

COVID-19: An Ophthalmologist's Perspective

COVID-19: A Perspetiva do Oftalmologista

João Paulo Cunha^{1,2}, Nuno Moura-Coelho^{3,4}, Rita Pinto Proença^{4,5}, Arnaldo Dias Santos^{3,4,6}, Joana Tavares Ferreira^{1,2,6}

Corresponding Author/Autor Correspondente:

João Paulo Cunha [joao.cunha@jmelloasaude.pt]
R. Fernão Lopes 60, 2750-663 Cobre, Cascais, Portugal
ORCID iD: 0000-0002-3162-0531

ABSTRACT

In just one hundred years, the world has been through five pandemics. Lessons of the past have not prevented a new virus from being responsible for a fifth wave of deaths worldwide, even with scientific advances and the rapid response of societies that, for the most part, anticipated the political and economic response. A century after the end of the Spanish Flu (1918/19), in December 2019, the world has watched the beginning of the second pandemic of the 21st century, coronavirus disease 2019 (COVID-19) caused by a new severe acute respiratory coronavirus syndrome-2 (SARS-CoV-2).

The eye can not only be the entry point for coronaviruses, but also a target organ. Conjunctivitis, uveitis, vasculitis, retinitis and optic neuritis have all been documented in animal models studies.

In this article, we review the possible roles of the visual system/ocular tissues as an entryway, and the potential ophthalmic manifestations of human SARS-CoV-2 infections. This review article will also highlight the most effective ways for protecting and preventing the spread of the virus.

KEYWORDS: COVID-19; Coronavirus Infections; Disease Outbreaks; Eye Diseases; Eye/virology; Ophthalmology; Pandemics; SARS-CoV-2

1. Ophthalmology, Hospital CUF Cascais, Cascais, Portugal. 2. Instituto Politécnico de Lisboa, Escola Superior de Tecnologia da Saúde de Lisboa, Lisbon, Portugal. 3. NOVA Medical School, Faculdade de Ciências Médicas - Universidade Nova de Lisboa, Lisbon, Portugal. 4. Ophthalmology, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal. 5. Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal. 6. Ophthalmology, Hospital CUF Descobertas, Lisbon, Portugal.

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RESUMO

Em apenas cem anos, o mundo registou 5 pandemias. As lições do passado não evitaram que um novo vírus fosse responsável pela quinta vaga de mortes a nível mundial, mesmo com os avanços científicos e a rapidez de resposta das sociedades que, na sua maioria, se anteciparam à resposta política e económica. Passado um século do final da Gripe Espanhola (1918-19), em dezembro 2019, regista-se o início da segunda pandemia do século XXI, a coronavirus disease 2019 (COVID-19) provocada por um novo coronavírus (CoV), severe acute respiratory syndrome coronavirus - 2 (SARS-CoV-2).

O olho poderá ser não só a porta de entrada dos CoV, como também um dos órgãos-alvo do mesmo. Conjuntivite, uveíte, vasculite, retinite e nevrite ótica foram documentadas em modelos animais.

Neste artigo, fazemos uma revisão dos possíveis papéis do sistema visual/tecidos oculares como porta de entrada, bem como das possíveis manifestações oftalmológicas da infeção humana por SARS-CoV-2. Este artigo de revisão também destacará as normas mais eficazes de proteção e evicção de propagação do referido vírus.

PALAVRAS-CHAVE: Coronavírus; Doenças dos Olhos; Infeção por Coronavírus; Oftalmologia; Olho/virology; Pandemia; Síndrome Respiratória Aguda Grave; Surtos de Doença

INTRODUCTION

HISTORICAL BACKGROUND: 100 YEARS OF PANDEMICS

The current COVID-19 pandemic is still far from being equated with other global public health crises. However, it worries both the authorities and scientific community, which have long tried to anticipate a new pandemic, and the population, which remains the key to flatten the pandemic's progression curve.

The H1N1 virus pandemic, widely known as Spanish flu, which began in 1918 and ended in 1919, killed more than 50 million Europeans, North Americans and Asians, taking many more lives than World War I.¹ Since then, 4 more deadly pandemics (1957, 1968, 2009 and 2019-20) have been recorded by the World Health Organization (WHO). Asian influenza, caused by an influenza A virus of the subtype H2N2, victimized about 2-4 million people in 1957-58, affecting mainly children of Southeast Asia. The Hong Kong flu (1968-69), caused by another influenza H3N2 virus, currently still in circulation, has a lower mortality rate (due to its genetic similarities to the Asian flu), with around 1 million deaths reported.² The H1N1 virus again emerged in 2009 as a combination of the swine, avian and human influenza viruses, originating in Mexico. It was responsible for what was initially called the swine flu pandemic and later type A flu. This pandemic made more victims in Argentina, Brazil and Mexico, with two hundred thousand deaths having been reported, and 62% to 85% of those being in people under 65 years.³

