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

Mohsen Farvardin · Mohammadkarim Johari · Mahshid Tahamtan · Mohammad-Taghi Najafi · Reza Farvardin · K. S. Jagannatha Rao · Mohammad Nami

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 extrapulmonary 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 evidence-based protective measures in today’s practice of ophthalmology and allied disciplines.
Keywords  COVID-19 · nCoV-2 · Ophthalmic manifestations · Conjunctivitis · Retinitis · Optic neuropathy · Chemosis

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 Yuyun 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
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
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

| 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 | NA | 1 | Conjunctivitis, eyelid dermatitis |
| #20 | N/A | N/A | 2228 | NA | 95 (4.12%) | N/A |
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 into 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.

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