betacoronavirus* genus of the *Orthocoronaviridae* subfamily. The name coronavirus derives from the Greek word κορώνη (korōnē) which means wreath and refers to the characteristic appearance of the infective form of the virus (virions) as seen under an electron microscope, resembling a crown which is created by the bulbous surface projections of the microorganism. The *Coronaviridae* family has in total four genera with a wide host range, with *Alphacoronavirus*, *Betacoronavirus* infecting mammals, while *Gammacoronavirus* and *Deltacoronavirus* primarily infect birds (2). Infection with bacteria from any of these genera can lead to diverse clinical syndromes, while subclinical infections are not uncommon in all species. SARS-CoV-2 is the seventh member of the coronavirus family that is able to infect humans (3). The other six are human coronavirus 229E (*Alphacoronavirus*), NL63 (*Alphacoronavirus*), OC43 (*Betacoronavirus*), HKU1 (*Betacoronavirus*), Middle East respiratory syndrome coronavirus (MERS-CoV) (*Betacoronavirus*), severe acute respiratory syndrome coronavirus (SARS-CoV) (*Betacoronavirus*).

With regard to the life cycle of a coronavirus, infection begins when the spike glycoprotein of the viral envelope attaches to the host cell receptor and then a host protease assists the entry of the virion (either by direct fusion or endocytosis) by cleaving and activating this receptor-spike protein. This interaction is key for the life cycle of the virus and it has been confirmed that, as in SARS-CoV, angiotensin-converting enzyme II (ACE2) receptor mediates virion entry (4). It has also been demonstrated that the genome sequence of this virus is 79.6% identical to that of SARS-CoV and 96% identical at the whole-genome level to a bat coronavirus (4).

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COVID-19 diagnosis is primarily based on clinical signs and radiological findings, with laboratory findings confirming the diagnosis. With respect to ocular tissues, little is known about the pathological mechanisms. The purpose of this article is to present the ocular manifestations that have been reported so far in COVID-19-positive patients, as well as to provide a critical review of the proposed treatments of COVID-19 with focus on their ophthalmic side-effects.

Epidemiology – Risk Factors

SARS-CoV-2 cases have been confirmed across the globe except in Antarctica. In general, males and people over the age of 65 years with comorbidities are more likely to develop more severe symptoms and die when infected compared to other people without these characteristics. Even though children are affected by COVID-19 at a rate of 1% to 5% of total cases, they tend to present with milder symptoms, are less prone to severe disease and deaths are infrequent (5). Vertical intrauterine transmission from infected mothers or transmission through breastfeeding have not been confirmed. However, infected mothers can transmit the virus through either direct or indirect routes of human-to-human transmission and they are at higher risk of developing severe illness (6).

Risk factors for in-hospital death include older age, D-dimer level $>1 \mu\text{g/ml}$ and higher Sequential Organ Failure Assessment (SOFA) score on admission (7). In addition, patients with severe illness were more likely to have increased levels of interleukin 6 (IL-6), lactate dehydrogenase and high-sensitivity cardiac troponin I, prolonged activated partial thromboplastin time (aPPT) ($>90\%$ positive for lupus anticoagulant) (7) and reduced lymphocyte count (8). In contrast, inflammatory biomarkers and lymphocytopenia are less common findings in children (5).

Routes of Transmission

It was observed that the early cases in Wuhan were linked to the seafood market suggesting that this is likely a zoonotic disease. However, as for today the route of transmission has not yet been fully elucidated. While bats have been considered a natural host of the novel virus, as they are for a wide variety of coronaviruses, the intermediate hosts that can infect humans still remain unknown (9).

The disease is known to be directly transmitted by human-to-human contact through droplet spread (coughing or sneezing) in contact with oral, nasal and mucous membranes and indirectly through fomites *i.e.* in surfaces or objects that an infected person has used (10, 11). Of note, it has been suggested that transmission of the virus can also occur through contact with asymptomatic patients (12). In addition, the virus has been also detected on the ocular surface of

COVID-19-positive patients and in conjunctival secretions (13). Nevertheless, while in the study of Xie *et al.* it was shown that even conjunctivitis-free patients can actually spread the virus (14), the study of Seah *et al.* demonstrated no evidence of viral shedding in tears (15). The proposed theories for ocular involvement in SARS-CoV might also apply to COVID-19 and include direct inoculation of conjunctiva by droplets, migration of upper respiratory infection through the nasolacrimal duct, and hematogenous infection of lacrimal glands (16). These studies have only partially increased our understanding regarding the transmission route of SARS-CoV-2 as still it is not clear whether the virus can be transmitted through tears and if positive conjunctival titers imply higher transmissibility.

