COVID-19 AND OPHTHALMOLOGY

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COVID-19 AND OPHTHALMOLOGY

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PREFACE

The COVID 19 pandemic first reported in the Hubei province of China has since spread to every corner of the world causing a human calamity of humungous proportions. High mortality, enormous morbidity, tremendous pressure on hospitals, shortage of personal protective equipment, economic regression, re- infections were some of the problems faced by governments, medics and public caught totally unawares. As humanity continues to battle the pandemic, medics need to continuously update their knowledge on the clinical manifestations of the disease and also brace up for operational challenges.

Our understanding of the disease continues to evolve. Numerous ophthalmic manifestations of the disease have been reported. In addition to managing the ophthalmic complications of the disease, ophthalmologists also need to adapt to a slew of preventive measures aimed at curtailing the spread of the disease. Lockdowns have delayed much needed eye care in emergency situations. Experts under the aegis of ARC AIOS have pooled together knowledge gleaned from published literature and their experience to bring out this book.

The first chapter is devoted to the operational challenges faced by ophthalmologists during the pandemic. It touches upon the difficulties in attending to ophthalmic emergencies, and challenges for eye donation programs. It briefly dwells on the guidelines issued by AIOS on triaging patients and also suggestions in improving resident education amidst the new “normal”. The next chapter summarizes the pathogenesis of ocular manifestations- retinal, conjunctival, mucormycosis, corneal graft rejections, neuroophthalmic to name a few. Almost every structure in the eye can be affected by COVID 19 and the chapter details the proposed mechanisms in a simple yet comprehensive manner. Ocular surface manifestations have kindled a lot of interest amongst ophthalmologists and the third chapter covers a lot of information on this topic. Also covered are concerns on the impact of COVID 19 and COVID vaccinations on corneal graft survival. Impact of the pandemic on eye donation is also touched upon. Retinal vascular occlusions, infective endophthalmitis, central serous retinopathy have all been reported following COVID 19 infection and the fourth chapter
dedicates itself to the posterior segment complications. The occurrence and management of these complications especially in patients admitted for systemic complications is detailed. Reactivation of retinochoroiditis and viral retinitis is also discussed. The second wave of the pandemic in India also piled in patients with mucormycosis. The fifth chapter deliberates on the management of this life threatening and debilitating condition. The chapter succinctly covers the risk factors, clinical features, applied anatomy, staging system, diagnostic modalities, treatment options, role of debridement, exenteration and prosthetic rehabilitation — a must know for every ophthalmologist in India. The neuroophthalmic manifestation of COVID 19 has always been an enigma and the sixth chapter is devoted to this. It begins with insights on the pathophysiology and follows it up with specific clinical entities believed to be associated with the disease or vaccination. The work up, investigations and treatment modalities are described in great detail.

We have released this work as an ebook to enable better reach during these difficult times. I firmly believe that learning is a continuous process. We eagerly await your comments — both positive and negative as we strive to better ourselves.

Please feel free to email me on the address given below.

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The COVID-19 pandemic has ravaged humanity like no other calamity before. The World Health Organization (WHO) was notified on 31st December 2019 about a cluster of 41 cases of unexplained pneumonia from the Hubei province of China. The phylogenomic analysis identified the pathogenic organism as a novel coronavirus (SARS-COV2), and the disease was called coronavirus disease 2019 or simply COVID-19. The WHO recognized COVID-19 as a pandemic on 11th March 2020. The virus has subsequently spread across all geographic regions of the planet. At the time of this writing, on 27th July 2021, the data from Johns Hopkins showed that there were 194.72 million confirmed cases of COVID-19 globally, with 4.16 million deaths worldwide.

Extrapulmonary manifestations of COVID-19 are not infrequent. Early studies rarely reported ocular manifestations. A large series of 1099 patients from China reported 0.8% to have conjunctival congestion. A recent meta-analysis reported a pooled prevalence of 11.03% among 7300 COVID-19 patients, with conjunctivitis being the most frequent presentation (88.8%), followed by dry eyes (16%), red-eye (13.3%), epiphora (12.8), and itching (12.6%). The ocular manifestations are a subject of intense debates and controversies. For example, the true nature of tissue involvement, potential ocular viral reservoirs, ocular surface and tears, and the direct linking of the virus to ocular tissues, etc. Few studies did not find or could not isolate the virus from anterior and posterior segments, whereas others demonstrated 21.4% positivity from cadaveric retinal samples. A meta-analysis has shown a positive rate of 7.4% from ocular surface samples triggering the belief of possible ocular transmission of SARS-COV2 virus and the need for public health measures to stem such a possibility if confirmed.
The pathogenesis of ocular manifestations of COVID is unclear. It is not surprising that fundamentals of pathogenesis take a backseat during overwhelming pandemics. The tissue tropism is currently believed to involve Angiotensin-converting enzyme (ACE2) receptors and protein transmembrane serine protease 2 (TMPRSS2).6,9,10 Direct cellular invasion and widespread cytokine-driven inflammation contribute to the virulence of the disease. The data presently is limited and molecular mechanisms, causative pathways, and interactions are yet to be deciphered.

Several ocular manifestations associated with COVID-19 have been reported in the literature, which includes but are not limited to conjunctival hyperemia, chemosis, epiphora, dacryoadenitis, tarsadenitis, follicular conjunctivitis, pseudomembranous conjunctivitis, keratoconjunctivitis, nodular episcleritis, anterior and intermediate uveitis, retinal nerve fiber layer thickness, retinal hemorrhages, retinal vasculitis, central retinal artery occlusion, ophthalmic artery occlusion, optic neuritis, papillophlebitis, Miller-Fisher syndrome, nystagmus, tonic pupils, 3rd, 4th and 6th cranial nerve palsies, and posterior reversible leukoencephalopathy.1,7,9 The epidemic of mucormycosis in the setting of COVID-19 pandemic is probably the grimmest of the ocular manifestation with a high incidence of visual loss and mortality11.

COVID-19 presented several challenges to the Ophthalmic practice and involved a broad spectrum of operational, clinical, research, and educational activities. Economic challenges were universally faced due to decreased patient footfall and increased expenditure due to the implementation of several new protocols. The ophthalmic community responded to this challenge effectively with the help of governments, innovations, and innate human resilience.12 The changes brought about include COVID-19 triage, upgrading the protective measures, inducting separate COVID-19 workflows for out-patients, operating rooms, and in-patients13,14.

