Peer Review File

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Reviewer Comments

Comment 1:
This is a review of various ocular sequalae associated to COVID-19. A review like this is not new and various other, similar articles have already been published. This paper is well written in English, but its contents require more attention. My main problem is there is no Methods section and that the included case reporte seem to be selcted at random. A lot of reports on diseases of the posterior segment are missing from the review, for example on VKH and CSCR amongst others. I would suggest the authors to write a structured methods section with a repeatable search strategy that is actually aimed at gathering all posterior segment sequelae of COVID-19.
Reply 1:
Thank you for your response
Changes in text
The following methods section was added:
"An extensive literature review was conducted at the time of the writing of this publication in January 2023. The PubMed search engine was used for this purpose. The terms "COVID-19," "SARS-CoV-2," "Coronavirus," "Ophthalmic," "Ocular," "Retina," and "Uveitis" were typed into the search engine in order to identify appropriate, relevant publications. Other associated terms were also used based on the results of the studies, for example to further explore specific ophthalmic manifestations that were reported, including "multiple evanescent white dots syndrome," "acute posterior multifocal placoid pigment epitheliopathy," "acute retinal necrosis." Reports exclusively related to vaccines rather than primary COVID-19 infection were excluded (lines 93-102).

Comment 2:
The title is too broad for the scope of the article, since it mainly focusses on the posterior segment.
Reply 2:
Thank you for your comment
Changes in text:
The title has been changed from "Ocular Manifestations of COVID-19" to "Ophthalmic Posterior Segment Manifestations of COVID-19" (line 1).

Comment 3:
Please mention the goal of this review early on. This is too much of an introduction and not a recapitulation of your paper.
Reply 3:
Thank you for your comment
Changes in text:

The following line was added to address the goal of this paper early in the abstract: "The aim of this review is to describe various posterior segment manifestations of the SARS-Cov-2 virus on the eye and discuss proposed pathophysiology and mechanisms of involvement of these ophthalmic structures" (lines 36-38).

Comment 4:
You mention you include neuro-ophthalmolical disease, but the section this is very minor.
Reply 4:
Thank you for the comment. We agree that the section on neuro ophthalmic disease is very minor.

Changes in text.
To keep focus on the posterior segment which is the primary component of this review, this line was changed to the following: "In this paper we explore various reported ophthalmic manifestations of COVID-19 infection, primarily involving the posterior segment" (lines 47-49).

Comment 5:
COVID-19 is not synonymous to the virus, but ratner the disease caused bij the SARS-CoV-2 virus. (Like HIV causes AIDS.)

Reply 5:
Thank you for the comment.
Changes in text:
This line was changed to the following: "The SARS-CoV-2 virus, which causes the clinical syndrome known as COVID-19, has impacted nearly every organ system…" (lines 63-64).

Comment 6:
Refrain from using the term "injury", as this implies a physical/traumatic origin.
Reply 6:
Thank you for the comment
Changes in text:
This phrase was changed to "The pathophysiologic mechanisms of involvement…" (line 65).

Comment 7:
Please explain why the anterior segment was omitted from your review.
Reply 7:
External eye and anterior segment involvement were recognized earlier on during the COVID-19 pandemic and were reported in association with other strains of coronavirus even prior to the pandemic. Therefore, we decided to focus on posterior

segment manifestations which are now being increasingly recognized and reported.
Changes to text:
To reflect this and the scope of our paper, the line was changed to the following: "While involvement of the external eye and anterior segment was recognized early on during the COVID-19 pandemic (e.g. dry eye, keratoconjunctivitis, episcleritis, etc.), this paper focuses on the likely vision impacting posterior segment manifestations which are less frequently reported" (lines 67-70).

Comment 8:
Why is this "major"? Please provide numbers for your statement.
Reply 8:
As these manifestations are rare and there is not well-established incidence data comparing various manifestations, we agree the term "major" is not appropriate.

Changes in text:
As such, the line has been changed to "One of the reported ways in which…" (line 105).

Comment 9:
How do you know for sure this is viral re-activation and not a primary infection? You only mention PCR and not Goldmann-Witmer.
Reply 9:
PCR studies were discussed in the cited reports, while Goldmann-Witmer was not mentioned.

Changes in text:
The following line was added to acknowledge the limitations in determining conclusively whether these were reactivations, as proposed by the majority of the cited cases, or primary infections: "…as is the proposed mechanism of microbial reactivation as opposed to potential primary infection" (lines 118-119). As PCR is used more widely than Goldmann-Witmer, we feel this is more likely to be reflective of current practices.

Comment 10:
Why do you suddenly decide to mention anterior segment symptoms?
Reply 10:
The sentence was changed to the following to better emphasize the posterior segment findings while also include a few interesting anterior segment findings within the classification of uveitis.

Changes to text:
"Beyond reactivation or predisposition to other infections, coronavirus itself is the presumed etiology of various posterior segment ophthalmic inflammatory disorders,

including acute posterior multifocal placoid pigment epitheliopathy (APMPPE), multiple evanescent white dot syndrome (MEWDS), Vogt-Koyanagi-Harada (VKH) syndrome, and punctate inner choroidopathy (both primary disease and reactivation); other reported uveitic presentations beyond the posterior segment include few reports of anterior and intermediate uveitis (presenting bilaterally in a pediatric patient with multisystem inflammatory syndrome in children, or MIS-C), bilateral acute depigmentation of the iris (BADI), and panuveitis" (line 123-129).

Comment 11:
Please add some background on the supposed ways COVID-19 causes thrombo-embolic events.
Reply 11:
Thank you for the comment
Changes to text:
The following was added to include background on proposed systemic thromboembolic mechanisms: "In addition to the direct inflammatory effects of COVID 19, retinal vascular events have been commonly reported with various proposed mechanisms, which have been further studied from an extraocular, systemic standpoint. These potential mechanisms include hemodynamic factors including stasis and turbulence, endothelial injury, shear stress-induced injury and platelet activation, and overall dysregulation of inflammation and coagulation leading to release of prothrombotic factors" (lines 160-165).

Comment 12:
Why do you mention vaccines just now? Please omit completely or add to your review.

Reply 12:
Vaccination was mentioned in line 146 as temporally associated with worsening of NAION.
Changes to text:
However, to focus on primary COVID-19 infection ocular presentations, the following phrase was omitted: "…that worsened with subsequent vaccine administration" (line 200). The sentence "Many of these presentations have also been demonstrated in association with COVID-19 vaccination, thus further alluding to an ocular immune or inflammatory response to the SARS-CoV-2 virus which requires further elucidation" has also been deleted (line 222).

We appreciate the opportunity to revise our manuscript and hope that it meets requirements for publication.
Thank you to the reviewers and editor for their time and effort helping us improve the manuscript.

Best,

Sapna Gangaputra