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BASIC SCIENCE

Ocular manifestations of coronavirus disease 2019

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Abstract

Purpose Coronavirus disease 2019 (COVID-19) is an ongoing global public health problem, and most of the COVID-19 research is focused mainly on the respiratory system because of life-threatening results. However, manifestations in other organs should not be ignored since they can also be a mode of transmission. We sought to describe the ocular manifestations of COVID-19 and investigate the association between ocular involvement and clinical presentation and laboratory outcomes.

Methods This cross-sectional study was conducted between March 1, 2020, and April 30, 2020. Ninety-three sequentially hospitalized and clinically confirmed COVID-19 patients were included in the study. The systemic and ocular symptoms, clinical findings, and laboratory outcomes were recorded.

Results Of the 93 COVID-19 patients, 54 (58.1%) were male, and 39 (41.9%) were female. Mean age of the patients was 39.4 ± 21.9 (min 7, max 88) years. Twenty patients (n 21.5%) had at least one ocular abnormality. Most common findings included hyperemia ($n = 20$), epiphora ($n = 9$), increased secretion ($n = 6$), chemosis ($n = 3$), follicular conjunctivitis ($n = 2$), and episcleritis ($n = 2$). The most common symptom was photophobia (n 15). Patients with ocular involvement were more likely to have higher neutrophil counts ($p = 0.001$), and increased CRP ($p < 0.001$), PCT ($p = 0.001$), and ESR levels ($p < 0.001$). Mean lymphocyte count was statistically lower in patients with ocular manifestations ($p = 0.001$). Mean age and number of patients with fever over 37.3 °C in the ocular involvement group was found to be higher ($p < 0.001$, $p = 0.006$, respectively).

Conclusion Older age, high fever, increased neutrophil/lymphocyte ratio, and high levels of acute phase reactants seemed to be risk factors for ocular involvement.

Keywords Acute phase reactants · COVID-19 · Conjunctivitis · Episcleritis · Eye · Neutrophil to lymphocyte ratio

Introduction

In December 2019, China reported a pneumonia outbreak in Wuhan, a city with more than 11 million people [1]. A new coronavirus (COV) was identified as the causative organism—namely, novel coronavirus, nCOV-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)—and the disease was named as the Coronavirus Disease 2019 (COVID-19) [2]. After its introduction, World Health Organization declared the situation as a public health emergency of international concern and published suggestions for protection and prevention of transmission [3].

The first case in Turkey was officially announced on March 11, 2020. To date, COVID-19 has confirmed to affect a total of 115000 patients in Turkey with more than 3000 deaths. Due to the life-threatening nature of its complications, most of the research about COVID-19 mainly focuses on respiratory system. However, since other organ involvements might be alternative routes of transmissions, they must not be ignored.

Seven types of CoVs are known to infect humans: 229E, NL63, OC 43, HKU, MERS-CoV, SARS-CoV, and the recent SARS-CoV-2 [4]. Most of these CoVs cause infections in the respiratory tract but also known to have manifestations in the gastrointestinal system and ocular tissues [5, 6]. HCoV-NL63 and SARS-CoV are known to affect the ocular system. There have been reports of cases with conjunctivitis and bronchiolitis between 2000 and 2003 with HCoV-NL63 [7]. In addition, in 2004, SARS-CoV-RNA was identified in tear samples of three patients suggesting that the virus can be

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present in tears [5]. Theories, including the conjunctiva being the direct inoculation site of pathogen-loaded droplets, migration of the infection from the respiratory tract through the nasolacrimal duct or even hematogenous infection of the lacrimal gland, were proposed [5].

Genomic and structural analyses show a similar receptor-binding motive between SARS-CoV and SARS-CoV-2 with resembling pathologic features and epidemiological characteristics [8, 9]. As a result, a similar involvement of the ocular tissues has been suspected. Nevertheless, there have only been few reports about the ophthalmic manifestations of the recent SARS-CoV-2 [10, 11]. The purpose of our study is to investigate ocular findings and symptoms of clinically confirmed COVID-19 patients and assess the relationship with those findings and laboratory results.

