Relations between the ocular surface and SARS-CoV-2

Relações entre superfície ocular e SARS-CoV-2

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ABSTRACT

Introduction: The SARS-CoV-2 pandemic has been a major challenge for the international scientific community. Since its inception, studies aiming to describe pathophysiological aspects and clinical manifestations of the disease have been conducted, raising hypotheses and confirming possible associations. One aspect of this scientific medical production is the role of the ocular surface as a means of transmission and clinical presentation of viral syndrome. **Objectives:** To analyze the role of the ocular surface in transmission, pathophysiology, and clinical manifestations of SARS-CoV-2, by means of a systematic review. **Methods:** The search was carried out in three databases: Cochrane, PubMed Central Journals and MEDLINE, using the following descriptors: "COVID-19, ophthalmology". The filters last five years and studies on humans resulted in 32 studies; in that 12 were excluded for not meeting the purpose of the study. **Results:** There are still few published studies on the relation between SARS-CoV-2 and the ocular route. Most studies showed an association between the presence of nonspecific ocular manifestations and infection by the new coronavirus, with limitations in the number of patients analyzed and the methodology adopted. Hypotheses about the pathophysiological role are largely anchored in the association of SARS-CoV and the ocular surface evaluated in the past. **Comments:** The results found are still not sufficient to confirm the role of the ocular surface in the pathophysiology of the disease. Most of these preliminary studies are of considerable importance in raising hypotheses based on the medical analysis of the patients studied. However, larger studies with standardized methodology for diagnostic protocol and laboratory analysis of the individuals assessed are required.

RESUMO

Introdução: A pandemia da SARS-CoV-2 tem sido um grande desafio para a comunidade científica internacional. Desde seu surgimento, estudos com a intenção de descrever os aspectos fisiopatológicos e as manifestações clínicas da doença vêm sendo conduzidos, levantando hipóteses e confirmando possíveis associações. Um dos temas dessa produção médica científica é o papel da superfície ocular como meio de transmissão e apresentação clínica da síndrome viral. **Objetivo:** Analisar o papel da superfície ocular na transmissão, na fisiopatologia e nas manifestações clínicas de SARS-CoV-2, através de uma revisão sistemática. Realizou-se a busca em três bancos de dados *Cochrane Database*, PubMed® e MEDLINE®, utilizando os descritores *"COVID-19 e ophthalmology"*. Foram definidos como filtros o artigo ter sido publicado nos últimos 5 anos e estudo realizado em humanos, tendo sido encontrados 32 artigos. Destes, foram excluídos 12 por não corresponderem ao objetivo do estudo. **Resultados:** Ainda são poucos os estudos publicados sobre a relação entre o coronavírus 2 da síndrome respiratória aguda grave (SARS-CoV-2) e a via ocular. A maioria dos estudos mostrou associação entre a presença de manifestações oculares inespecíficas e a infecção pelo novo coronavírus, com limitações no número de pacientes analisados e na metodologia adotada. Hipóteses sobre o papel fisiopatológico se ancoram, em grande parte, na associação estudada entre o SARS-CoV-2 e a superfície ocular no passado. **Comentários:** Os resultados encontrados ainda não são suficientes para confirmar o papel da superfície ocular na fisiopatologia da doença. Grande parte desses estudos preliminares têm importância considerável ao levantar hipóteses baseadas na análise clínica dos pacientes estudados. No entanto, são necessários estudos maiores e com metodologia padronizada para protocolo diagnóstico e análise laboratorial dos indivíduos avaliados.

INTRODUCTION

In December of 2019, a challenge arose in Wuhan, China, and changed the history of mankind. Reports of an outbreak of a new viral disease, with high infectious potential and capable of progressing within a few days to severe acute respiratory syndrome, causing death in part of the stricken patients, alerted the World Health Organization (WHO). It was a new beta coronavirus, causing a condition named coronavirus disease (COVID-19) by the WHO, which quickly spread to other continents, evolving into a worrying pandemic.

Infections by this pathogen, a single-stranded RNA virus of the *Coronaviridae* family, are already known by virologists, being more common in birds and mammals. However, in 2003, there was an outbreak of severe acute respiratory syndrome (SARS) caused by the severe acute respiratory syndrome coronavirus (SARS-CoV), which infected more than 8,000 people globally.[1] It led the scientific community to further discuss about the capacity of spillover transmission between species of this virus' family. In 2012, another outbreak occurred and was caused by the Middle East respiratory syndrome coronavirus (MERS-CoV), which infected more than 2,400 people worldwide.[2] In 2019, the new pathogen named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV), brought new discussions about the transmission and clinical manifestations of these infections. It is known that various manifestations, such as cough, fever and dyspnea are linked to the infection by SARS-CoV-2, but several case reports and directed studies suggested some ocular manifestations, like conjunctivitis, keratoconjunctivitis, and even a decrease in visual acuity, as possible symptoms, supporting conduction of further studies to clarify the patterns of these manifestations.

