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Research Article

Ocular Findings of Patients with Coronavirus Disease 2019 (COVID-19): A Literature Review

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Abstract

Background: COVID-19 pandemic has many clinical presentations not related to respiratory symptoms. Ocular symptoms are reported in many cases and conjunctivitis is now considered as one of the well-established symptoms in COVID-19 patients. However, the ocular pathologies in COVID-19 patients are not well studied. In this study, we reviewed the literature to stand on the epidemiology and clinical presentation of ocular pathologies in COVID-19 patients.

Methods: We searched the MEDLINE database using PubMed. Two independent reviewers reviewed the resulting papers and reviewed them based on our inclusion criteria.

Results: Based on the review results, many studies reported the presence of viral DNA in tears and conjunctival swabs. These studies implied a conjunctival route of infection to the respiratory system. The presence of ocular symptoms indicated a worse prognosis. The most common reported ocular diseases were conjunctivitis and ocular surface diseases. However, there is still no clear and proved evidence of the pathogenesis of these diseases.

Conclusion: The exact epidemiology and pathogenesis of the ocular diseases in COVID-19 patients is not clear and was not investigated thoroughly in the recent literature. However, many reports indicated the high prevalence of conjunctivitis and ocular surface infection in these patients. More studies are needed to identify the underlying pathogenesis of ocular diseases.

Keywords: *COVID-19; SARS-COV-2; Conjunctivitis; Retinitis; Ocular Diseases; Eye Infection*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is one of the coronaviruses infamously causing respiratory distress [1]. However, SARS-COV-2 is the most known for its high infectivity rate causing a worldwide pandemic [1]. Its structure is similar to SARS-

COV and it is formed of spike protein (S), transmembrane glycoprotein (M), an envelope protein (E), and nucleocapsid protein (N) [2,3]. S protein is essential for viral replication and it can bind to hACE receptors in human tissues. These receptors were expressed in many human tissues including retina and conjunctiva making these organs a potential entry point to the human bodies [4-6]. This explains the high prevalence of conjunctival symptoms in some COVID-19 patients [7-11].

In China, one of the physicians contracted the infection through conjunctiva after examining pneumonia patients without eye protection. Besides, it also explains the latest WHO guidelines to wear eye protection during the examination of COVID-19 patients [4].

The clinical presentation of COVID-19 is variable and not only limited to respiratory symptoms. The most common clinical presentations were fever (87%), cough (68%), and fatigue (38%); diarrhea (4%), and vomiting (5%) [1,12,13]. Other symptoms include the clinical presentation of liver injury, renal injury, and neurological manifestation [12,13]. Moreover, many patients had ocular surface manifestations and complications [7,14,15]. Despite being well known to be a respiratory virus, it caused a wide range of clinical presentations with no clue to underlying pathogenesis.

One of the most investigated clinical presentations is ocular manifestation. Conjunctival viral swab revealed the presence of viral DNA in tears [16-18]. It was hypothesized that eye infection can produce respiratory infection through the passage into the nasolacrimal duct followed by infection of nasopharyngeal cells. That is why conjunctiva is considered one of the viral entry points to human bodies [16-18]. Surprisingly, it was also found that conjunctival swab remained positive even after the negative throat [8,10].

There are no clear estimates of the incidence of eye infection in COVID-19 patients. Ocular surface infection is considered the most encountered complications followed by keratitis [4,9,19,20]. Retinitis and optic nerve neuropathy are not reported much in COVID-19 patients. They usually develop as a consequence of drug toxicity or autoimmune complications as in Guillain barre syndrome and Kawasaki disease [21-24]. Rarely, retinitis caused directly by SARS-COV-2 infection is reported [25].

The pathogenesis of eye manifestations in COVID-19 patients is not clear. Many studies found that complement based toxicity and inflammatory factors are responsible for the eye pathogenesis [26]. These factors caused eye injury and inflammation leading to various reported symptoms. Furthermore, coagulopathy was reported as one of the underlying pathogenesis for retinal diseases-causing thrombosis in the central retinal vein, thus, retinal pathology [27]. Moreover, drug toxicity was reported in many cases due to high doses of antimalarial drugs causing characteristic whorl-like corneal intraepithelial deposits and maculopathy [23,28,29].

This review was set out to report the latest research results to understand the pathogenesis and epidemiology of eye infection in COVID-19 patients.

