



Letter to the editor: Keeping an eye on the many symptoms of COVID-19

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Dear Editor,

We found the report on “Ocular manifestation of coronavirus disease 2019” by Bostanci Ceran B. and Ozates S. very interesting [1]. In fact, ocular symptoms may occur in COVID-19 since entry of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) into human cells occurs after viral protein binds to an angiotensin converting enzyme 2 (ACE2) receptor [2], also present on the ocular surface cells [3, 4]. There is, however, little information about the conditions that predispose or protect patients from ocular involvement during COVID-19 infections. We therefore share results of our study, conducted in order to confirm ocular symptoms occurring during acute COVID-19 and to investigate on correlations with both systemic symptoms and elements of ocular history.

A multicenter, retrospective, cross-sectional, descriptive study was conducted in May and June 2020 in five French university hospitals (Strasbourg, Dijon, Colmar, Nice and Brest) in accordance with the tenets of the Declaration of Helsinki. The study was approved by the national ethics committee. Symptomatic patients diagnosed positive for COVID-19 by polymerase chain reaction were eligible. We used a consecutive sampling method among those diagnosed at least 3 weeks earlier (each center had updated lists of patients having consulted for emergency care). We excluded patients who couldn't give consent or be joined by phone. Sample size was

calculated based on a previously suggested one-third frequency of ocular symptoms in COVID-19 infections[4].

Variables of interest were collected using medical records and phone interviews. Data was gathered using a standardized questionnaire and collated using a structured electronic collection form. Patients were asked to report the presence or absence of symptoms during the acute phase of COVID-19. All univariate statistical analyses (Pearson's χ^2 test) were performed using R version 3.6.3.

Four hundred eighty-one patients were assessed for eligibility. Twelve (2.5%) refused to participate, and 33 (6.9%) were unreachable. Thus, 436 patients were included. Patients' demographic and clinical characteristics are summarized in Table 1. Relations between general symptoms, ocular history, and the occurrence of ocular surface involvement during the infection are presented in Table 2.

Our results are consistent with those of Bostanci Ceran and Ozates. Ocular symptoms reported by COVID-19 patients resembled non-specific mild conjunctivitis. With an incidence of 36.7%, they were the fourth most frequent, on par with digestive symptoms. The fact that conjunctivitis is less common than pulmonary involvement is consistent with studies showing lower ACE2 protein levels on conjunctival epithelial cell membranes than in the lungs [5]. Another reason might be the protective effect of tears although dry eye disease was not associated with a higher ocular involvement rate.

Unlike Bostanci Ceran and Ozates, some authors like Xia J. et al. [6] found correlation between ocular symptoms and the severity of COVID-19. Our study is consistent with the results of Bostanci Ceran and Ozates: we did not find any such correlation.

As to the relationship between COVID-19 ocular symptoms and ocular history, the protective effect of contact lenses and spectacle wear [7] was not established. Results about the correlation of ocular symptoms with a history of infectious conjunctivitis and ocular allergy must be tempered as data might have been misreported (memorization bias) and allergy

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Table 1 Demographic and clinical characteristics of the COVID-19 symptomatic and PCR positive patients

Demographic characteristics	
Female sex, No. (%)	302 (69.27)
Age, mean (SD)	44,03 (16,15)
Systemic symptomatology, No. (%)	
Influenza-like illness	375 (86.01)
Fever	292 (66.72)
Muscle aches	224 (51.38)
Chills	160 (36.70)
Rhinopharyngitis	25 (5.74)
Pulmonary	330 (75.69)
Cough	258 (59.17)
Dyspnea	188 (43.12)
Thoracic pain	96 (22.01)
Neurological	361 (82.80)
Anosmia / ageusia	286 (65.60)
Headaches	268 (61.47)
Vertigo	13 (2.98)
Digestive (nausea, diarrhea)	160 (36.70)
Need for mechanical ventilation during admission	39 (8.94)
Systemic history, No. (%)	
Anti-inflammatory drugs taken prior or during the disease	56 (12.84)
Comorbidities	189 (43.34)
Ocular symptomatology, No. (%)	
Ocular discharge	42 (9.63)
watery	40 (9.17)
purulent	2 (0.46)
Burning, foreign body sensation	45 (10.32)
Itching	44 (10.09)
Ocular pain	40 (9.17)
Red eye	32 (7.34)
Eyelids stuck together	19 (4.36)
Eyelid swelling	5 (1.15)
Ocular History No. (%)	
Infectious conjunctivitis	131 (32.75)
Allergic conjunctivitis	76 (16.67)
Dry eye disease	119 (27.29)
Other ocular disease	46 (10.55)
History of eye surgery	33 (7.57)
Contact lenses wear	38 (8.71)
Glasses wear	326 (74.77)