Although there is no robust evidence to suggest ocular transmission of the new coronavirus, prodromal eye symptoms have been reported in infected patients.[3] In addition, there are reports of infected healthcare workers who used their personal protective equipment properly, but did not use eye protection,[3] making detailed investigation of this possible route of transmission of great importance, although few studies have managed to isolate the virus by reverse transcription polymerase chain reaction (RT-PCR) from conjunctival samples.

METHODS

Cochrane Database, PubMed® and MEDLINE® databases were used to select the articles analyzed for this review, by searching the keywords "COVID-19" and "ophthalmology".

Articles related to ocular manifestations in COVID-19 infection were selected. The search filters comprised studies published in the last 5 years (between April 2015 and April 2020) and carried out in humans. They included prospective and retrospective cohorts, systematic and non-systematic review articles, case series studies, clinical trials and letters to the editors. The Jadad and Newcastle-Ottawa scales were used for qualitative classification of the main articles on the subject. The selection of studies was independent, blind and peer-reviewed, according to the inclusion criteria. Initially, 32 publications were selected, and 12 of them did not correspond to the objective and were discarded. After this stage, 20 scientific articles were included in this review.

RESULTS

The details of the selected studies are described in Table 1.

Table 1. Description of selected articles

Article	Number of patients	Study methodology	Study variables
Seah et al.[1]	-	Review	Ophthalmological manifestations of SARS-CoV-2 infection
Hong et al.[2]	56	Case-control study	Ophthalmological manifestations of SARS-CoV-2 infection
Zhang et al.[3]	102	Cross-sectional study	Ophthalmological transmission and manifestations of SARS-CoV-2 infection
Wu et al.[4]	38	Clinical series study	Ophthalmological manifestations of SARS-CoV-2 infection
Chen et al.[5]	1	Case report	Ophthalmological manifestations of SARS-CoV-2 infection
Guo et al.[6]	-	Review	Ophthalmological manifestations of SARS-CoV-2 infection
Kuo et al.[7]	-	Review	Ophthalmological manifestations of SARS-CoV-2 infection
Liu et al.[8]	-	Review	Ophthalmological manifestations of SARS-CoV-2 infection
Liang et al.[9]	-	Review	Ophthalmological manifestations of SARS-CoV-2 infection
Xia et al.[10]	30	Prospective interventional case series	Ophthalmological manifestations of SARS-CoV-2 infection
Guan et al.[11]	1,099	Clinical series study	Ophthalmological manifestations of SARS-CoV-2 infection
Seah et al.[12]	12	Cohort study	Ophthalmological transmission of SARS-CoV-2 infection
Wu et al.[13]	1	Case report	Ophthalmological manifestations of SARS-CoV-2 infection
Liang et al.[14]	37	Case series	Ophthalmological manifestations of SARS-CoV-2 infection
Cheema et al.[15]	1	Case report	Ophthalmological manifestations of SARS-CoV-2 infection
Xie et al.[16]	-	Review	Ophthalmological transmission and manifestations of SARS-CoV-2 infection
Romano et al.[17]	-	Review	Ophthalmological transmission of SARS-CoV-2 infection
Jørstad et al.[18]	-	Letter to the Editor	Ophthalmological manifestations of SARS-CoV-2 infection
Zhang et al.[19]	-	Review	Ophthalmological manifestations of SARS-CoV-2 infection
Li et al.[20]	-	Review	Ophthalmological manifestations of SARS-CoV-2 infection

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

DISCUSSION

Some recently published studies have shown cases of ocular symptoms in patients with COVID-19, many of which have a small sample but they alert us about the possibility of these specific disorders and ocular transmission.[3] Most patients analyzed showed clinical manifestations compatible with viral conjunctivitis, such as conjunctival hyperemia, chemosis, epiphora, increased ocular secretions and absence of reduced visual acuity.[3-5]

The possibility of transmission via the eye is suggested in some studies due to infection of health professionals who cared for patients without proper eye protection.[3] Another point that corroborates the possibility of this type of transmission is the presence of positive RT-PCR for SARS-CoV-2 in conjunctiva swabs of patients with or without ocular manifestations.[6,7] However, there is still no significant scientific evidence to confirm this report.