Methods

A literature search was performed in PubMed and Google scholar. We used the following search terms: ("COVID-19" OR "SARS-CoV-2" OR "coronavirus") AND ("eye" OR "ocular" OR "ocular surface" OR "ophthalmic" OR "conjunctivitis" OR "Optic" OR "retinitis"). We included all studies that reported ocular symptoms in COVID-19 patients. No language or study design restrictions were included in the criteria.

Results and Discussion

Included studies

Seventeen studies reported the ocular manifestation in COVID-19 patients; six studies were case reports and eleven studies were prospective case series Table 1. We also included studies that reported ocular complications not specific to COVID-19 but can occur to COVID-19 patients during hospitalization or as side effects of the drug.

Ocular manifestation in COVID-19 patients

Epidemiology

The ocular infection was reported in 4% of the population diagnosed as COVID-19 [7,9-11,14,15,30-32]. Many of these patients had ocular symptoms as the first presenting symptoms of COVID-19 [14,33,34]. Surprisingly, the ocular swabs tested positive in many patients and other COVID-19 patients who did not report any ocular manifestation [14,16-18,31].

The incidence of the ocular symptoms in COVID-19 patients depends on the site of infection. For instance, Conjunctival symptoms were reported in many studies constituting about 15% of the population [33-35]. For ICU related ocular manifestation, it was highly present in many studies and was evident in up to 60% of patients [19,20,36]. For retinitis and neuropathy, there is no clear evidence on the real incidence in COVID-19 patients.

Conjunctival diseases

SARS-COV-2 is reported to infect the conjunctiva although it had a low replication rate in the conjunctival cells [4,16-18]. Also, conjunctivitis was reported in many physicians not wearing eye protection which implied the transmission of the disease through the eye [4]. It was also the first presenting symptom in these patients [33,34].

The manifestation of conjunctivitis in COVID-19 is similar to another infectious conjunctivitis. The common clinical presentations were bilateral redness of the eye, increased lacrimation, and swelling of the eyelid [10,30]. On Examination, there were bilateral conjunctival hyperemia, chemosis, the follicular reaction of the tarsal conjunctiva, epiphora, watery discharge, mild eyelid edema. Furthermore, enlarged preauricular and submaxillary lymph nodes [10,30]. No complications were reported in these cases; however, two unusual presentations were reported as unilateral keratoconjunctivitis and bilateral pseudomembranous conjunctivitis. Neither of these two conditions was complicated or progressed to sight-threatening condition [10,30].

The viral load in the conjunctiva is related to the severity of the disease. Based on a recent meta-analysis, conjunctivitis was associated with severe disease and worse outcomes [35]. In addition, a study investigated the cases of conjunctivitis and found that these cases had higher white blood cells, C-reactive protein, neutrophils, procalcitonin, and lactate dehydrogenase [10].

Investigation of the pathogenesis of conjunctival diseases, ACE2 receptor, and cell surface protease enzyme (TMPRSS2) are responsible for cell entry and invasion of the conjunctiva [5,6]. It was discovered that the ACE2 receptor was expressed in conjunctiva, limbus, and cornea. However, the protease enzyme (TMPRSS2) was not expressed in the conjunctiva [5,6]. Thus, the conjunctival injury was reported to be caused by an immune response to the virus entry or due to tissue damage [26]. The virus entry through conjunctiva is still under investigation and with no proven mechanism. Tears transfer the virus towards the nasolacrimal duct to the nasopharynx causing respiratory infections [16,17]. The case report also found that conjunctival viral swabs were positive despite the negative nasopharyngeal swabs [7,8,31].

The conjunctival diseases in COVID-19 patients are usually self-limited and respond well to antiviral treatment [8].

Retinal diseases

There are not many reported cases of retinal diseases; only one case of central retinal artery occlusion was reported. Thrombotic diseases and coagulopathy had been reported in many cases of COVID-19 patients. Deep venous thrombosis, pulmonary embolism, and large-vessel ischemic strokes were reported in many COVID-19 patients [27,37].

The pathogenesis of retinal injury in COVID-19 patients is still under investigation. Hyperreflective lesions at the level of the ganglion cell and inner plexiform layers were found on optical coherence tomography (OCT) in 12 COVID-19 patients from Brazil [25]. These findings were more distinguished at the papillomacular bundle. Microhemorrhage and subtle cotton-wool spots were found in the retina [25]. There were no signs of intraocular inflammation, visual acuity alteration, or abnormal pupillary reflexes were detected [25].

