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REVIEW

Ophthalmic manifestations of COVID-19; a less-appreciated yet significant challenge

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Abstract

Aim The current world has changed in all shapes since the emergence of the novel coronavirus (nCoV-2) also known as COVID-19. Among the extra-pulmonary manifestations of nCoV-2, ophthalmic symptoms have less been systematically studied. The so far existing body of evidence indicates that nCoV-2 has the potential to affect both anterior and posterior chambers of the eye. Albeit, the exact mechanisms which underlie ophthalmic manifestations of nCoV-2 are yet to be elucidated.

Methods The present brief review is an attempt to put together and highlight the significant yet limited number of studies which have spotlighted ophthalmic issues in nCoV-2 patients using a systematic literature search strategy.

Results All case series or reports (including both published and preprint articles) which described ocular manifestations of patients with COVID-19 and/or documented testing of SARS-COV-2 in ocular secretions via various sampling or detection methods were sought to be included.

Conclusion The ophthalmic presentations in SARS-COV-2 are often found to be salient. Raising awareness in this respect may help defining evidencebased protective measures in today's practice of ophthalmology and allied disciplines.

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Introduction

Since the emergence of nCoV-2, the need for dependable evidence-based data on the characteristic signs in afflicted patients has been rapidly rising [1]. Currently, the clinical considerations mainly stress on preventive measures at public level as well as remediating disease manifestations in hospitalized patients to decrease mortality. Given the life-threatening nature of the disease, a vast majority of recent reports have addressed the respiratory tract. Meanwhile, extra-pulmonary manifestations of nCoV-2 should not be overlooked as they often may be likewise a potentially alternative source of transmission and significant morbidity [2].

In other words, considering the fact that many individuals who contract the virus eventually recover, it is worth considering other systemic near-term and long-term consequences of the disease outside the respiratory issues caused by the nCoV-2.

Although the nCoV-2, also known as COVID-19, is essentially affecting the respiratory tract, it may often involve extra-pulmonary sites such as the digestive tract and other organ systems [3]. The extra-pulmonary symptoms may be substantially varied ranging from headache, diarrhea, nausea, and vomiting to ophthalmic symptoms or asymptomatic infection across patients [3].

Additionally, despite the intensive work done to unveil the routes and mechanisms of nCoV-2 transmission, the spread mode is partly unclear (3). In between the lines, some investigations have strived to define possible ophthalmic manifestations (both anterior and posterior segments) in nCoV-2 patients. To our knowledge, few studies are conducted to date into the clinical features of nCoV-2 from ophthalmologic perspective. Given the nCoV-2 potentials in developing in vivo mutations even the ocular manifestations of the disease may substantially vary [4]. Indeed, the virus is thought to be capable of causing a wide range of ocular manifestations from anterior segment pathologies like conjunctivitis and anterior uveitis to posterior pathologies including retinitis and optic neuritis [2].

Early on, when diagnostic kits were not readily accessible even for the old types of coronaviruses, studies aimed at collecting samples from various secessions including tears. Tears' reverse-transcription polymerase chain reaction (RT-PCR) which has been often done in research to detect and genotype viral infections with ophthalmic manifestations were examined for possible presence of the virus RNA in severe acute respiratory syndrome (SARS) hospitalized patients [5].

With the paucity of research on the ophthalmic manifestations in nCOV-2, existing data on the presence of CoV-2 RNA in tear are mixed and contradictory. While according one recent study there has been no discernible viral shedding and infectivity of tears in nCoV-2 patients [1], other studies have indicated the opposite [5, 6]. It has primarily been hypothesized that the nasolacrimal system acts as a passage to transfect the eye through the upper respiratory tract to the eye [1]. One study sampled tears using the Schirmer's test strip at several in between days 3 and 20 after nCoV-2 symptoms started to emerge. During the time-point evaluations, 17 patients who were recruited were examined for possible ocular symptoms such as red eye, discharge, tearing, blurred vision as well as desaturated color vision. Based on this observation, only one out of 17 patients demonstrated conjunctival injection and chemosis upon hospital stay [1]. Despite positive nasopharyngeal test results, all tear samples turned to be negative. As such, the hypothesis that nasolacrimal duct acts as a conduit to cause viral shedding in tears was found to be potentially untrue [1].

