Editorial

Role of ophthalmologists in combating with the Coronavirus disease 2019

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Abbreviations: nCoV, novel coronavirus; SARS-CoV, severe acute respiratory syndrome Coronavirus; *MERS-CoV,* Middle East Respiratory Syndrome-*Coronavirus*; 2019-nCoV, novel Coronavirus 2019; WHO, World Health Organization; ACE2, angiotensin-converting enzyme 2; reverse-transcription polymerase chain reaction (RT-PCR); CDC, Centers for Disease Control and Prevention; AAO, American Academy of Ophthalmology.

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Editorial

On December 31, 2019, a new Coronavirus (nCoV) was reported in the cases of pneumonia of unknown etiology in the city of Wuhan, China. This nCoV was named as 2019-novel CoV and Severe Acute Respiratory Syndrome Coronavirus–2 (SARS-CoV-2) and the name of the disease has been accepted as COVID-19. Li Wenliang, MD, an ophthalmologist working in Wuhan where the COVID-19 epidemic arose, took the virus from a glaucoma patient with conjunctivitis in January 2020. He was the first individual who announced this epidemic, and he has died on February 2020.[1–9] The virus responsible for the COVID-19 pandemic is the Sarbecovirus in the beta-CoV family which also contains SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). The 2019-nCoV may enter into the host through respiratory tract or tissues including mucosal surfaces such as conjunctiva and nose. The virus is transmitted to the nasal or ocular mucosa mainly through droplets, coughing sick individuals, sneezing the mouth drops by contact and the contact with sick or transporter individual's hands. Viruses can be detected in respiratory secretions of asymptomatic individuals.[1–9] The analysis of the epidemiological characteristics of COVID-19 demonstrates that the average incubation period is 5-6 days (2-14 days after a person is exposed), exactly un-known infectious time (range: from 1-2 days before the symptomatic period to the end with the disappearance of symptoms). COVID-19's highly possible symptoms are fever, cough and breathing difficulty. It causes death via pneumonia and severe respiratory failure and.[1–9]

What do we know about ocular transmission or involvement?

A. The recent data from China show that the frequency of conjunctivitis is about 1% in COVID-19 patients and only the tears from conjunctivitis in COVID-19 patients are responsible for viral transmission. The 2019-nCoV may be transmitted by aerosol direct or indirect contact with the conjunctiva.[3,7–19]

B. CoVs have been known to cause various ocular infections in animals. However, clinical entities such as conjunctivitis, anterior uveitis, retinitis, and optic neuritis have been documented in feline and murine models.[10]

C. There are some reports that the initial infection can take an ocular route or conjunctivitis may be the first presenting symptom of COVID-19. In a larger study, it has been reported that conjunctival injection/congestion in 9 of 1.099 patients (0,8%) with laboratory-confirmed COVID-19 from 30 hospitals in the whole of China.[8] In another report including a prospective interventional case series with 30 confirmed nCoV pneumonia patients, reverse-transcription polymerase chain reaction (RT-PCR) assay for a total of 60 tears and conjunctival secretions samples tear were performed with two samples from each patient collected at an interval of 2-3 days. The 2019-nCoV RNA was not detected in the samples from 29 COVID-19 patients without conjunctivitis, while as only one patient having conjunctivitis had detectable 2019-nCoV RNA in tears and conjunctival secretions.[14,15]

D. In a retrospective cohort study which was initiated to investigate the possible transmission of 2019-nCoV through aerosol contact with conjunctiva, the nasopharyngeal and conjunctival swabs of 67 cases including laboratory-confirmed 63 COVID-19 cases and 4 suspected COVID-19 cases were collected for real-time RT-PCR analysis to detect 2019-nCoV. Zhou et al reported that conjunctivitis was identified in only one case in this cohort. 2019-nCOV test in conjunctival swab samples was positive in only one case and probable positive in two COVID-19 cases without conjunctivitis. None of the three patients had ocular symptoms. The only one 2019-nCoV patient with conjunctivitis as the first symptom had a negative conjunctival test. Conjunctival swab samples from the four suspected cases of 2019-nCoV pneumonia were negative. 55 of the 60 sputum samples from 30 COVID-19 cases showed positive PCR results for 2019-nCOV.[16,17]

E. In another study, Sun et al reported that conjunctivitis was present in two patients out of 72 laboratory-confirmed COVID-19 cases while 2019-nCoV was detected in conjunctival swab samples by RT-PCR in only one patient.[18]

F. It has been considered that the onset of pneumonia in COVID-19 within 2-3 hours following the development of conjunctivitis is in low probability.

