original article

Conjunctivitis and other ocular findings in patients with COVID-19 infection

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BACKGROUND: COVID-19 is an acute respiratory illness caused by a novel coronavirus (SARS-CoV-2). COVID-19 that might affect the eye in the form of conjunctivitis and other ocular features.

OBJECTIVES: Assess the frequency and clinical profile of conjunctivitis and other ocular findings in Iraqi patients with confirmed COVID-19 infection.

DESIGN: Analytical cross-sectional study.

SETTING: Secondary care center.

PATIENTS AND METHODS: This study involved patients diagnosed with SARS-CoV-2 viral infection of variable disease severity from June 2020 to December 2020. Ocular history and the severity of SARS-CoV-2 viral infection was assessed for all of the patients.

MAIN OUTCOME MEASURES: Frequency of conjunctival inflammation and other ocular findings in patients with coronavirus infection.

SAMPLE SIZE:186 patients.

RESULTS: The patients had a mean (standard deviation, range) age of 44.4 (18.8, 18-78) years. Conjunctivitis was present in 25 patients (13.4%). There was no significant association between prevalence of conjunctivitis and patient gender (*P*=.868). However, conjunctivitis was significantly associated with the severity of the disease (*P*=.018): the rate of conjunctivitis was significantly higher in cases with severe disease (28%) in comparison with those with mild to moderate clinical presentation (9.3%). The natural course of conjunctivitis seemed to be mild with no effect on visual acuity and no short-term complications.

CONCLUSION: Conjunctivitis can occur in patients with SARS-CoV-2 viral infection, and could be a presenting sign. Conjunctivitis is more common in cases of severe COVID-19 infection and since it could be a presenting sign it might be of benefit in the early diagnosis and treatment of COVID-19.

LIMITATION: Single-center study, safety limitations in the examination of the patients.

CONFLICT OF INTEREST: None.

COVID-19 is an acute respiratory illness caused by the novel coronavirus (SARS-CoV-2). The first cases of what were later described as COVID-19 was reported by a Chinese ophthalmologist in Wuhan, China, in December 2019 (*https://en.wikipedia.org/wiki/Li_Wenliang*). The disease is now a global pandemic with serious effects on human health and the economy.[1] COVID-19 is highly contagious and transmissible through air droplets produced by an infected person. The fatality rate of up to 2-3% is cause for concern.[2] Systemic symptoms usually appear 2-14 days after exposure to the virus. The main symptoms are fever, headache, generalized malaise, cough, shortness of breath and sore throat, but it can also cause gastrointestinal tract symptoms and even blood dyscrasias and conjunctivitis.[3]

There have been a few reports in the literature describing ocular findings with SARS-CoV-2 viral infection.[4,5] Although the first cases were described by an ophthalmologist, insufficient data have been collected on the prevalence and severity of ocular findings and their relationship with the severity of systemic illness.[4,5] This paucity of data prompted the authors to conduct this study despite the logistical difficulties and safety issues involved in examining the ocular manifestations in patients with a confirmed SARS-CoV-2 infection, and to study the relationship between ocular symptoms and systemic illness. To the best of our knowledge, this is the first such study done in Iraq, and the authors hope the results will help in the early diagnosis and management of this serious disease.

PATIENTS AND METHODS

This observational, cross-sectional study was conducted at Al-Diwaniya Teaching Hospital, where 242 patients with confirmed SARS-CoV-2 infection through PCR nasal swab were recruited for the study (from the outpatient coronavirus clinics and isolation center). Some patients became critically ill, which made them difficult to follow, and some did not provide the authors with informed consent; thus only 186 patients participated in the study. The exclusion criteria were age younger than 18 years, being critically ill and in the intensive care unit, and not providing informed consent.