Unlike this very recent study suggesting that the likelihood of nCoV-2 transmission through tears is low(1), an investigation in 2004 by Loon et al. demonstrated the presence of viral RNA in the tears of SARS-CoV patients using the RT-PCR [5]. Either way, there seem to be a need to pursue disinfection and personal protective equipment (PPE) protocols in Ophthalmology [6]. In other words, while the data of viral shedding in tears is not conclusive, the questionable presence of the virus RNA in ocular secretions and tears is still considered a hazard [2, 5, 6]. This would in turn mandate a well-defined personal protective standards by wearing mask, gown, gloves, and goggles when ophthalmologist deal with

suspected nCoV-2 patients [6]. The practice of ophthalmology is entangled with inadvertent physical contact with patients' eyes. Over and above, the proximity between the patient and ophthalmologist upon slit lamp examination raises a particular concern (6).

The present brief review was an attempt to cement the link between the available concurrence and controversies in to-date's literature on ophthalmic manifestations in nCoV-2 patients. A primary literature search was performed in literature databases including PubMed, EMBASE, Google Scholar, and medRxiv. Keywords were used in combination, including "COVID-19," "SARS-CoV-2," "coronavirus," "eye," "ocular," "ocular surface," "ophthalmic," and "conjunctivitis," last accessed on 28 August, 2020. A secondary literature search was conducted by identifying relevant references of initially included articles. Inclusion criteria were as follows: All case series or reports (including both published and preprint articles) that described ocular manifestations of patients with COVID-19 and/or documented testing of SARS-COV-2 in ocular secretions via various sampling or detection methods. We excluded studies that described other systemic manifestations of COVID-19 but did not mention any ocular manifestations related to the disease, nor present original data related to the eye.

Anterior chamber ocular manifestations of nCoV-2

According to some recent report, conjunctival congestion, conjunctivitis, epiphora, or chemosis were among common ocular symptoms in in patients with more severe systemic manifestations due to nCoV-2[4, 7]. These patients are generally referred to as SARS-nCoV-2. According to Ping Wu et al., the presence of ocular symptoms was positively correlated with signs of more severe systemic disease including higher white blood cell and neutrophil counts and higher levels of procalcitonin, C-reactive protein, and lactate dehydrogenase [7]. In addition, their observation suggested that ocular symptoms commonly emerge in patients with severe pneumonia (7). In their study, over 90% of SARS-nCoV-2 patients turned to have positive RT-PCR from nasopharyngeal swabs. On the other hand, only around 15% were found to have concurrently positive RT-PCR from conjunctival and nasopharyngeal swabs (7). In line with the above, another recent investigation by Yunyun Zhou and colleagues concluded that while the transmission of nCoV-2 from conjunctiva is controversial, it still prompts public health implications [4]. They documented that the virus RNA can be detected in the conjunctival sac of patients with nCoV-2 pneumonia (4). Nevertheless, up till today, the route through which nCoV-2 ends up in tears has remained elusive. Some theories propose conjunctiva as the frontline inoculation site of nCoV-2 infected droplets. Others have suggested the migration of upper respiratory tract infection through the nasolacrimal duct or even hematogenous infection of the lacrimal gland [2–4, 7, 8]. That said, further empirical and observational studies need to further investigate the same.

While the patients' ocular symptoms are found to be generally mild and self-limiting, small pieces of conjunctival hemorrhage have also been reported [3].

With respect to the anterior chamber ocular manifestations of nCoV-2 in children, Nan Ma, et al., reported a 22% prevalence. In details, 55% presented with increased conjunctival discharge and congestion. Other ocular manifestations were eye rubbing (38.8%), ocular pain (8.2%), tearing (4.1%), and eyelid swelling (8.2%) [9].

The angiotensin-converting enzyme 2 (ACE-2) receptors are known to be abundantly distributed among many tissues and cell types such as conjunctiva. In addition, it has been shown that the nCoV-2 invades the host cells through recognizing and binding to its potential host receptor, i.e., ACE-2. Accordingly, some reports have indicated that nCoV-2 may potentially spread via direct or indirect contact with mucous membranes in the eyes [1, 3, 7]. Additionally, some recent reports have brainstormed on possible pathophysiology inspired by ocular models from the nCoV-2, eye, and immunity perspectives [10, 11].