G. Similar to SARS-CoV, 2019-nCoV uses angiotensin-converting enzyme 2 (ACE2) for recognizing and binding receptors to spike

protein on its surface to enter into host cells.[14,20] The expression and the binding capability of the ACE2 is highly expressed on the lung, small intestine, and the kidney while these properties are much less in conjunctival and cornea in humans. The involvement of ACE2 as the cellular receptor explains droplet transmission to the lower respiratory tract. *ACE2* is also found in the ocular tissues including the conjunctiva.[20]

H. The conjunctiva easily meets to infectious droplets during close contact with infected patients or contaminated hands. Thus, the conjunctiva may be an important entry route for CoVs, and tears and conjunctival secretions may contain the virus and may cause spread viral infection.[9–19]

I. Since COVID-19 patients have viremia during the acute phase, the positivity of SARS-CoV-2 RNA has likely resulted from the virus in the exudation of conjunctivitis. [9–19]

J. Previous reports showed that the sensitivity of RT-PCR in body secretions was ranged from 50%-60% and that a part of 2019-nCOV suspects often had 2-3 repeated RT-PCR tests of nasopharyngeal swabs before the positive results were obtained. It has been also demonstrated that the positivity of 2019-nCOV RNA in tears and conjunctival samples were detected in the early phase of the disease, and the negativity of 2019-nCOV RNA occurred in the later or convalescent phase. Thus, it has been considered that the 2019-nCOV and its RNA might be only present in a short period or that the secretion of the virus in tears occurs only during the early phase of the COVID-19.[9–19]

K. The liquid in the drop instilled to the eye is partially absorbed by the cornea and conjunctiva, but mostly drained into the nasal cavity, and then crossed to the lower part of the respiratory tract including nasopharynx and trachea. Thus, the conjunctiva may be a portal of entry gate or transfer station of the pathogens such as COVs to infect the respiratory tract.

L. This data shows that:

a. Conjunctivitis has been reported in only five cases in COVID-19 patients.

b. 2019-nCOV can infect the conjunctiva and cause conjunctivitis.

c. Virus particles may present in ocular secretions.

d. Tears and conjunctival secretions can be a medium for the 2019-nCOV spread.

Why are ophthalmologists at high risk?

A. Although conjunctivitis is an uncommon presentation in COVID-19, as COVID-19 patients may admit or projected to ophthalmology clinics or emergency service, it increases the likelihood ophthalmologists to first evaluate the patients possibly infected with COVID-19.[9–19]

B. Routine ophthalmic examinations such as slit-lamp examination and most ophthalmic examinations and treatment procedures which are much within the range of aerosol transmission are all performed by close contact. Additionally, there is almost no distance between ophthalmologist and patient during the direct ophthalmoscopy.[9–19]

C. The ophthalmologists are easily exposed to the droplets and tears or ocular secretions from the ophthalmic instruments contaminated by COVID-19 patients or suspects and so, ophthalmologists are at the high risk for the contagion of the disease.[9–19]

D. The patients who were directed to ophthalmology clinics for a consultation often stay for a longer duration in the hospital for multiple and systemic investigations. So, they can increase the risk of cross-infection to other patients and health care workers. The risk is higher with unsuspected asymptomatic patients with subclinical infections.[9–19]

The world health organization (WHO) and centers for disease control and prevention (CDC), and the american academy of ophthalmology (AAO) recommendations related pandemic:[1,2,5–7,21–23]

Inquiry: All the patients, especially with conjunctivitis should be inquired quickly by the ophthalmologist or the medical staff regarding whether or not the patient has a fever, cough, and difficulty or shortness in breath, and who have recently (in the last 14 day) traveled to abroad, particularly to areas with known outbreaks, or with family members recently back from one of these areas. A patient who presents to the ophthalmologist for conjunctivitis could be a case of COVID-19.

