OPO OPHTHALMIC & PHYSIOLOGICAL OPTICS
THE JOURNAL OF THE COLLEGE OF OPTOMETRISTS

Ophthalmic and Physiological Optics ISSN 0275-5408

GUEST EDITORIAL

COVID-19 and the eye

Introduction

In early December 2019, a cluster of cases of pneumonia of unknown origin were identified in Wuhan, the capital city of Hubei province in China. The clinical features of the condition included fever, shortness of breath and pneumonic infiltrates in both lungs,[1] which were similar to those seen in the severe acute respiratory syndrome (SARS) epidemic that occurred in Asia in 2003 and the Middle Eastern Respiratory Syndrome (MERS) identified in the Arabian Peninsula in 2010. Nucleic acid sequencing of lower respiratory tract samples from infected patients identified the causative agent as a previously unidentified coronavirus[2] that has been termed SARS-CoV-2, to distinguish it from the virus causing the earlier SARS epidemic (SARS-CoV). The Wuhan outbreak was declared a Public Health Emergency of International Concern by the WHO on 30 January 2020 and a pandemic on 11th March. The WHO designated 'Corona Virus Disease 2019' (COVID-19) as the official name for this new disease. At the time of writing this editorial in May 2020, there have been approximately 5.5 million COVID-19 cases globally with over 344 000 COVID-19 attributed deaths,[3] although it is widely acknowledged that these figures considerably underestimate the true scale of the pandemic.

Given the rapidly expanding literature on COVID-19, it is timely to summarise what we have learned so far about the effects of COVID-19 on the eye and discuss the implications of the current pandemic for eye care practitioners. To identify the relevant source literature, we used a database of COVID-19 citations that are most relevant to ophthalmology, which has been developed by the Cochrane Eyes and Vision (CEV) US satellite. The database uses a machine learning classifier to screen thousands of biomedical citations indexed in PubMed to identify relevant reports. Records that had any matching eyes and vision terms were verified by an ophthalmologist. Given the short timeline since the start of the pandemic, some of the included studies are preliminary reports that are yet to be certified by peer review. The search was last updated on 30th April 2020.

Ocular manifestations of COVID-19

Although coronaviruses are well known pathogens of birds and mammals, only seven coronaviruses were known to infect humans (Human Coronavirusus (HCoV)).[4] Four of these (OC43, 229E, HKU1, NL63) cause approximately 15% of common colds and some cases of pneumonia, particularly in children and the elderly. By contrast, SARS-CoV, MERS-CoV and the novel SARS-CoV-2 can result in life-threatening respiratory failure. A recent review, which summarised ocular implications of known coronaviruses in humans and animals[5] concluded that, although a wide spectrum of ocular manifestations of coronaviruses has been documented in animals, the literature on ocular involvement in humans is sparse. However, a retrospective case series of 18 hospitalized children diagnosed with respiratory tract infections and testing positive for HCoV NL63, reported the presence of conjunctivitis as an associated feature in 17% of children.[6]

At this relatively early stage of the COVID-19 pandemic, it is difficult to draw definitive conclusions on the prevalence of ocular involvement. There have been isolated case reports to suggest that conjunctivitis or keratoconjunctivitis can be the first clinical manifestation of the disease.[7-9] However, estimates for the prevalence of conjunctivitis in established COVID-19 comes predominantly from early reports from hospitalised patients in China and Singapore (*Table 1*).[10-18] The majority of studies reported on samples of <100 and in some reports 'conjunctival congestion' was used as a proxy diagnostic indicator of viral conjunctivitis. Based on the currently available evidence, we conclude that conjunctivitis is a rare complication of COVID-19, with an estimated pooled prevalence of 4% or less depending on the meta-analytical model used (*Figure 1*).

All of the included patients had a clinical diagnosis COVID-19, with the majority testing positive for SARS-CoV-2 by serology or nasopharyngeal swabs. Testing of conjunctival swabs or tear samples was performed on the minority of the included patients (8.7%), which confirmed the presence of the virus in approximately 3% of samples (*Table 1*, *Figure 2*).

