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Pattern of ocular manifestations and the prevalence of severe acute respiratory syndrome coronavirus-2 in tears of hospitalized coronavirus disease 2019 patients

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Abstract:

PURPOSE: Severe acute respiratory syndrome coronavirus2 (SARSCoV2) can affect eyes in various forms. Furthermore, ocular surface can act as potential port of entry and ocular secretions as possible route of transmission of SARSCoV2. The aims of the study are to identify ocular manifestation in confirmed coronavirus disease 2019 (COVID19) patients and to evaluate conjunctival secretions as the possible route of transmission of this disease.

MATERIALS AND METHODS: A prospective, populationbased, observational study was done. Ocular symptoms and signs of every hospitalized patient with SARSCoV2 infection between September 15, 2020, and November 15, 2020, were recorded. Tear samples of the first 60 participants (30 each of patients with severe and moderate illness, can be removed) with ocular manifestations were selected for real-time polymerase chain reaction (RTPCR). Data were analyzed using the Statistical Package for the Social Science Software (SPSS) program, version 23. When comparing mean values, ttest was used otherwise Chisquare test.

RESULTS: Out of 804 admitted patients during study period, 309 (38.4%) patients were identified with ocular manifestations, out of which 78% (241) had conjunctival hyperemia, 65.6% (203) had follicular reaction in palpebral conjunctiva, 58% (180) had chemosis, and 58% (99) had discharge and 18.4% (57) complained of burning in their eyes. Mean duration from systemic manifestation to onset of ocular symptoms was 4.52 ± 1.47 days while 8 patients (1%) had conjunctivitis as the presenting symptom. SARSCoV2 was detected in 18.3% patients (11 out of 60) using RTPCR.

CONCLUSION: The presence of SARSCoV2 in ocular secretions of patients with ocular manifestations suggests that COVID19infected patients with ocular manifestations should wear protective glasses to prevent secretions contamination to healthy persons.

Keywords:

Conjunctival secretions, coronavirus disease 2019, healthcare workers, ocular findings, ophthalmologist, severe acute respiratory syndrome coronavirus-2

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an enveloped RNA virus belonging to the same beta coronavirus family of zoonotic origin as SARS-CoV and Middle East respiratory syndrome-related CoV which previously caused epidemics in different parts of the world. Coronavirus disease 2019 (COVID-19) was first detected and reported in December 2019 in Wuhan, Hubei Province in the People's republic China which later quickly spread worldwide. On

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March 11, 2020, the World Health Organization declared coronavirus as a global pandemic.[1]

Although the most common presentation of COVID-19 at the outset includes respiratory symptoms with fever, myalgia, fatigue, and diarrhea.[2] The frequency of ocular symptoms is not uncommon.[3] In fact, Li Wenliang, an ophthalmologist was the first to voice concern regarding spread of COVID-19.[4] Due to predominant respiratory symptoms and life-threatening nature of complications involving lungs, research mainly revolves around respiratory system. The primary transmission of COVID-19 may be through respiratory droplets, but since other organs are also involved, alternate route of transmission should not be ignored. The eyes as a source of infection as well as an entryway for transmission have also been suggested.[1]

Ocular manifestations of COVID-19 have been reported between 0.8% and 31.6%.[5] Xia *et al*., 2020 revealed that out of 30 hospitalized COVID-19 patients, one patient had conjunctivitis who later tested positive for SARS-CoV-2 in ocular secretions.[6]

However, Sun *et al.*, 2020 concluded that the eye is rarely involved in human CoVs infections and is not a preferred portal for spreading the infection to the respiratory tract.[7] On the contrary, some clinicians have expressed concerns about the transmission of SARS-CoV-2 through tears and conjunctival secretions of infected patients.[8]

The American Academy of Ophthalmology in view of possible transmission, in its publication, has also advised all contact lens wearers to switch to glasses during this pandemic.[9]

Since ocular surface as a potential port of entry and ocular secretions as possible route of transmission of SARSCoV2[10] is under discussion, the objective of this study was to identify ocular manifestations in moderatetosevere SARSCoV2 positive patients and correlate it with the presence of SARSCoV2 in the tears. To the best of our knowledge, there is no study in the medical literature at this time which identifies a direct relationship between SARS-CoV-2 and its ocular manifestation in Indian population in this region.

Materials and Methods

After taking clearance from the Institutional Ethical Committee (approval number: IEC/GMC/IEC 2061), a prospective observational study was done by the Department of Ophthalmology in collaboration with viral research and diagnostic laboratory at Government Medical College, Amritsar. Laboratory (with a real-time polymerase chain reaction [RT-PCR] assay of both oropharyngeal and nasopharyngeal swab) confirmed novel coronavirus patients admitted in medical wards with moderate-to-severe disease between September 15, 2020, and November 15, 2020, were enrolled in the study. Written informed consent from enrolled cases willing to participate in the study was taken in their vernacular language in advance, in accordance with the declaration of Helsinki. Patients having preexisting ocular complaints were excluded from the study.

