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COVID-19: Ophthalmological Aspects of the SARS-CoV 2 Global Pandemic

COVID-19: ophthalmologische Aspekte der globalen SARS-CoV-2-Pandemie

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ABSTRACT

Purpose To perform a systematic analysis of articles on the ophthalmological implications of the global COVID-19 pandemic.

Methods PubMed.gov was searched for relevant articles using the keywords "COVID-19", "coronavirus", and "SARS-CoV-2" in conjunction with "ophthalmology" and "eye". Moreover, official recommendations of ophthalmological societies were systematically reviewed, with a focus on the American Academy of Ophthalmology (AAO) and the Royal College of Ophthalmologists (RCOphth).

Results As of April 16, 2020, in total, 21 peer-reviewed articles on the ophthalmological aspects of COVID-19 were identified. Of these, 12 (57.1%) were from Asia, 6 (28.6%) from the United States of America, and 3 (14.3%) from Europe. There were 5 (23.8%) original studies, 10 (47.6%) letters, 3 (14.2%) case reports, and 3 (14.2%) reviews. These articles could be classified into the topics "Modes and prevention of (ocular) transmission", "Ophthalmological manifestations of COVID-19", "Clinical guidance concerning ophthalmological practice during the COVID-19 pandemic", and "Practical recommendations for clinical infrastructure". Practical recommendations could be extracted from official statements of the AAO and the RCOphth.

Conclusion Within a short period, a growing body of articles has started to elucidate the ophthalmological implications of COVID-19. As the eye can represent a route of infection (actively via tears and passively via the nasoacrimal duct), ophthalmological care has to undergo substantial modifications during this pandemic. In the eye, COVID-19 can manifest as keratoconjunctivitis.

ZUSAMMENFASSUNG

Einleitung Ein substanzieller Teil der aktuellen Literatur zur COVID-19-Pandemie beschäftigt sich mit deren ophthalmologischen Aspekten. In diesem Übersichtsartikel soll ein Überblick über die bisher publizierten Studien gegeben werden, die für die Ophthalmologie relevant sind.

Material und Methoden PubMed.gov wurde systematisch nach Artikeln mit den folgenden Schlüsselwörtern durchsucht: „COVID-19", „Coronavirus" und „SARS-CoV-2" in Verbindung mit „Ophthalmology" und „Eye". Darüber hinaus wurde eine Analyse der Empfehlungen der ophthalmologischen Fachgesellschaften durchgeführt, insbesondere der American Academy of Ophthalmology (AAO) und des Royal College of Ophthalmologists (RCOphth).

Ergebnisse Es wurden 21 Artikel mit Peer Review zu den ophthalmologischen Aspekten von COVID-19 identifiziert (Stand: 16. April 2020). Davon stammten 12 (57,1%) aus Asien, 6 (28,6%) aus den Vereinigten Staaten und 3 (14,3%) aus Europa. Darunter befanden sich 5 Originalarbeiten (23,8%), 10 (47,6%) Briefe an den Herausgeber, 3 (14,2%) Fallberichte und 3 (14,2%) Übersichtsartikel. Es erfolgte eine Sortierung in folgende Themen: „(Okuläre) Übertragungswege und Prävention", „Ophthalmologische Manifestation von COVID-19", „Klinische Richtlinien für die ophthalmologische Praxis während der COVID-19-Pandemie" und „Praktische Empfehlun-

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gen für den klinischen Alltag“. Letztere wurden den Empfehlungen der AAO und des RCOphth entnommen.

Schlussfolgerungen Eine Vielzahl kürzlich erschienener Artikel befasst sich mit den ophthalmologischen Aspekten von COVID-19. Da COVID-19 über das Auge übertragen werden kann (aktiv über die Tränenflüssigkeit und passiv über den Ductus nasolacrimalis), ist eine sorgfältige Infektionsprävention in der ophthalmologischen Praxis von großer Bedeutung. Eine Augenbeteiligung kann sich als Keratokonjunktivitis manifestieren.