A century after the end of the Spanish flu, the second pandemic of the 21st century started in December 2019

in the city of Wuhan, China, due to a new coronavirus responsible for a severe acute respiratory syndrome (SARS). On the 30th of January of 2020, the WHO has declared this disease as the sixth public health emergency of international concern (PHEIC),⁴ following the 2009 H1N1 pandemic (2009), the 2014 polio outbreak in the Middle East (2014), the Ebola outbreak in West Africa (2014), the Zika outbreak in Brazil/South America (2016), and the 2019 Ebola outbreak in the Democratic Republic of Congo (2019).⁵

On the 11th of February of 2020, the WHO announced a new name for the epidemic disease caused by 2019-nCoV: coronavirus disease (COVID-19). Regarding the virus itself, the International Committee on Taxonomy of Viruses has renamed the previously provisionally named 2019-nCoV as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).⁶

One month later, on 11th March 2020, the WHO declared COVID-19 as the second pandemic of 21st century.⁷

This new pandemic has spread across the globe rapidly, affecting 2 108 897 people in the world as of the 16th of April 2020.⁸

METHODS

We searched the PubMed and Google Scholar databases to identify articles published up to 16th April 2020, using the following key terms: "COVID-19", "coronavirus", "pandemic". In addition, we manually searched the reference lists of most primary articles and reviewed articles.

CORONAVIRUS - VIROLOGY AND PROPOSED PATHOGENIC MECHANISMS

Coronaviruses (CoV) are enveloped, positive stranded RNA viruses that belong to the *Coronaviridae* family and the order Nidovirales.⁹ The CoV have been known to affect birds and mammals.¹⁰ Public opinion became aware of CoVs after the outbreak of the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003.¹¹ The SARS-CoV outbreak was responsible for more than 8000 infected patients and 774 deaths in 26 countries.¹²

In 2012, a new CoV variant was detected in Saudi Arabia which was responsible for the coronavirus-related Middle Eastern respiratory syndrome (MERS-CoV). MERS-CoV was isolated in the same year¹³ and has been responsible for more than 850 deaths.¹⁴ Of the 2223 confirmed cases in the MERS-CoV laboratory reported to the WHO, 415 were healthcare professionals, representing more than a third of all secondary transmission¹⁵ and a fifth of all cases. Both severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are caused by coronaviruses.

The entry of SARS-CoV in human host cells is mediated mainly by an angiotensin-converting enzyme 2 receptor (ACE2-R),¹⁶ which is expressed in the epithelium of human airways, in the lung parenchyma, vascular endothelium, kidney cells and intestinal cells.¹⁷ However, the presence of ACE2-R is neither enough nor necessary to make host cells susceptible to infection. For instance, in some scientific studies, endothelial cells that express ACE2 and human intestinal cell lines were not infected with SARS-CoV,¹⁸ while some cells with very low levels of ACE2 expression, such as hepatocytes¹⁹ or neuronal cells,²⁰ could also be infected with SARS-CoV.

The respiratory involvement of human CoV has been clearly established since the 1960s. Data reported in scientific literature has also demonstrated that, similar to other human viruses, CoV have naturally neuroinvasive and neurotropic capacities, with potential neuropathological consequences in genetically or otherwise susceptible individuals, with or without additional environmental insults. The presence of CoV in the human central nervous system (CNS) is now a recognized fact, either as a result of hematogenous or transneuronal spread.²¹

Increasing evidence shows that CoVs can first invade peripheral nerve endings and then gain access to the CNS. Trans-synaptic transfer has been well documented

for other CoVs, such as hepatitis E virus (HEV),^{22,23} and avian bronchitis virus.^{24,25}

It is known that interleukin 6 (IL-6) has neurotrophic and neuroprotective effects and can increase the permeability of the blood-brain barrier.²⁶ A high level of IL-6 leads to progressive neurological disorders with neurodegeneration and cognitive decline.²⁷ Although elevated serum levels of IL-6, interleukin 8 (IL-8) and monocyte chemoattractant protein 1 (MCP-1) in patients infected with SARS and MERS have been illustrated,²⁸⁻³⁰ there are studies in which there are no significant increases in the serum levels of these cytokines but they become significantly accumulated in the cerebrospinal fluid of patients with CoV infection.³¹

Moreover, Arbour *et al* showed that human CoV (HCoV) can infect human astrocytes and microglia in primary cultures and can acutely and persistently infect immortalized human glial cells.³²