Moderate cases were defined as those having clinical signs of pneumonia and with oxygen saturation (SpO2) measured by pulse oximetry <94% (90%–95%) on room air and respiratory rate ≥24/min while severe cases were mentioned if with clinical signs of pneumonia patient had one of the following signs: respiratory rate >30 breaths/min, severe respiratory distress, or SpO2 <90% on room air.[11]

After recording brief history and demographic profile of the enrolled patients, symptoms, ocular findings including ocular surface, anterior segment assessment was performed by the same experienced clinician and recorded. Results of blood tests and RT-PCR from nasopharyngeal and oropharyngeal swabs were noted.

The first 60 patients were selected for RT-PCR using conjunctival swab, out of which 30 patients had moderate COVID-19 disease while other 30 patients had severe illness. Regardless of unilateral or bilateral ocular involvement, the conjunctival swab was simultaneously taken from both the eyes within 48 h of onset of ocular complaints, For taking the swab, lower eyelid was retracted and inferior fornix was swept with sterile disposable nylon swab for 10 s and the procedure was repeated in the second eye. In addition, in an endeavor to increase the yield of viral RNA in precorneal tear film, samples were taken (within a gap of 2–5 min) using Schirmer paper strip (no 41 Whatman filter paper, 5-mm wide and 35-mm long). After taking all aseptic precautions, Schirmer strips were folded at one end and placed at the junction of middle and outer third of the lower lid of both eyes. The patient was asked to keep the eyes open and blink normally and after 3 min, the strips were removed. All the four samples were then placed in viral transport media tube which after proper sealing and labeling and while maintaining temperature of 4°C was transferred to VDRL Lab in a triple layer packing for evaluating the presence of SARS-CoV-2 by reverse transcription PCR. Allplex 2019-NCoV multiplex RT-PCR assay kits (Commercial kit, Indian Council of Medical Research approved) were used for detection of SARS-CoV-2 Virus. Reporting positive/negative was done by following manufacturer's guidelines. Sample was considered negative if cycle threshold (ct) value was ≥40 and positive if it was <40. Both screening

Table 1: Distribution of patients under study

Severity of disease	Moderate (%)	Severe (%)	*P*
Total number of patients (804)	259 (32.2)	545 (67.7)	<0.001
Patients with ocular manifestation (309)	102 (33)	207 (66.9)	
Number of patients selected for RT-PCR (60)	30	30	0.019
RT-PCR positive (9)	2 (6.6)	9 (30)	

RT-PCR=Reverse transcription polymerase chain reaction

Table 2: Demographic and clinical characteristics of patients with ocular manifestations

Parameters	Frequency
Number of patients with ocular symptoms (%)	309 (38.4)
Mean age	58.4±1.0
Sex (%)	
Males	175 (56.6)
Females	134 (43.4)
Mean duration from systemic manifestations to onset of ocular manifestations (days)	4.5±1.4
Ocular manifestations	
Conjunctival hyperemia	241 (77.9)
Unilateral/bilateral	90/151
Follicular reaction	203 (65.6)
Unilateral/bilateral	81/122
Chemosis	180 (58.2)
Unilateral/bilateral	75/105
Discharge	99 (32)
Unilateral/bilateral	19/80
Itching, burning	57 (18.4)
Unilateral/bilateral	11/46
Ocular manifestation as initial symptom	8 (1)
Comorbidity* (%)	
Yes	252 (81.5)
No	57 (18.4)
Mean total leukocyte count†	11,120.6±198.1
Mean D dimer‡	0.986±0.022

*Diabetes mellitus, hypertension, obesity, †Normal range - 5000-1000/mm, ‡Normal values - ≤500 ng/ml

(E gene) and confirmatory (orf/rdrp/Ngene) assays were done on each sample.

Results

Among 804 SARS-CoV-2-positive patients encountered during our study period, 545 (67.7%) had severe illness while 259 (32.2%) patients had moderate illness. 66.9% patients with severe illness (207/545) and 33% patients (102/259) with moderate illness had ocular manifestations [Table 1]. The difference was statistically significant ($P < 0.001$). When the first 60 patients (30 patients of severe and 30 of moderate illness) were tested for RT-PCR using conjunctival swabs, 9 patients (30%) with severe illness and 2 (6.6%) with moderate illness tested positive for SARS-CoV-2. The difference was not statistically significant ($P = 0.019$).

