



A Review on Novel Corona Virus SARS-CoV-2 and its Ocular Manifestations

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Abstract

A novel coronavirus (nCoV) pandemic named as coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) emerged from Wuhan, Hubei, China in December 2019, spread in almost all continents, countries, territories across the world and became a threat to human population. Some reports of ocular infections along with respiratory infection in the patients of COVID-19 were also reported during this pandemic. The ocular manifestation of this virus has not completely been established yet; hence more research is needed to confirm the association of SARS-CoV-2 with ocular infections. However few reports have already been published about the association of corona virus infections in various animals. Clinical symptoms such as conjunctivitis, retinitis, and anterior uveitis are documented in feline and murine models, which on diagnosis were proved due to the corona virus infections. In this review article, some evidences of the association of SARS-CoV-2 with ophthalmic infections in the current pandemic and some published reports of corona virus infections in some animals has been briefly highlighted. Simultaneously we have tried to explain briefly about some research ideas that may establish the ocular association of this virus. We have also tried to suggest some new visitor's policies in ophthalmic settings and some preventive measures those can be obeyed by an Ophthalmologist and other associated staffs during consultation to prevent themselves and to break spread of infections. We hope that, this article will inspire some researchers and Ophthalmologists to establish the exact pathophysiology behind the SARS-CoV-2 infections in ocular system.

Keywords: COVID-19; SARS-CoV-2; Ocular Manifestation of SARS-CoV-2; Review on novel Corona Virus SARS-CoV-2; Pathophysiology

Abbreviations: PHEIC: Public Health Emergency Of International Concern; WHO: World Health Organization; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; PPE: Personal Protective Equipment; AAO: American Academy of Ophthalmology; RAS: Renin Angiotensin System; ACE2: Angiotensin Converting Enzyme-2; FIPV : Feline Infectious Peritonitis Virus.

Introduction

The recent outbreak of novel corona virus SARS-CoV-2

has become a pandemic threat to human population across the world, hence declared as a public health emergency of international concern (PHEIC) by World Health Organization (WHO) on 30th January 2020 [1]. There are more than 200 strains of corona viruses known earlier; this SARS-CoV-2 belongs to the beta coronavirus family [2,3]. These viruses always exist in nature and sometimes infect free living animals, birds and also humans and the infection is usually mild. As the immunity power of human is less compared to free living animals and birds, whenever these viruses enters in the human system from the animals or birds, they create threat and the infection may become pandemic. As per the past published

reports, new coronaviruses emerge periodically and infects humans, due to its high prevalence, wide distribution, large genetic diversity and frequent recombination of their genomes and simultaneously the increase of human-animal interface activities [4,5]. This situation is not new to us and two major epidemics had emerged in the past two decades from two different beta-coronaviruses; severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) which had resulted >10,000 cumulative cases, with fatality rates of 10% for SARS-CoV and 37% for MERS-CoV [5-7]. This time the particular strain “SARS-CoV-2” has entered in to the human population through bats and made a pandemic COVID-19, more severe than earlier [8].

Corona viruses and the Evidence for Ocular Manifestations

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 most recent SARS-CoV-2 [9,10]. It is well known that, CoVs cause respiratory tract infections with several clinical symptoms such as; runny nose, sore throat, fever, cough and breathing problem. However if a person is immunocompromised or has underlying any kind of cardiopulmonary disease, than it can results in pneumonia or bronchitis and severity will be much more [10]. If the infections are not detected and treated early can lead to life-threatening respiratory failure and even death [11].

Apart from respiratory tract infections the presence of coronaviruses were also reported in tears and gastrointestinal tract [12,13]. On the 22nd of January 2020, Guangfa Wang an expert on pneumonia during an inspection to Wuhan, the epicenter of the outbreak, had developed conjunctivitis with the symptoms of redness in the eyes, several days before the onset of pneumonia. He wore an N95 mask but did not wear anything during his visit to Wuhan to protect his eyes. He was subsequently tested positive for the SARS-CoV-2 due to unprotected exposure of the eyes but recovered from the infection eventually [14]. This suggests that, respiratory viruses such as nCoV are capable of inducing ocular infections such as conjunctivitis or uveitis if not protected, which later leads to respiratory infection and may become fatal. In another incident; the death of the Chinese 33 years Ophthalmologist Li Wenliang in Wuhan during the current epidemic also cannot be ignored. He was the whistle-blowers who had first warned about the outbreak of a novel virus and sent a message to a group of fellow doctors warning them about a possible outbreak of an illness that resembled severe acute respiratory syndrome (SARS) on 30th December 2019.