Eye transmission

In 2004, at the end of the SARS-CoV crisis, a new human coronavirus was identified. It was the HCoV-NL63. The virus was first isolated in a 7-month-old infant, and later identified in seven individuals. In the same year, a series of cases was published highlighting the presence of SARS-CoV RNA in tears, in which conjunctival samples were collected from 36 patients with suspected SARS-CoV and were sent to try to isolate the virus through RT-PCR. Viral samples were found in the conjunctiva of three patients.[8]

Another study[12] evaluated tears and conjunctival specimens of 17 patients with confirmed SARS-CoV infection and did not demonstrate any positive results from RT-PCR. The authors attributed the results to three possibilities: first, the RT-PCR was not sensitive enough to capture small amounts of SARS-CoV RNA; second, the samples were collected in a single process, which may not have coincided with the viral load period in the ocular tissue, due to the short interval within which the pathogen would remain in the conjunctiva; third, there is also the possibility that SARS-CoV was not present in eye tissue. However, when the SARS-CoV epidemic disappeared, these crucial questions were left unanswered. Thus, even today, it is still unclear if this virus can be located in the tear and how would that be. The proposed theories have included the conjunctiva as the site of direct inoculation of SARS-CoV from infected droplets, migration of the upper respiratory tract infection through the nasolacrimal duct, or even hematogenous infection of the lacrimal gland.[8]

Thus, from genomic and structural analyses, it has been reported that SARS-CoV-2 has a receptor-binding mechanism similar to SARS-CoV, which allows it to infect host cells by binding to the the pathogen's S protein by means of the angiotensin-converting enzyme 2 (ECA2). Hence, the hypothesis raised was transmission through the eye would be possible given the expression of ECA2 in aqueous humor, cornea and conjunctiva.[8-10] However, no study has confirmed this correlation with strong scientific evidence. Further studies are warranted to explore this hypothesis.

Ocular manifestations

Several ophthalmological manifestations of varying intensities, at different stages of SARS-CoV-2 infection, have been described in the scientific articles analyzed in this study. The manifestations ranged from irritation and mild conjunctival hyperemia, to keratoconjunctivitis and chemosis. Severe eye manifestations put vision at risk were not observed in the articles evaluated.

In the largest non-specific cohort ophthalmology study, Guan et al. observed the clinical progression of 1,099 laboratory-confirmed COVID-19 patients, followed up at 552 hospitals, in 30 provinces of China. The study aimed to statistically analyze the main clinical manifestations of the disease, and found conjunctival congestion in only nine patients (0.8%). The study did not include other ophthalmic signs and symptoms in the analysis, nor specifically described the clinical development of reported ocular manifestations.[11]

Unlike the result found by Guan *et al*.[11] in a specific ophthalmology study, with 56 patients diagnosed with COVID-19, Hong et al. reported the onset or worsening of general eye symptoms in one out of four participants. The patients´ medical records were reviewed, comparing the results of the Ocular Surface Disease Index (OSDI) questionnaires applied before the pandemic and during the study. An increase by 8.96% in total score of the applied questionnaires was observed, suggesting a possible association between SARS-CoV-2 infection and ocular surface manifestations. In addition, 27% of patients reported the onset of ocular symptoms during some stage of the disease, and 11% presented ocular symptoms before the onset of fever or respiratory manifestations. General manifestations have been reported, including eye pain, itching, tearing and dry eye.[2]

In a study conducted by Wu et al., with 38 hospitalized patients diagnosed as COVID-19, ocular manifestations suggestive of conjunctivitis were observed in 12 patients (31.6%). Ocular manifestations included conjunctival hyperemia, chemosis, epiphora and ocular congestion.

In addition, only 5% of conjunctival swabs from patients with ocular manifestations were positive for SARS-CoV-2 by RT-PCR. The findings were most commonly seen in patients during the middle stage of the disease or with severe pneumonia already installed. Interestingly, patients with eye symptoms had higher white blood cell and neutrophil counts, in addition to higher levels of procalcitonin, C-reactive protein and lactate dehydrogenase. Since these markers have a strong correlation with severity of disease, a possible association between presence of ocular symptoms and moderate or severe courses of the disease should be evaluated in future studies.[13]

In another study, Seah et al. found ocular manifestations in one out of every 17 laboratory-diagnosed COVID-19 patients (5.8%), none of whom were positive on the RT-PCR test and lacrimal sample viral isolation.[12] In published case reports, ophthalmic manifestations, such as conjunctivitis and keratoconjunctivitis have also been reported, with variable time of onset.[3-13]

COMMENTS

There are several reports of ocular symptoms in COVID-19 patients; however it is still unclear whether presence of the pathogen occurs in tears or in conjunctival secretions, if positive detection of virus in these secretions is transient, or if there is ocular transmission.[6] Some hypotheses have been raised to try to clarify these issues.

First, the diagnostic criteria used by the authors were not standardized - each author used protocols from their countries and are different. In addition, the articles diverged in the exact definition of confirmed and suspected cases. As a result, different patient populations were analyzed and this may impact on RT-PCR results of tear samples and conjunctiva swabs.[7]

Second, RT-PCR is a very specific test. Therefore, negative results may not be false negative. Another point to be considered is the lower sensitivity of the test for samples of ocular secretions, when compared to respiratory specimens.[7]

Hence more in-depth studies and with a larger sample of patients are necessary to properly understand this important public health problem.

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