Out of 804 patients confirmed COVID-19 patients, 309 patients (38.4%) were identified with ocular manifestations. 56.6% (175/309) were males and 43.3% (134/309) were females. Their mean age was 58.48 ± 1.09 years (range: 27–89 years). The mean duration from systemic manifestation to the onset of ocular complaints was 4.52 ± 1.4 days. The ocular findings included conjunctival hyperemia in 77.9% patients (241), follicular reactions in palpebral conjunctiva in 65.6% patients (203), chemosis in 58.2% (180) patients, watery discharge in 32% (99), and itching or burning in 18.4% (57) patients. One percent (8 of 804) patients had conjunctivitis as the initial symptom, even before the onset of fever, malaise, or pulmonary symptoms. Of 309 patients with ocular symptoms, 207 patients (66.9%) had severe disease while 102 (33%) had moderate disease. Mean total leukocyte count and D-dimer values in these patients were higher than normal values [Table 2].

Only 18.33% patients (11 out of 60) tested positive for SARS-CoV-2 in tears while 81.6% (49) showed no signs of viral shedding. It was significantly less than nasopharyngeal SARS-CoV-2 detection rate. Of the 11 patients who showed positive conjunctival swab for SARS-CoV-2, 2 had moderate and 9 had severe COVID-19 disease.

Discussion

There is a high heterogeneity in studies of ocular manifestation and tear SARS-CoV-2 virus in COVID-19 disease. A systematic review and meta-analysis reported prevalence range of ocular manifestations among COVID-19 patients between 1% and 32% and the overall pooled prevalence as 7%.[12]

We observed ocular manifestations in 38.4% patients. In accordance with our findings, Hong *et al*. reported 15 patients (27%) with ocular symptoms including sore eyes, itching, foreign body sensation, tearing, redness, and eye secretions.[13] Similarly, a study on 38 SARS-CoV-2 patients also reported that one-third of their patients (31.6%) had ocular manifestations which included hyperemia, chemosis, epiphora, or increased ocular secretions.[3] The only reported case of eyelid dermatitis related to COVID-19 was also described in a 2-year-old male child with contact history with infected family members.[3] On the contrary, a study on 72 laboratory-confirmed patients for COVID-19, only 2.7% patients (2) reported with conjunctivitis[14] and a study on 30 patients found only 1 patient with conjunctivitis.[6] A meta-analysis also confirmed that although the incidence of ocular manifestations in COVID-19 patients ranged between 0.8% and 64%, majority recorded a percentage close to 3% only.[15] In wake of more severe and disturbing symptoms of COVID-19-positive patients, under

reporting of ocular symptoms might be the reason for low incidence of ocular manifestation in COVID in literature.

The mean time of presentation of ocular complaints after the onset of COVID-19 systemic manifestations in the current study was 4.52 ± 1.4 days. A meta-analysis concluded that timing of appearance of conjunctivitis during course of COVID-19 disease was uncertain. It varied between synchronous onset with systemic manifestations to late-onset conjunctivitis (10–13 days).[15] A 30-year-old male presented with bilateral follicular conjunctivitis 13 days after the onset of COVID-19[16] while Navel *et al.* observed hemorrhagic conjunctivitis and pseudomembrane in an intubated patient 17 days after the onset of the disease.[17] Furthermore, ocular manifestation may even be the presenting feature of this illness. Wu *et al.*, 2020 reported 1 patient (2.6%) out of 38 patients[3] and Hong *et al*. 6 patients (11%) out of 55 who presented with ocular symptoms before the onset of fever or respiratory symptoms.[17,13] In the present study also, 1% patients (8 out of 804) presented with conjunctivitis as the first symptom of COVID-19 disease even before they had fever or body aches. Similar to these observations, five cases of nonremitting conjunctivitis without any malaise, fever, or respiratory symptoms were reported which subsequently turned out to be positive on RTPCR of nasopharyngeal swabs.[18] Likewise, conjunctivitis was a sole symptom in a 32yearold, COVIDpositive healthy nurse working in the emergency department.[19] In view of this, any patient visiting eye care professional or emergency physicians with clinical features suggestive of viral conjunctivitis during pandemic era must be inquired for flu-like symptoms, travel history, or history of contact with COVID-positive patient so as to take general measures for prevention of infection transmission.