As an ophthalmologist, he might have ocular exposure while consulting a patient with acute angle-closure glaucoma, manifested disease symptoms on January 10, 2020, which later converted to severe acute respiratory problem and died [15]. He is the first ophthalmologist who will be remembered for first case of a patient-to-ophthalmologist transmission of the SARS-CoV-2.

In a case study in 2004 at Singapore, among 36 patients who were suspected of having SARS virus infection over a period of 12 days, 3 were found to be positive for SARS-CoV with PCR from their tear samples. SARS-CoV binds to its receptors expressed on the outer membrane of epithelial cells at mucous membrane of mouth and nose, and severity occurs when the lungs gets infected [16]. Then the virus is internalized by endocytosis, replicates within the cell and finally comes out by breaking the cell membrane of host cell to further infect other nearby cells. A new strain of corona virus “HCoV-NL63” was identified to cause ocular infections towards the end of 2004. This virus was isolated from a 7-month-old child with the symptoms of bronchiolitis and conjunctivitis before being identified in seven additional individuals [17]. In a retrospective study conducted in 2005 over children with respiratory tract infections, 17% of were also suffering from conjunctivitis which proves its association with ocular tissues [18]. When these positive patients were further investigated, presence of “HCoV-NL63” was reported from these samples, whose association with ocular tissue was earlier reported. Some reports have highlighted the ocular association of SARS-CoV-2, with ocular samples, which gives an urgent call for research that “ocular tissue may be an entry point for these viruses in to human body” like nasal and oral route [18]. All these studies suggest that, corona virus may attack the ophthalmic epithelial cells, but it is not established yet and measures should be taken to prevent the spread of the infections through tears or ocular secretions.

Corona viruses are known to infect a wide range of birds and mammals, which includes household animals such as the cat (feline) and dog (canine) to large animals such as elephant and whales [19-21]. Clinical symptoms such as conjunctivitis, retinitis, anterior uveitis, and optic neuritis have been documented in feline and murine animals [19,20]. In a study conducted in feline infectious peritonitis virus (FIPV) infected cats and their offspring, it was observed that, ~90% of the conjunctival swabs collected from infected cats were positive for feline CoV (FCoV) which suggest that ocular secretions were potentially infectious [21,22]. It was also observed that, when the healthy cats were kept with infectious cats for 100 days they developed several ocular manifestations such as; conjunctivitis, pyogranulomatous anterior uveitis, choroiditis with retinal detachment and retinal vasculitis [21,22].

Future Prospect of the Concept of Association of SARS-Cov-2 with Ocular Infections

As reported earlier that, angiotensin-converting-enzyme-2 (ACE2) is the active receptor binding motif of host cells membrane for the attachment of SARS-CoV-2, in lung tissue, hence any tissues that express ACE2 enzyme receptors on their outer cell membrane are targets and entry points for these viruses [23,24] The gene for this ACE2 enzyme is present in epithelial cells of all organs of our body but, the expression of ACE2 enzyme related to all organs is not established yet. It has been established in the epithelial cells of oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain, with high expression noticed in the epithelial cells of lungs and enterocytes of the small intestine [23,25]. These ACE2 receptor binding motifs are seen in aqueous humor of eyes [25]. Expression of ACE2 protein in the epithelial cells of external ophthalmic parts like cornea, conjunctiva is yet to be established to confirm the association of this deadly corona virus with ophthalmic tissues.

The renin-angiotensin system (RAS), apart from its well-known endocrine role in blood pressure regulation, also has complicated autocrine functions within specific tissues. Human eye has its own intraocular RAS, however is yet to be established if there is any association of RAS with SARS-CoV-2 ocular infections. Ocular manifestations of SARS-CoV-2 in domestic animals like cats and dogs has already established, but more research be needed for establishing the association in humans [26,27].

Policies for Managing COVID-19 Pandemic in an Eye Hospital

In an ophthalmic hospital, Ophthalmologists are the first health care providers to evaluate whether patients are potentially infected or not with SARS-CoV-2. As slit-lamp examination is the most important and unavoidable part of ophthalmic evaluation and treatment procedures that is within the range of aerosol transmission, so preventive measures must be followed by an ophthalmologist and related hospital staffs to avoid the chance of infection. In comparison to other consultations, ophthalmic consultations involves multiple investigations, hence the patients usually stay for a long time inside the hospital campus that increases the risk of cross-infection to other patients as well as to health care workers. As per the ratio of current positivity among symptomatic and asymptomatic patients, asymptomatic patients are more dangerous than symptomatic patients with subclinical infections as they are the active spreaders of the society. American Academy of Ophthalmology (AAO)

has issued guideline to wear masks for mouth, nose, and eyes for the ophthalmologists while consulting patients with conjunctivitis with any symptoms of COVID-19 or having history of international/interstate travel in near past [28].