Presentation – Non-ocular Manifestations

The mean incubation period is of 5 to 6 days but affected people can experience symptoms anywhere from 2 to 12 days and only rarely after day 14 (17). Typical clinical symptoms of patients affected by COVID-19 are fever, dry cough, dyspnea, headache, pneumonia and myalgia. Nevertheless, a small fraction of patients have presented with diarrhea, hemoptysis and sputum production (18).

Diarrhea may be the only initial manifestation and fecal-oral transmission has been also suggested as viral RNA has been detected at high levels in stool samples of infected individuals (19, 20). Additionally, olfactory (anosmia, phantosmia, parosmia) and taste (ageusia, dysgeusia) disorders have been also reported in case reports and small cohort studies (21-23). Anosmia of new onset is currently considered a criterion for COVID-19 assessment (24).

Regarding the neurological manifestations of patients with COVID-19, these can be classified as mild and severe. Mild symptoms include headache, dizziness, nausea/vomiting and muscle aches, while in more severe cases acute neurological events such as stroke (ischemic, hemorrhagic) and acute necrotizing encephalopathy and even altered mental status, Guillain-Barre syndrome and myelopathy have been reported (25-27).

In severe cases myocarditis, cardiac arrhythmias and heart failure have been also observed. In addition, coagulopathy is a common abnormality in COVID-19 positive patients and as a result early therapeutic anticoagulation has been suggested in ICU patients in order to prevent venous thromboembolism complications (28-30).

Ocular Manifestations (Case Reports/Series)

A retrospective study of three hospitals in Wuhan presented the neurological manifestations of 214 patients (January 16-February 19, 2020). Among other important findings, this study demonstrated that 1.4% of patients (three out of 214)

had visual impairment, without specifying the nature of the impairments (31).

In addition, Wu *et al.* performed a preliminary investigation about the prevalence of ocular manifestations in patients with COVID-19 and reported that chemosis, epiphora, and conjunctival hyperemia were present in one-third of the patients. Moreover, they observed that these manifestations most commonly occurred in patients with severe systemic disease. Even though the sample size was relatively small (n=38), the study showed that white blood cell and neutrophil counts, as well as levels of procalcitonin, C-reactive protein and lactate dehydrogenase, were higher in patients who presented with ocular symptoms when compared to those without any ocular sign or symptoms. Of note, as no ophthalmic examination was performed by a specialist, clear conclusions cannot be drawn in regard to intraocular involvement or not. Overall, this study also suggested that even if only two conjunctival specimens (5.2%) from patients with ocular abnormalities yielded positive findings for SARS-CoV-2 on reverse transcription polymerase chain reaction (RT-PCR), COVID-19 can potentially also be transmitted through the eyes (32).

Keratoconjunctivitis as initial presentation with only mild respiratory symptoms was first reported in Canada in a young patient (33). Dinkin *et al.* also reported two cases of ophthalmoparesis consistent with abducens nerve palsies that developed within a few days of mild respiratory symptoms associated with SARS-CoV-2 (34). In addition, neurological deficits, as well as abnormal perineural or cranial nerve findings on magnetic resonance imaging were documented in both patients.

Ocular manifestations secondary to COVID-19 can even develop in the middle phase of the disease as suggested by Chen *et al.* (35). In their case report, a young COVID-19-positive male presented with bilateral acute follicular conjunctivitis that developed 13 days after illness onset. The patient reported eye redness, excessive tearing and foreign body sensation and his examination was significant for conjunctival injection, watery discharge, inferior palpebral conjunctival follicles and palpable preauricular lymph nodes without anterior chamber inflammation or corneal defects. Viral RNA for SARS-CoV-2 was detected in conjunctival swabs (RT-PCR) on day 13. Ribavirin eye drops were administered four times a day and in less than a week (day 19), resolution of symptoms was noted and RT-PCR was negative (35).

Furthermore, pseudomembranous and hemorrhagic conjunctivitis was reported in a patient with severe COVID-19 19 days after the beginning of symptoms. Azithromycin along with dexamethasone eye drops and daily debridement of pseudomembrane in order to avoid conjunctival fibrosis and contraction were introduced and improvement of symptoms was noted from day 21 to day 26 (36).

Hyper-reflective lesions at the level of the inner plexiform and ganglion cell layers have been also described in COVID-19-positive patients (37). Based on murine models of other CoVs, viral-induced retinitis and optic neuritis secondary to autoantibody production against neuroretina should also be included in the differential diagnosis and infected patients should be monitored for signs of neuroretinal degeneration in the long term (16, 37, 38).