Introduction

Since the first diagnosis of a novel severe acute respiratory syndrome (SARS) in Wuhan, China, in late 2019, the disease now known as COVID-19, caused by the SARS-Coronavirus (CoV) 2, has evolved into a global pandemic [1]. The ophthalmologist Dr. Li Wenliang, who tragically died from COVID-19 in February 2020, was among the first to warn of the disease [2,3]. Indeed, ophthalmologists seem to rank among the medical specialties with the highest risk for COVID-19 infection, probably due to close patient contact during examination, e.g., at the slit lamp [4], and possible conjunctival involvement during the course of the disease [5,6]. In a recent survey of ophthalmology practitioners in the UK, 80% of participants stated that they felt at high risk of COVID-19 transmission [7].

In this paper, a systematic review of current COVID-19 literature relevant for ophthalmological practice is performed, with a special focus on modes of transmission, the prevention thereof, structural adjustments of clinical care required during the pandemic, and possible ocular manifestations of this novel disease.

Methods

The database PubMed.gov was searched for peer-reviewed articles including the keywords “COVID-19” and “SARS-CoV-2” in conjunction with “ophthalmology” and “eye”. Depending on the article type, they were stratified as “Original article”, “Case report”, “Review”, or “Letter to the Editor/Comment”. Depending on their content, they were summarized into the categories “Modes and prevention of (ocular) transmission”, “Ophthalmological manifestations of COVID-19”, “Clinical guidance concerning ophthalmological practice during the COVID-19 pandemic”, and “Practical recommendations for clinical infrastructure”. Due to the rapidly evolving situation, recommendations from non-peer-reviewed articles were also included where appropriate, e.g., recommendations from professional societies.

Results

As of April 16, 2020, in total, 21 articles on the ophthalmological aspects of COVID-19 were identified. Of these, 12 (57.1%) were from Asia, 6 (28.6%) were from the United States of America, and 3 (14.3%) were from Europe. There were 5 (23.8%) original studies, 10 (47.6%) letters, 3 (14.2%) case reports, and 3 (14.2%) reviews. A structured summary of the literature follows, along with an implementation of recommendations by the American Academy of Ophthalmology (AAO) and the Royal College of Ophthalmologists (RCOphth).

Modes and prevention of (ocular) transmission of SARS-CoV 2

SARS-CoV-2 is believed to spread mainly due to close contact with an infected person, exposing the subject to respiratory droplets during coughing, sneezing, talking, or breathing [8]. Transmission from asymptomatic and presymptomatic carriers has been reported [9,10]. For this reason, some experts and institutions advocate the widespread use of surgical face masks to prevent both viral spreading from those possibly infected and infection in healthy individuals [8,11,12]. In ophthalmological practice, the working distance at the slit lamp between patient and examiner varies between 20 and 40 cm. Therefore, protective shielding attached to the slit lamp has been suggested (see below, “Practical recommendations for clinical infrastructure”) [13,14].

In addition to direct patient-to-patient transmission, contact with infectious particles can be established through surfaces. In an experimental study, van Doremalen et al. found stable virus particles on surfaces after up to 72 hours, with greater stability on plastic and stainless steel than on copper or cardboard [15]. Therefore, thorough disinfection of surfaces and equipment after each patient is essential. If possible, single-use tonometer tips are preferred over reusable tips. To inactivate SARS-CoV 2, disinfection with > 70% alcohol-based solutions has been shown effective. Common protocols, including the inactivation of adenoviruses, e.g., bleaching (8.25% sodium hypochlorite), also seem to exhibit sufficient virucidal activity.

