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REVIEW

The eye: ''An organ that must not be forgotten in coronavirus disease 2019 (COVID-2019) pandemic''

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Abstract The coronavirus family is a group of zoonotic viruses with some recognized reservoirs particularly some bats. A novel coronavirus emerged in the province of Wuhan (China) in December of 2019.The number of infected patient with serious respiratory infection quickly spread around the world to become a global pandemic. The clinical presentation and viral pathogenesis of the coronavirus disease named COVID-19 indicated that the virus is transmitted from person to person through infected droplets entering the respiratory mucosa. Close contact with infected individuals particularly in crowded environments has characterized the rapid spread of the infection.

Clinical manifestations of the viral infection have mentioned the presence of some ocular findings such as conjunctival congestion, conjunctivitis and even corneal injury associated with the classical COVID-19 infection. Some animal models of different coronaviruses eye infections have described the viral pathogenesis through tear and conjunctival sampling. On the other hand, we are recommended protective measure to prevent contagion and limit the spread of the virus in health care professionals and contact lenses wearers.

Introduction

Multiple outbreaks in humans and animals have occurred in the last centuries. Many of them due to unrecognized viruses who had the ability to produce emerging or reemerging diseases affecting large populations worldwide.[1]

Many of these zoonotic viral infections have been caused by the dynamic interactions of humans with multiple ecosystems, flora and fauna. The close contact between humans and wild life, the globalization of the economies and the facilities of international travel have contributed to the spread of new viruses around the world.[1]

Multiple preventive strategies have been recommended for regional outbreaks of zika, dengue, and chikungunya infections.[2] In Colombia these infections continue to pun-

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ish children and other vulnerable populations. We are now facing a new pathogen that is not in the group the of arborvirus: a novel coronavirus, a microorganism easily transmitted from person to person leading to a world pandemic as declared by the World Health Organization (WHO): the COVID-19 Pandemic.[3]

SARS-CoV-2 overview

In late December 2019 a number of individuals presenting serious respiratory disease were reported by the health authorities of the province of Wuhan (China). Clinical specimens collected from the patients with the pneumonia and like illness resembling the clinical syndrome respiratory allowed the isolation of a novel Coronavirus (CoV).[4]

Chinese investigators published the genomic characteristics of the novel virus obtained from patients affected with the clinical picture identifying a different novel virus from the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) coronaviruses of 2003 and 2012 respectively. The virus was initially named novel coronavirus 2019 (2019-nCoV).[3]

The route of contagion was speculated as bats from a wet market in the city of Wuhan.[5] Further, phylogenetic analysis compared with sequencings of the pangolins virus and infected bats showed an intermediary animal host. There was similarity of 91% in pangolin and 90.5 in infected bats. Homology of the genomic sequences of pangolin and 2019-nCoV were highly conserved in the protein S amino acid sequences, suggesting the pangolin as the possible intermediary host. The common trafficking of jungle animals in China, such as the pangolin, gave some credibility to this analysis.[6]

The virus was subsequently classified as SARS-CoV-2 by the International Committee on taxonomic of viruses (ICTV) and the WHO named the official coronavirus disease 2019 (COVID-19)[7,8] SARS-CoV-2 has now being reported in all continents and 192 countries, reaching an incredible 4 million infected individuals, close to 70.000 deaths and 260.000 recoveries.[9]

Who is SARS-CoV-2?

The coronavirus family and the Coronavirinae subfamily contains 4 genera: alpha, gamma, delta and beta coronavirus that includes the SARS-CoV, MERS-CoV, MHV (mouse hepatitis virus) and the novel SARS-CoV-2 which in turn presents 2 types L (7% more frequent) and type S (30% more frequent).[10]

SARS-CoV-2 is a positive sense RNA virus with a genome of 27 o 32 kb (being the largest of the RNA viruses) with a diameter of 125 nm. It has an enveloped core associated with a crown form from which it gained its name.[11] The virus contains in its genome a 5′ cap structure with a 3′ poly (A) tail, allowing it to act as a viral mRNA (messenger RNA), serving as a template for replication of new viral particles. A region encoding a polyprotein (pp) pp1a is found at 5′ followed by pp1b, for the encode of nonstructural proteins (NSP) involved in virus replication and a region that encodes the structural proteins as the Spike protein (S), the envelope (E), nucleocapsid (N) and membrane (M) in the 3′ region.[12]