Materials and methods

This cross-sectional study was conducted at the Kars Harakani State Hospital, Kars, Turkey, in accordance with the ethical standards of the Declaration of Helsinki. The study protocol was approved by the institutional board of the Okan University Medical Faculty ethics committee.

Between March 11th and April 30th, 2020, 93 consecutive patients who were hospitalized in Kars Harakani State Hospital with the diagnosis of COVID-19 were included. The COVID-19 diagnosis was made according to real time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of respiratory specimens which revealed positive results for SARS-CoV-2 nucleic acid and thorax CT findings consistent with viral pneumonia [12]. The COVID-19 diagnosis was confirmed with RT-PCR in all included patients in this study. The patient symptoms, fever at presentation, thorax computerized tomography (CT) scans, neutrophil, lymphocyte and monocyte counts, C-reactive protein (CRP), pro-calcitonin (PCT), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), creatine kinase (CK), and D-dimer levels were recorded. Older age was accepted as 65 years or older. Fever was classified as 37.3 °C or higher.

Ocular findings and symptoms were evaluated at hospital admission. Ophthalmological examination including ocular surface and anterior segment assessment was performed by the same experienced clinician using a binocular indirect ophthalmoscope. Ocular symptoms and findings were recorded.

Statistical analyses were performed with SPSS Statistics (Version 22.0, Armonk, NY: IBM Corp). The assumption of normal distribution of data was tested by the Kolmogorov-Smirnov test. Association of descriptive data was tested with the chi-square test. Differences in the outcomes between the groups were tested with the Mann–Whitney U test. A p value less than 0.05 was considered statistically significant.

Results

Ninety-three patients with clinically confirmed COVID-19 were included in the study. Of the 93 patients, 54 (58.1%) were male and 39 (41.9%) were female. Mean age of the patients was 39.4 ± 21.9 (min 7, max 88) years. Ninety-two patients (98.9%) tested positive for SARS-CoV-2 by RT-PCR of nasopharyngeal swabs; while 1 (1.1%) was positive in the RT-PCR of the endotracheal aspirate. Twenty (21.5%) patients had fever, 18 (19.4%) patients had cough, 3 (3.2%) patients had respiratory distress, 2 (2.2%) patients had headache, and 50 (53.8%) patients had no symptoms at presentation to the hospital. Fifty-eight (62.4%) patients had no sign of abnormality at thorax CT, whereas 23 (24.7%) patients had typical CT findings of SARS CoV-2 pneumonia, and 12 (12.9%) patients had possible SARS CoV-2 pneumonia according to the CT findings. Five patients were intubated due to respiratory distress and 4 of them died due to SARS CoV-2 pneumonia and comorbidities.

Table 1 represents age, fever, and the laboratory findings of the patients with and without ocular involvement. Mean neutrophil count, neutrophil to lymphocyte ratio, CRP, PCT, and ESR levels were significantly higher in patients with ocular involvement; whereas, mean lymphocyte count was significantly lower. No significant difference was observed between patients with and without ocular involvement regarding mean monocyte count, LDH, CK, and D-dimer levels.

Table 2 represents ocular findings and symptoms of the patients. Hyperemia was found to be associated with high fever (p = 0.006), typical radiological findings of SARS CoV-2 pneumonia (p = 0.046), high ESR and CRP ($p <$ 0.001 for all), PCT levels (p = 0.001) and neutrophil to lymphocyte ratio (NTL) ($p <$ 0.001). Epiphora and increased secretion were found to be associated with high fever (p = 0.012, p = 0.006, respectively), high ESR (p = 0.001, p = 0.023, respectively), CRP ($p <$ 0.001, p = 0.001 respectively), PCT (p = 0.002, p = 0.004 respectively), and NTL (p = 0.001, $p <$ 0.001 respectively). Chemosis was positively correlated with high CRP (p = 0.017), PCT (p = 0.39), and NTL (p = 0.008). Follicular conjunctivitis was also correlated with high fever (p = 0.037), high neutrophil count ($p <$ 0.001), ESR (p = 0.001), and CRP ($p <$ 0.001), PCT (p = 0.001) and high NTL (p = 0.001). Episcleritis was found to be associated with higher D-dimer (p = 0.017), PCT (p = 0.045), and CRP (p = 0.020). No ocular finding was associated with gender, LDH or CK levels, and monocyte count ($p >$ 0.05 for all).