When faced with an unprecedented COVID-19 challenge, several industries innovated digital solutions and the health care industry is not an exception. The ophthalmic community well embraced telemedicine and the advent of the digital doctor. Digital health models like teleconsultations, virtual hospitals, patient-friendly mobile-device applications, utilization of artificial intelligence (AI) in patient care, e-pharmacies, robotic interventions, virtual educational and research platforms and digital data management are some of the numerous initiatives that catapulted telemedicine to newer frontiers.15-17
The search for the right answers starts from framing the right questions. What do we know about the virus and its ocular cellular interactions? How often and what factors influence the ocular shedding of the virus? Are ocular manifestations the direct result of virus invasion? What are the mechanisms of virus transfer from respiratory to ocular tissues? What is the detection window, and how good are our detection systems? What is the reliability and limitation of the current evidence? How can we best utilize the current evidence for better ophthalmic practice? These and many more would be discussed in the subsequent chapters of this book. This treatise aims to equip both general ophthalmologists and subspecialists with an armamentarium to not only diagnose and treat the ocular manifestations of COVID-19 but also emphasize several logistic measures that would positively impact their clinical practice. While the COVID-19 outbreak remains one of the most significant challenges faced in the history of Medicine, it has also provided significant momentum to innovative practices. In a way, whenever the history of the world will be written for posterity, it would be divided into the pre-COVID and post-COVID eras. The same would be valid for the history of Medicine.

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OPERATIONAL CHALLENGES IN OPTHALMOLOGY DUE TO COVID-19 PANDEMIC: IMPACT ON ALL FRONTS, FROM SERVICE DELIVERY TO RESEARCH

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The COVID-19 pandemic has changed the world and ushered in the “New Normal” that the world is still coming to terms with.\(^1\) The sudden onset of the pandemic had brought in significant challenges both in terms of access to health care including increasing gender disparity and placing vulnerable groups of children and the elderly at risk. While the pandemic rapidly forced the governments to rethink the strategies to fight the increasing numbers, care givers to adapt to new approaches to provide uninterrupted health care services, it still forced citizens into the confines of their homes. This heralded a significant limitation of movement of patients who needed healthcare services. The Government of India had enforced a national-wide lockdown across the country on March 25\(^{th}\), 2020 that resulted in a massive migration of individuals back to their home in the rural hinterlands.\(^2\) This also had a profound effect on the access to health care for these individuals as the hospitals were flooded with the COVID-19 cases.

Eyecare services were also affected in multiple ways — reduction in patient volumes (including those with lower socio-economic status), including specialty as well as emergency care, lower compliance to treatment and increase in teleconsultation. Apart from this, it also impacted eye banking as well as corneal donation program. There is limited evidence that harvested cornea from COVID-19 patients can contain the virus thus leading to systemic infection.\(^3\) Those blind and visually impaired as well as those requiring rehabilitation services were more impacted that their normal counterpart.\(^4\) Hospitals saw a significant reduction of the patient volumes and care being provided due to the travel restrictions and regulations that were imposed in various geographies.\(^5\) Specialty care as well as compliance to therapy were also impacted.\(^6-8\) In terms of compliance, in a survey conducted for glaucoma patients from April-July 2020, nearly 58% of patients were not adherent to treatment.\(^9\) Risk factors included long distance to hospital, lower socio-economic status, use of more than one anti-glaucoma medication, lack of awareness of glaucoma, non-compliant before COVID-19 and stress due to pandemic.\(^9\) Similarly, Bhalerao et.al found that the compliance to treatment for post-keratoplasty patients was also reduced.\(^7\)
The All-India Ophthalmology Society (AIOS) guidelines also helped to triage the patients into emergency, urgent and routine categories to effectively ensure that they are treated on a priority basis.\textsuperscript{[10]} Patients with emergency conditions were able to access care while there was a significant decrease in the routine patients who did not travel to the hospital. Similarly, guidelines from AIOS as well as Eye Bank Association of India (EBAI) helped in laying down the protocol for restarting eye banking and cornea collection services as well as carry out corneal procedures.\textsuperscript{[11]} The unlock also saw a gradual recovery of the patients with the easing of the travel regulations across the country.\textsuperscript{[12]} The sudden inability of patients to visit the hospital forced health care providers to quickly adapt to the rapidly changing scenario with the rising COVID-19 cases in the community. There were many protocols and policies that had to be enforced across healthcare organizations that included re-designing the appointment systems, implementation of personal protective equipment, establishing protocols to possible dissemination of the COVID-19 infection and the development of innovative products including face shields to protect the frontline workers in the hospital.\textsuperscript{[13]} The use of electronic medical records (EMR) in healthcare organizations enables access to information on patient records for decisions at the right time.\textsuperscript{[14]} When the national lockdown prevented patients to reach the hospital, the use of teleconsultations saw a massive increase in adoption of EMR and teleconsultations. This enabled the healthcare providers to have access to the medical records of the patients during telephonic or video consults which greatly ensured efficient care. The use of teleconsultation technology was made possible due to the implementation of the electronic medical records as the use of paper-based records prevented access to right information at the right time for the right advice for the patients.\textsuperscript{[15]} The patient database was utilized to effectively communicate with them regarding the change in the protocols at the hospital due to the restrictions posed by COVID-19 pandemic. The use of SMS through the mobile phones ensured that the modified clinical schedules of the clinicians and appointments status was made possible for timely communication which ensured that the patients were informed of the latest updates. The use of technology tools such as
the EMR and teleconsultation platform enabled organizations to continue to provide the much-needed care for the patients who had to adapt to the changing scenario due to the rising and falling waves of the COVID-19 pandemic. Model for telerehabilitation was also established.\textsuperscript{[16]} The accurate documentation of the clinical condition of the patients ensured that the clinicians had access to the latest scenario of the ocular status of the patient to provide the advice both during a physical consult or a tele-consult interaction. There is a need to invest in digital systems to digitize the clinical, operational and financial aspects of providing eyecare services that helps in the extra-ordinary challenging times such as this COVID-19 pandemic. The “New Normal” is to adopt new technologies to the changing times and to be prepared beforehand to handle situations that do not allow the patients to access healthcare services in the years to come.