Viral cycle

Viral entry into the host cells requires the interaction of Protein S (spike) with specific receptors on the respiratory cell. Several receptor have been identified: aminopeptidase N, (APN), dipeptydyltranferase 4 (DPP4) and the angiotensin converting enzyme receptor (ACE2) being the ACE2 the main receptor.[4,13] Some cellular peptydases mediate protein S cleavage as a cellular transmembrane like serine protease 2 (TMPRSS2) and furin (necessary for cleavage site to membrane fusion and virus.[14,15] Once the virus is recognized, it enters by endocytic pathway, undergoes encapsidation process that results in the release of the genetic material that starts the proteins translation involved in the viral replication and structural proteins generation processes and subsequently package the encapsidated genome into viral particles that are finally transported by vesicles to the cell membrane and released by exocytosis.[16,17]

Cellular tropism

In a study they showed that SARS-CoV-2 infected pneumocytes and enterocytes and non-infective in cells such as macrophages, bronchial epithelial and endothelial cells.[18] However, other studies support that SARS-CoV can replicate efficiently in lung epithelial cells, endothelial cells that also express ACE2 receptor, explaining to a certain extent the pulmonary pathogenesis related to SARS-CoV-2.[19]

Tissue samples of SARS COV have shown infection in the lung and alveolar cells primarily, but it is also apparent that cells that express the ACE 2 receptor can also replicate the virus such as the conjunctival epithelium.[20] A study was recently published, they found that VeroE6 cell line expressed TMPRSS2 and inoculated with samples from patients infected with SARS-CoV-2 were highly susceptible to infection, demonstrating that expressing TMPRSS2 has an important role not only in understanding cell tropism, an also in the pathogenesis and therapeutic treatment against the virus.[14] Furthermore, RNA viral has been detected in the fecal samples of COVID-19 patients[21]; this may be due to the fact that the virus travels from the lungs to the blood and afterwards infects the gastrointestinal system, an aspect that is associated with other studies with SARS-CoV.

On the other hand, Coronaviruses can infect a variety of animals and various genera of coronaviruses can cause human disease ranging from the common cold (HCoV229E, NL63, OC43, HKU1 to the known epidemic strain SARS and MERS).[17]

Clinical manifestations

Typical manifestation of COVID-19 infection are fever >38 °C (83%), sore throat, non-productive cough (76%), myalgia's shortness of breath (31%), skin rashes, anosmia, ageusia, headaches and fatigue also lymphopenia and thrombocytopenia and abnormal liver function studies.[3,22,23] A very high number of the pathophysiological problems of the infection are associated with a significant immune response provoked by the virus.[24] On the other hand, efficient replication (high viral titers) has been documented into of the possible pathophysiological processes of COVID-19, accompanied

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by a reduced response of interferon type I (IFN), leukocyte infiltration and exacerbated release of inflammatory cytokines called ''cytokine storm'', that induces apoptosis of alveolar, endothelial and epithelial cells, pneumocytes, causing increased vascular permeability, coagulopathy, multiple organ failure and death.[25]

Similarly, other extra-respiratory manifestations such as neurological damage should be evaluated. Among the risk factors smoke could be an important factor in COVID-19, vulnerability to respiratory infection and it may be decisive for the developmental of neural injury. Even studies support that smoking can promote the entry of the virus through the signaling of the nicotinic acetylcholine receptor (nAChR), receptors that are found in the lungs but also in the kidney, circulation and brain, in nerve cells that express ACE2[26,27] so, it would be important to consider brain damage within the manifestations. Furthermore, a small percentage of people infected with SARS-CoV-2 manifest conjunctivitis, which could indicate ocular manifestations with this novel virus.[20]

Eye manifestations in COVIDs-19 disease

Preclinical and animal models

Coronaviruses can induce infectious symptoms in mammals and birds, different than those in humans. Several studies suggest ocular tropism in respiratory disease In murine coronavirus infection conjunctivitis, with visual alteration, was associated with retinal vasculitis and subsequent retinopathy likely all related with higher expression of tumor necrosis factor alpha (TNF-α) and declined production of Nitric Oxide (NO).[28,29] It has been postulated that the virus has the ability to infect cells of the retinal pigment epithelium, ciliary body, Muller cells[30,31] inducing apoptosis thus contributing to retinal degeneration.[32] The rat sialo dacryoadenitis virus (SDAV) infects acinar and epithelial cells of the lacrimal gland with high viral load causing degenerative and atrophic alterations in the gland.[33]