Discussion

Ocular involvement with Coronavirus family has been shown in various publications [10, 13, 14]. On January 22, 2020, when a visiting doctor in Wuhan developed conjunctivitis,

Table 1 Age, fever, and the laboratory findings of the patients with and without ocular involvement

	Patients with ocular involvement (n = 20)	Patients without ocular involvement (n = 73)	P value
Age (years)	60.7 ± 19.8	33.6 ± 18.6	<0.001*
Fever over 37.3 °C (n)	12 (60.0%)	8 (11.0%)	0.006*
Neutrophil (/mm^3)	6453.0 ± 4856.7	3662.2 ± 2132.3	0.001*
Lymphocyte (/mm^3)	1368.0 ± 680.2	2246.5 ± 1173.3	0.001*
Neutrophil/lymphocyte ratio	7.5 ± 11.5	2.3 ± 2.8	<0.001*
Monocyte (/mm^3)	471.5 ± 194.4	480.8 ± 207.5	0.918
CRP (mg/L)	55.4 ± 48.6	6.1 ± 8.8	<0.001*
PCT (μg/L)	0.30 ± 0.47	0.08 ± 0.11	0.001*
ESR (mm/hr)	42.7 ± 20.6	15.1 ± 13.3	<0.001*
LDH (U/L)	308.6 ± 132.8	242.1 ± 97.6	0.094
CK (U/L)	109.7 ± 105.9	110.1 ± 97.9	0.389
D-dimer (μg/L)	1314.2 ± 611.3	789.9 ± 658.4	0.492

CRP C-reactive protein, *PCT* pro-calcitonin, *ESR* erythrocyte sedimentation rate, *LDH* lactate dehydrogenase, *CK* creatine kinase

*Statistically significant

and later yielded positive for SARS-CoV-2, call for research on ocular transmission and involvement of SARS-CoV-2 was made [14]. In a prospective study by Xia et al. [10], tear and conjunctival secretions of 30 COVID-19 patients were collected, and the presence of the virus was evaluated by RT-PCR [10]. Virus was detected in only one patient's conjunctival scrapes who had conjunctivitis at the time of specimen collection; therefore, it was proposed that the virus only existed in the tear and conjunctiva of the patients with conjunctivitis. On the other hand, in the same study, it was stated that the sample volume of tear and conjunctival secretion might be insufficient for RT-PCR detection, and therefore, the possibility of viral particles' presence in tears and conjunctiva should not be ignored in patients without conjunctivitis.[10]

Table 2 Ocular manifestations of the patients

	Value (n)
Ocular findings	
Hyperemia	20 (21.5%)
Epiphora	9 (9.7%)
Increased secretion	6 (6.5%)
Chemosis	3 (3.2%)
Follicular conjunctivitis	8 (8.6%)
Episcleritis	2 (2.2%)
Ocular symptoms	
Photophobia	15 (16.1%)
Itchiness	13 (15.7%)
Burning sensation	7 (8.4%)
Gritty feeling	5 (6.0%)
Blurred vision	4 (4.8%)

In the present study, we reported the ocular findings and symptoms of COVID-19 patients and risk factors associated with those ocular manifestations.

Results of our study suggest that 20.5% of the COVID patients had at least one ocular abnormality. Mean age, fever, neutrophil count, CRP, PCT, and ESR levels were significantly higher in patients with ocular involvement; whereas, mean lymphocyte count was significantly lower.

The aggressive inflammatory response is a significant component in the pathophysiology of SARS-CoV-2 infection, strongly implicated in the resulting airway damage [15]. Severity of the disease is reported to be not only due to the viral infection but also the host response [16]. There are many studies highlighting the role of inflammatory markers such as ESR, CRP, and PCT to predict the onset of an inflammatory process or infection [17]. In the case of SARS-CoV-2 infection, many studies demonstrated that most of the patients present with elevated levels of acute immune markers [18, 19].