Apart from this, there was huge impact on resident education. Most of the residents were deployed to COVID-19 duties, which not only had psychological impact on them, but also had impact on their routine clinical as well as surgical training.\textsuperscript{[17]} In a survey done by Mishra et al involving residents, nearly 80.7% of trainees felt that COVID-19 has negatively impacted their surgical training and 54.8% felt increased stress levels.\textsuperscript{[17]} Most of them however felt online classes and webinars were useful.\textsuperscript{[17]} Moving ahead, we recommend a hybrid model of teaching need to be evaluated, including physical and virtual classroom training as well as simulation based training. Similarly, most of the conferences were modified to either completely online or hybrid mode as well as there was increased use of social media for increasing participants.\textsuperscript{[18, 19]} Online mode of conferences, also had significant impact on carbon footprint.\textsuperscript{[20]} As most of the education, including school education went digital, there is also likelihood of increase in myopia epidemic due to increase screen time, near work and limited outdoor activities.\textsuperscript{[21]} Hence, there is need to identify suitable digital device as well as outdoor activities to prevent myopia pandemic.\textsuperscript{[21]}

Last but not the least is the psychological as well as financial impact – Impact on funding for eye research, future science career as well as financial sustainability of eye
COVID-19 has huge psychological impact and it was found that nearly 33% of practicing ophthalmologists had some kind of depression.\(^{[22]}\) COVID-19 has also impacted lab work, including in-person meeting as well as some lab closures.\(^{[23, 24]}\) In terms of financial impact on practicing ophthalmologists, in a survey from India, nearly 59% reported that they can suffer from serious financial distress in near future.\(^{[25]}\)

In summary, COVID-19 has impacted delivery of eye care services at various fronts and moving ahead, we need to quickly adopt to ‘New Normal’ to combat the impact of COVID-19.

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PATHOPHYSIOLOGY AND BASIS OF OCULAR INVOLVEMENT IN COVID-19

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The prevalence of ocular manifestations in patients with COVID-19 ranges from 2% to 32%. The SARS-CoV-2 virus can affect all the ocular tissues and produce inflammatory or infectious sequelae. There are several proposed mechanisms for ocular involvement. Most widely accepted among the ophthalmological community is the theory that the ocular surface represents a site of inoculation for this airborne virus via inoculation of the conjunctiva by droplets. Other plausible mechanisms include migration of the virus from the nasolacrimal duct, hematogenous infection of the lacrimal gland, and/or inoculation of the regional mucosal immune system in the nasal cavity. An aberrant immune response induced by molecular mimicry and bystander activation has also been proposed. This review aims at understanding the pathophysiologic basis of eye involvement in COVID-19. The review is presented with an outline of each anatomic structure of the eye that can get involved and the pathophysiologic mechanism for the same. Table 1 presents the most important pathologic mechanisms involved in COVID-19 related eye disease.

1. Conjunctiva and Cornea

1.1 Presentations: Acute conjunctivitis, relapsing viral keratoconjunctivitis, haemorrhagic pseudomembranous conjunctivitis, Kawasaki disease.

Symptoms of conjunctivitis are seen more commonly in patients with severe systemic symptoms of COVID-19, though they can rarely present as an initial manifestation of the disease. A 30-fold increase in the incidence of Kawasaki disease-like condition has been reported in children in some parts of Italy with strong association with COVID-19. This atypical presentation is known as multisystem inflammatory syndrome in children (MIS-C). Kawasaki disease, presents with subconjunctival hemorrhages and conjunctival injection, iridocyclitis, punctate keratitis, vitreous opacities and papilloedema. There are reports on corneal graft rejection following COVID-19 vaccination.

1.2 Pathophysiology: The SARS-CoV-2 virus requires the Angiotensin converting enzyme 2 (ACE2) host receptor to infect the host cell, however, ACE2 expression alone is not enough to infer SARS-CoV-2 transmissibility in ocular structures. This is because the penetration of SARS-CoV-2 into the host cell requires the viral spike proteins to undergo proteolytic cleavage by the serine protease, transmembrane serine protease 2 (TMPRSS2) before they can use the ACE2 receptor to internalise. Zhou et al. analysed post mortem eyes as well as surgical specimens and concluded that expression
of ACE2 and TMPRSS2 occurs in the conjunctiva, limbus, and cornea, with especially prominent staining in the superficial conjunctival and corneal epithelial surface. Thus ocular surface cells including conjunctiva are susceptible to infection by SARS-CoV-2, and could therefore serve as a portal of entry as well as a reservoir for person-to-person transmission of this virus. COVID-19 vaccines have been shown to induce SARS-CoV-2 neutralising antibodies and elicit strong Th1-biased CD4+ responses in human. CD4+ Th1 cells have been shown to be the main mediators of corneal graft rejection.\textsuperscript{17} The development of autoimmune diseases has been reported after SARS-CoV-2 infection. Vaccination against SARS-CoV-2 could also trigger auto-immunity, as it has been described with other vaccines. An aberrant immune response induced by molecular mimicry and bystander activation, especially in predisposed individuals, is a potential mechanism.\textsuperscript{20}

2. Sclera and Episclera

2.1 Presentation: Episcleritis and scleritis.\textsuperscript{21,22}

Acute nodular episcleritis, necrotizing anterior scleritis and sectoral anterior scleritis have been reported.

2.2 Pathophysiology: Scleritis is a destructive and vision-threatening ocular disorder that involves deep episclera and sclera. It is mostly an autoimmune disorder, which in half of the cases is associated with an underlying systemic immune-mediated disease. Scleritis has also been reported as an ocular manifestation of viral diseases. The relatively late-onset of the reported episcleritis and scleritis cases suggests a postinfectious immune-mediated response rather than a direct viral infection resulting in the inflammation in the episcleral and sclera.\textsuperscript{21,22} However in all these reported cases, conjunctival sampling for viral nucleic acid was not performed and hence direct inoculation of the virus cannot be ruled out.
3. Anterior chamber

3.1 Presentations: Acute anterior uveitis and reactivation of serpiginous choroiditis. Uveitis can occur either in isolation or in association with COVID-19 related multi-system inflammatory disease.\textsuperscript{23,24}