Patient isolation: When seeing positive or suspicious cases or the patients potentially infected with 2019-nCOV, a facemask should be placed on the patient and they should be isolated in an examination room with the door closed or airborne infection isolation rooms. These patients, especially older patients should not be included in the routine patient waiting room. It is also very important that not to take to the examination room of the patient's surroundings which will not be of benefit to the patient.

No-touch: It should be noted that the patient's hand should not be clenched or otherwise contacted by an ophthalmologist. Also, the doctor should not discreetly touch own face, particularly eyes, nose, and mouth during the examination. Ophthalmologists are also recommended not to touch their goggle, face shield, surgical/N95 mask, eye, head, and neck region before the hand-washing procedure is completed.

Wash: Ophthalmologist should wash own hands in detail and frequently with soap and water with soap for at least 20 seconds after each examination. Hand washing using chlorhexidine alcoholic hand rub after each ophthalmic examination or therapeutic procedure is highly recommended to prevent cross-infection. Additionally, she/he should especially wash own hands before eating, after using the restroom, sneezing, coughing or blowing the nose.

Mask: Ocular examination is performed by the approximation to less than 1 meter from the patient almost, thus, the mask use during examination is mandatory. All ophthalmologists are warned about wearing the masks for mouth, nose, and eye to protect during the examination or care of the patients with conjunctivitis with respiratory symptoms and a history of international travel or potentially infected with 2019-nCoV and to prevent air contamination. The recommended masks are N95 (USA standard) ve FFP2 ve FFP3 (EN149) (EU standard). However, FFP1 masks cannot obtain appropriate protection. FFP3 has the most protective property. The blockade ability for 0, 6-micron particles of these masks is %80 for FFP 1, %94 for FFP2 and %99 for FFP3. As the pores in the masks can be large or collapsed with the time, it is recommended to be changed every 4 or 24 hours in different reports without re-use after washing.

Gloves: The gloves should be used only during the handling to all the body secretions or fluids or lesions, and also the examination of

the eyelids or periorbital tissues and fundus or iridocorneal angle with the contact three-mirror lens or goniolens, and the fornices with the pulling or eversion of eyelids and the removal of the cilia in the eyebrow. As soon as the ocular examination is completed, the gloves should be un-weared and the handling to own face and eye should be avoided while wearing gloves.

Googles: The entry or transmitting route of the disease for the people to people is the conjunctiva by aerosol (droplet) or by hand transfer of the virus to the eye. Although the possibility of the eye route is much lower than the passage by the nasopharyngeal route, it is also recommended to use eye protection glasses with a wide frame or googles. However, as there is usually a narrow gap between the upper edge of the mask and the eyes, pathogen virus may transfer to the eye. Thus, a protective goggle can prevent this handicap.

Shields: Slit-lamp barriers or breath shields with Plexiglas and plastic structure attached to slit lamp biomicroscope will be useful to prevent airdrop contamination of viruses. A large A4-sized clear plastic sheet made for bookbinding covers or plastic radiology scans may be used for this purpose. However, as these materials can easily be infected by touching of the staff or by the patients who talk, cough, sneeze, after each examination, they should be cleaned with an alcohol-based disinfectant (alcohol, chlorhexidine, sodium hypochlorite) and should be dried in room air to prevent contamination of equipment and surfaces on the patient's side of the barrier.

Gowns: It has been recommended that ophthalmologists and healthcare workers wear gowns, especially ocular invasive procedures or processing in conjunctival secretions.

Silence: To minimalize the risk of viral transmission and to prevent air droplet contamination, ophthalmologists should warn the patients regarding minimal speaking during the slit-lamp examination.

Fast work: Ophthalmologists should act quickly and efficiently in the works as they may be the first specialists to evaluate the possibly infected patients.

Examination devices: It is also important to use as many non-contact devices as possible such as air-puff tonometer in ocular examinations, and to clean the contact-devices without neglect after each examination. Many ophthalmic instruments such as the ultrasound probes, ocular contact lenses such as Goldmann three-mirrored lens and goniolens, trial frames, slit-lamp microscope, direct ophthalmoscope, automatic perimeter, corneal topography, fundus camera, and optical coherence tomography, are frequently used by direct or close contact with patients and may play as a medium for virus spread. Non-contact tonometer may also cause aerosol during the measurement and may also facilitate virus spread by aerosol transmission. Previous experiences on 2019-nCOV infection control, it has been accepted that 2019-nCoV is sensitive to ultraviolet irradiation and heating. Ophthalmic instruments after each use should be sterilized by heating at 56°C for 30 minutes and by lipid solvents including 75% ethanol, chlorine-containing disinfectant, peroxyacetic acid, hydrogen peroxide or chloroform, but not chlorhexidine.