Although there is accumulating evidence that COVID-19 predisposes patients to thrombotic disease that involves both the arterial and venous circulations,[19] evidence for a causal relationship between SARS-CoV-2 and ischaemic stroke is equivocal due to competing vascular risk factors in most patients. The same would apply in the case of a putative increased risk of retinal vascular occlusions. With regard to other retinal findings, a recently published case series reported bilateral OCT abnormalities in 12 patients with confirmed COVID-19. These included hyper-reflective lesions at the level of ganglion cell and inner plexiform layers of the retina, particularly within the papillomacular bundle. In four of these patients cotton wool spots and

Table 1. Prevalence of conjunctivitis in COVID 19

Study	Location	Sample size	Cases of presumed conjunctivitis	Conjunctival swab/tears taken	Positive result
Chen 2020[10]	China	534	25	No	N/A
Guan 2020[11]	China	1099	9	No	N/A
Lan 2020[12]	China	81	0	Yes	0/3
Seah 2020[13]	Singapore	17	1	Yes	0/17
Wu 2020[14]	China	38	12	Yes	2/28
Xia 2020[15]	China	30	1	Yes	1/30
Ye 2020[16]	China	30	3	Yes	5/27
Zhang 2020[17]	China	72	2	Yes	l/2
Zhou 2020[18]	China	63	1	Yes	3/63

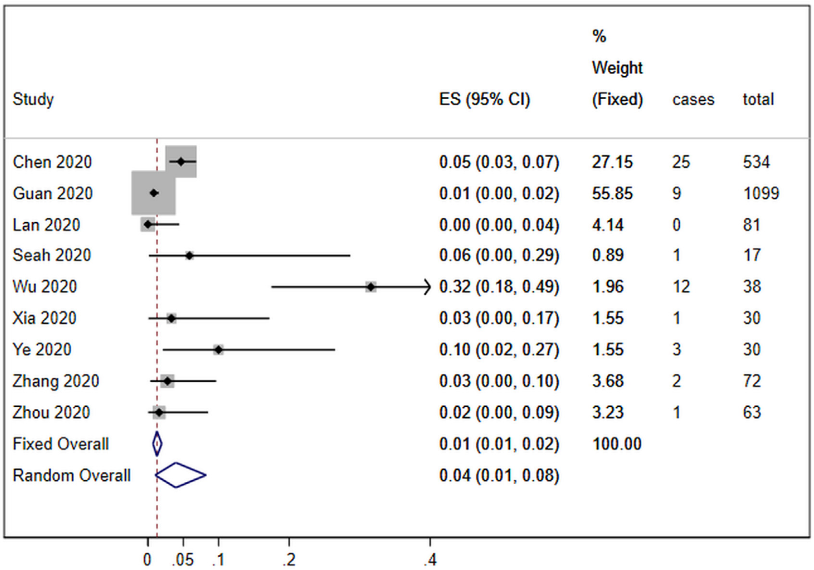

Figure 1. Forest plot of the prevalence of presumed conjunctivitis in hospitalised patients with COVID-19. The Freeman-Tukey Double Arcsine Transformation was used to stabilize the variances prior to pooling using fixed and random effects models.

microhaemorrhages were also observed on fundus examination. All patients had normal visual acuities and pupillary reflexes.[20]

Infectivity of the tears and conjunctival transmission

In order to replicate in a host animal, viruses must first adhere to receptors on host cells. In coronaviruses this is achieved via the spike proteins that protrude through their lipid envelopes (and which give them their familiar 'crown-like' ultramicroscopic appearance). The SARS-CoV-2 virus uses the angiotensin converting enzyme-2 (ACE2) receptors present on human cells to bind to them, being primed to do so by the serine protease TMPRSS2.[21] Current belief is that the normal human conjunctiva possesses ACE2 receptors but not the priming protease[22], so it should not be theoretically possible for the SARS-CoV-2 virus to bind to the ocular surface and hence to initiate infection. It would however be possible for viruses reaching the ocular surface to be washed with the tears along the nasolacrimal ducts into the nasopharynx and from there to the respiratory and gastrointestinal tracts, where membrane-bound priming proteases are abundant, facilitating adherence.[23] In that sense, infection with the SARS-CoV-2 virus via the ocular surface is possible. As to why coronaviruses should be found in tears, apart from direct inoculation from infected droplets reaching the eye surface (for example from a cough or sneeze of an infected person), there are the theoretical possibilities of migration from the nasopharynx via the nasolacrimal duct and haematological infection of the lacrimal gland.[5] Given that SARS-CoV-2 virus has been detected in stool samples, the possibility of faecal to hand to eye transmission also exists.[24]

