



Coronavirus disease 2019 (SARS-CoV-2) and colonization of ocular tissues and secretions: a systematic review

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Abstract

Coronavirus disease 19 (COVID-19) has been described to potentially be complicated by ocular involvement. However, scant information is available regarding severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and ocular structures tropism. We conducted a systematic review of articles referenced in PubMed, Cochrane Library, Web of Science and Chinese Clinical Trial Register (ChiCTR) from December 20, 2019 to April 6, 2020, providing information on the presence of SARS-CoV-2 in cornea, conjunctiva, lacrimal sac, and tears. We excluded ongoing clinical studies as for unobtainable conclusive results. Of 2422 articles, 11 met the inclusion criteria for analysis and were included in the study. None of the studies were multinational. Among the 11 selected papers there were three original articles, one review, four letters, two editorials, and one correspondence letter. Globally, 252 SARS-CoV-2 infected patients were included in our review. The prevalence of ocular conjunctivitis complicating the course of COVID-19 was demonstrated to be as high as 32% in one study only. Globally, three patients had conjunctivitis with a positive tear-PCR, 8 patients had positive tear-PCR in the absence of conjunctivitis, and 14 had conjunctivitis with negative tear-PCR. The majority of the available data regarding SARS-CoV-2 colonization of ocular and periocular tissues and secretions have to be considered controversial. However, it cannot be excluded that SARS-CoV-2 could both infect the eye and the surrounding structures. SARS-CoV-2 may use ocular structure as an additional transmission route, as demonstrated by the COVID-19 patients' conjunctival secretion and tears positivity to reverse transcriptase-PCR SARS-CoV-2-RNA assay.

Introduction

Coronaviruses (CoVs) are enveloped, non-segmented, positive-sense RNA viruses belonging to the family of *Coronaviridae* [1]. Although they were not considered as highly pathogenic, mostly causing mild infections in immunocompetent people, in the last 20 years they have been responsible for the outbreak of two epidemic, zoonotic, and respiratory syndromes. In 2002 and 2003

CoVs were responsible of the severe acute respiratory syndrome (SARS) [2–6] and in 2012, of the Middle East Respiratory Syndrome (MERS) [7, 8]. Altogether, they have caused more than 10,000 cumulative cases, with mortality rates of 10% for SARS-CoV, and 37% for MERS-CoV [9].

In more recent times, another CoV hit the headlines for having been described as the cause of a cluster of pneumonia cases in Wuhan, Hubei, China, from December 2019 [9, 10]. On January 31, 2020, the outbreak has been declared by the World Health Organization (WHO) as a Public Health Emergency of International Concern [11]. On February 11, 2020, the WHO officially named the infection due to the virus as coronavirus disease 2019 (COVID-19) [12]. The Coronavirus Study Group of the International Committee on Taxonomy of Viruses named the etiologic agent of COVID-19 as “severe acute respiratory syndrome related coronavirus 2”, or SARS-CoV-2 [13]. On March 11, 2020, the WHO declared COVID-19 a pandemic. As of April 06, 2020, a total of 1,136,862 laboratory-confirmed

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cases had been documented, with 63,025 confirmed deaths, in 208 countries [14].

SARS-CoV, MERS-CoV, and SARS-CoV-2 etiologic agents belong to the subfamily of *betacoronavirus*. Interestingly, both SARS-CoV and SARS-CoV-2 uses angiotensin converting enzyme-2 (ACE2) receptor to primarily infect ciliated bronchial epithelial cells and type 2 pneumocytes [15–17]. In addition, it has been shown that SARS-CoV and Human Coronavirus NL63 (HCoV-NL63) infections are associated with conjunctivitis, hence suggesting that CoV can shed and even infect ocular tissue [18–20].

However, it is still unclear if SARS-CoV-2 can infect or spread through the mucous membranes of the eye. This systematic review will firstly attempt to analyse the current knowledge on SARS-CoV-2 colonization of ocular and periocular tissues and secretions (i.e., cornea, conjunctiva, lacrimal sac, and tears), in order elucidate if conjunctival transmission occurs, and secondarily aims to propose a potential diagnostic tool in the evaluation of suspected, infected patients.

