Important COVID-19 Updates for Ophthalmologists

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an ongoing global emergency public health problem. In this review, we aimed to systematically summarize what should be known by ophthalmologists about the transmission characteristics, diagnosis, and ophthalmic manifestations of the virus in order to provide reference for the prevention and control of the COVID-19 outbreak.

Key words: COVID-19, Coronavirus, SARS-CoV-2, pandemic, ophthalmology.

INTRODUCTION

On December 31, 2019, China reported an unknown pneumonia epidemic to the World Health Organization (WHO) in Wuhan, a city with a population of 11 million- in Hubei province.[1] A new Coronavirus (COV) was identified as the causative organism –namely, novel coronavirus: (nCOV) and the disease was named as the Coronavirus Disease 2019 (COVID-19) on February 11, 2020 by WHO.[2] On the same day, the Coronavirus Working Group of the International Committee of Virus Taxonomy named 2019-nCoV as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

The first confirmed case in our country was announced on March 11, 2020. By April 6, 2020, there was a total of 30.217 cases of SARS-CoV-2 infection in Turkey with 1415 patients requiring intensive care. This disease, also known to cause conjunctival involvement, may progress asymptomatically, putting the ophthalmologists who work in close contact with patients, and the following patients they examine at risk.[3] In this review, we aim to summarize the articles on COVID-19 that may be of interest to ophthalmologists about the SARS-CoV-2 virus, transmission routes and ocular involvement.

SARS-CoV-2

A new betacoronavirus called SARS-CoV-2 is the causitive organism of COVID-19.

Coronaviruses are a family of zoonotic pathogens that include the Middle East Respiratory Syndrome (MERS CoV) and four other viruses that cause common cold.[4]

There are seven types of CoVs known to infect humans: 229E (alphacoronavirus), NL63 (alphacoronavirus), OC43 (betacoronavirus), HKU1 (betacoronavirus), MERS-CoV (betacoronavirus), SARS-CoV (betacoronavirus) and the latest SARS-CoV-2.[5]

Most of these CoVs cause infections in the respiratory tract but they are also known to have manifestations in the gastrointestinal system and ocular tissues.[6,7] Most of the CoV research focuses on the respiratory system due to the life-threatening results. However, CoV manifestations in other organs should not be ignored since they can also be a mode of transmission.

Similar to SARS and MERS, SARS-CoV-2 virus, belongs to the β Coronavirus cluster of the Coronavirus family. Wu et al.[8] and Zhou et al.[9] found that the sequence homology between the SARS-CoV-2 virus and SARS-CoV, which caused a major epidemic in 2002-2003, was 79.5%. In the same studies it was also found that SARS-CoV-2 has high homology with bat Coronaviruses. Accordingly, the first cases have emerged in relation to the South China Seafood Market, where a wide variety of live or freshly cut animals are sold, including poultry, bats and snakes.

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The incubation period for COVID-19 has been reported between 2 to 14 days, according to Centers for Disease Control (CDC),[10] but in rare cases this period can last up to 24 days.[11]

Symptoms of infection are fever, cough, fatigue, muscle pain, anorexia, dyspnea and diarrhea.[12] While mild forms may present in the absence of pneumonia, in severe cases, shortness of breath and hypoxemia develop within 1 week from the onset of the disease. [13] Computerized tomography (CT) scans show irregular shadows or ground-glass opacities in the lungs.[14] Complications of the disease include acute respiratory distress syndrome, arrhythmia, shock, multiple organ failure, and the mortality rate is reported between 5 to 7%. [15]

Routes of Transmission

An important study from the University of Hong Kong provided the first concrete evidence of human to human transmission of SARS-CoV-2 virus and laid out some important clinical features of COVID-19.[16]

In this study, three important conclusions about COVID-19 were drawn. The first is the high virulence of SARS-CoV-2, as the viral transmission can be as high as 83% in the infected family. The second important feature is the diversity of the clinical signs of COVID-19 in this family; generally from mild to moderate; severe radiological abnormalities were seen in elderly family members with systematic disease. The third important feature was the detection of SARS-CoV-2 RNA in the sputum samples and irregular opaque shadows in thorax-CT of an asymptomatic child in the family. This finding of asymptomatic virus shedding indicates that asymptomatic carriers of SARS-CoV-2 are likely to infect others and this has been confirmed by subsequent studies. [11,12,17]