*Comorbidities included history of chronic diseases (obesity, hypertension, diabetes mellitus, oncological history, auto-immune diseases, immunosuppressive treatments)

might also be a confounding factor as the study was conducted in spring. However, previously aggressed conjunctiva might be more susceptible, via the upregulation of

Table 2 Relations between systemic symptomatology, ocular history and ocular involvement during COVID-19 acute phase

Systemic symptomatology and history	OR (IC 95)	p
Influenza-like illness	1,10 (1,02 – 1,19)	0.0163 *
Pulmonary	1,15 (1,04 – 1,28)	0.0173 *
Neurological	1,18 (1,02 – 1,65)	0.0355 *
Digestive	1,31 (1,04 – 1,65)	0.0340 *
Need for mechanical ventilation	0,68 (0,35 – 1,32)	0.2489
Comorbidities	0,90 (0,72 – 1,13)	0.3822
Anti-inflammatory drugs	0,75 (0,45 – 1,25)	0.2917
Ocular history		
Infectious conjunctivitis	1,35 (1,04 – 1,76)	0.0355 *
Allergic conjunctivitis	1,65 (1,13 – 2,39)	0.0151 *
Dry eye disease	1,27 (0,94 – 1,71)	0.1342
Other ocular disease	1,11 (0,64 – 1,90)	0.7173
History of eye surgery	0,86 (0,43 – 1,73)	0.6767
Contact lenses wear	0,89 (0,48 – 1,69)	0.7392
Spectacles wear	0,97 (0,86 – 1,08)	0.5469

* p < 0.05. All of the systemic manifestations of COVID-19 were statistically associated with occurrence of ocular symptoms. Previous infectious conjunctivitis and ocular allergy were correlated with the presence of ocular symptoms

ocular surface receptors as ACE2; this offers a subject for further investigation that might allow for deeper understanding of a complex illness.

Acknowledgment Zsolt Böcskei had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Conflict of interest for authors: none

Authors' contribution All authors contributed to the study conception and design. The first draft of the manuscript was written by Zsolt Böcskei, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

- Bostanci Ceran B, Ozates S (2020) Ocular manifestations of coronavirus disease 2019. *Graefes Arch Clin Exp Ophthalmol* 258:1959–1963. <https://doi.org/10.1007/s00417-020-04777-7>
- Grajewski RS, Rokohl AC, Becker M et al (2020) A missing link between SARS-CoV-2 and the eye?: ACE2 expression on the ocular surface. *J Med Virol*. <https://doi.org/10.1002/jmv.26136>
- Peng Y, Zhou YH (2020) Is novel coronavirus disease (COVID-19) transmitted through conjunctiva? *J Med Virol*. <https://doi.org/10.1002/jmv.25753>
- Wu P, Duan F, Luo C et al (2020) Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province, China. *JAMA Ophthalmol*. <https://doi.org/10.1001/jamaophthalmol.2020.1291>

5. Liu Z, Sun C-B (2020) Conjunctiva is not a preferred gateway of entry for SARS-CoV-2 to infect respiratory tract. *J Med Virol*. <https://doi.org/10.1002/jmv.25859>
6. Xia J, Tong J, Liu M et al (2020) Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. *J Med Virol* 92:589–594. <https://doi.org/10.1002/jmv.25725>
7. Zeng W, Wang X, Li J et al (2020) Association of daily wear of eyeglasses with susceptibility to coronavirus disease 2019 infection. *JAMA Ophthalmol*. <https://doi.org/10.1001/jamaophthalmol.2020.3906>

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