It is hypothesized that micro circular damage in COVID-19 patients is complement-mediated thrombotic vasculopathy [27,37,38]. ACE receptors are expressed in the ciliary body, choroid, retina, and retinal pigment epithelium [39]. This may give an insight into how SARS-COV-2 infects retinal cells and cause complement-mediated cell injury.

The incidence of retinal disease is still not actively reported nor calculated in many studies which may indicate the rarity of these diseases in COVID-19 patients.

Optic neuropathy and ocular nerves diseases

It is considered very rare and was only found in two cases. Miller Fisher syndrome and polyneuritis cranialis were reported in two COVID-19 patients. Both patients had fever and areflexia before the SARS-COV-2 infection [40].

Diplopia, ophthalmoparesis, and abnormal perineural or cranial nerve injury were reported in COVID-19 patients [41]. Oculomotor nerve palsy was also reported which may result in ptosis and other manifestation [22]. No studies have reported optic neuritis in COVID-19 patients.

The pathogenesis of these disorders is still under investigation. It could be caused by direct virus invasion as it was found that the virus is neurotropic and cause nerve damage. Besides, it is caused by inflammatory factors released in response to viral infection [26].

Ocular complications related to COVID-19 associated diseases

Kawasaki disease

Kawasaki disease is considered one of the most reported autoimmune diseases associated with COVID-19 [42]. It is a vasculitis of the medium-sized blood vessels usually affecting the children and young adults [42]. Kawasaki disease is well known for its influence on the eye and its clinical presentation. It is usually presented by iridocyclitis, punctate keratitis, vitreous opacities, papilledema, subconjunctival hemorrhage, and conjunctivitis [21].

Guillain Barre syndrome

Guillain Barre syndrome was associated with polyneuropathy affecting the oculomotor nerve. It was associated with abnormal perineural or cranial nerve MRI findings. Also, inflammatory optic neuritis is usually reported [22,24].

Other Ocular complications

Patient admitted to ICU has increased incidence of ocular complications. 3% to 60% of patients admitted to ICU had reported ocular diseases including ocular surface disorder as the most common presentation [20].

Ocular surface disorders

Ocular surface disorders are considered the most commonly reported complications in ICU patients [9]. It ranges from mild conjunctival irritation to infectious keratitis [20]. Exposure keratinopathy usually develops in these patients because of the use of muscle relaxants [19,36]. As a result, this will lead to weakened lid muscle and lagophthalmos. Furthermore, it will decrease tear production causing dry eye and keratitis [19,20,36]. In addition, Continuous positive airway pressure (CPAP) and oxygen masks have a drying effect on the eye. This will increase the incidence of complications on the top of exposure keratinopathy like conjunctivitis and keratitis [20,36].

Conjunctival chemosis and subconjunctival hemorrhage were also reported in ICU patients as it is usually caused by increased intrathoracic and central vein pressure caused by the ventilator and CPAP [20,43]. These symptoms are non-specific to COVID-19 patients, but we consider it one of the crucial things that should be mentioned in the review.

Drug-related ocular complications

Chloroquine and hydroxychloroquine were extensively used for the treatment of COVID-19 and it successfully decreased the viral load in COVID-19 patients [28]. However, high doses were associated with whorl-like corneal intraepithelial deposits, which are usually reversible, posterior subcapsular lens opacity, ciliary body dysfunction, and a bilateral maculopathy [23,29]. The maculopathy was distinguished by a ring of parafoveal retinal epithelium depigmentation. Unfortunately, these retinal injuries are not reversible and associated with loss of visual acuity. It can also persist even after discontinuation of the drug [23,29].

These retinal damages usually occur after toxic doses of Chloroquine and hydroxychloroquine for a prolonged duration which usually happens in COVID-19 patients [23,29].

Other drugs associated with ocular complications are interferon and second-generation antiviral like lopinavir and ritonavir [44-47]. These drugs usually are associated with retinopathy and posterior segment. However, ocular complications require a high dosage of these drugs which is unlikely to occur in COVID-19 patients [44-47].

Conclusion

In this review, Conjunctivitis and ocular surface diseases are the most encountered eye disease in COVID-19 patients. In some cases, these diseases are the first presentation of COVID-19 so ophthalmologists can be the first physicians to diagnose the disease. However, retinitis and optic neuropathy are rarely reported. In addition, Conjunctival swabs tested positive even after negative throat swabs indicating the importance of conjunctival swabs to rule out the diseases as the virus can pass to the respiratory system through the conjunctival infection.

Conflict of Interest

None.

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