C-reactive protein begins to rise within 4–6 h in settings of inflammation and has a half-life of 4–7 h [20]. Therefore, serum level of CRP is considered to be a measure of active inflammation. CRP levels were found to be positively correlated with the diameter of lung lesions and severity of the presentation in COVID-19 patients [21]. In our study, all of the ocular findings were correlated with high CRP levels which may indicate active inflammatory response and severity of the disease.

Procalcitonin is a peptide precursor of calcitonin, released primarily by lung and intestine, in response to bacterial toxins and cytokines. Production of PCT is amplified during bacterial infections but downregulated during viral infections which make it a particularly interesting acute inflammatory marker [22]. Levels of PCT become detectable in patient's serum in

3–6 h after onset of inflammation and remain elevated for 12–36 h after resolution [22]. A metaanalysis of the literature suggests that serial PCT measurement may be beneficial to evaluate progression towards a more severe form [23]. The production of PCT is inhibited by interferon-γ, whose concentration increases during viral infections [24]. PCT levels remain within the reference range in several patients with noncomplicated SARS-CoV-2 infection, whereas substantially increase in the severe form of the disease, possibly secondary to a bacterial coinfection which contributes to complicate the clinical picture. Procalcitonine levels of the patients with ocular symptoms were higher than the patients without ocular involvement, which may also be indicative for the severity of the disease in those individuals.

Patients with ocular manifestations had higher ESR levels according to the results of our study. Erythrocyte sedimentation rate typically begins to increase within 24 h after the onset of inflammation. ESR can be a useful tool to aid in the diagnosis and management of certain specific situations, like inflammation or infection, but like CRP it lacks specificity [25].

Elder patients seemed to be at certain risk for developing ocular symptoms. This may be secondary to the already existing age related changes in the ocular tissues of the older population such as dry eye disease, meibomian gland dysfunction, or demodex infestation [26]. It may be expected that ocular problems would be exacerbated in older adults, where the communication between innate and adaptive immunity is known to be compromised [27].

The pathogenesis and organ manifestations of SARS-CoV-2 virus are not fully understood [28]. Cytokine storm and viral evasion of cellular immune responses are considered to have crucial roles in the severity of COVID-19 [29]. In this study, patients with COVID-19 who had ocular manifestations had significantly high levels of CRP, PCT, and ESR, perhaps as a result of the active immune response of the host and disease severity. This may partly explain the positive association between high fever and ocular manifestations.

Lymphocytopenia and increased levels of neutrophils have been reported to reflect an enhanced inflammatory process and suggest a poor prognosis in COVID-19 [28]. In our group, patients with higher neutrophil-to-lymphocyte ratio seemed to be in higher risk for developing ocular manifestations. This can also be secondary to the severity of the disease with generalized aggressive inflammatory response.

Limited sample size and absence of conjunctival RT-PCR evaluation are the limitations of our study. A larger cohort study of patients with COVID-19 from multiple centers would help to further define the ocular manifestations and risk factors of the disease. Regardless, the findings of our study are the preliminary results shared in an effort to serve as a starting platform for research into ocular involvement immunological responses of COVID-19.

Older age, high fever, increased neutrophil/lymphocyte ratio, and high levels of acute phase reactants were associated with greater risk of developing ocular manifestations. Care must be taken when evaluating patients with those characteristics to prevent ocular complications and viral spread, since other organ involvements might be alternative routes of transmissions. As the current pandemic continues, a better understanding of both the transmission routes and manifestations of COVID-19 will emerge.

Availability of Data and Material The data supporting the findings of this study are available from the corresponding author on request.

Authors' contribution All authors contributed to the study conception, design, material preparation, data collection, and analysis. The first draft of the manuscript was written by Basak Bostanci Ceran, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethics Approval The study protocol (Number: 91412548-899) was approved by the institutional board of the Okan University Medical Faculty ethics committee.

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