Severely affected patients are more likely to develop neurological symptoms, including headache, disturbances in consciousness and paresthesia, than patients with mild or moderate disease.³³ Autopsy reports have revealed brain tissue edema and partial neuronal degeneration in deceased patients with COVID-19.³⁴ Another study has reported a case of viral encephalitis, caused by a new CoV with confirmation of the presence of SARS-CoV-2 in cerebrospinal fluid by genome sequencing.³⁵ In addition, an increasing number of patients with COVID-19 report a sudden loss of smell or taste. Therefore, anosmia and dysgeusia are likely to be seen in patients with COVID-19.^{36,37}

In addition to hematogenous dissemination, a second form of viral dissemination to the CNS is through the neuronal retrograde pathway.³⁸ After an intranasal infection, both HCoV-OC43³⁹ and SARS-CoV⁴⁰ have been shown to infect the respiratory tract in mice and to have neuroinvasive behavior.^{41,42} Interestingly, several viruses, including the neurotropic strains of murine coronavirus (MuCoV) and the mouse hepatitis virus (MHV) reach the CNS through the olfactory nerve.⁴³ However, Brann *et al* concluded that mouse and human olfactory sensory neurons do not express two key genes needed for SARS-CoV-2 entry, ACE2 and transmembrane serine protease 2 (TMPRSS2). On the other hand, olfactory support epithelial cells and stem cells express these two genes, as well as cells in the nasal respiratory epithelium. These findings suggest possible local mechanisms through which SARS-CoV-2 infection can lead to anosmia or other forms of olfactory dysfunction.⁴⁴

CORONAVIRUS AND THE EYE

Although COVID-19 is transmitted mainly by respiratory droplets and direct contact, a recent report has raised the question of whether ocular surfaces could be a potential site for SARS-CoV-2 invasion, in part, due also to virus hepatitis murine aerosols.⁴⁵

As previously mentioned, many studies have described the binding of SARS-CoV-2 to human ACE2-R, resulting in the invasion of host cells.^{46,47} In the eye, the ACE2-R is expressed mainly in the posterior tissues, namely in the retinal pigment epithelium. Whether ACE2 /ACE2-R expression and activity are present in the ocular surface cells of humans and rabbit models (including cornea and conjunctiva) remains controversial.⁴⁸

The polymerase chain reaction (PCR) technique in human tears has been widely used by ophthalmologists to diagnose eye infections, especially of the *herpesviridae* family, such as the herpes simplex virus types 1,⁴⁹⁻⁵¹ the Epstein-Barr virus⁵² or even adenovirus.⁵³ There is also evidence that some coronaviruses can occasionally cause conjunctivitis in humans. In fact, the human coronavirus NL63 (HCoV-NL63) was first identified in a baby with bronchiolitis and conjunctivitis.⁵⁴ Later, in a study of twenty-eight cases of children with confirmed HCoV-NL63 infection, 17% had conjunctivitis.⁵⁵

Guan *et al* reported nine cases of conjunctival congestion in 1099 studied cases of COVID-19 positive patients.⁵⁶ However, other ocular manifestations of COVID-19 are still unknown and can include as increased conjunctival secretion, epiphora and decreased vision. In a study by Chen *et al* of 534 patients with COVID-19, twenty-five (4.68%) had conjunctival congestion and in three patients this was the initial symptom. That same study also found that ocular dryness, foreign body sensation and blurred vision were the three main eye symptoms in these patients (20.9%, 11.8% and 13.9%), which may be due to the fact that these patients spend much time using electronic devices.⁵⁷

In another study with thirty patients, there was only one patient with conjunctivitis. Viral RNA was isolated in his tear fluid and conjunctival secretion twice. Its clinical signs were similar to a common viral conjunctivitis, with conjunctival congestion and watery discharge. The patient did not have severe fever or respiratory symptoms when his samples were collected. No viral RNA was detected in the tear fluid and conjunctival secretions of critically ill or common patients without conjunctivitis.⁵⁸ These findings have led to the speculation that the virus present in tears can reach the respiratory system through the nasolacrimal ducts.⁵⁹