A feline coronavirus (FCoV) infects domestic and wild cats; however, there has been no evidence of human transmission. A study described the presence of viral antigens on the conjunctiva surface, as well as detection in conjunctival swabs suggesting that ocular secretions are potentially infectious.[34] Ocular complications have been described in FCoV infection such as retinal vasculitis, anterior uveitis and chorioretinitis.[30]

The AC2 receptor is present in ocular tissues and expression in retina is seen in some animal models (rats, chicken).[35,36] In primary retinal culture angiotensin 2 and it receptor were detected in Muller cells and ganglion cells.[36] In pigs ACE 2 activity was found in retinal, ciliary and vitreous tissues suggesting its role in modulate ocular circulation and pressures.[37] Previous research had found ACE2 in aqueous humor as well as other components of the renin-angiotensin system appear to have some role in the control of the intraocular pressure.[38]

CoV in human

he ocular findings of coronavirus infection in humans are not clear. Human coronavirus infection was first reported in the Netherlands (HCoV-NL63) as a cause of respiratory infection.[39] In subsequent studies of coronavirus infections, the clinical manifestation of eye involvement was conjunctivitis in 17% of the cases, presenting primarily in children.[40]

In cases of human coronavirus infection SARS, HCOV-NL63 and SARS-CoV-2 in adults involvement of the anterior segment of the eye, such as conjunctivitis, they have been postulated an infection route in the conjunctiva with the virus migrating in the lacrimal fluid through the duct inferior meatus until the respiratory epithelium to start its replication.[41,42] It is noteworthy that the ocular mucosa and the respiratory epithelium share many characteristics such as the receptor alpha2−3 linked to sialic acid, it found in the tract lower respiratory and ocular tissue mainly in epithelial cells of the conjunctiva, could be related to the tropism of many viruses such as Influenza virus.[43]

During the SARS epidemic infected patients reported cases of conjunctivitis where viral RNA was detected from tears 2 of 32 patients.[44] It should have related with some studies showed that main receptor for the entry of the virus into cells is ACE2 located in the alveolar, pulmonary and conjunctival epithelium. Hence, the location of this receptor contributes to severe respiratory disease and conjunctival mucosa.[45]

The appearance of ocular manifestations in COVID-19 disease has been conjunctivitis even though in low percentages. In mild January 2020 a pulmonologist visiting Wuhan developed conjunctivitis and later tested positive for COVID-19. Later a Chinese ophthalmologist develop conjunctivitis during routine care of reportedly healthy patients, bringing again the question of as the eye being a possible source of contagion.[20] Tears have a wide variety of antimicrobial peptides and immunoglobulin however, several viruses have been detected in this fluid.[46,47]

In a recent publication of 1099 patients with SARS-CoV-2 from Wuhan 9 showed a positive test for the virus in conjunctival samples.[22] A second cohort of 21 patients, 1 patient with conjunctivitis had a positive test reverse transcription polymerase chain reaction (RT-PCR) assay from the conjunctival samples.[48] It will be possible to collect tears for testing with a micro-capillary tube or perhaps with a Schirmer strip to obtain a larger volume of fluid.[49]

A Singapore study of 17 COVID-19 patients with positive tests of nasopharyngeal swabs had the tears tested with a Shirmer strip with negative results suggesting that transmission of the virus is low through of tears regardless of the stage of infection.[49] In another report of 38 severe cases of COVD 19, twelve (31%) had ocular manifestations such as conjunctival hyperemia, chemosis and tearing) and 16.7% had positive conjunctival swabs.[50] Another recent case reports a 29 year old female presenting hyperemia photophobia ocular discomfort and watery discharge without any other classical symptoms of COVID-19 disease. A known epidemiological link was diagnosed as a keratoconjunctivitis in the form of pseudo dendrites and epithelial infiltrates in one eye. She tested positive in a nasopharyngeal swab and weakly positive in the conjunctival swab.[51] Chinese studies of 534 COVID cases reported ophthalmic findings in 4.68% of conjunctival congestion and 11.8% of foreign body sensation added to the classical disease. Respectively, and 67% had a positive nasopharyngeal swab.[52] In another case report of

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a patient with COVID-19 and acute bilateral follicular conjunctivitis 13 days post onset of the original symptoms, his conjunctival sample was positive by PCR.[53] A specific consideration of the conjunctiva and tear being a source of contagion was again raised.