An ophthalmologic examination was performed for all patients enrolled in the study, including patients with no respiratory symptoms but having a positive PCR swab test. The exams were performed by two experienced ophthalmologists using a slit lamp in a separate examination room in the ophthalmology department for outpatients or a portable slit lamp in the ward for inpatients. They wore complete personal protective equipment for safety. The examination included a visual acuity examination using the Snellen chart with refraction and an external eye examination using a slit lamp (Haag Streit) for signs of inflammation and other related signs. A dilated fundus examination was also done for all patients. All patients were evaluated for signs of conjunctival inflammation such as conjunctival edema, redness, tearing, itching, discharge, foreign body sensation, non -specific conjunctival follicular reaction and sometimes corneal epithelial infiltrates. All patients were also evaluated using essential laboratory tests such as blood gas analysis, complete blood count with differential, LDH (lactate dehydrogenase), CRP (C-reactive protein), CPK (creatinine phosphokinase), serum ferritin, D-dimer, chest X-ray and CT scan which were recommended by the internist. A clinical evaluation of the severity of COVID-19 symptoms was also conducted.

All asymptomatic subjects with a positive PCR test were asked to return for reevaluation in 3-5 days to check for the presence of signs and symptoms of conjunctival inflammation. All staff members involved in the care of the inpatients in wards were asked to notify us if a patient developed any signs of eye problems (excluding critically ill patients in the ICU). COVID-19 infection status was classified as mild, moderate or severe. Mild cases usually presented withcough without shortness of breath, fever, non-specific flu-like symptoms, a respiratory rate less than 16 breaths per minute, a heart rate less than 100 beats per minute and SpO_2 more than 94%, and LDH less than 220 U/L, CRP less than 10 mg/L, CPK less than 200 mcg/L, serum ferritin less than 250 ng/L, D-dimer less than 500 µg/mL, absolute lymphocyte count more than 0.8 uL and less than 20% involvement of the lung on CT scan by ground-glass appearance. Moderate cases usually had cough with shortness of breath, fever, profound fatigability, dyspnea on exertion with a respiratory rate more than 16 breaths per minute, a heart rate more than 100 beats per minute and Spo_2 of 90-94%. Prothrombin time (PT) was less than 16 seconds, LDH more than 220 U/L, CRP more than 20 mg/L, CPK more than 200 mcg/L, serum ferritin more than 250 ng/L, D-dimer more than 500 µg/mL, absolute lymphocyte count less than 0.8 uL and more than 20% involvement of the lung on CT scan by ground-glass appearance. Severe cases usually presented with cough with shortness of breath, decreased SpO_2 or shortness of breath on movement; walking a few steps left the patient out of breath, fever, profound fatigability, dry secretion, vasculitis signs, a respiratory rate more than 24 breaths per minute, pulse rate more than 120 per minute, SpO_2 less than 90%, with PT less than 16 seconds, LDH more than 220 U/L, CRP more than 20

mg/L, CPK more than 200 mcg/L, serum ferritin more than 250 ng/L, D-dimer more than 500 µg/mL, absolute lymphocyte count less than 0.8 uL and more than 50% involvement of the lung on CT scan by ground- glass appearance. Critically ill patients were not involved in this study. The study was conducted in accordance with the tenets of the Helsinki Declaration and was approved by the ethical committee of Al-Qadisiyah University College of Medicine; informed consent was obtained from all participants.

Data were analyzed using IBM SPSS version 16 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp) and Microsoft Office Excel 2007. Continuous variables were expressed as mean with standard deviation and range. Categorical variables were expressed as number and percentage. The comparison of mean values was done using an independent sample t test. The association between categorical variables was examined using a chi-square test with Yates correction for continuity. The level of significance was considered $P<.05$.

Table 1. The characteristics of patients with conjunctivitis (n=25).

Characteristics	Results		
Cases with conjunctivitis	25 (13.4)	Male	14 (56.0)
		Female	11 (44.0)
Conjunctivitis as presenting sign	3 (1.6)		
Previous ocular disorders	5 (20.0)	Chalazion	2 (40.0)
		Pterygium	3 (60.0)
Peripheral corneal infiltrates	3 (12.0)		
Pseudomembrane	0		
Petechi	0		
Reduced vision	0		

Data are number (%).

Table 2. Association between conjunctivitis and age and gender of patients with COVID-19.