Taken together, it appears that a properly institutionalized PPE and disinfection protocols would be expected to cut off transmission routes and avert cross infection in favor safety in ophthalmology practice.

Posterior segment manifestations of nCoV-2

There are some reports highlighting the neurological manifestations of nCoV-2 [12, 13]. Since retina is considered as an outpouching of the central nervous

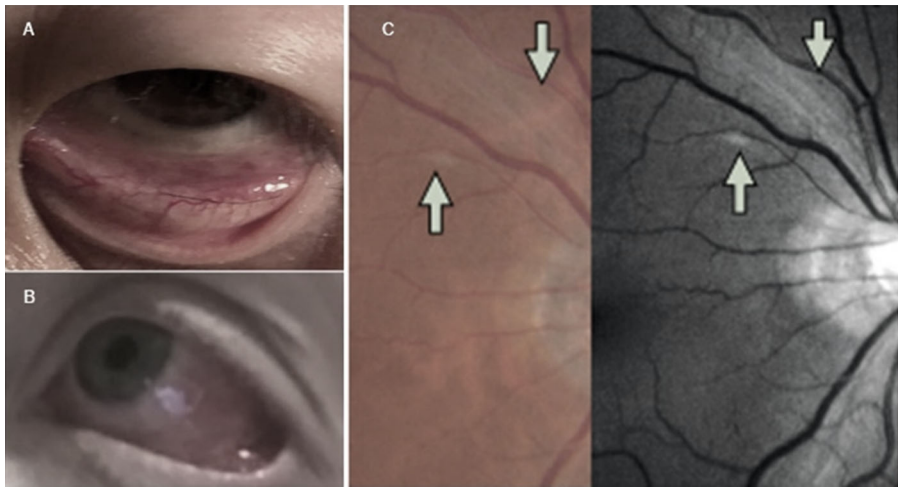

Fig. 1 Snapshots from ocular manifestations of nCoV-2. The left eye photograph of an 81 year-old nCoV-2 male patient showing a significant conjunctival congestion **a**, courtesy of [8]. Examination revealed unilateral eyelid edema and moderate conjunctival hyperemia. A few hours later, the patient experienced intense headache and developed fever, cough and severe dyspnea. A nasopharyngeal swab proved positive for SARS-CoV-2 **b.**, Courtesy of [21]. Color fundus photography and red-free imaging showing a cotton wool spot at the superior retinal arcade with subtle microhemorrhage (C-arrows), courtesy of [18].

system (CNS), there could possibly be a link to justify involvement of not only the optic nerve (optic neurites), but also the retina (retinitis) in neuroinflammatory processes, including CNS infections [14]. The CNS is protected from viruses with its multilayer barriers and its immune response system. However, different viruses can affect the brain through a variety of mechanisms. Some proposed mechanisms by which the virus can cause infection include direct brain injury, hypoxic damage, upregulated ACE-2 receptors, and immune insufficiency [13]. The virus can potentially cause direct CNS (including retinal and optic nerve) injury through different mechanisms [15], i.e., via blood circulation where the virus is released into the blood causing an increase in the permeability of the blood–brain barrier leading to the virus-related insults [15, 16]. Some viruses can also cause direct damage to the CNS by involving the nerve endings [17].

Paula M Marinho and colleagues used optical coherence tomography (OCT) to examine patients with SARS-nCoV-2. This has been done 11–33 days after the onset of symptoms. All patients showed hyper-reflective lesions at the level of ganglion cell and inner plexiform layers predominantly at the papillomacular bundle in both eyes. Nonetheless, the results of the OCT-angiography and the analysis of ganglion cells complex were found to be within normal limits. Some patients were also found to present cotton wool spots and microhemorrhages along the retinal arcade (Fig. 1). Authors inferred that their findings in ganglion cell and plexiform layers could potentially be associated with CNS manifestations [18]. Meanwhile, a recent commentary by Vavvas and his colleagues argued such findings, as they believed those OCT findings were resembling cotton wool spots (CWSs) which could be identified in a wide range of pathologies including diabetic retinopathy or hypertensive retinopathy. Also, they showed that normal inner retinal vessels in terms of the morphology, reflectivity, location, and associated posterior shadowing can mimic Marinho et al., COVID-19 OCT findings [19].

