Review Article

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Ocular Manifestations of COVID-19: An Update and A Review of Current Literature

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ABSTRACT

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization (WHO) in March 2020. It was caused by the highly pathogenic SARS-Cov-2 virus. Although the majority of its clinical manifestations are associated with airway involvement, extrapulmonary damage does occur in some situations. In light of the above discussion, this study of the literature tries to identify the ophthalmological disorders produced by infection with the new coronavirus. Although ocular symptoms do not correspond to the disease's standard clinical presentation, there are reports of some ophthalmological alterations in COVID-19 individuals, the most prevalent of which is conjunctivitis.

KEYWORDS: Ophthalmology; Conjunctivitis; Coronavirus infections; Pandemic; Sars-CoV-2; Indocyanine Angiography; Multiple evanescent white dot syndrome (MEWDS); Non-infectious uveitis; Retinal lesions

INTRODUCTION

Viruses spread in humans, birds, and other animals, resulting in epidemics and pandemic breakouts throughout history, such as the 1968 H1N1 (Spanish flu) and H3N2 (Hong Kong fever) pandemics, which killed over 1 million people [1]. The World Health Organization (WHO) announced a pandemic on March 11, 2020, due to the novel coronavirus NCOV-19, which produces Sars-COV-2, severe acute respiratory syndrome with systemic complications such as organ failure and septic shock [2-4].

The condition was first documented in the Chinese city of Wuhan, where patients presented with symptoms such as a dry cough, dyspnoea, fever, and bilateral lung infiltrates on imaging studies. In addition to identifying these symptoms and clinical signs, the Chinese Centre for Disease Control and Prevention also identified the causative agent as Sars-CoV-2 following a more extensive study using nasopharyngeal swabs [3,4]. As of the 28th of December 2021, there were 252,976,252 documented cases worldwide, and 5,099,860 reported deaths [5]. The death rate varies by country and 'appears' to be low in those with effective public health and primary healthcare systems [6]. The SARS-CoV-2 virus is transmitted mostly by respiratory droplets during close face-to-face contact, with an average time interval of five days between exposure and symptom onset [7]. Initial reports from China indicated a high incidence of symptoms, with fever accounting for 98% of cases, cough accounting for 77%, and myalgia accounting for 44% of patients evaluated [8]. However, the literature is beginning to reveal a more nuanced semiology [9¬-16]. Along with the cardinal signs of COVID-19 (fever (88-100%), cough (68-85%), and sputum (23-41%)), several other signs have been reported [9-16]: anorexia (84%), asthenia (70-80%),

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headache (52-55%), ageusia (43%), anosmia (37%), abdominal pain (25%), neuromuscular involvement (19%), dyspnoea (18-85%), Subsequent research has revealed that the majority of infected individuals remain asymptomatic or slightly symptomatic [17]. Additionally, the COVID-19 pandemic had a long-term impact on people's lives, particularly on education, business, and the economy, as well as on social life, politics, and entertainment [18-30]. Sars-CoV-2 is a single-stranded RNA virus that resembles Sars-CoV-1 immunologically [31]. This pathogen is a member of the beta-coronavirus family and possesses a large number of non-structural proteins and spike proteins that interact strongly with the angiotensin-converting enzyme 2 (ACE2) receptors found in the human body [31]. The lung, heart, kidney, and intestinal tissues contain a higher concentration of ACE2 [32]. The receiver gene is expressed in epithelial cells in the lung, implying a link between ACE2 and the distinctive alveolar damage seen in COVID-19 patients [33,34].

T-lymphocytes mediate the immunological response to the virus via antigen-presenting cells and alveolar macrophages that express ACE2 receptors. Thus, there is an inflammatory process sustained by CD-4 and cytotoxic CD8-mediated cellular death [35]. Additionally, the ocular tissue expresses ACE2, which is found in the cornea and conjunctiva epithelial cells [35,36]. This receptor is involved in the maintenance of intraocular pressure and plays a significant role in the COVID-19 physiopathology [37]. Because the ocular surface can act as a gateway for a variety of infections, including the coronavirus, it is hypothesized that this includes the coronavirus [38]. Given that this is a perfect environment for virus adhesion due to the virus's affinity for the surface receptor, some scientists hypothesize that contact of the ocular surface with infected items and hands may serve as the first site of infection, from which the virus spreads [38,39].