Characteristics	Total (n=186)	Conjunctivitis (n=25)	No conjunctivitis (n=161)	*P*
Age (years)	44.4 (18.8, 18-78)	43.4 (18.3, 18-76)	44.6 (18.9, 18-78)	.781
Gender				
Male	107 (57.5)	14 (56.0)	93 (57.8)	.868
Female	79 (42.5)	11 (44.0)	68 (42.2)	

Data are mean (standard deviation, range) or number (%).

RESULTS

The 186 patients with COVID-19 had a mean age of 44.4 years (median] 45.0 years, range of 14 to 78 years). Conjunctivitis was reported in 25 patients (13.4%) (**Table 1**). There was no significant difference in mean age between patients with conjunctivitis and those without conjunctivitis (P=781). There was also no significant correlation between conjunctivitis and the gender of patients (P=.868) (**Table 2**). Conjunctivitis was the presenting sign in 3 cases, only 1.6% (3/186) and among all cases of conjunctivitis, only 3 cases 12% (3/25) presented with peripheral corneal infiltrates. There was no significant correlation between conjunctivitis and symptomatic COVID-19 or the presence of pneumonia (**Table 3**). However, conjunctivitis was significantly correlated with the severity of COVID-19 (P=.018): the rate of conjunctivitis was significantly higher in cases with severe disease (28%) in comparison with those with mild to moderate clinical presentation (9.3%). Conjunctivitis was not significantly correlated with high CRP, high D-dimer, high serum ferritin or leukocytosis; however, it was significantly correlated with high serum LDH (P=.008) (**Table 4**).

DISCUSSION

The most common and life-threatening symptoms of COVID-19 are respiratory, gastrointestinal, neurological, and ocular; other manifestations have been increasingly reported.[4,5,8-10] Since the disease is highly transmissible even by asymptomatic patients, the detection of any symptoms that can aid in early diagnosis is vital. Eye manifestations were one of the early presenting signs of COVID-19.[19] However, there have been only meagre data reported on the incidence and severity of eye manifestations in COVID-19 infection.

Studies of conjunctivitis in coronavirus infection report an incidence less than 0.8%, or in one small series, around 3%,[5-7] while a study conducted in China reported an incidence of 31.8%.[8] The logistical limitations and safety issues involved in the examination of patients with highly infectious disease might affect the results and lead to such variation. Furthermore, the absence of a sophisticated test to diagnose with certainty that the conjunctivitis was caused by the coronavirus is also a factor. The yield from a PCR is poor with the use of tears or conjunctival secretions.

A systematic review and meta- analysis study by Cao K et al showed that 10% of patients with a positive PCR test for COVID-19 had conjunctival inflammation and conjunctival swabs were positive in 3% of cases. These data might have given rise to the idea of ocular transmission of virus since corneal epithelial cells express

Table 3. Association between conjunctivitis and severity of COVID-19.

Characteristics	Total (n=186)	Conjunctivitis (n=25)	No conjunctivitis (n=161)	*P*
COVID-19				
Symptomatic	136 (73.1)	21 (84.0)	115 (71.4)	.187
Asymptomatic	50 (26.9)	4 (16.0)	46 (28.6)	
Pneumonia				
Positive	31 (16.7)	5 (20.0)	26 (16.1)	.848
Negative	155 (83.3)	20 (80.0)	135 (83.9)	
Severity of COVID-19				
Mild/moderate	164 (88.2)	18 (72.0)	146 (90.7)	.018
Severe	22 (11.8)	7 (28.0)	15 (9.3)	

Data are number (%).

Table 4. Association between conjunctivitis and laboratory investigations in patients with COVID-19.