As for the retinal damage, one more thing has sadly added upon challenges in today's nCoV-2 crisis. Following the spread of rumors that alcohol consumption reduces the risk of nCoV-19, the overuse of alcohol became an issue. This has become even more problematic when homemade alcoholic drinks which often contained methanol raised the red flag of high incidence of methanol toxic optic neuropathy (mTON) and ultra-low vision or often legal blindness seen in a large number of individuals who came to our doors. This might has been an issue in similar regions where

Table 1 Outline of to-date studies reporting ocular manifestations of COVID-19. The summarized data indicate that putatively over 4% of the cases with confirmed COVID-19 (95outof2228) across studies were found to demonstrate ocular signs and symptoms requiring clinical attention. NCOM: Number of nCoV-2 cases with Ocular Manifestations, PCS: Prospective Case Series, RCS: Retrospective Case Series, RS: Retrospective Survey, CR: Case Report

Ref	Authors	Study type	No. of subjects	nCoV-2 Detection Method	NCOM (%)	Ocular manifestations
[1]	Jun et al	PCS	17	Schirmer's test strip, RT-PCR	0 (0%)	Conjunctival injection, chemosis
[22]	Xia et al	PCS	30	Conjunctival swab, RT-PCR	1 (3.33%)	Conjunctivitis
[23]	Deng et al	PCS	114	Conjunctival swab, RT-PCR	0 (0%)	None
[24]	Guan et al	RCS	1099	NA	9 (0.81%)	Conjunctival congestion
[25]	Wu et al	RCS	38	Conjunctival swab, RT-PCR	12 (31.57)	Conjunctival hyperemia, chemosis, epiphora
[4]	Zhou et al	RCS	63	Conjunctival swab, RT-PCR	1 (1.47)	Conjunctivitis
[26]	Sun et al	RCS	102	Conjunctival swab, RT-PCR	2 (0.01%)	Conjunctivitis
[27]	Liang et al	RCS	37	Conjunctival swab, RT-PCR	3 (8.1%)	Conjunctival congestion and other inflammatory appearance
[28]	Chen et al	RCS	534	NA	25 (4.68%)	Dry eye, blurred vision, foreign body sensation
[29]	Parmet et al	RCS	121	Conjunctival swab, RT-PCR	8 (6.61%)	Itching, redness, tearing, discharge, foreign body sensation
[30]	Lescure et al	RCS	5	NA	1 (20%)	Conjunctivitis
[31]	Scalinci et al	RCS	5	NA	5 (100%)	Conjunctival hyperemia, epiphora, discharge, photophobia
[8]	Hong et al	RS	56	NA	21 (37.5%)	Itching, foreign body sensation, tearing, redness, dry eyes, eye secretions, floaters
[32]	Chen et al	CR	1	Conjunctival swab, RT-PCR	1 (100%)	Bilateral follicular conjunctivitis, foreign body sensation, epiphora
[33]	Colavita et al	CR	1	Conjunctival swab, RT-PCR	1 (100%)	Bilateral conjunctivitis
[34]	Guillen et al	CR	1	NA	1 (100%)	Conjunctivitis
[35]	Cheema et al	CR	1	Retrospective testing of conjunctival swab, RT-PCR	1 (100%)	Unilateral conjunctivitis, photophobia, epiphora
[36]	Salducci et al	CR	1	NA	1 (100%)	Bilateral conjunctivitis, photophobia, aqueous secretion, chemosis, pseudo-membranes
[37]	Daruich et al	CR	1	NA	1 (100%)	Foreign body sensation, red eye
[25]	Wu et al	CR	1	N/A	1	Conjunctivitis, eyelid dermatitis
#20	**N/A**	**N/A**	**2228**	**NA**	**95 (4.12%)**	**N/A**

alcohol is banned or not readily accessible (20). As such, public awareness campaigns and academic efforts need to get synergized to reduce such an ongoing catastrophe.