Due to the presence of ACE2 in the corneal limbus, the beta-coronavirus is able to traverse the ocular surface and move to other areas of the body *via* the hematogenic route or the neurological system via the trigeminal nerve [40]. The existence of ocular signs and symptoms, as well as the likelihood of contracting NCOV-19 via contaminant droplets in the conjunctiva, has piqued medical institutions' interest. Individual eye protection measures and early detection of ocular symptoms in individuals with suspected COVID-19 have thus been indicated as critical [39,41]. Although this is a very recent event, there have been reports of ocular symptoms in COVID-19 patients [41]. Ocular involvement is most frequently manifested by viral conjunctivitis, which manifests as redness, lacrimation, and a foreign body sensation on the 13th day of the sickness or as the initial symptom of infection [42]. While conjunctivitis is not a traditional or usual presentation of the new coronavirus, clinicians and ophthalmologists should be mindful of patients who arrive with this symptom. The purpose of this study is to identify and assess the most common ocular problems associated with viral infection with Sars-Cov-2.

METHODS

The current work is a literature review of the main ocular manifestations found in COVID-19 patients. A search was carried out in the PubMed, Medline and Google scholar databases using keywords such as "ocular findings" and COVID-19, as well as "ocular manifestation" and "coronavirus." As a result, we found some initial studies from 2019-2021 and selected those that fit into the proposed theme.

RESULTS AND DISCUSSION

The novel coronavirus-induced acute respiratory disease extended outside Chinese boundaries and garnered international attention. NCOV-19 utilizes ACE2 to connect to the respiratory epithelium in particular and establish systemic circulation in the animal [43]. SARS-CoV-2 pathogenesis and tissue tropism are linked to the viral spike protein binding to its corresponding receptor on human host cells, the angiotensin-converting enzyme 2 (ACE-2) receptor. Cleavage of the protein transmembrane serine protease 2 is required for efficient cell entrance (TMPRSS2). ACE-2 is expressed predominantly on respiratory mucosal and alveolar epithelial cells but has also been found in other tissues such as the gastrointestinal tract, kidney, vascular endothelial cells, immunological cells, and even neurons. Virulence is established through direct cellular invasion and death, as well as through the production of broad cytokine-mediated inflammation and vascular leakage [44].

The possibility of infection via ocular secretions is unknown at the moment, as is the mechanism by which SARS-CoV-2 accumulates in ocular secretions. Several possible explanations include direct inoculation of ocular tissues by respiratory droplets or aerosolized virus particles, migration from the nasopharynx via the nasolacrimal duct, or even hematogenous dissemination via the lacrimal gland [45]. The data on ACE-2 and TMPRSS2 expression on the ocular surface is inconsistent. Both of these proteins are expressed on the cornea and limbus, but in very low quantities on the conjunctiva [46]. Lange et al. [47] also discovered that the human conjunctiva had low ACE-2 levels.

In a case report from Rome, Italy [48], SARS-CoV-2 was identified by RT-PCR from conjunctival swabs in a COVID-19 patient with ocular symptoms. From hospital days 3 to 27, conjunctival swabs were taken. Although the conjunctivitis improved clinically on day 20, the patient exhibited detectable viral SARS-CoV-2 RNA in conjunctival samples on day 21 and then on day 27 after a nasopharyngeal swab tested negative for SARS-CoV-2. Due to the inability of SARS-CoV-2 to be cultivated successfully from human tears or conjunctival swabs, the virus's survival and transmissibility in human ocular secretions remain unknown [49]. Tears may be a source of infection transmission both early and late, even after the patient becomes asymptomatic [48,50].

Azzolini et al. [51] discovered SARS-CoV-2 on the ocular surface of 52 of 91 COVID-19 patients (57.1 percent) using a reverse transcription-polymerase chain reaction test. They discovered that in ten of seventeen cases, even when the nasopharyngeal swab was negative, the virus was detected on the ocular surface. It has been hypothesized that viral particles in tears originate in the lacrimal gland via diffusion from a systemic viral load or via direct contact with airborne droplets. It has been hypothesized that Dr. Li Wenliang, a deceased ophthalmologist from Wuhan, China, caught the virus by ocular transmission [51]. Ocular symptoms occur in between 2% and 32% of patients with COVID-19 [52-56].

Conjunctiva

SARS-CoV-2 infection can cause acute conjunctivitis symptoms such as eye redness, ocular irritation, eye discomfort, foreign body sensation, weeping, mucoid discharge, eyelid swelling, congestion, and chemosis. These symptoms have been reported to occur more frequently in patients with severe systemic symptoms of COVID-19, albeit they can seldom emerge as the disease's initial manifestation

[57]. In five patients with confirmed SARS-CoV-2 infection using nasopharyngeal RT-PCR, non-remitting conjunctivitis was identified as the sole manifestation of COVID-19; these patients did not develop fever, general malaise, or respiratory symptoms during their illness [58].

