



Ophthalmic posterior segment manifestations of COVID-19

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Abstract: Since the onset of the coronavirus disease 2019 (COVID-19) pandemic, numerous reports of associated ocular manifestations have emerged. Involvement of nearly every ocular structure has been reported. The aim of this review is to describe various manifestations of the severe acute respiratory disease coronavirus 2 (SARS-CoV-2) virus on the eye, focused primarily on the posterior segment, and discuss proposed pathophysiology and mechanisms of involvement of these ophthalmic structures. Proposed mechanisms of ocular involvement of COVID-19 parallel those of systemic manifestations and include viral and other microbial reactivation, primary infection, inflammation, and thromboembolism. Viral reactivation of Herpes Simplex Virus, Varicella Zoster Virus, and Epstein-Barr Virus has been presumed in cases of acute retinal necrosis (ARN), while bacterial and parasitic infections have also been reported albeit less commonly. Primary infection has also been thought to contribute to various inflammatory presentations. Thromboembolic manifestations include various retinal artery and vein occlusions among other less visually significant signs such as cotton wool spots. Cranial neuropathies including optic neuropathy, as well as optic neuritis have also been widely reported. COVID-19 vaccines are increasingly associated with ocular signs and syndromes. In this paper we explore various reported ophthalmic manifestations of COVID-19 infection, primarily involving the posterior segment. Given the novel nature of the virus and overall paucity of cases, further study is required to better elucidate the causal relationship between the virus and its ophthalmologic effects.

Keywords: Coronavirus disease 2019 (COVID-19); coronavirus; posterior segment; uveitis

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Introduction

Background

The severe acute respiratory disease coronavirus 2 (SARS-CoV-2) virus, which causes the clinical syndrome known as coronavirus disease 2019 (COVID-19), has impacted nearly every organ system of the human body ranging from pulmonary to neurological. The pathophysiologic mechanisms of involvement are highly variable and include thrombotic, inflammatory, and neural mechanisms. A similar wide range of ocular manifestations of the disease has been reported since the onset of the pandemic. 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.) (1), this paper focuses on the posterior segment manifestations which are increasingly recognized and reported.

Rationale and knowledge gap

Involvement of the posterior segment has been more anecdotal in nature with some reports suggesting visually devastating and irreversible effects of COVID-19. Marinho *et al.* reported a case series of 12 patients with cotton wool

spots and intraretinal hemorrhages on OCT and fundus examination in patients with COVID-19 infection (2), but critics point out that these findings are non-specific and can be seen in a variety of retinal disorders (3). Although these anecdotal reports can only demonstrate correlation without causality, the abundance of literature that has emerged strongly suggests a relationship between COVID-19 and various ocular manifestations as described below.

Objective

In this review, we discuss these ocular manifestations related to viral reactivation, primary COVID-19 infection, inflammation, and thrombosis.

Methods

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”, etc. Reports exclusively related to vaccines rather than primary COVID-19 infection were excluded.

Viral reactivation in COVID 19

One of the reported ways in which COVID-19 infection manifests in the eye is through a reactivation of indolent infections and viruses in the setting of concurrent or recent COVID-19 infection. Multiple cases of acute retinal necrosis (ARN) have been reported in both immunocompromised and otherwise healthy patients infected with SARS-CoV-2 (1). ARN in this setting is hypothesized to be secondary to an immune dysregulated state that may have predisposed to reactivation of other viruses classically known to induce ARN, including Herpes Simplex Virus, Varicella Zoster Virus, and Epstein-Barr Virus, found in vitreous samples via polymerase chain reaction (4-6). Reactivation of other infections has also been reported including toxoplasmosis-retinochoroiditis,

in addition to a *de novo* toxoplasmosis retinochoroiditis, and endogenous bacterial endophthalmitis in an otherwise healthy patient, potentially supporting a theory of immune dysregulation (7,8). While these case reports suggest a possible association based on the temporality of the inflammatory response and COVID-19 infection, direct causality is still yet to be established, as is the proposed mechanism of microbial reactivation as opposed to potential primary infection.

Primary COVID-19 infection

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) (9), multiple evanescent white dot syndrome (MEWDS) (10), Vogt-Koyanagi-Harada (VKH) syndrome (11), and punctate inner choroidopathy (both primary disease and reactivation) (12); 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 (MIS-C)] (13), bilateral acute depigmentation of the iris (BADI) (14), and panuveitis (15,16). Ocular treatments reported for these cases included standard of care for uveitis including topical steroids, systemic steroids, and cycloplegics, except for a reported case of MEWDS, which was observed without treatment and subsequently improved. Systemic treatment of COVID-19 was also initiated in some cases with concurrent systemic (i.e., non-ocular) findings and consisted of intravenous immunoglobulins (IVIG), aspirin, and prophylactic antivirals in some uncertain cases (9,10,12-16). The paucity of cases, however, makes it difficult to rule out concurrent, undiagnosed viral illnesses that may be the true etiology of these presentations, as Kawali *et al.* underscore in a review of presumed post-COVID retinitis cases (17).

