

Review



COVID-19 and conjunctivitis: A contemporary literature review

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Abstract

Coronavirus disease 2019 (COVID-19) is a viral respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since its first appearance in December 2019, COVID-19 has been responsible for a number of global outbreaks and has claimed the lives of nearly three million people as of April 2021. High infection rate, loss of taste and smell, fever, cough, and severely adverse effects on the respiratory system have been the chief attributes of the virus. However, SARS-CoV-2 has been linked to other symptoms, many of which are extra-pulmonary or not directly related to the respiratory system. The impact of SARS-CoV-2 on various ophthalmic outcomes has been manifested in many reports and literature tracing the link between COVID-19 and ocular findings in patients suffering from COVID-19. One recurrent case report presented in the literature is related to the presentation of conjunctivitis in COVID-19 patients. Conjunctivitis is a viral infection causing inflammation in conjunctiva, episclera and eyelids resulting in a change of color in eyes, called *pink eyes*. Swelling, itching, pain, and eye burn are some of the common symptoms. The present study reviews the latest literature on the subject by focusing on the reports of conjunctivitis symptoms in patients with COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is a viral disease that brought about a global outbreak followed by a pandemic and is known for a wide array of symptoms from mild to severe respiratory issues and body pain to more complicated seemingly unrelated digestive and ocular conditions.¹ The total number of laboratory-confirmed cases by August 2020, exceeded over 19.4 million patients in the world.^{2,3} Clinical manifestations of the virus in patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have ranged from being asymptomatic to ARDS-induced severe respiratory problems. Symptoms usually appear within 12 days after the initial exposure to the virus with a mean incubation period of 5.1 days.^{1,4}

Shortness of breath, fever, chills, cough, and malaise are reported as the most common symptoms among the patients infected with SARS-CoV-2.⁵ According to the latest research, some patients showed a complete or partial sense of smell loss in addition to the more common symptoms.⁶ These reports were corroborated by a phone survey conducted from a group of asymptomatic or mild SARS-CoV-2 infected patients. Almost 36.6% of the surveyees reported a lost or weakened sense of smell and taste.⁷ To confirm the diagnosis, however, a laboratory

test using polymerase chain reaction (PCR) is required.⁸

Conjunctivitis is inflammation of the conjunctiva which is a thin clear tissue covering the white of the eye and the lining inside the eyelids.⁹ Children are most at risk of developing conjunctivitis due to permanent exposure to contagious environments such as schools and daycares.⁹ Despite its prevalence, conjunctivitis is rarely a critical medical issue and it is very unlikely to cause serious damage to the vision, especially if diagnosed and treated in the early stages.⁹ Several conditions could lead to conjunctivitis, including viruses (including the common cold causes), bacteria, irritants (shampoos, swimming pool chlorine, smoke, and dirt), eye drops, hypersensitivity, allergic reaction to pollen, dust, smoke, contact lenses, parasites, amoebas, fungi, and sexually transmitted disease (STD) (chlamydia, gonorrhea, etc).¹⁰

Five major types of conjunctivitis are viral, bacterial, allergic, ophthalmia neonatorum, and giant papillary conjunctivitis.¹¹ The viral form, the most common and contagious type, usually affects one eye followed shortly after by the second and is characterized by watering eye and swollen lymph nodes under the jawbone or in front of the ear.^{12,13}

Symptoms depend on the cause of the inflammation and may include redness in the inner eyelid and/or

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sclera, swollen conjunctiva, burning, watery or itchy eyes, eyelashes with a thick yellow discharge, presence of green or white discharge, blurred vision, sensitivity to light, and swollen lymph nodes (due to viral infection).¹⁴

The examination process begins with asking the patients about symptoms followed by a thorough examination. If necessary, the ophthalmologist may use a cotton swab to take some fluid sample from the patient's eyelid to be tested in a lab. This will determine the exact viral or bacterial cause of the infection (including infections caused by STDs).¹⁵

Treatment will also depend on the cause of infection. In viral forms, the best option is to let the infection run its course which lasts about 4 to 7 days similar to that of a common cold. In the bacterial form, however, a prescription of antibiotics (eye drops, ointments, or pills) is suggested. If an irritant causes conjunctivitis, the first necessary step is to wash the affected area of the eye and if not treated seek medical help. And finally, in seasonal allergic conjunctivitis antihistamines are the most common prescriptions and in the majority of the cases treat the symptoms.¹⁵

As data regarding the presentation, diagnosis, and treatment of COVID-19 has been accumulating in the literature since the start of the outbreak, authors started to report ocular involvement by SARS-CoV-2 prior to any other manifestations.^{16,17} However, given that our understanding of COVID-19 is still evolving, an all-encompassing and meticulous review of the latest literature on the subject is required more than ever.

The demand for the most updated studies regarding the appearance of ocular presentations, especially conjunctivitis in COVID-19 patients was the motivating force behind the present review which renders a thorough summary of the studies describing the link between the emergence of conjunctivitis and confirmed COVID-19 patients.