In several studies, SARS-CoV 2 RNA has been detected in tear film and/or conjunctival swabs by reverse transcription polymerase chain reaction (RT-PCR) [5,6,16]. Xia et al. examined 60 tear and conjunctival samples of 30 patients, of which two samples from one single patient were positive for SARS-CoV 2 RNA; of note, this also was the only patient with clinical symptoms [16]. However, Xia et al. could not isolate the virus [16]. Wu et al. examined 38 patients, of which 2 (5.3%) had detectable SARS-CoV 2 RNA in a conjunctival specimen, while 12 (31.6%) had ocular symptoms consistent with conjunctival involvement. A case report documenting the clinical course of a 30-year-old patient with COVID-19 with ocular involvement (follicular conjunctivitis) confirmed viral RNA on days 13, 14, and 17, while further testing on day 19 revealed a negative result [6]. Of note, the viral load in conjunctival swabs was markedly lower than in nasopharyngeal swabs or sputum [6]. In contrast, another study by Seah et al., analyzing 64 samples from 17 patients in weeks 1, 2, and 3 of the disease, could not detect viral RNA, with only 1 patient having ocular symptoms [17].

Cellular entry of SARS-CoV 2, and hence infection, takes place via the angiotensin-converting enzyme II (ACE-2) receptor [18]. In contrast to ACE-1, which is almost ubiquitously present in ocular tissue, ACE-2, interestingly, is only present in the retina [19] and

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aqueous [20]. Therefore, it is currently unclear if sole ocular contact with SARS-CoV 2 can manifest in an infection [17]. Based on the current literature, exposure of the ocular surface to SARS-CoV 2 might confer infection most probably due to drainage of virus particles via the nasolacrimal duct into the respiratory tract [21, 22]. Therefore, the use of protective glasses or shields is recommended [23 – 25].

Concerning airborne infection, most studies have not been able to demonstrate infectious particles in air samples; however, virus particles might be distributed by small virus-laden droplets or aerosols, which might be displaced by airflow [26]. Virus stability in aerosols might exceed 3 hours [15].

Ophthalmological manifestations of COVID-19

So far, the ophthalmological manifestations of COVID-19 have been described in two original studies, and three case reports. In general, ocular involvement seems to be rare. In the largest non-ophthalmology-specific study, Guan et al., reporting a cohort of 1099 patients with COVID-19, found conjunctival congestion in 0.8 % of cases [27]. As stated by the AAO, "conjunctival congestion", however, represents a rather unspecific finding, which can also be caused by mechanical ventilation, which was used in 6.1 % of patients in this study.

In the largest ophthalmology-specific study, Wu et al. found ocular symptoms in 12 (31.6 %) out of 38 patients with COVID-19; SARS-CoV RNA was found in 2 of these (5.8 %). Symptoms included hyperemia, chemosis, epiphora, and increased secretion, while none of the patients experienced blurred vision [5]. Interestingly, patients with ocular symptoms were more likely to have higher white blood cell and neutrophil counts and higher levels of procalcitonin, C-reactive protein, and lactate dehydrogenase [5]. Since these markers have been found to correlate strongly with disease severity [28], a possible correlation between the presence of ocular symptoms and moderate or severe courses of the disease should be evaluated in future studies. In another study, Seah et al. found similar symptoms in 1 out of 17 patients (5.8 %) who developed conjunctival injection and chemosis [17]. Similarly, in a case report, Chen et al. reported again similar clinical findings in a patient with redness, foreign body sensation, and tearing [6]. Additionally, Chen et al. found inferior palpebral conjunctival follicles. In this case report, ocular symptoms were first reported on day 13 after symptom onset, which improved by day 15, and completely resolved on day 19 [6]. Analogously, another case report by Cheema et al. found similar conjunctival signs, however, also noted were lid swelling, 3+ follicles, and additional keratitis, which presented with subepithelial infiltrates with overlying epithelial defects [29].

In a review on the pathogenicity of coronaviruses in general, Seah and Agrawal elucidate that conjunctivitis, anterior uveitis, retinitis, and optic neuritis have been documented in feline and murine models [30]. At the moment, it is unclear whether SARS-CoV 2 can cause more severe eye disease beyond keratoconjunctivitis. Due to the presence of ACE-2 in the retina [19] and aqueous [20], uveitis or involvement of the posterior pole might, however, be possible – and maybe even linked to an increased viral load. As patients with a high viral load are, however, also more likely to develop severe or critical illness, severe eye problems might, at the moment, largely go unnoticed as these patients are often treated in intensive care units for much more severe, life-threatening conditions.