Materials and methods

We performed a systematic review of the Medline (PubMed), Cochrane Library, World of Science (WoS), and Chinese Clinical Trial Register (ChiCTR) [21] from December 2019 to April 05, 2020 to find papers providing information on the presence of SARS-CoV-2 in cornea, conjunctiva, lacrimal sac, and tears (view “Supplementary Material”). PRISMA guidelines were used for this systematic review [22]. Reference lists of identified articles were independently hand-searched by two authors (GGA, CG). Abstracts were examined, and if eligible, full texts and associated reference lists underwent further evaluation for eligibility. The search was then expanded using a snowballing method applied to the references of retrieved papers, which, once identified, were also screened for accordance to our inclusion criteria. Authors were contacted when necessary. All the results were merged using the reference management software Mendeley (V.1.19.4, Mendeley Ltd). All publications were then reassessed by a third reviewer (FA). According to Cohen’s Kappa, interrater agreement was excellent ($\kappa = 1$). Notably, though the majority of publications on COVID-19 are from Asia, no language restrictions were imposed, in order to minimize language bias. Due to the scant evidence, both original articles, editorials, letters, and reviews providing evidence (i.e., prevalence, anecdotal report) about SARS-CoV-2 colonization of ocular and periocular tissues and secretions were all included in the study. In addition, both published and unpublished papers were examined in our analysis, but we excluded ongoing clinical studies as for unobtainable

conclusive results. To assess risk of bias and quality of primary studies or systematic reviews identified from database searches, we used the Newcastle–Ottawa Scale for cohort studies, the highest score on which is 9 points [23]. After extensive discussion among reviewers, we decided to include also studies with high risk of bias. We did not register the systematic review protocol because we anticipated the paucity of available information on the subject and due to the urgency of the matter.

Results

The initial search identified 2422 articles (2403 from PubMed, 0 from Cochrane Library, 15 from WoS, 0 from ChiCTR, and 4 through other sources). Following the initial screening of titles, abstracts and removal of duplicates, we included 11 articles in our review. None of the studies was multinational. Among the 11 selected papers there were three original articles, one review, four letters, two editorials, and one correspondence letter (Table 1) [24–33]. Because of the heterogeneity of studies, no meta-analysis was performed.

Wu et al. investigated ocular manifestations and viral prevalence in the conjunctiva of 38 patients with COVID-19 (mean age: 65.80 ± 16.60 years). Among them, 12 eyes (31.58%) presented with signs suggestive of conjunctivitis and 2 up to 38 conjunctival specimens (5.26%) yielded positive findings for SARS-CoV-2 at RT-PCR. Notably, the two positive conjunctival swabs (2/12, 16.66%) were sampled from patients with ocular symptoms [32].

Fang et al. enrolled 32 COVID-19 patients (age range from 34 to 54). They collected nasal, blood, faecal, urine, saliva, and tears samples to detect SARS-CoV-2 RNA via RT-PCR. Conjunctival swabs resulted as positive in five samples (15.63%). Remarkably, the presence of conjunctivitis or other ocular manifestation was not reported in their letter [33].

Mungmungpantipantip and Wiwanitkit in their letter to editor did not report any ocular manifestation among the 48 patients met in their practice. However, no conjunctival swab has been sampled and analysed [34].

Xia et al. attempted to elucidate in a prospective study the presence of the novel coronavirus in conjunctival secretions of confirmed SARS-CoV-2-infected patients at the First Affiliated Hospital of Zhejiang University from January 26, 2020 to February 9, 2020. Authors tested a total of 60 tear samples and conjunctival secretion samples from 30 patients (mean age = 54.50 ± 14.17 years). Reverse-transcription polymerase chain reaction (RT-PCR) assay resulted positive for SARS-CoV-2 RNA in two swabs (2/60, 3.33%) from a single patient with conjunctivitis symptoms. The other 58 samples yielded negative RT-PCR

Table 1 Full list of the selected papers analysed in the systematic review.