Therapeutic Options Under Investigation and Potential Ocular Toxicity

Several treatment options have been reviewed but none of these therapies have been proven effective. In general, supportive treatment which includes oxygen and mechanical ventilation is of key importance in patients presenting with severe respiratory deterioration. We should highlight that no single medication or combination has shown efficacy in humans to date. Thus, the medications discussed in this section are candidate therapies.

Remdesivir. Remdesivir (GS-5734) is a nucleotide analog which inhibits RNA-dependent RNA polymerase with broad-spectrum antiviral activity. It is considered the most promising treatment so far based on its potent *in vitro* activity against SARS-CoV-2 but also on its *in vivo* and *in vitro* activity against SARS and MERS (39-41).

Of note, this medication was originally developed against Ebola virus (42). The first reported patient with COVID-19 in the United States received intravenous remdesivir on day 7 and clinical improvement was noted on day 8 without any adverse effects (43). The medication is currently under investigation in several clinical trials across the world and no ocular or severe adverse effects have been reported thus far (44).

Chloroquine and hydroxychloroquine. Chloroquine and hydroxychloroquine are two agents that have been widely used to treat malaria, systemic lupus erythematosus and rheumatoid arthritis. These medications have antiviral and immunomodulatory effects and are in general well tolerated. Their role in COVID-19 treatment is currently under investigation in several randomized clinical trials while recent reports have shown promising results (45, 46). More specifically, high doses have been recommended based on pharmacokinetic, clinical and safety studies and more typically involve an up to 10-day course of 500 mg chloroquine twice daily chloroquine or 400 mg of hydroxychloroquine four times daily (47).

It has been well established that chloroquine and hydroxychloroquine can result in serious, although rare, adverse effects. Long-term usage of these medications can lead to retinal toxicity but this only rarely occurs in cases with less than 10 years of usage at recommended doses (48).

Even though the doses currently used for COVID-19 treatment can be up to five times higher than the recommended ones, it seems that the brief period of treatment course is not a concern for retinal damage and no screening is yet suggested. Nevertheless, the results of future studies or even newer recommendations may provide more useful information (49). Interestingly, the most recent observational study of Geleris *et al.* showed that hydroxychloroquine use was not associated with a change in risk of intubation or death (50).

Lopinavir/ritonavir. The oral combination of protease inhibitors lopinavir/ritonavir has been used for human immunodeficiency virus treatment. This antiretroviral therapy has demonstrated *in vitro* activity against SARS-CoV-2, possibly through inhibition of 3-chymotrypsin-like protease which plays an important role in viral RNA processing. The most commonly used regimen in patients with COVID-19 patients is 400 mg lopinavir with 100 mg ritonavir twice daily for up to 14 days (51). There are studies which support the belief that early treatment may improve clinical outcomes (52, 53). Nevertheless, a randomized trial showed that this treatment was not associated with either clinical improvement or mortality in patients with severe COVID-19 (51).

There are no direct ocular side-effects in patients treated with this combination treatment. However, lopinavir/ritonavir can lead to resurgence of autoimmune conditions such as Grave's orbitopathy due to immune reconstitution inflammatory syndrome (IRIS) (54).

Ribavirin. Ribavirin is a guanine analog that tightly binds to and inhibits SARS-CoV-2 RNA-dependent RNA polymerase. Due to inconsistent efficacy of this medication whether as a monotherapy or in combination with other drugs such as interferon in MERS and SARS, ribavirin has not been widely recommended for COVID-19. Additionally, its use has been linked to severe dose-dependent adverse events such as hematological toxicity and bradycardia, making it a less attractive option for further investigation (55). Studies have shown that there may be severe ophthalmic adverse effects associated with ribavirin, interferon or their combination, especially when treating hepatitis C-positive patients. Retinopathy, retinal vein occlusion, serous retinal detachment, non-arteritic anterior ischemic optic neuropathy (NAION), and Vogt-Koyanagi-Harada disease are among the complications of these medications that can potentially lead to irreversible visual loss (56-59).

Interferons. Interferons are a group of cytokine mediators that exhibit important antiviral activity while playing a major role in the quality of both innate and adaptive cellular immune system responses (60).