Clinical guidance concerning ophthalmological practice during the COVID-19 pandemic

At the core, all measures taken to slow the spread of COVID-19 aim at "flattening the curve", i.e., reduce the maximum number of patients falling ill simultaneously (and in a certain fraction requiring intensive care), thus protecting health care systems from breakdowns [31].

Due to the high daily patient throughput in eye clinics, ophthalmological caretakers face particular responsibility to reduce exposure in waiting rooms and during physical examination, including the prevention of patient-to-physician transmission. Both the AAO and RCOphth have given extensive recommendations concerning patient care during the COVID-19 pandemic.

(Re)Scheduling of appointments

Both literature and organizations, such as the AAO and the RCOphth, advise all ophthalmologists to perform urgent care only [25, 32, 33]. The RCOphth has issued specific recommendations for most subspecialties, including medical retina, vitreoretinal surgery, glaucoma, and pediatric ophthalmology including retinopathy of prematurity management, uveitis, and oculoplastic surgery [33].

The recently published Moorfields Ophthalmological Risk Stratification and Implementation Guidance offers in-depth recommendations for all ophthalmological subspecialties based on a three-level risk score and previous in-clinic patient history (new patient, follow-up, surgery) [34]. In high-risk patients, face-to-face consultation is recommended to be maintained (e.g., acute angle closure glaucoma, newly diagnosed neovascular AMD, new active panuveitis). In medium-risk patients, remote consultation via telephone or video call might effectively substitute face-to-face consultation while lowering the transmission risk (e.g., mild thyroid eye disease, amblyopia treatment). In low-risk patients (cataract with mild visual impairment, recent onset central serous chorioretinopathy), deferral by 6 months is recommended.

Surgical procedures

As with outpatient care, all non-urgent surgical procedures are recommended to be deferred. In general, the assessment of surgical "emergencies" has been performed rather strictly by the professional societies (e.g., recommendation by the RCOphth to defer vitrectomy for unilateral diabetic vitreous hemorrhage by 6 months [34]). As further guidance, the AAO has published a list of emergency surgical procedures that should not be withheld in spite of the current pandemic [35].

Clinical trials

Widespread agreement concerning clinical trials suggests that all observational studies should be suspended. Patients receiving investigational substances should continue the study treatment, if withdrawal thereof might cause harm. In most cases, the recruitment of new patients into investigational drug trials should, however, be paused [36].