Studies including prospective and retrospective case series, retrospective surveys or case reports (both published and preprint document) which described ocular manifestations of patients with COVID-19 and/or documented testing of SARS-COV-2 in ocular secretions via various sampling or detection methods were sought to be included. Table 1 summarizes data which putatively suggest an overall prevalence of

4.12% for ocular signs and symptoms requiring clinical attention in nCoV-2 patients (Table 1).

Concluding remarks

Though the existing body of evidence reassures that the transmission of nCoV-2 via ocular surface is low, nosocomial routes of the virus spread to the eyes after occupational exposure is still a potential concern. Due to the sampling time lag and the fact that diagnostic methods are often inefficient; like other health care providers, ophthalmologists need to strictly follow the PPE protocols [6].

Taking the so far evidence in to account, conjunctivitis seems to be an initial ocular symptom of nCoV-2. It has been shown that nCoV-2 patients with conjunctivitis tend to spread the virus in the tears. Regardless of symptomatic or asymptomatic ophthalmic profile of patients with nCoV-2, the risk of patient-to-ophthalmologist disease transmission should always receive attention.

Compliance with ethical standards

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

References

1. Jun ISY, Anderson DE, Kang AEZ, Wang L-F, Rao P, Young BE et al (2020) Assessing viral shedding and infectivity of tears in coronavirus disease 2019 (COVID-19) patients. Ophthalmology 127(7):977–979
2. Seah I, Agrawal R (2020) Can the coronavirus disease 2019 (COVID-19) affect the eyes? A review of coronaviruses and ocular implications in humans and animals. Ocular immunol inflammation 28(3):391–395
3. Sun X, Zhang X, Chen X, Chen L, Deng C, Zou X, et al. The infection evidence of SARS-COV-2 in ocular surface: a single-center cross-sectional study. MedRxiv. 2020.
4. Zhou Y, Zeng Y, Tong Y, Chen C. Ophthalmologic evidence against the interpersonal transmission of 2019 novel coronavirus through conjunctiva. MedRxiv. 2020.
5. Loon S, Teoh S, Oon L, Se-Thoe S, Ling A, Leo Y et al (2004) The severe acute respiratory syndrome coronavirus in tears. Br J Ophthalmol 88(7):861–863
6. Seah I, Su X, Lingam G. Revisiting the dangers of the coronavirus in the ophthalmology practice. Nature Publishing Group; 2020.
7. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L et al (2020) Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei Province. China, JAMA ophthalmology
8. Hong N, Yu W, Xia J, Shen Y, Yap M, Han W (2020) Evaluation of ocular symptoms and tropism of SARS-CoV-2 in patients confirmed with COVID-19. Can J Ophthalmol. https://doi.org/10.1016/j.jcjo.2020.11.006
9. Ma N, Li P, Wang X, Yu Y, Tan X, Chen P et al (2020) Ocular Manifestations and Clinical Characteristics of Children With Laboratory-Confirmed COVID-19 in Wuhan. China. JAMA ophthalmol 138(10):1079–1086
10. Neri P, Lamperti M, Pichi F, SARS-COV-2 and eye immunity: the lesson was learned but we are not done yet, (2020) Brainstorming on possible pathophysiology inspired by ocular models. Int Ophthalmology. 40(8):1879–1883
11. Neri P, Pichi F (2020) COVID-19 and the eye immunity: lesson learned from the past and possible new therapeutic insights. Int Ophthalmol 40(5):1057–1060
12. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q et al (2020) Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan. China, JAMA neurology
13. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L et al (2020) Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain, Behav Immunity. 87:18–22
14. Afarid M, Torabi-Nami M, Zare B (2016) Neuroprotective and restorative effects of the brain-derived neurotrophic factor in retinal diseases. J Neurol Sci 363:43–50
15. Koyuncu OO, Hogue IB, Enquist LW (2013) Virus infections in the nervous system. Cell Host Microbe 13(4):379–393
16. Unni SK, Růžek D, Chhatbar C, Mishra R, Johri MK, Singh SK (2011) Japanese encephalitis virus: from genome to infectome. Microbes Infect 13(4):312–321
17. Swanson PA II, McGavern DB (2015) Viral diseases of the central nervous system. Current opinion in virol 11:44–54
18. Marinho PM, Marcos AA, Romano AC, Nascimento H, Belfort R (2020) Retinal findings in patients with COVID-19. The Lancet. https://doi.org/10.1038/s41433-020-01283-2
19. Vavvas DG, Sarraf D, Sadda SR, Eliott D, Ehlers JP, Waheed NK, et al. Concerns about the interpretation of OCT and fundus findings in COVID-19 patients in recent Lancet publication. Nature Publishing Group; 2020.
20. Lankarani KB, Afshari R (2014) Alcohol consumption in Iran. Lancet 384(9958):1927–1928
21. Daruich A, Martin D, Bremond-Gignac D. Ocular manifestation as first sign of Coronavirus Disease 2019 (COVID-19): interest of telemedicine during the pandemic context. Journal Français d'Ophtalmologie. 2020.
22. Xia J, Tong J, Liu M, Shen Y, Guo D (2020) Evaluation of coronavirus in tears and conjunctival secretions of patients with SARS-CoV-2 infection. J Med Virol 92(6):589–594
23. Deng C, Yang Y, Chen H, Chen W, Chen Z, Ma K, et al. Ocular Dectection of SARS-CoV-2 in 114 cases of COVID-19 pneumonia in Wuhan, China: An observational study. China: an observational study (2/19/2020). 2020.
24. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x et al (2020) Clinical characteristics of coronavirus disease 2019 in China. New England J Med 382(18):1708–1720