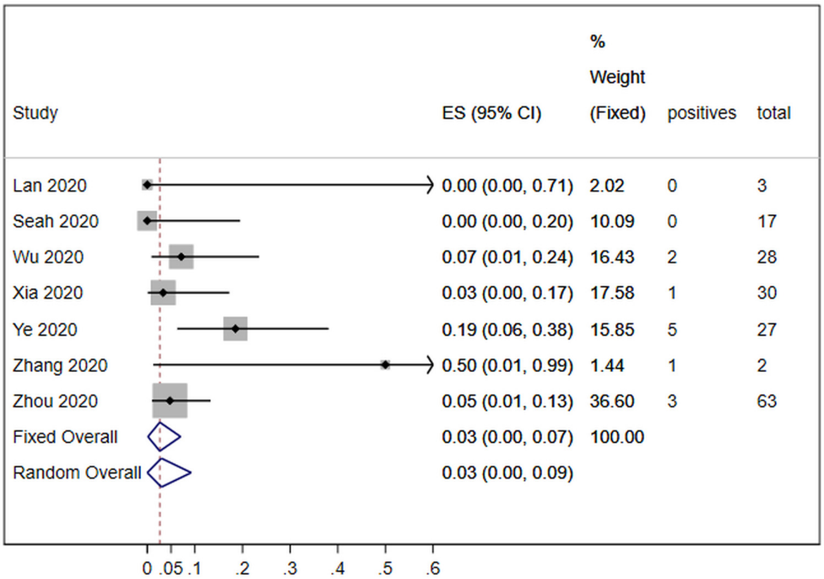

Figure 2. Forest plot of the proportion of positive tests from conjunctival swab/tear samples in hospitalised patients with COVID-19.

Conjunctival swab samples from the tears of infected individuals have proved positive for SARS-CoV-2 RNA, using the reverse-transcription polymerase chain reaction (RT-PCR), whether or not there are ocular manifestations. Similar findings were made during the SARS-CoV pandemic, though it is interesting to note that neither conjunctival inflammation nor other ocular manifestations were reported during either the SARS-CoV or the MERS-CoV pandemics.[25] A recent paper concluded that the risk of SARS-CoV-2 transmission through tears is low.[13]

Though it remains theoretically possible, transmission of coronavirus infection from the conjunctival surface of one individual to that of another, during the course of a clinical examination, has not so far been documented.

Personal protective equipment and implications for ophthalmic service delivery

On 30th December 2019 Li Wenliang, an ophthalmologist working at Wuhan Central Hospital, warned fellow doctors about a possible outbreak of an illness that resembled severe acute respiratory syndrome (SARS). He was summoned to the Public Security Bureau and made to sign a document which accused him of making false statements that disturbed the public order. He was, in fact, one of the first to recognise the outbreak of the novel coronavirus disease COVID-19. He contracted the disease from a patient and died of the infection on 7th February. His case illustrates the need for us all to speak out if we are faced with new and disturbing clinical situations, and reminds us that, as eye care practitioners, we are at personal risk in the face of emerging respiratory virus infections, of which there is no reason to believe that COVID-19 will be the last.

The provision of eye care involves, at times, close physical proximity between practitioners and patients and this is why ophthalmologists, optometrists, orthoptists and other eye care workers can be considered to be at special risk of contracting infection with the SARS-CoV-2 virus. It is believed that the virus is transmitted in exhaled liquid droplets of 5 μm diameter or larger, such as are generated during coughing, sneezing, singing and speaking. Transmission may also occur via aerosols (i.e. droplets smaller than 5 μm)[26] a mechanism that has been established for influenza viruses.[27] It is not known what concentration of coronavirus particles, or the length of exposure, is necessary to produce an infection. The concept of 'viral load' may be helpful. It is intuitive and probably correct that the viral load to which a person is exposed should influence the incidence and severity of infection, though direct evidence is hard to obtain.[28] Strategies to minimise the potential viral load should be kept constantly in mind during eye examinations.

In addition to inoculation from droplets and aerosols, SARS-CoV-2 infection is also transmitted via contaminated surfaces, where the viral concentration shows an exponential decay, with the median half-life varying with the nature of the surface, ranging from 6.8 h on plastic to 5.6 h on stainless steel, with lower values on cardboard and (especially) copper.[29] For this reason, instruments that come into contact with the eye surface, such as diagnostic lenses (gonioscopes, 3-mirror and similar lenses, pachymetry and ultrasound probes) should be disinfected with ethanol-based solutions, and disposable alternatives, such as singleuse applanation tonometer tips and iCare tonometer probes, used whenever possible.