3.2 Pathophysiology: Looking at the retinal degeneration in the experimental coronavirus retinopathy (ECOR) model,\textsuperscript{25} the impression is given that coronavirus creates two different phases: the first represented by the primary infection which induces the triggering of the immune system, while the second phase is likely to be an autoimmune disease. Both these mechanisms can lead to uveitis. Reactivation of serpiginous choroiditis has also been reported and is attributed to a drop in a predisposed patients’ immunity secondary to SARS-CoV-2 infection.\textsuperscript{26}

4. Retina

4.1 Presentations: Cotton wool spots, retinal haemorrhages, premacular sub-hyaloid haemorrhage, paracentral acute middle maculopathy (PAMM), acute macular neuroretinopathy (AMN), acute retinal necrosis, dilated and tortuous retinal veins have been reported. Retinal vascular occlusions have been reported.\textsuperscript{15} Endogenous endophthalmitis, retinal candidiasis, chorioretinitis and choroidal abscesses have been reported.\textsuperscript{32,34}

Retinal manifestations are either due to direct inflammatory infiltration of the retina or microangiopathic disease from viral infection.\textsuperscript{27-32}

4.2 Pathophysiology: The primary cellular receptor for the entry of SARS-CoV-2 is the ACE2 receptor, which has been detected in the aqueous humour and retinal tissue in humans.\textsuperscript{33} Casagrande et al.\textsuperscript{33} evaluated retinal biopsy samples of 14 eyes of COVID-19 patients and demonstrated viral-RNA of SARS-CoV-2 in three of them. Based on the available literature and current knowledge about the disease and its pathogenesis, the retinal vasculitis could be either because of the thrombo-inflammatory cascade secondary to the “cytokine-storm” immune response or because of direct involvement by the virus. Similar occlusive retinal vasculitis has also been described in other viral infections such as dengue and chikungunya. Considering that posterior segment involvement is usually seen in 1 to 4 weeks following the onset of fever in these diseases, many authors suggest that the immune-mediated pathogenesis as compared to direct virus infection.\textsuperscript{34} COVID-19 viral infection causes a significant strain on the immune system of a patient which could predispose to opportunistic infections. Although the use of steroids is necessary for systemic disease management, this could
further worsen an already compromised immune system, making it susceptible to secondary infections. This is the presumed pathogenesis for endogenous endophthalmitis following COVID-19 infection.\textsuperscript{34}

5. Optic nerve

5.1 Presentation: Optic neuritis, papilledema from raised intracranial pressure and papilophlebitis have been reported.\textsuperscript{35-37}

5.2 Pathophysiology: Optic nerve can get involved by direct neuronal invasion, endothelial cell dysfunction leading to ischemia and coagulopathy, or a widespread inflammatory "cytokine storm" induced by the virus.\textsuperscript{38}

6. Extraocular Motility and Cranial Nerves

6.1 Presentation: Cranial nerve III, IV, and VI palsy associated with COVID-19 have been reported in the literature within a few days of fever and cough onset, most without remarkable radiological features.\textsuperscript{39-41} Post infectious demyelinating conditions such as Miller-Fisher and Guillain Barre syndrome with ocular cranial neuropathies have been reported.\textsuperscript{42} Ocular myasthenia gravis has been described as a post-infectious sequela of COVID-19.\textsuperscript{43} Oscillons and central vestibular nystagmus have been reported in several cases of COVID-19 with neurologic involvement.\textsuperscript{44}

6.2: Pathophysiology:
The virus has not been isolated from the CSF of the patients presenting with optic neuritis and cranial nerve palsy following COVID-19. This indicates that the virus may not be directly involved, rather it may be an immune-mediated insult.\textsuperscript{15} Ocular myasthenia gravis following COVID-19 is proposed to occur due to the presence of antibodies directed against SARS-CoV-2 proteins which may cross-react with acetylcholine receptors and similar components at the neuromuscular junction.\textsuperscript{43}

7. Pupils

7.1 Presentation: Pupillary changes such as mydriasis and cholinergic supersensitivity indicative of tonic pupils and post-ganglionic parasympathetic pupillary nerve fibre damage have been reported.\textsuperscript{45,46}

7.2 Pathophysiology: Adie’s tonic pupil is known to occur after viral infections.\textsuperscript{45} The reported case had a short duration of presentation and hence direct viral infection of the nerves was postulated. However, there is conflicting evidence on the presence of ACE2 receptor and transmembrane protease serine 2 (TMPRSS2) in the ciliary ganglion. This particular reported case\textsuperscript{45} also had the presence of bilateral chorioretinopathy and hence
an immune mediated pathogenic mechanism seems to be more likely. A few other case reports describe suggest a delayed onset Tonic pupil. The proposed mechanism in these cases might be a delayed onset immune response.46

8. Visual Cortex

8.1: Presentation: Usually patients present as acute stroke affecting the posterior visual pathways.47 The incidence of stroke in these patients has been found to be 7.6 times higher than that of patients with influenza. Also, post COVID-19 stroke has been occurring in a far younger than average patient population without classic vascular risk factors.47 These patients may present with homonymous visual field deficits prompting ophthalmologic consultation.

8.2: Pathophysiology: Implicated mechanisms include inflammation, prothrombotic coagulopathy and endothelial injury.47 COVID-19 infection in particular is associated with a vigorous inflammatory response accompanied by coagulopathy, with elevated D-dimer levels and the frequent presence of antiphospholipid antibodies, which may explain the high prevalence of thromboses seen in these patients.48 Secondly, patients with COVID-19 infection are at heightened risk for medical complications, such as atrial arrhythmias, myocardial infarction, heart failure, myocarditis and venous thromboses, all of which likely contribute to the risk of ischemic stroke.48 Thirdly, baseline stroke risk factors, such as hypertension, diabetes, and coronary artery disease, are more common in the cohort of patients with COVID-19.48

9. Orbit

9.1 Presentation: Direct orbital involvement in cases of COVID-19 is very rare. Orbital cellulitis and sinusitis in adolescents have been reported.49 However there has now been a large number of cases reported with COVID associated Mucormycosis involving the orbit paranasal sinuses and the brain (CAM).50 Acute dacryoadenitis has also been reported.51

9.2 Pathophysiology: Orbital cellulitis, especially fungal cellulitis following SARS-CoV-2 is believed to be caused by a compromised initial adaptive immune response in early viral replication, followed by an unleashed innate immune response. COVID-19 likely plays a role in the development of ROCM due to its effects at the entry point of the fungus in the respiratory mucosa where the 78 kDa glucose-regulated protein (GRP78) is upregulated. Additionally the effects on the innate immune system, creation of an
environment of iron overload, propagation of hyperglycemia and the effects on the adaptive immune system all play a role in the increased incidence of mucormycosis that is being seen in the current times.\textsuperscript{51-56}

Diaz et al\textsuperscript{7} reported a case of acute dacryoadenitis in a case with positive SARS-CoV-2 antibodies who developed partial ophthalmoplegia. It was postulated that since patients with COVID-19 can have SARS-CoV-2 in the tear film, retrograde spread to the lacrimal gland via the ductules may lead to dacryoadenitis or the cause may be an immunological response of the lacrimal gland as the patient had positive IgM coronavirus antibodies.