Recombinant forms of interferons have been used to treat several types of viral infections as well as neoplastic diseases. Evidence of activity of interferon β against MERS has led interferons to be considered an alternative treatment for COVID-19, usually in combination with other medications. Studies have demonstrated that interferon β 1 is a more potent inhibitor of coronaviruses and can be a safe and promising treatment against SARS-CoV-2, and it has been suggested that its efficacy might be improved when combined with lopinavir/ritonavir, ribavirin or remdesivir (61, 62). Interferons have also been used in ophthalmology in a wide range of anterior and posterior chamber pathologies such as ocular surface neoplasias and macular edema (63, 64). Adverse ocular side-effects have been described in literature and can present either as complications during monotherapy and combined treatment as already highlighted. Besides interferon-associated retinopathy and Vogt-Koyanagi-Harada, blurred vision, ocular pain, conjunctivitis, uveitis, optic neuropathy and corneal disorders including ulcers, epithelial defects and Sjogren's syndrome, have been reported, with the more severe ones presenting after long-term treatment with interferons (65-67).

Tocilizumab. Tocilizumab is an immunomodulatory agent that has recently received FDA approval for phase III clinical trial for the treatment of critically ill COVID-19 patients. In general, this drug has been used as a monotherapy or in combination with other medications against several autoimmune diseases such as rheumatoid arthritis. In addition, in ophthalmic practice it has been recommended for the treatment of moderate or severe thyroid eye disease as well as for the treatment of giant cell arteritis (68, 69). In a small cohort, tocilizumab, which blocks IL-6 was tested in critically ill patients or in patients with extremely high levels of IL-6, and the study demonstrated that these patients benefited from repeated doses of oral 80-600 mg per administration (70). In 2012, Tada *et al.* first reported the occurrence of ocular adverse events in a middle-aged woman with rheumatoid arthritis who was treated with tocilizumab infusions (8 mg/kg) (71). More specifically, bilateral retinopathy with multifocal cotton-wool spots and retinal hemorrhages along with skin manifestations were observed 20 days after the first infusion. Gradual resolution of cutaneous and ocular findings was noted after treatment with antibiotics and corticosteroids and discontinuation of tocilizumab. The authors suggested that the abovementioned effects were secondary to modified leukocyte adhesion to vascular endothelial cells and resultant retinal capillary occlusion. Hence, it is important that ocular adverse events are always considered in patients treated with tocilizumab.

Oseltamivir. Oseltamivir is a neuraminidase inhibitor which is widely used for the treatment of influenza. This medication was introduced early in the treatment of COVID-19 patients as empirical management (influenza peak period). However, once influenza is excluded, oseltamivir is discontinued (41). Although rare, ophthalmologists should be aware of the side-effects of this medication. More specifically, Lee *et al.* reported a case of bilateral acute angle closure glaucoma and transient myopia after a 4-day treatment with oseltamivir. The authors postulated that these acute changes were related to the presence of cilioretinal effusion which caused anterior displacement of the lens-iris diaphragm. Moreover, cilioretinal effusion has been associated with the use of dopaminergic drugs and oseltamivir might have played a key role in the alteration of the membrane potential in the ciliary body (72).

Umifenovir. Umifenovir is an antiviral medication which inhibits spike protein–ACE2 interaction (73). It has been widely used for the treatment and prophylaxis of influenza and currently is being studied in COVID-19 patients at the same dose as for influenza (200 mg/8 h; per os). While umifenovir has shown promising results in small non-randomized studies, further evaluation is needed (74). Similar to other medications, no ocular side-effects associated with its use have been reported.

Nitazoxanide. Nitazoxanide and its active metabolite tizoxanide are known to inhibit the replication of a wide range of RNA and DNA viruses. It has shown action against several viruses including SARS and MERS and currently its action against SARS-CoV-2 is under investigation either as monotherapy or in combination with hydroxychloroquine. The only reported ocular-related side-effect of nitazoxanide is eye discoloration (75, 76).

Favipiravir. Favipiravir is a pyrazine derivative which acts as an inhibitor of viral RNA-dependent RNA polymerase thus, preventing RNA elongation. It has been widely used and shown remarkable activity against influenza virus but also in oseltamivir-resistant cases. It is a teratogenic medication and should be avoided in pregnant women (77). However, ophthalmic side-effects have not been reported thus far. Further studies are needed in order to determine its toxicity profile.

Camostat mesylate. Camostat mesylate is a protease inhibitor that targets the host serine protease transmembrane serine protease 2 (TMPRSS2) preventing viral entry. This drug has been approved in Japan for the treatment of pancreatitis and had also demonstrated partial activity against other coronaviruses but there is no clear evidence that it can fight SARS-CoV-2 (78). No studies have reported any severe

ocular side-effects other than conjunctival discoloration secondary to liver dysfunction (jaundice) (70).