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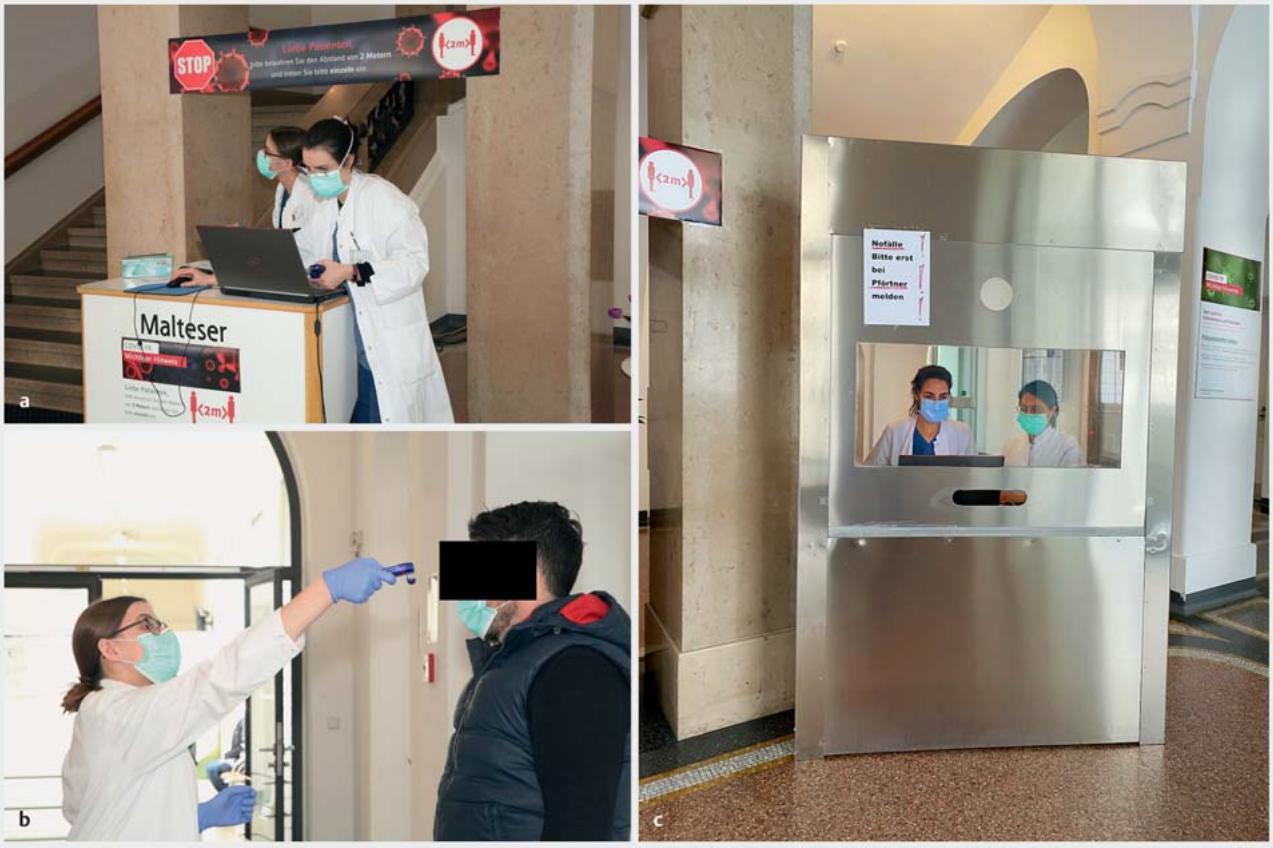

▶ **Fig. 1** Implementation of triage during the COVID-19 pandemic in the University Eye Clinic Munich, Ludwig Maximilians University, Germany. **a** Triage at the main entrance of the clinic is essential to directly isolate patients showing symptoms of COVID-19, and to evaluate the urgency of the requested ophthalmological consultation, especially in patients presenting without a prior appointment. All patients are provided with surgical masks. **b** Non-contact thermometers can be implemented to screen for (largely) asymptomatic patients who, however, present with fever. **c** Custom cabins limiting direct health care worker/patient interaction can be constructed to reduce contagion. Since implementing these measures in the beginning of March, no case of patient-personnel-related COVID-19 transmission was documented as of April 16, 2020.

Practical recommendations for clinical infrastructure

Screening for COVID-19 and triage

For all patients entering the clinic for consultation, screening for COVID-19 by trained staff directly in the entrance hall, prior to fully entering the facilities, has been implemented by many clinics and offices (▶ **Fig. 1 a, c**) [25, 37, 38]. This requires reducing all gateways to the clinic or office to a minimum amount. Staff should be kept safe behind protective shielding or in custom cabins (▶ **Fig. 1 c**). Patients should be asked the following:

- Have you been in contact with people diagnosed with or showing symptoms of COVID-19 within the last 14 days?
- Have you travelled internationally within the last 14 days?
- Do you show any of the following COVID-19 symptoms [39 – 42]?
  - Fever, dry cough, dyspnea, sore throat, runny nose, myalgia, fatigue, headache, diarrhea, loss of smell, loss of taste, nausea.