Author	Publication date	Article type	Journal	No. of patients tested	No. of patients with conjunctivitis	No. of patients with positive RT-PCR RNA assay	Study quality
Wu et al. [32]	31.03.2020	Original article	JAMA Ophthalmology	38	12 (32%)	2 (5%)	7
Mungmungpantip and Wiwanitkit [34]	25.03.2020	Letter to the editor	Graef's Archive for Clinical and Experimental Ophthalmology	48	0 (0%)	n/a	n/a
Peng et al. [30]	16.03.2020	Letter to the editor	Journal of Medical Virology	None	n/a	n/a	n/a
Fang et al. [33]	Pre-proof	Letter to the editor	Journal of Infection	32	n/a	5 (16%)	n/a
Seath and Agrawal [31]	02.03.2020	Review article	Ocular Immunology and Inflammation	None	n/a	n/a	n/a
Liang and Wu [28]	01.03.2020	Editorial	Acta Ophthalmologica	37	3 (8%)	1 (3%)	n/a
Qing et al. [25]	01.03.2020	Letter to the editor	Acta Ophthalmologica	None	n/a	n/a	n/a
Xia et al. [29]	19.02.2020	Original article	Journal of Medical Virology	30	1 (3%)	1 (3%)	n/a
Li et al. [26]	13.02.2020	Editorial	British Journal of Ophthalmology	None	n/a	n/a	n/a
Zhou et al. [24]	Unpublished	Original article	Unpublished	67	1 (1%)	3 (4%)	5
Lu et al. [27]	06.02.2020	Correspondence	The Lancet	None	n/a	n/a	n/a

RT-PCR reverse transcriptase-polymerase chain reaction, n/a not available.

results (58/60, 96.66%) and did not show signs of conjunctivitis [29].

Zhou et al. conducted a similar prospective study at Renmin Hospital of Wuhan University from 17 Jan to 28 Jan 2020 on 67 COVID-19 patients (mean age: 35.70 ± 10 years; male/female ratio of 1/1.68). Authors demonstrated conjunctival swab samples positive for SARS-CoV-2-RNA in one and weakly positive in two patients (3/67, 4.48%). None of the aforementioned patients had conjunctivitis at the time of conjunctival swab collection. In the single patient with conjunctivitis, conjunctival swab was negative for RT-PCR (1/67, 1.50%) [24].

Liang and Wu analysed 37 conjunctival swabs from confirmed SARS-CoV-2-infected patients at Yichang Central People's Hospital, Hubei. Three out of 37 patients (8.11%) had conjunctivitis. Only one swab (1/37; 2.70%) from a severe patient (as for the Chinese COVID-19 diagnosis protocol [9]) not suffering from conjunctivitis, had positive RT-PCR assay [28].

Peng and Zhou, due to the aforementioned contrasting results, described conjunctivitis as a "coincident event, rather than a causal event of SARS-CoV-2 infection of the conjunctiva." [30].

Qing et al. speculated the possibility that SARS-CoV-2, as a droplet, could mix with tears, and then access the respiratory tract via the nasolacrimal duct, further suggesting that conjunctivitis during the course of COVID-19 may be an incidental event [25].

Li et al. strongly suggests physician to "take particular care when examining patients, because of both the proximity to patients' nose and mouth, and the potential exposure to tears which may contain the virus" [26, 35]. This hypothesis was used to suggest the need for ophthalmologist to wear goggles during clinical encounter, as expressed by Lu et al. and Li et al. [26, 27].

However, as analysed by Seah and Agrawal, not only is it still unclear whether SARS-CoV-2 may colonize ocular tissue, but we may also speculate upon other ocular manifestations based on the confirmed expression of ACE2 in different other structures of the eye [24, 30, 31].

Discussion

To the best of our knowledge this is the first systematic review summarizing all the data regarding SARS-CoV-2 colonization of ocular and periocular tissues and secretions (i.e., cornea, conjunctiva, lacrimal sac, tears).