Contact lenses and SARS-CoV-2

The some authors mentioned have raised the possibility of transmission of the virus through the tears and the conjunctiva. To date no infection has been reported in contact lenses wearers and its use carries a particular risk of COVID-19 infection. However, is necessary to emphasize the recommendations in the use of contact lenses promoted by the different societies: change the maintenance solution frequently, maintain the cleaning conditions, hand washing before and after manipulation of the lenses and suspension of its use in case of any flu symptoms.[54,55] The Spanish Association of Ophthalmology recommends that the adaptation of any type of lenses should be postponed until resolution of the symptoms.[56]

There no evidence those multipurpose disinfectants solutions are effective in clearing the SARS-CoV-2 from the ocular surface. Antimicrobial solutions with antibacterial and antiviral efficacy are used for disinfection of contaminated fomites or other surfaces that may have been contaminated with viral particles. For instance, several studies demonstrate that solutions can give protection against viral DNA as herpes simplex virus.[57] Furthermore, the most of multipurpose disinfecting solutions for contact lenses containing chlorhexidine digluconate, benzalkonium chloride, aminopropylbiguanide etc, which has been reported as antimicrobial, included viruses.[58,59] It has demonstrated that different forms of inactivating viral particles have been showed by the use of disinfectants including hydrogen peroxide, an usual cleaner.[60,61] That molecule has efficacy in the inactivation of the virus such as influenza, adenoviruses (serotype 3 and 6) and respiratory syncytial virus,[62] therefore, it is probable that, from the properties of ethyl alcohol and isoprolipilic of many of these disinfectants, can inactive naked virus as well as wrapped ones like SARS-CoV-2.

Several studies demonstrate that the porcine transmissible gastroenteritis virus (TGEV), with similar structure to SARS-CoV and Avian Influenza Virus, when they are exposed with hydrogen peroxide vapor, decreased the number of viral particles.[63] In another report, it demonstrates that disinfecting solutions as hydrogen peroxide decreased the viral particles of the porcine epidemic diarrhea virus.[64] The hydrogen peroxide, a coadjutant substance in contact lenses cleaning, it has been effectively performed in a rigid and soft contact lenses.[58] Hence, it is possible to think that in pandemic time, the interaction of disinfecting agent together with multipurpose solution and hand washing should minimize the infection risk in that population. Despite, until the date of writing of this manuscript, it did not have information contagion of the SARS-CoV-2 from contact lenses wearers. For that reason, it could be interesting to determinate if the virus adhere to contact lenses material and how much is the quantity of the viral particle detected, in order to generate strategies and protocols in the contact lenses wearers and visual health professionals.

Health care measures and prevention

The number of COVID-19 patients will continue to be present all over the world with areas going out of control until a preventive vaccine or a therapeutic treatment can convert the infection in endemic, similar to the influenza virus. Periodical measures to control the spread of the virus will continue for many months. In regard, some of the ophthalmologic care entities as the Chinese ophthalmologic society have intensified the measures of social distancing starting in the reception and clinical areas with protocols of frequent disinfection, hand washing, hand sanitizer, N95 masks and protection tools for the slit lamps and the ophthalmoscope retinoscope, foropter equipment.[65]

The Spanish Society of Ophthalmology, the American Academy of ophthalmology (AAG) and Optometry (AOA) suggests prevention measures, biosafety guidelines and the development of protocol to prevent the viral spread. One suggestion is the adoption of a triage before visual evaluation to decrease risks of exposure to SARS COV-2, and evaluation with only one companion when It is necessary. Another suggestion is the use of personal protective equipment (protective goggles, face shield gloves and N95 mask) by the health professional who will have contact with secretions[55,56,65]

Conclusions

The pandemic caused by the coronavirus SARS-CoV-2 has challenged the scientific world to find the means to control it. Large amounts of information about the agent have been collected related to the clinical infection. The immune response that ensues but we are still searching for better diagnostic tests therapeutics to control it and ultimately vaccines.

Several models of viral transmission regarding the ocular structures as possible transmission routes have been described. The findings described correlated with clinical findings have only begun to open a small understanding of the ocular manifestations of COVID-19 infection. If the virus can enter through the conjunctiva it will be necessary to advise precautions in contact lenses wearing and extend the precaution about eye touching. Future investigations will determine the role of the conjunctiva and lacrimal mucosa in the pathogenesis and transmission of the virus. We invite the scientific community to set up protocols for the evaluation and testing of the ocular samples as tear and conjunctiva of suspected infections information provided by the scientific associations of visual health care professional will continue to strengthen the preventive measures to minimize the risk contagion in professional and patients.

Authors' contributions

Sandra Carolina Duran Cristiano, performed of the writing, revised the manuscript Diana Carolina Mayorga.

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