**Conclusions**

Ophthalmic manifestations may be the presenting feature of COVID-19 infection or they may develop several weeks after recovery from COVID-19. Direct infection due to the SARS-CoV-2 virus is possible as the receptors that are required for the entry of the virus into the eye i.e., ACE 2 receptor and the transmembrane serine protease 2 are found in the ocular tissues. Immune mediated tissue damage, activation of the coagulation cascade and prothrombotic state induced by the viral infection can also lead to eye disease. The associated comorbidities and drugs used in the management of COVID-19, especially steroids can worsen the immune system of a patient and are responsible for infections in the eye and the orbit. Finally, though the viral ribonucleic acid (RNA) has been isolated from ocular tissues, the role of the eye as a route for infection has not been conclusively proven.
References

11. Scalinci SZ, Trovato Battagliola E. Conjunctivitis can be the only presenting sign and symptom of COVID-19. IDCases. 2020;20:e00774.


<table>
<thead>
<tr>
<th>Authors</th>
<th>Tissue involved</th>
<th>Presentation(s)</th>
<th>Proposed Pathophysiologic mechanism</th>
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<td>Dou D et al\textsuperscript{14} Gwan WJ et al\textsuperscript{16} Bal et al\textsuperscript{18} Zhou et al\textsuperscript{19}</td>
<td>Conjunctiva and Cornea</td>
<td>Acute conjunctivitis Hemorrhagic pseudomembranous conjunctivitis Relapsing viral keratoconjunctivitis Phlyctenular keratoconjunctivitis Kawasaki disease Corneal graft rejection post COVID-19 vaccination</td>
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|         |                |                                                                                                                                                                                                              | • Penetration of SARS-CoV virus into host cells requires 2 processes  
• First is proteolytic cleavage by the serine protease i.e., transmembrane serine protease 2 (TMPRSS2)  
• Second is interaction with the ACE2 host receptor, facilitating viral envelope/cell membrane fusion and infection of the host cell  
• Expression of ACE2 and TMPRSS2 has been demonstrated in the conjunctiva, limbus, and cornea, with especially prominent staining in the superficial conjunctival and corneal epithelial surface  
• Hence local invasion and inflammation of the ocular surface can be caused by the virus  
• A local cytokine surge caused by an autoimmune response mediated by the virus may lead to corneal and conjunctival involvement  
• COVID-19 vaccines have been shown to induce SARS-CoV-2 neutralising antibodies and elicit strong Th1-biased CD4+ responses in human. CD4+ Th1 cells have been reported to be the main
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<th>Authors</th>
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| Zhou et al\textsuperscript{17} Feizi S et al\textsuperscript{21} Méndez Mangana C et al\textsuperscript{22} | Sclera and Episclera | Scleritis and episcleritis | • Circulating immune complexes containing antibodies to the virus  
• Induction of secondary vasculitis  
• Episcleral inflammation due to direct inoculation as listed for conjunctiva |
| Mazzotta C et al\textsuperscript{23} Bettach E et al\textsuperscript{24} Hooper LC et al\textsuperscript{25} | Anterior chamber | Acute anterior uveitis Panuveitis | • Coronavirus creates two different phases: the first represented by the primary infection triggers the the immune system  
• The second phase is proposed to be an autoimmune disease resulting in uveitis  
• Aberrant immune response induced by molecular mimicry and bystander activation, especially in predisposed individuals, is a potential mechanism for autoimmune diseases including uveitis triggered by SARS-CoV-2 infection or vaccination for COVID-19 |
| Vinores SA et al\textsuperscript{21} Goyal M et al\textsuperscript{22} Casagrande M et al\textsuperscript{23} Shroff D et al\textsuperscript{24} | Retina | Hemorrhages Exudates Cotton wool spots CRVO CRAO OAO PAMM AMN ARN | • Blood retinal barrier breakdown and inflammatory infiltration of the retina following cytokine storm  
• Direct microangiopathic disease from viral infection  
• Severe superimposed infections such as ARN, endophthalmitis in otherwise healthy patients could be as a result of |
<table>
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<tr>
<th>Authors</th>
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<th>Other Observations</th>
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| Sawalha K et al\(^{15}\) Baccarella A et al\(^{16}\) Insausti-Garcia A et al\(^{17}\) Luís ME et al\(^{18}\) | Optic nerve | Optic neuritis Papilloedema Papillophlebitis | • Direct neuronal invasion by the virus  
• Endothelial cell dysfunction leading to ischemia and coagulopathy  
• Widespread inflammatory response i.e., multisystem inflammatory response induced by the virus |
| Belghmaidi S et al\(^{19}\) Oliveira RMC et al\(^{20}\) Greer CE et al\(^{21}\) Dinkin M et al\(^{22}\) Restivo DA et al\(^{43}\) | Extraocular motility, Cranial nerves | Cranial nerve III, IV and VI palsies Miller-Fisher and Guillain Barre syndrome Ocular myasthenia gravis | • Immune mediated insult  
• Virus has not been isolated in CSF hence the above theory is proposed  
• For myasthenia gravis, aberrant immune response induced by molecular mimicry and bystander activation, especially in predisposed individuals, is a potential mechanism for autoimmune diseases triggered by SARS-CoV-2 infection or vaccination |
<p>| Ortiz-Seller A et al(^{45}) | Pupils | Mydriasis Adie’s tonic pupil | • Immune mediated insult |</p>
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<th>Author(s)</th>
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<th>Additional Comments</th>
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<td>Ordás CM et al&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Visual cortex</td>
<td>Oscillopsia Central vestibular nystagmus Acute stroke affecting the posterior visual pathways</td>
<td>• Controversy over possible direct viral insult to the ciliary ganglion vs. autoimmune response</td>
</tr>
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</table>
| Merkler AE et al<sup>47</sup> Panigada M<sup>48</sup> | Orbit | Covid associated mucormycosis Dacryoadenitis Orbital cellulitis | • Vigorous inflammation seen in COVID-19 with elevated D-dimers  
• Prothrombotic coagulopathy due to frequent presence of antiphospholipid antibodies  
• Endothelial injury  
• Direct injury to the cardiac muscle increasing the risk of ischemic stroke |
| Dave TV et al<sup>50</sup> Brosnahan et al<sup>51</sup> Koseler et al<sup>52</sup> López-Muñoz et al<sup>53</sup> Barr FD et al<sup>54</sup> Huang C et al<sup>55</sup> Hollstein T et al<sup>56</sup> Turbin RE et al<sup>49</sup> | | | • Infection with the SARS-CoV-2 virus causes damage to the function and structure of the respiratory mucosal cells allowing the ubiquitous mucor to become invasive  
• GRP78 level was found to be significantly higher in the COVID-19 infection group than the control group. GRP78 is also a receptor that mediates invasion of Mucorales  
• Coronaviruses can infect the macrophages and interfere in their normal functioning. Macrophages are unable to mount the innate immune response against Mucorales  
• Hyperglycemia, either due to steroid treatment or due to insulin resistance that develops following COVID-19, deactivates the |
neutrophils. Neutrophils are the second line of defense Mucorales.