In addition, measurement of body temperature has been advocated by some authors, which, however, might additionally expose health personnel to infection (▶ **Fig. 1 b**) [43]. If patients, after answering the above questions, are not presumed to carry SARS-CoV 2, ophthalmological triage according to the suggestions made above (urgency, risk, etc.; see "Scheduling of appointments") is performed. When patients are admitted to entering the clinic, hand disinfection is required, and mandatory surgical face masks are handed out [43]. If patients have symptoms of COVID-19, they should be urgently isolated by personnel in personal protective equipment (PPE).

Waiting room

To reduce contagion, waiting rooms should be kept as empty as possible. This requires optimization of patient flow (defer non-urgent appointments, staff ambulance appropriately). Within the waiting room, patients should be kept at a minimum distance of 1.5 to 2.0 m. Removing chairs (and spacing them) by an appropriate amount can facilitate "social distancing".

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Staff reorganization

To reduce contagion within the medical personnel, working in separate teams has been suggested and implemented in many clinics [43]. These teams should be in minimum face-to-face contact, and some clinics have implemented 50 % home office time for the team currently not serving the facilities. Since home confinement further reduces the risk of infection even beyond the sheer risk at work (less commuting, etc.), many authorities have implemented 1 week at the clinic/office, followed by 1 week of home office, alternating between the 2 teams.

Face masks and protective shielding

Many clinics in Germany, including ours, have implemented mandatory surgical face masks for medical personnel and all patients entering the clinic. It is important to note that masks with exhalation valves (e.g., FFP2, FFP3) do not protect the opposite individual, and that additional surgical face masks on top of the exhalation valve might be reasonable. Possible protective effects of widespread use of face masks have to be weighed against the problem of temporary or local shortage, and strict hygiene, e.g., concerning reuse of masks, has to be implemented.

Additionally, protective breath shields attached to the slit lamp have been suggested. They can be ordered from various slit lamp manufacturers, or self-made from flexible plastic file folders attached to the slit lamp after the eyepiece has been removed [13]; detailed instructions can be found online [14]. Of note, thorough disinfection of flexible self-made shields may be challenging. In general, professional societies like the AAO, the RCOphth, and the German Ophthalmological Society (DOG) recommend limiting time spent in front of the slit lamp to a minimum, with the patient advised to refrain from talking to avoid the spread of respiratory droplets.

Conclusion

The novel coronavirus SARS-CoV 2, currently causing the COVID-19 pandemic, has severe implications for ophthalmology – be it because the eyes represent an important route of infection, most probably through lacrimal drainage into the nasal mucosa, or because of ocular manifestations, which, even if rather rare, can represent the first symptoms of this novel disease [29]. Within short notice, the worldwide ophthalmological society has generated substantial insight into this new entity and offered important guidelines on how to adjust our daily duties to preserve eyesight in this complex situation. While SARS-CoV 2 continues to spread around the globe, leaving many unanswered questions behind, hope is on the horizon that continued international collaboration will soon provide us with tools to beat this pandemic.

Conflict of Interest

J. Siedlecki: Speaker honoraria and travel reimbursement from Carl Zeiss Meditec AG, Novartis Pharma GmbH, Bayer AG, Pharm-Allergan GmbH, Oculentis OSD Medical GmbH. Travel reimbursement: Roche AG. W. Mayer: Personal fees and travel reimbursement from Carl Zeiss Meditec, Alcon, Oculentis OSD Medical, Oertli AG, Staar Surgical, Pharm-Allergan, Ziemer, Ophthec, D. O. R.C, Bausch & Lomb. Advisory Board: Carl Zeiss Meditec, Alcon. T. Kreutzer: Speaker honoraria from Alcon Pharma GmbH. Personal consultation fees from Novartis Pharma GmbH and Bayer AG. Travel reimbursement from D. O. R. C. (International). B. Schworm: Speaker honoraria and travel expenses from Novartis Pharma GmbH and Topcon. S. Priglinger: Speaker honoraria and travel reimbursement from Novartis Pharma GmbH, Oertli AG, Bayer AG, Alcon Pharma GmbH, Pharm-Allergan GmbH, Bausch & Lomb GmbH, Carl Zeiss Meditec AG.

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