Examination findings include unilateral or bilateral bulbar conjunctival injection, follicular response of the palpebral conjunctiva, watery discharge, and minor eyelid edema. Bilateral chemosis alone may be a sign of third-spacing in a severely unwell patient rather than a real viral ocular presentation. Cheema et al. [59] presented the first instance of keratoconjunctivitis as a presenting symptom of COVID-19 in North America [59]. The patient's chief symptoms were redness and lacrimation in his eyes. The examination was notable for conjunctival injection, palpebral conjunctival follicular reaction, and the rapid development of corneal lesions over three days, including transitory pseudo dendritic lesions and widespread subepithelial infiltrates with overlaying epithelial defects. Navel et al. [60] reported a case of acute haemorrhagic conjunctivitis with pseudo membrane formation in a patient 19 days after the onset of systemic symptoms and 11 days after intensive care unit admission [60]. A 46-year-old male presented with minor respiratory symptoms and a positive COVID-19 nasopharyngeal test. He had haemorrhagic bilateral conjunctivitis with pseudo membrane development and chemosis five days following the positive test. Several years prior, the left eye had been removed due to melanoma. The conjunctiva of the socket exhibited the same haemorrhagic conjunctivitis with chemosis and pseudo membrane development as the conjunctiva of the right eye. His symptoms resolved in four weeks after he was treated empirically with topical antibiotics. He did not acquire any other COVID-19 symptoms.

Episclera/Sclera

At least two cases of episcleritis have been recorded in the context of COVID-19 infection. Otaif et al. [61] described a 29-year-old male with unilateral episcleritis as the primary symptom of SARS-CoV-2 infection, while Mangana et al. [62] characterized a 31-year-old female with nodular episcleritis [61,62].

Anterior Chamber

Beyond the ocular surface, acute anterior uveitis has been reported both independently and in combination with COVID-19-associated multisystem inflammatory illness [63,64].

Retina

Changes in the retina may also be related to COVID-19 infection. In 12 adults examined after systemic disease onset, optical coherence tomography (OCT) revealed subclinical hyperreflective lesions at the level of the inner plexiform and ganglion cell layers; dilated fundus examinations revealed cotton wool spots and microhaemorrhages in four of these patients [65]. Invernizzi and colleagues discovered retinal haemorrhages (9.25%), cotton wool spots (7.4%), dilated veins (27.7%) and tortuous vessels (12.9%) in 54 individuals with COVID-19 during fundus photography screening [66]. Additionally, these authors discovered a direct correlation between retinal vein diameter and disease severity, implying that this may be a non-invasive metric for monitoring inflammatory response and/or endothelial injury in COVID-19. On FLAIR-weighted images, Lecler et al. [67] observed aberrant MRI findings in the posterior pole of nine patients with COVID-19, consisting of one or more hyperintense nodules in the macular region. These lesions were hypothesized to be caused by either direct inflammatory infiltration of the retina or by viral infection-induced microangiopathic disease.

A further case of suspected retinal changes following prior infection with COVID 19 has been reported. De Salvo et al. [68] reported a case that presented with visual loss and unusual new retinal manifestations in the form of Multiple Evanescent White Dot Syndrome (MEWDS). Resolution of the visual loss was noted with normalization of ancillary testing, including visual fields [68]. Additionally, animal model studies have demonstrated that the retina is involved in the development of retinal vasculitis [69], retinal degeneration [70], and the collapse of the blood-retinal barrier [71]. The majority of these symptoms are related to demyelinating disease. While the mechanism of these manifestations is uncertain, possible explanations include direct neural invasion, endothelial cell failure leading to ischemia and coagulopathy, or a virus-induced broad inflammatory "cytokine storm" [72]. Optic neuritis has developed in a number of infected patients, accompanied by neuromyelitis optica spectrum disease and anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies [73]. Following a COVID-19 infection, patients presented with subacute vision loss, a relative afferent pupillary defect, pain with eye movements, optic disc edema, and radiographic abnormalities consistent with acute optic neuritis. In another report, Palao et al. [74] reported a case of multiple sclerosis following COVID-19 infection in a 24-year-old patient who presented with right optic neuritis; MRI revealed inflammation of the right optic nerve and supratentorial periventricular demyelinating lesions [74]. These instances indicate that SARS-CoV-2 may initiate or aggravate inflammatory or demyelinating illnesses.

Ophthalmologists may also be consulted to assess for papilledema in individuals infected with SARS-CoV-2, as there have been reports of increased intracranial pressure caused by extensive inflammation and dural venous sinus thrombosis [75]. Multisystem inflammatory syndrome in children (MIS-C) caused by COVID-19 is also gaining recognition as a distinct condition resembling Kawasaki disease and has been associated with increased intracranial pressure [76]. Verkuli et al. [77] documented a 14-year-old girl who developed pseudotumor cerebri syndrome in association with MIS-C due to COVID-19. Symptoms included a new right abducent nerve palsy, papilledema with disc haemorrhages, and lumbar puncture with an opening pressure of 36 cm H2O [77].