Several studies demonstrated that the viral transmission may occur via droplets, close contact or common use of infected items,[18] while there are reports about zoonotic,[19], nosocomial,[20] and feco-oral passage of the virus.[21]

Epidemiological features

Li et al., [8] reported that the mean age of SARS –CoV-2 patients was 59 years. They found that 56% of the cases were male and almost half of the adult patients were 60 years of age or older. The average incubation period of the virus was reported as 5.2 days. In the early stages of the disease, the number of infected patients doubled in 7.4 days, and an infected patient was found to transmit the disease to an average of 2.2 people. [21]

In a patient group with a median age of 49 years, 73% of patients were male, and 32% had a systemic disease such as diabetes, hypertension, or cardiovascular disease according to Huang et al's study.[22]

In large epidemiological studies, the female to male ratio of the patients was similar, 86% of the patients were between 30-79 years old and the median age was 49 years. [17]

Ocular Involvement of the Virus

Ocular involvement of Coronavirus family has been shown in various publications. The first of these studies was related to a new human coronavirus called HCoV-NL63, which appeared towards the end of the SARS-CoV epidemic in 2004. This study, evaluating HCoV-NL63 patients with respiratory disease between 2000 and 2003 in France, revealed that conjunctivitis developed in 17% (n=3) of the infected children (n=18).[22]

Following this study, in 2004, SARS-CoV RNA was identified in three tear specimens collected from 36 SARS-CoV patients and it was stated that SARS-CoV could be found in tears and therefore, measures should be taken to prevent transmission through ocular tissues and secretions.[23]

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 haematogenous infection of the lacrimal gland, were proposed.[24]

However, there are publications in the literature that reveal conflicting results.[25,26]

In a study evaluating both tear and conjunctival swabs of 17 patients with confirmed SARS-CoV infection, viral RNA was not detected by reverse transcriptase polymer chain reaction (RT-PCR).[26]

The authors proposed three theories for the absence of viral RNA in the conjunctiva. First, RT-PCR may not be sensitive enough to detect small amounts of SARS-CoV RNA. Second, if viral shedding in ocular tissue continues for a short time, this window period may be missed during sample collection. Finally, there is the possibility that SARS-CoV is absent in the ocular tissue.

There are also reports about ocular involvement of the latest SARS-CoV-2 epidemic in the literature. First, it is worth noting that in the light of genomic and structural analysis, SARS-CoV-2 has a similar receptor binding motif with SARS-CoV, which allows it to infect host cells via angiotensin-converting-enzyme-2. In the light of this information, it can be assumed that the ocular involvement characteristics of SARS-CoV-2 might be similar to SARS-CoV.[27]

On January 22, 2020, when a visiting doctor in Wuhan developed conjunctivitis, and later yielded positive for SARS-CoV-2, call for research on ocular transmission and involvement of SARS-CoV-2 was made.[28,29]

In a prospective study by Xia et al.,[30] tear and conjunctival secretions of 30 COVID-19 patients were collected in every 2-3 days and the presence of the virus was evaluated by RT-PCR.[11] 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.

Ocular findings in Coronavirus disease

Retrospective analysis made by Wu et al[31] contains the first data on ocular involvement of patients with COVID-19. Of 38 COVID-19 patients included in the study, virus was detected in the nasopharyngeal swab samples of 28 (73.7%) patients, and two (5.2%) of the conjunctival specimens.

Ocular findings suggesting conjunctivitis such as conjunctival hyperemia, chemosis, epiphora and increased secretion were detected in 12 patients. The first symptom of one of those patients was recorded as epiphora. None of the patients had blurry vision. In the same study, ocular symptoms were found to be higher in patients with increased procalcitonin, C-reactive protein and lactate dehydrogenase with high leukocyte and neutrophil counts. As a result of this study, it was suggested that the SARS-CoV-2 virus may have ocular manifestations.