25. Wu P, Liang L, Chen C, Nie S. A child confirmed COVID-19 with only symptoms of conjunctivitis and eyelid dermatitis. Graefe's Archive for Clinical and Experimental Ophthalmology. 2020:1.
26. Sun Y, Liu L, Pan X, Jing M (2006) Mechanism of the action between the SARS-CoV S240 protein and the ACE2 receptor in eyes. Int J Ophthalmol 6(4):783–786
27. Liang L, Wu P. There may be virus in conjunctival secretion of patients with COVID-19 (2020). Acta ophthalmologica, 93(3): 223
28. Chen L, Deng C, Chen X, Zhang X, Chen B, Yu H, et al. Ocular manifestations and clinical characteristics of 534 cases of COVID-19 in China: A cross-sectional study. MedRxiv. 2020.
29. Parmet WE, Sinha MS (2020) Covid-19—the law and limits of quarantine. N Engl J Med 382(15):e28
30. Lescure F, Bouadma L, Nguye n D. case series. Lancet Infect Dis. 2020.
31. Scalinci SZ, Battagliola ET (2020). Conjunctivitis can be the only presenting sign and symptom of COVID-19. ID Cases.20:00774.
32. Chen L, Liu M, Zhang Z, Qiao K, Huang T, Chen M et al (2020) Ocular manifestations of a hospitalised patient with confirmed 2019 novel coronavirus disease. Br J Ophthalmol 104(6):748–751
33. Viral R. Observation: Brief research report.
34. Guillen E, Pineiro GJ, Revuelta I, Rodriguez D, Bodro M, Moreno A, et al. (2020). Case report of COVID-19 in a kidney transplant recipient: does immunosuppression alter the clinical presentation? American Journal of Transplantation.
35. Cheema M, Aghazadeh H, Nazarali S, Ting A, Hodges J, McFarlane A, et al. Keratoconjunctivitis as the initial medical presentation of the novel coronavirus disease 2019 (COVID-19): A case report. Canadian Journal of Ophthalmology. 2020.
36. Salducci M, La Torre G (2020) COVID-19 emergency in the cruise's ship: a case report of conjunctivitis. Clin Ter 171(3):e189–e191
37. Daruich A, Martin D, Bremond-Gignac D (2020) Unilateral conjunctivitis as first presentation of Coronavirus Disease 2019 (COVID-19): A telemedicine diagnosis. J Français d'Ophtalmologie. 43(5):1–2