- Hyperglycemia, insulin resistance and diabetic ketoacidosis in COVID-19 result in ubiquitous Mucorales becoming invasive
- COVID-19 causes increased ferritin synthesis by proinflammatory cytokines. Any pathway or milieu that increases iron availability, helps in vital process of Mucorales and contributes to the increased virulence of the Mucorales
- Retrograde spread of SARS-CoV-2 virus via tear film can produce dacyroadenitis
- Immunological response of the lacrimal gland to SARS-CoV-2 infection may also lead to dacyroadenitis

<table>
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<th>Table 1: Literature review on the involved eye tissues with the pathological mechanisms postulated</th>
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OCULAR SURFACE AND ANTERIOR SEGMENT MANIFESTATIONS OF COVID 19 DISEASE

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INTRODUCTION

Coronavirus disease (COVID-19) is an infectious respiratory illness caused by a newly discovered coronavirus, SARS COV-2. The novel RNA encapsulated corona virus (SARS COV-2) was first detected in Hubei Province of China on December 31, 2019.¹ In the next few weeks, it spread rapidly around the globe as a public health emergency of international concern (PHEIC). It was declared as a pandemic by WHO on March 11, 2020.² Wu et al reported that 91.7% of all COVID patients who developed ocular symptoms were positive for SARS COV-2 by RT-PCR from nasopharyngeal swabs while 16.7% had SARS COV-2 isolated from conjunctival swabs.³ It is not uncommon that patients with SARS COV-2 have the live virus in the ocular secretions which may affect transmission and can lead to novel clinical manifestations on the ocular surface.⁴,⁵ Blurring of vision, foreign body and burning sensations have been reported to be the most common symptoms amongst COVID patients who exhibit ocular manifestations.⁶,⁷ These patients also have been reported to have a higher incidence of hand eye contact of 22% versus 7.9% of those who do not have ocular symptoms.¹ In some cases, conjunctivitis has been the presenting feature of the disease even before the respiratory symptoms have set in.⁴,⁵ Xerophthalmia has been reported to be another major feature in COVID related eye disease with an incidence of 4.5%.¹ Corneal involvement and keratitis is reported as a rare manifestation in coronavirus disease.¹ In most reported cases it is believed to be viral or neurotrophic in etiology.⁸ The effect of SARS-2 Cov-19 infection and vaccines on cornea transplant especially in terms of causing early graft rejection is also coming to the fore.⁹,¹⁰ With vaccination against COVID made available, the pattern and onset of rejection in transplanted cornea needs to be looked out for. This chapter provides a comprehensive review of existing literature on ocular surface and anterior segment manifestations of COVID, corneal and ocular surface features seen in the convalescence phase at our institute and a brief mention of implication of COVID 19 on eye banking and keratoplasty practices in this era of ongoing pandemic.

BASIC SCIENCE

The pathogenesis of coronavirus disease is described in detail in the chapter 3 (pathophysiology). In brief, it involves the binding of the viral spike protein to the angiotensin converting enzyme 2 (ACE 2) receptors on human host cells, following which the target cell proteases such as transmembrane serine protease 2 (TMPRSS2) and Furin (a protease enzyme that in humans is encoded by the FURIN gene) interact.
with the spike protein to facilitate the internalization of the virus into the cell. Based on this pathogenic mechanism, presence of these receptors favors the potential of viral localization on the cells that carry the ACE-2 receptors. The amount of expression of ACE 2 receptors on ocular surface remains uncertain and is variably reported. Zhou et al demonstrated the expression of this enzyme on cornea and limbus but lower levels were observed on the conjunctiva.\textsuperscript{11} While SARS COV-2 ribonucleic acid (RNA) has been isolated from conjunctival swabs of patients with active coronavirus disease but direct culture of the virus from the swabs or tear has not been possible.\textsuperscript{12} This may seem to question the transmissibility of the virus via ocular secretions. In contrast, some reports have suggested that tears can be a source of infection even after the patient turns asymptomatic as viral RNA has been detected on ocular surface even after the nasopharyngeal swab turned negative.\textsuperscript{12,13}

CONJUNCTIVA AND COVID 19 DISEASE

Conjunctivitis is the most reported ocular manifestation of coronavirus disease.\textsuperscript{14} Redness, soreness, irritation, and foreign body sensation are the usual symptoms. Conjunctivitis is usually seen in middle stage of the disease.\textsuperscript{1} Rarely it may be the presenting feature of the disease and may be seen in the absence of any other systemic symptoms. Chen et al evaluated 535 patients with active coronavirus disease, out of which 27 patients (5.0\%) had conjunctival congestion with 4 patients reporting it as the initial symptom.\textsuperscript{1} Hand eye contact was noted to be an independent risk factor in these patients.\textsuperscript{1} Examination findings in most cases of conjunctivitis with coronavirus disease are suggestive of mild follicular reaction with minimal watery discharge and significant redness. The affliction could be both unilateral and bilateral.\textsuperscript{15} Navel et al reported a case of severe hemorrhagic conjunctivitis with pseudo-membrane formation 19 days after onset of systemic disease and 11 days after intensive care unit admission.\textsuperscript{16} In a case series from India, Sindhuja et al reported that 8.66\% (11/127) patients with mild to moderate coronavirus disease developed conjunctivitis.\textsuperscript{2} Conjunctival congestion was reported to correlate with the presence of respiratory symptoms, but hand eye contact was not found to be a significant independent risk factor.\textsuperscript{7} Cheema et al reported a case where the patient presented with redness, discharge and photophobia without any respiratory symptoms and COVID testing revealed positive reports on both nasopharyngeal and conjunctival swabs. This patient was treated on lines of viral
keratoconjunctivitis initially with oral valacyclovir and topical moxifloxacin with good outcomes.  