Characteristics	Total (n=186)	Conjunctivitis (n=25)	No conjunctivitis (n=161)	*P*
C-reactive protein (mg/mL)	11.0 (15.0, 1.0-66.0)	11.0 (17.50, 1.0-44.0)	11.0 (13.50, 2.0-66.0)	.927
D-dimer (ng/mL)	395.0 (450.0, 45.0-3200.0)	300.0 (435.0, 100.0-1200.0)	400.0 (440.0, 45.0 -3200.0)	293
Serum ferritin (ng/mL)	140.0 (202.5, 20.0 -1000.0)	150.0 (155.0, 30.0-450.0)	130.0 (210.0, 20.0-1000.0)	.884
Lactate dehydrogenase (ug/L)	100.0 (140.0, 25.0-350.0)	200.0 (185.0, 50.0-340.0)	100.0 (130.0, 25.0-350.0)	.040
Absolute lymphocyte count ($\times 10^9$/L)	1.0 (0.50, .50-2.10)	1.0 (0.45, .60-1.60)	1.0 (0.55, .50-2.10)	.350

Data are median (interquartile range, minimum-maximum).

ACE2 receptors on their external surface, which is the attachment site for the coronavirus; however, the transmission rate would be low since the overall incidence is low.[9] Another systematic review done by Inomata et al reported a frequency of ocular symptoms and signs to be 11.2%, most commonly ocular pain and conjunctival inflammation.[10] The authors also reported painful preauricular lymph nodes in three patients. In our study, the PCR positive rate was 16.7% from conjunctival swabs, which is higher than other reports. For example, Aggarwal and colleagues described only a 3.5% positive rate for conjunctival swab in their meta-analysis.[11] This variation might be due to the low yield of conjunctival swab. In addition, the natural history of COVID-19 could affect the incidence rate since the disease is asymptomatic in most patients and simple conjunctivitis could pass unnoticed by most subjects and even medical staff. Thus, in our study, we tried to find evidence for the presence of conjunctivitis as a presenting sign for COVID-19 infection, which could be useful in diagnosing COVID-19, especially in otherwise asymptomatic patients. However, we found no statistical evidence to support this hypothesis. In addition, no age or gender variation was found between patients with conjunctivitis and patients without conjunctivitis, whereas other studies[12,13] found conjunctivitis to be more common in males with moderate disease. This difference might be due to the more profound biochemical abnormalities usually found in males compared with females with such infections.

In our study, we found a statistically significant relationship between the severity of systemic infection

in COVID-19 patients and the presence of conjunctivitis. This finding is important because COVID-19 is a serious disease with a potentially fatal outcome and no proven treatment; therefore, the presence of any sign that might be an indication of severe disease should be taken into consideration by physicians treating such patients. Our study differs from other studies that have shown no relationship between the presence of conjunctivitis and severity of systemic disease.[14,18]

We found a significant relationship between conjunctivitis and elevated levels of LDH but not elevated levels of other biochemical markers that are usually elevated in patients with COVID-19 infection, such as WBC count, D-dimer and serum ferritin.[15] With full safety protection suits and masks, we successfully examined all patients carefully, and sometimes we re-examined a patient a few days later if we suspected new signs had appeared. We found inflammatory reactions similar to those found with any type of viral infection, but no pseudomembrane formation, which is an important distinguishing difference from adenovirus infection. Surprisingly, we found no cases with conjunctival petechiae or hemorrhage, which is unexpected given the thrombotic nature of the infection, which affects small vessels.[16] There were some cases with peripheral subepithelial corneal infiltrates, but there was no frank corneal ulceration or epithelial hypertrophy. There was no effect on visual acuity, which was also reported by Cheema et al in a case study.[17]

The natural course of the disease seems to be mild inflammation with disappearance of all symptoms in a few days without treatment. Thus, COVID-19 might be overlooked by many patients focusing on more obvious and critical systemic symptoms. Coupled with the absence of a definitive laboratory test to detect SARS-CoV-2 in conjunctival secretions, the incidence of conjunctivitis might be underestimated. These two observations are the main limitations of our study.

In conclusion, conjunctivitis may present as a manifestation of COVID-19 infection, possibly as a presenting sign or at any time during the course of the disease. Therefore, care should be taken by medical staff in ophthalmology departments when dealing with patients with red eyes during the COVID-19 pandemic. The diagnosis of nonspecific conjunctivitis in patients with confirmed SARS-CoV-2 infection might be a sign of disease severity, although this conclusion requires further study for confirmation.

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