Schedule: If ophthalmic staff phones on the patients, it should be rescheduled for the examinations of the patients with nonurgent ophthalmic complaints. They should warn patients to stay at home. If these patients have also a respiratory illness or fever or a return story from a high-risk area within the recent 14 days, they should be directed to the infection control section in a pandemic hospital.

Contact lens wearers: As a contact lens wearer touches own eyes more frequently than an individual without a contact lens. Substitution of the contact lenses with the glasses can reduce ocular irritation and prevent the person from touching the eyes. Additionally, wearing glasses may add a layer of protection. However, wearing glasses causes them to touch it for repositioning. All the contact lens users should be warned about this subject.

Ophthalmic consultation: All ophthalmic consultations in patients with confirmed COVID-19 should be completed within the quarantine ward to avoid cross-infection. Disposable caps and gloves, N95 respirator, goggles, face-shields, and protective gowns should always be worn.

Specimen sampling: Droplet, contact, and airborne precautions should be applied during all specimen collection procedures, and especially sputum induction should be avoided. WHO recommends using only synthetic fiber swabs with plastic shafts instead of calcium alginate swabs or swabs with wooden shafts which may contain substances that inactivate some viruses and inhibit the PCR test in specimen sampling procedures. Additionally, in tears and conjunctival scrapings sampling procedures, topical anesthesia is not recommended as an anesthetic agent may affect negatively the viral viability and may cause to take a negative result. The volume of tears collected in the sampling procedure may also affect the positivity of the RT-PCR test. On the other hand, the antimicrobial agents in tears including lactoferrin (via inhibiting ACE-2, by preventing the attachment of the virus to heparan sulfate proteoglycans) and secretory IgA (via killing virus) may cause to eliminate the virus on the ocular surface.

Ophthalmic surgery: Regional and local anesthesia are strictly recommended instead of general anesthesia to avoid aerosol transmission during tracheal intubation in ophthalmic operations. Surgeon and patient should also wear N95 respirators during ophthalmic surgeries under local anesthesia. Nonurgent or elective ocular surgeries ophthalmic procedures such as cataract operations, oculoplastic surgeries, extraocular muscle surgeries, intravitreal injections, ophthalmic laser procedures should be postponed as possible, particularly in elderly patients and those with comorbidities. However, if direct ophthalmoscopy, lacrimal irrigation/probing, intraocular pressure measurement, ophthalmic laser therapy or surgery in COVID-19 patients is mandatory, N95 respirator, gloves, goggles or face shield are strictly recommended. Because these are high-risk ophthalmic procedures.

Surgical rooms: Complete sterilization using a chlorine-containing disinfectant, peroxyacetic acid, and hydrogen peroxide is mandatory for ophthalmology clinics and operating rooms.

Ophthalmic emergencies: When ophthalmic emergency surgeries such as acute angle-closure glaucoma and severe ocular injury are performed in patients with confirmed or suspect COVID-19, proper personal protective equipment similar to those for ophthalmic consultation should be strictly used.

Outdoor clothes: When the ophthalmologist reached to the home, he/she should not forget that there is a possibility of carrying the virus. Additionally, outdoor clothes should be removed quickly, put in an isolated environment and quickly showered without getting close contact with the household people within social distance.

Fever: The doctor should measure own temperature at least 2 times a day. In case of a fever, a diagnostic PCR test should be performed immediately.

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Conclusion

In conclusion, (1) the patients with COVID-19 conjunctivitis may carry the virus in their tears; (2) conjunctivitis may be the first presenting symptom of COVID-19; (3) asymptomatic COVID-19 patients or the patients in incubation period can transmit the disease; (4) ophthalmologists may play important roles in both the transmission and prevention of the disease and (5) they have some responsibilities in the combating with COVID-19 and the notification and warning the patients about patient-related subjects.

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Conflicts of interest

The author declares that there is no conflict of interest regarding the publication of this paper.

Authorship contributions

The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, takes responsibility for the integrity of the work as a whole, and has given final approval to the version to be published.

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