Risks of COVID-19 for ophthalmologists and patients

Many healthcare workers have been infected with COVID-19 since the first day of the disease, and a considerable portion has lost their lives. One of them was an ophthalmologist working at the Wuhan Central Hospital, Li Wenliang who got the infection from an asymptomatic glaucoma patient in early January, and a month later died.[32]

Nosocomial transmission was an important transmission route both in SARS-CoV outbreak in 2003 and the MERS-CoV outbreak in 2012. When the similarity in the genomic sequence between SARS-CoV-2 and these Coronaviruses are taken into account, the nosocomial propagation tendency should not be underestimated for the current COVID-19.

There are case reports presenting doctors infected by patients with subclinical infection through droplets or contact with mucous membranes and secretions.[33] In these publications, it is also suggested that when eye protection is not used, the virus can be transmitted by aerosol contact of the conjunctiva and cause infection.

As ophthalmologists, we have to stay in close proximity to the nose and mouth of our patients, especially during biomicroscopy and fundus examination. In addition, ocular evaluation often includes numerous examination steps, including visual acuity, intraocular pressure measurement, pupillary dilation, and fundus examination. Since patients stay in the clinic for a long time to complete the entire examination, the risk of infection increases in ophthalmology outpatient clinics, both between patients in the waiting area, and also between healthcare professionals and patients.

Additionally, a significant part of our patient group consists of an aging population, and this group of patients appears to be at risk for severe COVID-19 infection and mortality.[34]

Immediately after identification of the disease, the American Academy of Ophthalmology (AAO) issued an alert to the ophthalmologists to wear a mask and eye protection when examining patients with conjunctivitis who have respiratory symptoms and an international travel history.[35] In anecdotal reports following this warning, it has been demonstrated that conjunctivitis may be the first symptom of COVID-19 before cough and fever occur.[28,3]

Various precautions are needed to prevent virus transmission in ophthalmology outpatient clinics. Lai et al.[37] described the 3-step infection control measures taken in public hospitals in Hong Kong during the COVID-19 epidemic in their report. These steps were as follows: Administrative control, environmental control and the use of personal protective equipment. In order to prevent cross-infection, within the framework of administrative control, appointments were rescheduled by sending a text message to the patients to reduce the number of outpatient treatments, and if necessary, drug prescriptions were renewed. This is an important public health measure, especially considering transmission of the virus from subclinical patients.[38]

For patients who did not accept postponement of the appointments, a separate triage system was established to identify patients with fever, respiratory symptoms, acute conjunctivitis and history of travel to epidemic sites recently, and these people were directed to the emergency departments. At the triage stations in the entrance of the eye clinics, all patients and their relatives were scanned using infrared thermometers and then accepted.

One of the precautions to be taken during the ophthalmic examination is to avoid the applications that produce aerosol.[39] Since COVID-19 is known to transmiss through aerosol delivery, procedures that produce aerosol in ophthalmic practice such as puff tonometry should be suspended.[40] Goldmann applanation tips should be disinfected by 70% alcohol solutions and left to dry in air, in line with AAO recommendations, to prevent the SARS-CoV-2 transmission. However, since alcohol is insufficient to provide effective sterilization against adenoviruses, using disposable tonometer tips would be a safer approach for preventing pathogen transmission.[41]

Since nasal endoscopy before or after endoscopic dacryocystorhinostomy may cause sneezing by irritating the nasal mucosa, this practice should be avoided as much as possible to reduce the risk of contamination of the operator.[42]

Non-urgent elective surgeries should be postponed to reduce human contact and also in order to spare hospital beds, manpower and personal protective equipment for the combat with COVID-19.