**EPISCLERITIS IN COVID 19 DISEASE**

Episcleritis has been described as an initial symptom of COVID-19 disease in two case reports. Otaif et al reported a case of a 29-year-old male who presented with unilateral episcleritis three days before the onset of respiratory symptoms. Mangana et al also described a case of a 31-year-old female with nodular episcleritis in the setting of active COVID disease. Both cases were managed with topical low dose steroids along with systemic management for pulmonary COVID disease.

**CORNEA AND COVID 19 DISEASE**

Keratitis in COVID 19 disease is a rare occurrence. It is not often associated with conjunctival congestion. Chen et al reported keratitis in 13/508 patients without conjunctival congestion as opposed to 1/27 patients with conjunctival congestion. COVID patients can present as keratoconjunctivitis and non-specific corneal cellularity with associated conjunctival congestion but are negative on microbiologic evaluation. These lesions are persistent and may have recurrent episodes. SARS COV-2 may often decrease the innate immunity and increase inflammatory mediators, like cytokines, and thus allow reactivation of HSV keratitis. A report by Majtanova et al suggested a two-fold increase in the incidence of HSV 1 keratitis amongst COVID patients compared to pre COVID times. The study population was positive for SARS COV-2. Seasonal variation with predilection for winter months were noted. They described various ocular manifestations due to HSV which included blepharitis, conjunctival hyperemia, dendritic keratitis, corneal haze, uveitis, trabeculitis with raised intraocular pressure. All patients resolved with topical and systemic acyclovir. Peripheral corneal involvement with recurrent keratoconjunctivitis and seronegativity to adenovirus and HSV has also been reported. The patient was COVID positive with recurrent keratoconjunctivitis in left eye, virus was isolated in the tear and conjunctival swabs. The initial ocular samples from the first two weeks of illness were positive for SARS COV-2 which was followed by rapid clearance of the virus from the conjunctiva. One week after symptoms subsided the patient presented with recurrent red eye and ocular discomfort in the left eye with a sterile peripheral corneal epithelial involvement and with increasing levels of
inflammatory cytokines, supportive treatment, and control of inflammation with topical steroids leading to resolution.\textsuperscript{21} Transient keratoconjunctivitis with corneal haze that resembles adenoviral keratoconjunctivitis has been described in a series from Brazil.\textsuperscript{22} In this series, Keratitis developed in 3.7\% of patients with bilateral involvement and had rapid clinical cure within one week following instillation of topical steroids.\textsuperscript{22}

SARS COV 2 has also been reported to cause conjunctivitis, keratoconjunctivitis, anterior uveitis, optic neuritis and retinopathy which may be sight threatening. These manifestations are similar in clinical profile to those caused by HSV, Echoviruses, Enteroviruses, Cox-sackie and Influenza viruses.\textsuperscript{17,23}

The pandemic also provided a unique opportunity to study the demographics and outcomes of infectious keratitis. While microbial keratitis (MK) remains the leading cause of ophthalmic emergencies, changes in social behavior, travel restrictions led to decreased presentation to the emergency department (ED). The possible reduced chances of trauma, use of local or traditional medications, local physician consultation and use of teleophthalmology services where available might be the reason for the decreased presentation to ED.\textsuperscript{24} A study from India noted decreased rate of presentation during the initial stage of infection and rather most patients presented with advanced disease which could account for worse outcomes of infectious keratitis. There was a reported a seven-fold increase in the use of traditional medications and twice the rate of delay in presentation to the ED.\textsuperscript{24} The delay was more in patients from orange and red zones compared to green zones.\textsuperscript{25} The chance for presentation with perforation, need for surgical intervention was reportedly higher. Further, the lack of availability of donor cornea led to subsequently worse outcomes in such patients.\textsuperscript{26,27}

**COVID 19 AND GRAFT REJECTION**

Studies have hypothesized that COVID 19 induces a pro inflammatory cytokine storm, and the virus is known to enter tissues that have an expression of ACE2 receptors. Infection with subsequent immune dysregulation makes the graft liable to rejection. Jin et al\textsuperscript{9} reported graft rejection in a 31-year-old African American woman with a previously clear graft for PKP for left eye keratoconus. The patient had an uneventful post-operative course and was compliant to the post-operative regimen. Three months after surgery the patient presented with new onset of decreased vision, redness, and pain. There was conjunctival congestion, full thickness graft edema, diffuse keratic precipitates involving the graft. Five days after the onset of ocular symptoms, the
patient tested positive for COVID RT PCR. She had no other symptoms other than dysgeusia, fever and eye involvement. The patient was started on topical steroids, which controlled the graft rejection but subsequently led to failed graft and required a re-graft. In another report, a 32-year-old man presented three weeks after testing positive for COVID. The patient had a right eye clear graft following optical keratoplasty for corneal scar and had normal IOP and stable vision of 20/60. After contracting COVID-19 infection, the patient needed hospitalization for respiratory distress and developed subsequent decrease in vision in the right eye. The presenting vision three weeks later was counting fingers and IOP was normal, the graft was hazy with epithelial bullae and stromal edema, Descemet’s folds and keratic precipitates. The topical steroids were stepped up and graft rejection episode subsided, but the graft eventually failed. The above two case reports suggest that the immune dysregulation due to COVID-19 infection may lead to increases in pro-inflammatory cytokines levels and loss of immune privilege of the cornea. While the definitive cause effect relationship is lacking the possibility of a temporal association and the underlying heightened immune response is hypothesized as the possible mechanisms for triggering acute graft rejection in above cases.