Acute macular neuroretinopathy (AMN), however, may be more plausibly related to COVID-19 given the multitude of cases reported that have been temporally related to SARS-CoV-2 infection (18,19). A large case series by Dinh *et al.* reported 14 cases of AMN with onset shortly after COVID-19 diagnosis. In this cohort, 67% of cases presented with bilateral features (18). A poorly understood disease, AMN in these cases may alternatively be related to microvascular damage and ischemia, a plausible theory given the known systemic prothrombotic nature of COVID-19

(20-22). The abundance of case reports in a variety of immune mediated manifestations of uveitis combined with the known pro-inflammatory systemic effects of COVID-19 suggest a possible causation or at least predisposition.

Thromboembolic manifestations

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 (23,24). Reports of vascular effects have ranged from cotton wool spots to central retinal artery occlusion (RAO) with subsequent rapid onset neovascular glaucoma (25,26). Several case reports and series have reported RAO and retinal vein occlusion (RVO) in the setting of COVID-19. One case report describes consecutive central and branch RVOs four months apart in the same eye of an otherwise healthy patient (27-32). A case series by Yeo *et al.* reported 13 cases of RAO and 14 cases of RVO in patients diagnosed with COVID-19, with ocular symptoms comprising the initial presentation of the disease in five patients (33). The patients with RAO presented with ocular symptoms within 1–2 weeks of COVID-19 diagnosis while cases of RVO ranged from few days to several months after COVID-19 diagnosis. Most patients had abnormal coagulation and inflammatory markers, suggesting either a systemic prothrombotic state, an inflammatory response which some have likened to a disseminated intravascular coagulation-like syndrome, or a combination of these two mechanisms (25,33). In addition to the abundance of anecdotal reports, a prospective case-control study was conducted in COVID-19 patients with and without pulmonary involvement that demonstrated subclinical changes on OCT including statistically significant choroidal thinning and thinning of the ganglion cell and retinal nerve fiber layer in those with pulmonary involvement, suggesting a possible predisposition to ocular ischemia (34).

It is important to note that further studies on the incidence of RVO and RAO in the period of COVID are conflicting. A prevalence study by Al-Moujahed *et al.* demonstrated no increase in the incidence of RVO and RAO during the time of COVID-19 (35). As most reports of thromboembolic complications in the eye are limited to

case reports and case series, the definite association remains unclear and further research will be needed to fully establish causation.

Other posterior segment manifestations of COVID-19

A broad range of inflammatory and ischemic optic neuropathies and other cranial nerve palsies has also been reported, possibly related to a neurotropic propensity of the SARS-CoV-2 virus. Among the optic neuropathies reported include retrobulbar optic neuropathy; anterior ischemic optic neuropathy; including both arteritic and non-arteritic; papillitis; neuroretinitis; optic neuritis; and myelin oligodendrocyte glycoprotein (MOG) optic neuritis (36-42). Among the non-arteritic ischemic optic neuropathy (NAION) cases included one reported in the setting of prone positioning for acute respiratory distress syndrome and another case in the setting of prolonged, severe epistaxis (36,39). Another report described a case of bilateral sequential NAION over one month after acute viral infection, with lab work-up including unremarkable coagulation panel, supporting an immune over a thrombotic mechanism (43). There has also been report of NAION temporally associated with COVID-19 (37). In addition to neuropathy, several cases of optic neuritis have been reported, supporting a profound immune response to the SARS-Cov-2 virus, with a unique MOG-IgG antibody positive case reported in a young man with rapid onset severe bilateral sequential vision loss that significantly improved with systemic corticosteroid treatment (36,42).

Cranial nerve palsies of the oculomotor, trochlear, and abducens nerves (i.e., cranial nerves three, four, and six) have been implicated in acute ophthalmoplegia and diplopia in COVID-19 infection. A systematic review by Meshref *et al.* summarized 29 patients with SARS-CoV-2 infection, with a distribution as follows: 41.4% with unilateral sixth nerve palsy, 24% with bilateral sixth nerve palsy, 27.6% with third nerve palsy, and 17% with fourth nerve involvement (44).

Conclusions

Research continues to emerge on the various systemic and ocular manifestations of COVID-19. This paper focusses on posterior segment manifestations of COVID-19, but involvement of nearly every segment of the eye has been reported. Ocular manifestations are more commonly reported in adults but can also be seen in children as part

of MIS-C (45,46). Further research is needed to fully determine the causal relationship between COVID-19 and the various ocular presentations described in this paper. However, acknowledging the possibility of these findings is important to further promote research of this novel virus and its effects on the eye.

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