Of 309 patients with ocular manifestations, 67% patients (207) had severe and 33% (102) had moderate COVID-19 illness. It was in similar to a study which affirmed frequent ocular manifestation in patients with more severe disease.[3,20] Zhou *et al*., 2020 also observed that of 8 patients with ocular symptoms, 7 were severe or critical cases.[21] Contrary to this, a study from Spain found that 33% of their COVID19 patients with conjunctivitis had mild disease and only 17% of them had severe disease.[22] A comprehensive meta-analysis also concluded that this controversial issue requires further investigation.[15]

Studies in literature have assessed and confirmed the presence of SARS-CoV-2 RNA in nasal secretions, saliva, and tears of COVID-19 patients, but the route of transmission of COVID-19 is not yet fully clarified and is thought to be mainly respiratory. Research into determining the presence of COVID-19 virus in conjunctival secretions and establishing tears as contagious to serve as an alternate route of transmission for SARS-CoV-2 would be valuable and help in developing preventive strategies.

Xia *et al.,* 2020 in his research concluded that tear and conjunctival secretions were not a common route of coronavirus transmission as majority of COVID-19 patients do not manifest conjunctivitis, nevertheless, he also mentioned that this route of transmission could not be completely eliminate.[6] On the contrary, a recent report raised doubts when one-third of eye professionals accidentally acquired COVID-19 as severe as resulting in three deaths while managing patients during this pandemic.[23] Nonetheless, PCR on tears from patients with SARS-Co V infection has also demonstrated the presence of virus even in the absence of conjunctivitis.[24,25] Patients with features consistent with acute bilateral viral conjunctivitis and positive SARS-CoV-2 in ocular secretions have also been reported in literature.[14]

In the present study also, 18.3% patients (11 out of 60) with ocular complaints tested positive for SARS-CoV-2 virus in their conjunctival secretions while another 81.6% (49) did not show signs of viral shedding. Similarly, Zhou *et al.,* 2020 observed ocular symptoms in their 8 patients out of 121 (6.6%). One patient among these 8 patients (12.5%) tested positive for virus.[21] Another study on 38 COVID-19 patients, 12 patients (31.6%) reported ocular symptoms and 2 out of them (16.7%) tested positive for SARS-CoV-2 in tears. It concluded that although there is a low prevalence of SARS-CoV-2 in tears, transmission of the disease through ocular secretions cannot be ruled out.[3] A study from Italy observed ocular manifestations in 26.2% of their hospitalized patients and in spite of negative conjunctival swabs for SARS-CoV-2 in all of them, it recommended possible transmission through ocular secretions.[20] Low incidence of positive conjunctival swab in COVID-19 patients in these studies may be accounted to low sample size or insufficient tear material to detect the virus. A study stated that if they had identified conjunctivitis in the initial period, their RNA results might have been higher as conjunctivitis-induced inflammatory response suggested that it might relate to the death of infected cell.[3] In contrast to these observations, another study concluded that out of 2 patients who reported conjunctivitis, one tested positive through RT-PCR from conjunctival swab. She was a 29-year-old nurse and while working in the emergency department at Tongji hospital, Wuhan City, China, she continuously wore N-95 respirator but often removed her goggles and touched her eye lids.[16] In another prospective interventional study performed at Zhejiang University, the sole patient who had conjunctivitis tested positive conjunctival swab.[6] All these observations though variable suggest that tears

can be a potential source of infection for health-care workers. An extensive meta-analysis also concluded that mechanism of viral shedding from tears of SARS-CoV-2 is not clear yet and need to be further investigated to confirm transmission risk of COVID-19 infection through tears and to establish conjunctiva as a possible portal of entry for SARS-CoV-2.[15]

Until we learn more and is confirmed, it is imperative for everyone, especially the health-care workers in hospital environment to remain vigilant and avoid touching the eyes. Ophthalmologists in particular should take care and wear protective gear when examining patients with conjunctivitis specifically when accompanied by other respiratory tract symptoms or fever.

Limitations

Our study has several limitations. First, we did not include asymptomatic, mild, and very severe cases who were intubated. Second, we did not have a control group. Furthermore, due to risk to the examining doctor, we did not do slit lamp or posterior segment examination of these patients. Due to financial constraints, we could not do RTPCR tests of all enrolled participants, and finally, possible contamination of Schirmer strips from environment could not be avoided.

Conclusion

Ocular data related to COVID-19 seems to be under reported. To limit potential ocular transmission of virus through tears in health-care workers in health-care facilities and in offices of ophthalmologists, precision in accuracy of ocular data of COVID-19 patients needs to be increased by adding questions related to eye portion while reviewing them at the time of admission in emergency room. All patients presenting with red eye during pandemic, COVID-19 should be kept in differential diagnosis. In view of detection of SARS-CoV-2 in ocular secretions of patients with ocular manifestations, COVID-19-infected patients with ocular symptoms should wear protective glasses to prevent secretions contamination to healthy persons.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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