Methods

The present study offers a narrative review on current literature of SARS-CoV-2 infection, especially its ocular manifestations including conjunctivitis. Data and descriptions were gathered from clinical studies that evaluated confirmed SARS-CoV-2 infection and its correlation with severe pneumonia, mortality, ocular manifestations, and ocular viral load measurement. However, there were no restrictions regarding publication date, status, and language. The selection was implemented through searching in electronic databases including PubMed, ISI Web of Science, SCOPUS, and Cochrane library and using a combination of the following MeSH terms: COVID-19, severe acute respiratory syndrome coronavirus 2, 2019-nCoV, SARS-CoV-2, conjunctivitis, eye, ophthalmic, ocular.

Discussion

Conjunctivitis in COVID-19

There are several reports regarding the correlation between SARS-CoV-2 infection and conjunctivitis (Table 1). Although conjunctivitis has been implicated

Table 1. Demographic and clinical characteristics of studies on conjunctivitis in SARS-CoV-2 infected patients

Study	Country	Number of patients	Age	Gender	Ocular symptoms (primary or secondary symptom)	PCR result
Xia et al ¹⁹	China	30	54.5	F(9) and M(21)	1 of 30 primary 29 of 30 none	1 of 30: + 29 of 30: -
Chen et al ²⁷	China	535	50-40	F (271) and M (264)	3 of 534 primary 25 of 534 secondary	NA
Hong et al ²⁸	China	56	48	F (25) and M (31)	6 of 56: primary 9 of 56: secondary	1 of 56: +
Wu et al ²⁰	China	38	65.8	F (13) and M (25)	1 of 38: primary 11 of 38: secondary	2 of 38: +
Zhou et al ²¹	China	121	48	F (68) and M (53)	8 of 121: secondary	3 of 121: +
Zhang et al ¹⁸	China	1	29	F	Case report: secondary	+
Cheema et al ²³	Canada	1	29	F	Case report: primary	+
Chen et al ²²	China	1	30	M	Case report: secondary	+
Colavita et al ²⁹	Italy	1	65	F	Case report: primary	+
Salducci and La Torre ³⁰	Diamond Princess ship	1	72	M	Case report: primary	NA
Khavandi et al ¹⁶	Iran	1	65	M	Case report: primary	+
Navel et al ²⁴	France	1	63	M	NA	-
Wu et al ²⁵	China	1	2	M	Case report: primary	NA
Daruich et al ²⁶	Argentina	1	27	M	Case report: primary	NA
Ya et al ³¹	China	3	16-67	F (1) and M (2)	Case report: 1 of 3: primary 2 of 3: secondary	NA

NA, not available.

in COVID-19, it is not a well-established finding whether eye secretions are contagious.³² Also, the prevalence of conjunctivitis among SARS-CoV-2 infected patients has not been fully quantified. A large study on 1099 severe cases of SARS-CoV-2 infection showed that the prevalence of conjunctivitis among patients was only 0.8% while other studies with a small sample size have reported greater prevalence.^{18,19,33} One particular study on 30 laboratory-confirmed SARS-CoV-2-infected patients showed that conjunctivitis was present as a symptom only in one patient.¹⁹ The main laboratory technique for the detection of SARS-CoV-2 was the reverse transcriptase PCR, in which the specimen obtained from the patient with conjunctivitis showed a positive result on days 3 and 5, with the remainder of the patients having a negative PCR result. Additionally, the PCR of the ocular secretions for other viruses capable of causing conjunctivitis such as adenovirus was negative. This implicated SARS-CoV-2 as a contributing cause of conjunctivitis.²⁰ Another study showed more COVID-19 patients with ocular symptoms including two cases of conjunctivitis (5.3%) confirmed by conjunctival PCR. Additionally, a blood test in conjunctivitis-confirmed cases showed a higher level of C-reactive protein (CRP), procalcitonin C, and white blood cell and neutrophil counts.²¹

Furthermore, the study showed the conjunctival source of SARS-CoV-2 in 2.5% of the patients with a significantly lower rate than patients with respiratory symptoms. However, it was suggested that testing the conjunctival specimen may enhance the detection rate of the virus.²¹ Results of the tests conducted on the specimen obtained from patients with ocular symptoms of conjunctivitis showed that SARS-CoV-2 RNA can be detectable in the ocular secretions up to 27 days, whereas nasal specimen remains positive only for a few days.³⁴ These findings suggest that ocular secretions might be an important source of transmission for SARS-CoV-2.