In cases that require urgent surgery, performing surgeries under local anesthesia is recommended if possible, instead of general anesthesia with endotracheal intubation, which produces aerosol.[42]

If the operation must be performed under general anesthesia, ophthalmologists should be in contact with anesthesiologists and internal medicine specialists, and rapid COVID-19 testing should be performed when in suspicion.[43]

For emergent surgical procedures, if test results are positive, or negative but in case of clinical suspicion, or for cases where it is not possible to wait for the test result, the operation must be performed in an isolated operating room and all staff must wear N95 masks and protective glasses.[37] All clinical staff should undergo infection control training to learn the appropriate steps of hand hygiene with installation and removal of personal protective equipment. Hospital workers need to measure and report their body temperature before work and report symptoms such as fever, chills, muscular pain, sore throat, runny nose, cough, vomiting, diarrhea or pneumonia.

In Lai et al's study,[37] the first precaution taken under the name of environmental control was to install protective shields on the slit lamps and frequent disinfection of the equipment to reduce COVID-19 contamination with droplets. Since the proximity between ophthalmologists and patients during the slit lamp examination is sufficient for the transfer of droplets while coughing or sneezing, (droplets are reported to be projected up to 183 cm) [44] ophthalmologists are at risk for COVID-19 infection. Even when a protective breath shield is used, it is recommended that both the patient and the physician should wear a mask, and the physician should also wear protective glasses and gloves.

Usage of chloroquine / hydroxychloroquine in COVID-19 treatment: our responsibility as an ophthalmologist

Chloroquine and hydroxychloroquine show antiviral features against SARS virus and are included in the current treatment of COVID-19 from the initial step.[45] These two drugs are known to cause retinal toxicity depending on their long-term use for diseases like systemic lupus erythematosus (SLE) and other rheumatoid diseases. However, the risk of retinopathy to be seen before 10 years at the dose of <5 mg / kg as recommended by AAO is rather weak.[46]

Although the treatment dose administered at the beginning of COVID-19 treatment in China is above the daily dose recommended by AAO, (500 mg chloroquine twice daily or 400 mg hydroxychloroquine four times daily), the total duration of treatment is short (10 days).

There are other situations where hydroxychloroquine is used at a higher dose than recommended. The use of 1200 mg/day hydroxychloroquine as a loading dose for 6 weeks in the treatment of rheumatologic diseases was investigated and detailed ophthalmologic examinations of the patients revealed no retinal pathology or vision loss.[47,48] In addition, no visual loss was reported after the use of 1200 mg hydroxychloroquine per day for 4-8 weeks in the treatment of myeloma and solid tumors, which is among the publications reported on high dose of hydroxychloroquine.[49,50] Leung et al[51] evaluated 7 patients using 1000 mg hydroxychloroquine per day for 7 to 25 months for small cell lung cancer by optic coherence tomography (OCT) at 3-month intervals. Mild changes were detected in the parafoveal ellipsoid region in two patients after 11 and 17 months, and at the end of 15 and 25 months, retinal toxicity verified with OCT was reported in these patients. No signs of toxicity were detected in the rest of the patients,.

Therefore, in the light of scientific evidence obtained so far, it can be stated that high doses of these drugs accelerate retinal toxicity, however, this will occur in months rather than days.

The recommended dosage of Hydroxychloroquine in uncomplicated cases in the current treatment is 2x200 mg/day for 5 days following the 2x400 mg/day loading dose. This dose is less than twice the dose recommended by AAO and does not seem to carry the

risk of retinopathy during short-term use in the light of the information provided.

During a pandemic, where medical staff, funds, hospital beds, equipment and screening tests are limited, it will not be cost-effective to examine all the patients who will use Chloroquine and Hydroxychloroquine for less than 2 weeks by the ophthalmologists.

However, individuals using these medications may need to be examined at regular intervals in line with the AAO recommendations, if the treatment algorithms change and switch to longer-term use. At this point, the responsibility of the ophthalmologists should be to evaluate the changing treatment algorithms in terms of dose/weight and duration to perform risk analysis.

RESULTS

In this review, we tried to list the infection control measures that can be taken in ophthalmology clinics by summarizing the features of COVID-19 infection, groups at risk, transmission routes and ocular involvement in the light of current publications.

We hope that the information presented in this review can help our colleagues to be prepared for a community epidemic or pandemic.

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