Corticosteroids. Corticosteroids have been widely used for the treatment against cytokine storm syndrome which is characterized by hyperinflammation secondary to overproduction of immune cells and cytokines (80). This syndrome can occur in many infectious or autoimmune processes and a significant increase of several cytokines has been detected in a subgroup of patients with COVID-19 (81). However, the high doses and long duration which are required for treatment of severe or chronic diseases with corticosteroids can lead to a wide range of side and adverse effects including but not limited to delayed viral clearance and increased risk of secondary infection. In addition, no proven benefit has been documented so far (82). As a result, studies have focused on introducing corticosteroid-sparing medications (immunomodulatory) or alternatively using corticosteroids as adjunctive treatment in order to minimize the doses used and subsequent drug-related risks (41).

Ocular complications of corticosteroid use have been well documented. The incidence of corticosteroid-induced cataracts increases after long-term (at least 1 year) and high oral dose (≥ 10 mg/day) of any type of steroid. In addition, glaucoma is another daunting complication and patients who develop glaucoma may need long-term anti-glaucoma treatment in order to control the intra-ocular pressure (83). Exogenous steroid use has been linked to the development of central serous chorioretinopathy (CSR) (84). While, this condition can be self-limiting, it can recur in up to one-third of treated patients and irreversible visual deterioration has also been reported in long-standing cases (85). Overall, it is recommended that every patient on long-term therapy with corticosteroids, regardless of route of administration and whether are prescribed or over-the-counter, should be routinely screened and offered ophthalmological evaluation (82).

Immunoglobulin therapy. Hyperimmune immunoglobulins or use of convalescent plasma have been proposed as adjunctive treatment based on the results in patients with SARS, and MERS (86, 87). In general, these treatments are safe although better outcomes are expected when viremia is at its peak (41). Thromboembolic events have been reported including cerebrovascular accidents, myocardial infarction and deep vein thrombosis (88).

Interestingly, iatrogenic bilateral central retinal vein occlusions were reported in a young patient who received intravenous immunoglobulins but resolved after discontinuing their administration (89). Ophthalmologists should be aware of this rare and preventable side-effect in order to minimize the incidence of visual deterioration by proposing different management plans, including dose or interval adjustments of immunoglobulins.

Prevention

As there is clear evidence of patient-to-ophthalmologist transmission, prophylactic measures are also vital in ophthalmic practice. Efforts to contain the viral spread are of immense importance and effective containment requires a solid understanding of all possible routes of transmission, as well as timely interventions to break the chain of infection. The World Health Organization has provided guidance on the type of protection that is needed in a healthcare setting (90). Meticulous hand hygiene, use of facial and eye protection (face mask, goggles), gown and gloves are required in order to minimize transmission and exposure.

Based on the results of the clinical trials that have been published to date, no single treatment has been proven effective in increasing the likelihood of survival. More than one hundred vaccine candidates are under development, of which 78 are confirmed as being active against the novel coronavirus. However, even though all research processes have been accelerated, it is postulated that it may take up to 2 years to create a new and effective vaccine (91).

Regarding contact lens wearers, while currently there is no evidence that lenses can increase the risk of COVID-19 nor that they can provide protection against it, it is imperative for all wearers to continue strictly following appropriate hygiene practices in order to minimize the risk of infection and transmission. In fact, contact lens wearers should be encouraged to use their spectacles instead, a practice which is consistent with the guidance mainly for respiratory illnesses (92).

Conclusion

The COVID-19 pandemic has presented immense challenges worldwide. Social and physical distancing, and travel restrictions are among the strategies that have been implemented and are inevitably forcing a dramatic decline in the workforce, with negative impacts on the economy. The effect of COVID-19 on global healthcare systems is undoubtedly detrimental. There is an imperative need for multidisciplinary collaboration involving healthcare institutions, governments, pharmaceutical industries and academics in order to improve outcomes.

Even though from an ophthalmological perspective, it is essential for proper assessment of underlying ocular conditions, as medical doctors we must not forget that we are obliged towards our patients and society to provide a comprehensive evaluation of a patient's health status even beyond our field of expertise.

Accurate and early diagnosis, appropriate individualized therapeutic strategies, preventative measures and effective communication with healthcare and non-healthcare

professionals are key steps for preventing further spreading of this novel coronavirus.

Conflicts of Interest

The Authors state that they have no conflicts of interest to declare.

Authors' Contribution

KAAD and VPD were involved with designing of the work, data collection, analysis and interpretation and drafting of the article. MMM supervised the study and was involved in the critical revision of the article.

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