This systematic review analysed 252 SARS-CoV-2-infected patients globally who underwent conjunctival swab, and demonstrates the prevalence of ocular conjunctivitis complicating the course of COVID-19 to be as high as 32% (12 patients out 38), differently as what

previously stated by the “Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)” as low as 0.8% [36]. Altogether, three patients had conjunctivitis with a positive tear-PCR, eight patients had positive tear-PCR in the absence of conjunctivitis, and 14 had conjunctivitis with negative tear-PCR [24, 28, 29, 32, 33]. This inconsistency may be due to a number of factors, including low viral load in conjunctival secretion, inappropriate sample collection or handling leading to sample contamination, and damage to genetic material. Though current RT-PCR is considered an effective technique, it could inevitably lead to false positive and false negative results [37, 38].

The caution for potential ocular transmission of SARS-CoV-2 was first highlighted by one of the experts of the task force who visited Wuhan on early 2020. Despite being fully gowned with protective coat and N95 mask, he was still infected and reported his first symptom being unilateral conjunctivitis, with subsequent fever and catarrhal symptoms 2–3 hours later. The latency period of a few hours from conjunctivitis to respiratory symptoms does not aid in the determination of the route of transmission, since the virus may have entered via the unshielded ocular surface and caused respiratory symptoms around the same time as conjunctivitis, but masking may also have been ineffective, and conjunctivitis was merely a manifestation of SARS-CoV-2. It would be useful to further elucidate SARS-CoV-2 binding to the surface of ocular tissues. It has been shown that SARS-CoV-2 cell entry depends on SARS-CoV-2 S protein/ACE2 receptor interaction [39]. Key proteins crucial to the renin–angiotensin–aldosterone system (RAAS) have been widely described in many ocular structures, including the aqueous [40], the pigmented epithelium [41], and the retina [31, 42–45].

Evidence of the expression of such proteins both in the conjunctiva and in the cornea are limited. The only study trying to address this question with an *in vitro* model demonstrated ACE2 expression on both corneal and conjunctival cells and also showed effective binding of the S240 proteins of SARS-CoV with ACE2 receptor on both cells and tissues [46].

Furthermore, given the high vascularity of conjunctiva, along with the expression of ACE2 on the surface of endothelial cells [44, 45], it cannot be excluded that the ocular manifestation of SARS-CoV-2 infection may in fact manifest in the form of a local, transient vasculitis [47].

Due to the presence of RAAS proteins expression in different ocular tissues, it can also be speculated that, even in the form of anecdotal event, SARS-CoV-2 may be responsible for other possible ocular manifestations as anterior or posterior uveitis, iridocyclitis, vitritis, or retinal vasculitis [31, 40, 42–45].

Given the scarce nature of the available evidence regarding SARS-CoV-2 transmission through ocular tissue, no conclusions could be reached either regarding its ability to infect ocular structures or to use the lacrimal duct to reach the respiratory tract, as a novel transmission route [25].

In addition, due to inconsistency in RT-PCR assay results, conjunctival-swab RT-PCR should not be proposed as a standard diagnostic technique for COVID-19.

As it emerged from this analysis, evidence is not only limited, but sorely conflicting too, which determines low strength of the actual available data. In fact, no comparable results emerged in terms of both mean age at recruitment, number of recruited patients, and male/female ratio. In the two original articles and in the editorial reporting clinical data, only RT-PCR was run, while none of the studies reported viral culture [24, 28, 29]. Hence, it cannot be established whether SARS-CoV-2 only colonizes ocular structure or it is able to invade them, inducing conjunctivitis.

It is desirable that, as the current pandemic continues, a better understanding of the viral features with a focus on the viral tropism for ocular structures will emerge.

In the meantime, physicians should stay highly vigilant in recognizing patients with any previous contact at risk and early manifestation of COVID-19, including systemic symptoms and fever. A specific consideration must be dedicated to any ocular inflammatory involvement as a possible presentation. Individual protection kits including goggles are strongly recommended, especially in at risk clinical encounters [35, 48, 49].

Compliance with ethical standards

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

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