Strategies to control the risk of infection in the eye clinics of two Hong Kong hospitals have been described by Lai and colleagues.[30] They adopted a three-level hierarchy of control measures: (1) Administrative control, (2) Environmental control and (3) The use of personal protective equipment (PPE). Administrative control involved lowering patient attendance, suspending elective clinical services, patient triage and the use of patient questionnaires. Environmental control included fresh air access, shields and the frequent disinfection of surfaces that were often touched by health care workers, and video-conferencing between members of staff. Eye protection equipment was provided to all ophthalmologists and surgical masks were worn by both ophthalmologists and patients. Hand hygiene was regarded as particularly important; ophthalmologists were to practise hand hygiene using the WHO formula alcohol hand rub or hand washing after every patient encounter, and if gloves were worn, they were removed followed by hand hygiene between cases.

The challenges special to eye care practitioners are dictated by the anatomy of the eyes, which are situated within a short distance of the nose and mouth, with physical connection between the ocular surface and the nasopharynx via the nasolacrimal duct. Certain modes of examination, such as direct ophthalmoscopy, contact lens intervention and the need to touch the eyelids during examination can be regarded as potentially hazardous, as is the short interpersonal distance at the slit lamp. Conversation at the slit lamp is not recommended, because of the inevitable generation of droplets and/or aerosols. A simple home-made slit lamp breath shield has been described.[31]

The College of Optometrists Guidance for Optometrists (Coronavirus (COVID-19) pandemic: Guidance for Optometrists),[32] last updated on 19th May 2020, is a comprehensive guide to working with patients at this time, and should be referred to by all practitioners. It addresses issues that have been controversial, including the wearing of PPE (disposable aprons, gloves and surgical masks), and advises: 'Do not deliver face-to-face care at less than two metres if you do not have appropriate PPE. Instead, direct the patient to a service that does.' This Guidance also recommends against the use of pneumo- (air puff) tonometry on the grounds that the instrument may generate aerosols which could pose a risk to eye-care practitioners and their other patients. This potential problem was identified many years ago.[33]

A brief joint statement on viral conjunctivitis and COVID-19 by the Royal College of Ophthalmologists (RCOphth) and the College of Optometrists was issued on 19th March 2020.[34] The British Contact Lens Association has also issued guidance, both for eye care practitioners and for consumers.[35] On 25th March, the RCOphth updated its guidance to ophthalmologists.[36] The guidance recommends that clinicians should wear standard surgical masks when examining or treating patients at the slit lamp and the use of plastic breath shields, which must be disinfected between patients, attached to slit lamps. In addition, they recommend that the clinician should avoid speaking at the slit lamp. The College of Optometrists continues to provide advice and guidance on PPE and working practices in relation to COVID 19.[37] Professional bodies in the USA and Australia have similarly collated evidence and provided similar guidance on patient management in relation to COVID-19, including recommendations on the use of PPE.[38,39]

Conclusion

The evidence base for the SARS-CoV-2 virus and COVID-19 disease is expanding at a phenomenal rate. We are now much better informed on all aspects of the new virus, and the pandemic that it has caused, than we were earlier in the year. This has led to a wider understanding of the risks to both patients and practitioners of eye care procedures and how these risks can be minimised. We all look forward to the advent of effective anti-viral therapies and/or vaccines, but until they are available, it is likely that these alterations to our professional practice will remain in place.

Acknowledgements

We would like to thank Dr Tianjing Li, Coordinating Editor Cochrane Eyes and Vision USA, for access to the database of published studies on COVID-19 and the eye. We are also grateful to Professor Gianni Virgili, Associate Professor of Ophthalmology at the University of Florence, for his help with the meta-analyses.

John G Lawrenson[1] and Roger J Buckley[1,2]
[1]Centre for Applied Vision Research, Division of Optometry and Visual Science, City, University of London, London, UK
and [2]Vision and Eye Research Institute, Anglia Ruskin University, Cambridge, UK
E-mail address: J.G.Lawrenson@city.ac.uk

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John G. Lawrenson is Professor of Clinical Visual Science at City, University of London. He trained as an optometrist at Aston University and Moorfields Eye Hospital, London. He holds a PhD in Visual Science from City, University of London and a Master's degree in Evidence-based Healthcare from the University of Oxford. His primary research interests lie in the field of ophthalmic public health. He is a Co-ordinating Editor for the Cochrane Eyes and Vision Group

Roger J. Buckley is Professor Emeritus of Ocular Medicine at Anglia Ruskin University's Vision and Eye Research Institute, Honorary Visiting Professor in the Department of Optometry & Visual Science at City, University of London and an Honorary Consultant Ophthalmologist at Moorfields Eye Hospital, London. His primary research and clinical interests are ocular surface disease, including ocular allergy and contact lens medicine. He is proud to have been appointed an Honorary Fellow of the College of Optometrists.