To prevent transmission inside an eye hospital at Hong Kong a three-level hierarchy of control measures such as; administrative, environmental, and use of personal protective equipment (PPE) has been adopted [29]. Patient attendance was lowered and elective clinical services were suspended at administrative level [30]. In a symptomatic patient, as fever is the initial symptom of COVID-19 infections, all patients and their attendants were screened with infrared thermometers. Those who had symptoms of fever were consulted at administrative level to find, if there was any emergency or not. If there was no emergency at that time, further consultation with ophthalmologist was suspended and next appointment was rescheduled after at least 7 days. If the patient has developed fever and having some respiratory complications then they were referred to the COVID hospital. If the patient has really emergency, then they are further screened through a set of questionnaire such as: travel history to affected areas in near past, occupation, if any contact of suspected or confirmed cases etc. and referred to the respective OPD [23]. It is also mandatory for all the clinical staffs to measure their body temperature and report if any COVID related symptoms such as cough, problem in breathing, chest pain or travel to affected areas is there or not [30].

To control the hospital environment from viral transmission, air ventilation in patient waiting areas was sterilized by putting up HEPA units and to lower the risk of aerosol/ droplet transmission, a protective shield was installed on slit-lamps [30]. All the hospital equipment such as slit-lamps, retinoscopes, ophthalmoscopes, computers, sample processing area, finger printing machine and all doorknobs that were frequently touched by the staff were disinfected as per the hospital disinfection guidelines [30]. All clinical as well as non-clinical staffs are instructed to use N95 face masks and to practice hand hygiene as per the WHO protocol during the stay in hospital campus. All clinical staffs were suggested to wear full PPE including isolation gowns, gloves, caps, eye protection glasses, and N95 masks during the patient consultation [30].

Some Mandatory Measures Suggested in an Ophthalmology Setting

- a) Patients with one attendant (only in case of emergency) should be strictly allowed to the hospital campus. They must be screened by infrared thermometer and questionnaire such as: history of travel to red or orange zone or during quarantine period, occupation, if any

contact of suspected or confirmed cases in near past at the point of entry to the hospital campus.

- b) All patients and attendees must be instructed strictly to use masks before entering the hospital campus and their hand should be sanitized before entering and leaving a patient room. They must be instructed to maintain at least 1 meter distance among them inside the OPD and all other places within campus. Tissue paper should be provided to each patient, so that if he/ she will sneeze or cough during consultation will use that and through in dustbin before leaving the room.
- c) Patients who tested positive with infra-red thermometer and without any emergency must be referred to the COVID hospital immediately. Patients who will be tested negative should be allowed to enter the campus from entry point for further consultation with administrative staffs.
- d) Administrative staffs should consult the patient with some more questions to know the past history, symptoms and severity of infections. They may reschedule the consultation as per the answers to his queries.
- e) Patients with conjunctivitis, with or without any COVID-19 symptoms, should be seen by the ophthalmologists and other related staffs with personal protective equipment in an isolated designated examination room.
- f) Air ventilation unit with HEPA filter in patient waiting areas should be there. All the hospital equipments such as slit-lamps, retinoscopes, ophthalmoscopes, computers, sample processing area, finger printing machine and all doorknobs that were frequently touched by the staff should be disinfected at least twice as per the hospital disinfection.
- g) Slit lamp examination should be performed by an ophthalmologists or optometrist keeping distance as far as possible with minimum interaction with the patient.

Conclusion

COVID-19 has become a recent pandemic that made a significant impact worldwide in daily routine, health of individuals and economy of a country. As of now although excellent tools such as; rapid diagnostic kits, immunological assays, and rRT-PCR are used in the diagnosis of symptomatic patients in well-equipped laboratories, a difficulty exists in screening asymptomatic persons, individuals in the window period who later develops symptoms and accurate determination of live viral particles in the body of a quarantine person to end isolation and allow him to maintain his daily routine. This pandemic can be controlled with the timely interference of the Government to break the community transmission by reducing the number of susceptible persons in the population by quarantine or to reduce the active cases by immediate treatment. Ocular complications due to SARS-CoV-2 during this pandemic

has been reported. Infection due SARS virus in the eyes of some animals has already been established and there are evidences of the presence of SARS virus in tears of patients having symptoms of SARS infections. Hence more research is needed to confirm the association of this deadly virus SARS-CoV-2 with ocular system, which will have a major impact in the field of ophthalmology in terms of managing a patient in an ophthalmic care setting. As unprotected eyes always increases the risk of SARS-CoV-2 transmission, it should be mandatory for the Ophthalmologists and health-care workers to wear safety goggles along with gloves and masks while consulting a patient to prevent themselves and to break the community transmission of the virus.

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