Another study on 17 SARS-CoV-2 infected patients showed ocular symptoms only in one of the cases. Conjunctival tests on days 3 and 20 showed negative results in all patients. Also, the cell culture test showed no cytopathogenic effect.¹⁷

A published case report presented a 70-year-old man with symptoms including dry cough, fever, and fatigue, and nasolacrimal duct stenosis in one eye. The Nasopharyngeal RT-PCR result was negative while the conjunctival RT-PCR results remained positive for two weeks. Nasolacrimal duct stenosis was still present even after the patient's recovery from SARS-CoV-2. This was explained by the presence of lacrimal drainage system obstruction and reduction of the viral clearance.³⁵ In most of the studies focused on SARS-CoV-2 patients with symptoms of conjunctivitis, SARS-CoV-2 RNA was detected in the conjunctival specimens.^{16,18,22,23} Ocular manifestations included pink eye, eyelid edema, watery discharge, foreign body sensation, and photophobia.

Also, slit-lamp examination showed other symptoms including keratoconjunctivitis, serous secretion, the follicular reaction in the conjunctiva, pseudomembranous inflammation, and chemosis. Another study concluded that conjunctivitis was the only symptom of five SARS-CoV-2 infected patients in Italy. Since none of them reported fatigue, fever, or respiratory problems, the scholars concluded that ocular manifestations may be the only symptoms in patients with no other medical manifestations.³⁶

Some studies have shown that SARS-CoV-2 depends on ACE-2 receptors in the target cells for invasion. The ACE-2 receptors are located in both human type-2 alveolar epithelial cells and the cornea and conjunctiva. Hence, it is hypothesized that the ocular surface may be a potential transmission pathway for SARS-CoV-2. A possible mechanism for this transmission is as follows: when SARS-CoV-2 contacts with the ocular surface, it is transmitted to the conjunctiva, and virus particles can spread to the nasopharyngeal system via nasolacrimal canal and cause a critical respiratory infection.^{17,37,38}

There is evidence that SARS-CoV-2 leads to severe forms of conjunctivitis such as keratoconjunctivitis. In a case report of a 63-year-old woman, ocular examination showed major ocular findings including petechial, tarsal hemorrhage, and pseudomembranes. Conjunctival specimen tested negative for bacteria or viruses other than SARS-CoV-2.³⁹ This is especially worth a closer look since there is a possibility that a major eye problem might skip medical attention in high viral load patients who are hospitalized in intensive care units.²⁴ In a report of a 2-year-old infected child with SARS-CoV-2, the ocular symptoms included conjunctivitis and eyelid dermatitis on the 7th day of the infection. However, due to a lack of conjunctival specimen testing, the main cause of ocular manifestation remained unknown.²⁵ A community-based survey of SARS-CoV-2 infection identified a 27-year-old male with symptoms of pink eye and excessive tearing. Ophthalmic examination showed conjunctival hyperemia and eyelid edema. The next day, he experienced fever, dry cough, and respiratory symptoms.²⁶ Another community-based survey reported that the ocular problems were common among mild-to-moderate forms of SARS-CoV-2 infected patients.⁴⁰ These might suggest that conjunctiva is a serious transmission root for SARS-CoV-2.

Some studies focus on SARS-CoV-2 presence in ocular tissues. Other viruses of the Coronaviridae family have also been reported to have the potential to cause ocular surface symptoms. A seven-month-old child was the first patient recognized as coronavirus HCoV-NL63 infected patient with bronchiolitis and conjunctivitis in 2000-2003.⁴¹ Other studies reported that 17% of HCoV-NL63 infected children developed ophthalmic symptoms such as conjunctivitis.⁴² The presence of SARS-CoV-1 in ocular tissues and secretions was evaluated in one study conducted in 2003, showing the presence of SARS-CoV-1

in tear samples of 8.3% of patients.⁴³ One study attributes the negative results of SARS-CoV-1 in ocular tissues and secretions to test timing, viral load, and method of measurement.⁴⁴ A follow-up survey on seventeen SARS-CoV-2 infected patients found no ophthalmic symptoms as well as negative results regarding the presence of SARS-CoV-2 in ocular secretions.⁴⁵ In contrast, another study on thirty SARS-CoV-2 patients and 29 samples showed signs of infection caused by conjunctivitis and other ocular symptoms.¹⁹

Studies reported that SARS-CoV-2 related conjunctivitis is cured without the need for any specific treatment. Also, viral conjunctivitis may be aggravated within the first few days of infection and could last for two weeks.^{20,46}

Considering the bulk of the studies and the respective data discussed above, we may finally come to the conclusion that mucous membranes such as conjunctiva are transmission roots for SARS-CoV-2 and this should be announced as a health hazard for ophthalmologists during routine visits and treatment in all health-care centers. As previously demonstrated, many viral infections can cause ocular involvement. However, due to the novelty of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it seems important to review the articles in this field. Moreover, several studies have suggested the positive PCR of eye secretions in patients with COVID-19, but whether these secretions play a role in the transmission of the infection in this way is disputable.

Conclusion

Conjunctivitis is the main ocular presentation of COVID-19, thus patients referring to health centers complaining of pink eyes during the pandemic should be evaluated for COVID-19.

Author Contributions

All authors participated in conducting the literature review and preparing the manuscript draft.

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Conflict of Interests

There is no conflict of interests in any form.

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