It is known that the virus can trigger other pathological processes in the eye besides conjunctivitis and keratitis. In fact, the herpes simplex virus and the varicella zoster virus have been implicated in acute retinal necrosis^{60,61} and cytomegalovirus is capable of inducing retinitis in immunosuppressed individuals.⁶² Degenerative changes in the retina have also been observed in Creutzfeldt-Jakob disease and in subacute sclerosing panencephalitis due to rubella infection.⁶³ Also, it is common for a viral or flu-like illness to precede Multiple evanescent white dot syndrome (MEWDS), acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and acute macular neuroretinopathy, which led some to suspect of a viral etiology.^{64,65} In addition, the MuCoV and the MHV, induce an acute and chronic eye disease in BALB/c mice.^{66,67} In the early acute phase, 1 to 7 days after inoculation, mild retinal vasculitis is observed and in the second stage, on the 10th day and progressing for several months, retinal degeneration can be observed in the absence of vasculitis or inflammation. It is interesting that the development of the degenerative phase is controlled by a genetic predisposition of the host and it has been associated with the development of anti-retinal and anti-retinal pigment epithelium (RPE) autoantibodies.⁶⁸

Murine coronavirus infections can be modified or regulated by several factors including virus serotype, route of inoculation, genetic and age or stage of development of the host.⁶⁹ In fact, the host's genetic context can influence the type and intensity of the immune response, the presence of cell membrane surface molecules used for viral adsorption and penetration, and the intracellular composition of the cell that allows viral replication.

In the retina, the RPE cell is a potent regulatory cell and appears to play a critical immune role, probably presenting foreign proteins, retinal proteins and viral RNA present in the infected cells to helper T cells.⁷⁰⁻⁷³ Several studies indicate that MHV can cause acute and persistent infections in the central nervous system, such as acute necrotizing encephalitis followed by chronic CNS demyelinating disease.⁷⁴⁻⁷⁶

In fact, according to Bergmann *et al*, despite the T cell-mediated control of acute virus infection, host regulatory mechanisms, probably designed to protect the integrity of the CNS, contribute to the failure in eliminating the virus.⁷⁷

Moreover, hypoxia, ischemia and edema may also be implicated in retinal vasculitis as reported in patients infected with Rift Valley fever virus^{78,79} and West Nile virus.^{78,80-82}

If observed, retinal vasculitis in CoV Infected patients may be due to a cytokine storm associated with elevated IL-6, which can lead to edema and increased permeability of vascular walls as proposed in cases of myocarditis.⁸³ In Portugal there are already unpublished reports of retinal vasculitis and a VI cranial nerve palsy in patients that tested positive for SARS-CoV-2.

STANDARDS FOR PROTECTING AND PREVENTING THE SPREAD OF SARS-CoV-2

Ophthalmologists examine patients at close distances and inadvertent physical contact with patients' eyes is almost inevitable. This is a potential hazard to health-care workers given the close contact with the face, including the nose, mouth and the eyes of SARS patients. Therefore, particular care is advisable when examining any patient. There is a potential possibility of transmission to other patients with reusable eye equipment such as the Goldmann applanation tonometer, trial contact lenses, trial frames, and even reusable pinhole devices which come in close contact with the patient's eyes.^{84,85}

According to Lian *et al*, no virus particles were detected in the tears and conjunctival secretions in patients without conjunctivitis.⁸⁶ However, the low abundance of the virus in tear and conjunctival secretions does not eliminate the risk of transmission through conjunctival tissue. For the same reasons, the use of contact lenses should be discontinued until the COVID-19 emergency comes to an end.

Moreover, the most commonly used noncontact tonometer for ophthalmologic examination, the air puff tonometer, forces an air puff during the examination, which produces a large amount of aerosols in the local area. Aerosols may be concentrated in the local air for a long time, and general alcohol wipe disinfection is ineffective, causing widespread concern in the field of ophthalmology.⁸⁷ The noncontact tonometer, ultrasound biomicroscopy, corneal confocal microscope, and others do not theoretically cause cross-infection.⁸⁸⁻⁹¹

During an ophthalmological examination the use of adequate protections, including gloves, eye protection devices (eye shields), adequate protective masks (FFP2 and FFP3 or N95 and N99) and protective shields to be mounted on slit lamps is mandatory for community safety and to limit the risk of disease transmission between ophthalmologists and patients. Should the lack or incomplete availability of such devices be verified, ophthalmological practice ought to be suspended.^{92,93}

CONCLUSION

The eye can be not only the entry point for CoV, but also one of its target organs. Conjunctivitis, uveitis, vasculitis, retinitis, optic neuritis and other neuro-ophthalmological diseases will be probably reported in the future.

Knowing that especially the most serious forms of COVID-19 infection have neurological semiology, we believe that concurrent neuro-ophthalmological findings are likely underdiagnosed and undervalued because this disease is life-threatening. We also believe that, in the future, and particularly in survivors of intensive care, there will be reports of neurodegenerative and demyelinating eye pathologies linked to the previous infection with SARS-CoV-2.

ETHICAL DISCLOSURES

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