Extraocular Motility, Cranial Nerves

In addition, palsies of the third, fourth, and sixth cranial nerves linked with COVID-19 have been documented in the literature within a few days after the onset of fever and cough, with the majority of cases exhibiting no notable radiological findings [78]. Ocular cranial neuropathies and binocular diplopia with nerve augmentation on magnetic resonance imaging have also been found in connection with post-infectious demyelinating disorders such as Miller Fisher and Guillain Barré syndrome. Dinkin et al. [79], for example, documented a 36-year-old male with left mydriasis, ptosis, as well as contemporaneous MRI enhancement of the left oculomotor nerve [79]. Additionally, he was found to exhibit hyporeflexia and ataxia in his lower extremities, consistent with Miller-Fischer syndrome. Ocular myasthenia gravis has been documented as a post-infectious sequela to COVID-19, with investigators hypothesizing that antibodies directed against SARS-CoV-2 proteins may cross-react with acetylcholine receptors and other neuromuscular junction components [80]. Huber and

colleagues documented a 21-year-old patient who presented with variable vertical binocular diplopia and ptosis four weeks after COVID-19 infection and was successfully treated with intravenous immunoglobulins and oral pyridostigmine [81].

Pupils

Additionally, changes in the pupillary structure have been detected Ortiz-Seller et al. [82]; Ordas et al. [83] both documented patients with mydriasis and hypersensitivity to cholinergic stimuli, indicating tonic pupils and postganglionic parasympathetic pupillary nerve fibre injury. In some cases of COVID-19 infection involving the nervous system, nystagmus and oscillopsia have been observed. Malayali described a 20-year-old woman who came with persistent vertigo, nausea, and vomiting and was diagnosed with viral-induced vestibular neuritis secondary to COVID-19 [84]. Furthermore, central vestibular nystagmus has been linked to clinical and imaging symptoms of rhombencephalitis [85,86].

Visual Cortex

An acute stroke affecting the posterior visual pathways is perhaps the most serious neuro-ophthalmic consequence of severe COVID-19 infection. Stroke was shown to be 7.6 times more common in these patients than in patients with influenza, and it occurred in a much younger than normal patient population without conventional vascular risk markers [87]. These patients may present with homonymous visual field impairments, necessitating evaluation by an ophthalmologist.

Orbit

Direct orbital involvement is quite rare in cases of COVID-19. Two cases of sinusitis, orbital cellulitis, and cerebral abnormalities in adolescents infected with COVID-19 have been reported.

Lacrimal Gland

Diaz et al. [88] described a case of acute dacryoadenitis in a 22-year-old man who experienced partial ophthalmoplegia after testing positive for SARS-CoV-2 antibodies. The patient was otherwise asymptomatic with COVID-19. Of course, there is no way to prove a causal relationship between the two situations. It is hypothesized that because patients with COVID-19 may have SARS-CoV-2 in their tear film, retrograde spread to the lacrimal gland via the ductules may result in dacryoadenitis. Alternatively, the cause may be an immune response of the lacrimal gland in response to the patient's positive IgM coronavirus antibodies. When painful ophthalmoplegia developed, this patient was treated with oral antibiotics followed by steroid therapy. The patient healed after a month-long decrease in the steroids. We treated one patient who presented with typical symptoms and signs of dacryoadenitis and had a positive COVID-19 nasopharyngeal test. The patient responded well to a six-week decrease in steroids.

CONCLUSION

As evidenced by the aforementioned publications, despite the fewer number of reported cases of COVID 19 related ocular signs and symptoms, (compared to the number of respiratory and general systemic cases) our literature review demonstrates that ocular manifestations may be one of the early or exclusive manifestations of the new coronavirus, though not the most typical or well-known standard presentation with respiratory symptoms. Viral conjunctivitis is one of these ophthalmologic abnormalities that may manifest as hyperaemia, foreign body sensation, swollen eyelid, epiphora, increased conjunctival secretions, in addition to dry eyes and reduced vision. As a result, it is critical to expand our awareness of this novel condition and identify its extrapulmonary manifestations in order to thoroughly evaluate patients and grasp the role of ophthalmic symptoms and the ophthalmologist on the frontline. Additionally, because viral RNA has been detected in the conjunctiva in several investigations, the involvement of healthcare practitioners in educating the public about proper ocular surface handling and personal hygiene, has been demonstrated to be critical.

CONFLICTS OF INTEREST/COMPETING INTERESTS

Declaration of competing interest GDS reports consultant fees from Allergan, Bayer, Heidelberg Engineering and Novartis, outside the submitted work. AM declares no competing interests.

AVAILABILITY OF DATA AND MATERIAL

All data analysed and reported in this study are available from the first author on reasonable request.

CONSENT FOR PUBLICATION

All authors approved of the final version to be published and agree to be accountable for any part of the work.

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