COVID VACCINATION and KERATOPLASTY

A few case reports describe acute graft rejection following COVID-19 infection showing a temporal relationship. However, a recent study of COVID mRNA vaccine amongst solid organ transplant recipients did not list acute rejection or major allergic reactions amongst reported side effects. Vaccination for COVID-19 triggers a humoral and adaptive cell mediated immune response. This is evident from the elevation of anti-spike protein neutralizing antibody. Further, there is an increase in the titers of CD4+, CD8+ T cell responses and levels of proinflammatory cytokines IFNα. However, a causal relationship between vaccination for COVID-19 and development of acute graft rejection might not be possible.

Ravichandran et al reported acute graft rejection in a 62-year-old man 3 weeks after first dose of COVID-19 recombinant mRNA vaccine. The patient had undergone penetrating keratoplasty (PKP) two years earlier for corneal scar in his right eye. The graft was clear prior to rejection episode and did not have any loose sutures, vascularization and synechiae and the patient was maintained on topical steroids once a day. 3-weeks post vaccination the patient experienced acute endothelial graft
rejection with corneal stromal edema and anterior chamber reaction. Treatment was initiated for graft rejection.\textsuperscript{30} Pylactou et al reported two cases of DMEK rejection after administration of COVID vaccine.\textsuperscript{31} In their first patient, rejection occurred 7 days after the first dose and in second patient 3 weeks after second dose. The first patient had surgery done 3 weeks earlier and was on a regimen of topical steroids. The second patient had bilateral DMEK three years earlier and was off steroids. She experienced bilateral graft rejection. Both patients were treated with stepping up of topical steroids with reduction in corneal edema and subsidence of rejection.\textsuperscript{31}

Cornea is an immune privileged organ, nonetheless, post vaccination an increase in the CD4+, CD8+ T cells and possibly an antibody mediated response by pro inflammatory cytokines is possible. In this scenario, it is hypothesized that the hyperactivation of the immune mechanisms may trigger acute graft rejection, and such episodes require enquiring for a history of vaccination, early diagnosis and initiating specific treatment for control of such episodes. As the growing pandemic warrants timely mass vaccination, it is important for physicians to be aware of the possibility of triggering graft rejection and the need to step up steroids and keep transplant patients under close follow up during and after vaccination.

**POST COVID CONVALESCENCE PHASE**

Some patients in the post recovery phase of COVID have been seen in cornea with ocular surface and corneal manifestations. These are likely related to sequelae of the illness or secondary to the management therapy and treatment in the active phase of the disease. The clinical manifestations we have observed has been conjunctivitis, episcleritis, keratitis, Herpes zoster reactivation and dry eyes (unpublished data).

**EYE BANKING IN THE COVID ERA**

India has ranked as an “almost sufficient” country in the recent global survey on eye banking and corneal transplantation and is second to the United States in terms of corneal collection and utilization.\textsuperscript{32} Eye banking services were severely affected in the wake of COVID 19 pandemic. A survey of eye banks registered with EBAl and with a collection >500 per year suggested that 8/20 eye banks did not collect tissues during April–June 2020 and 41/62 corneal surgeons did not perform corneal transplantation.\textsuperscript{33} The significant drop in the corneal retrieval and utilization provided a felt need for exploring alternative sources of storage of corneal tissues such as glycerol preservation.
In the Indian context the most important indication for corneal transplantation is therapeutic penetrating keratoplasty (TPK). Eyes with a large perforation, diffuse corneal melt with poor tectonic support of cornea and involvement of infiltrates to corneal limbus are likely to require a TPK. In the times of a pandemic with restricted eye banking activities there is a definite need to triage patients. With lockdown exit, eye banks need to develop robust recovery guidelines and initiate stringent biosafety measures for eye bank technicians and recipients. These include developing a medical history-based algorithm to exclude retrieval from COVID positive donors. Hospital cornea retrieval program (HCRP) can be restricted to non-COVID hospitals. Minimizing voluntary or home-based retrieval where medical history might be insufficient as regards to cause of death. Opinion of eye bank medical directors needs to be sought to resolve queries on donor medical history and screening if needed. The lessons learnt from the pandemic included development of robust biosafety guidelines for tissue collection and distribution, and adherence to defined screening algorithms for donor tissue retrieval, triaging patients based on priority for TPK, and having standby glycerol preserved tissues for emergency use.34,35

Another issue of concern is the risk of transmission of the virus through the route of corneal transplantation from COVID-19 affected donors. Presently, the eye banking practices do not mandate RT-PCR testing of the donors and rely on the medical history to rule out the donors where there is a risk of COVID-19 infection. While a meticulous history from records and from the family members of the deceased is an efficient method, the asymptomatic donors can be missed. In the study conducted at Ramayamma International Eye Bank, LVPEI, the overall prevalence of SARS-CoV-2 was 1% (2% for conjunctival, and 0% for corneal samples, p value=0.5) in the donors who were found suitable for cornea recovery and transplantation (article in press).35 The findings of exceptionally low positive rates in the donors’ samples validate the criticality of history-based donor screening and does not support the necessity of post-mortem PCR testing as a criterion for procurement and subsequent use for corneal transplantation.
CONCLUSION

The ophthalmic features may develop at any stage of the COVID 19 disease. A definite cause effect relationship is difficult to determine. Mild follicular conjunctivitis is the most common ocular manifestation. Xerophthalmia may also occur. Rarely, episcleritis and keratitis may be seen in the setting of COVID 19 disease. Both COVID 19 disease and vaccination has been seen to trigger graft rejection, hence it is imperative to step up steroids in these circumstances.

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COVID-19 AND POSTERIOR SEGMENT MANIFESTATIONS

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**Introduction**

Ever since the outbreak of COVID-19 pandemic multiple ocular manifestations have been reported, suggesting involvement of the ocular surface, anterior segment, posterior segment and the orbit. These manifestations may be due to direct invasion by the virus, secondary build-up of inflammatory cascades, the related systemic stress, management of the disorder and its complications.\(^1\) This chapter focuses on posterior segment involvement by COVID-19. The pathologies discussed briefly include retinal vascular occlusion, central serous choroidopathy, uveitis and endophthalmitis.

**Retinal vascular occlusions**

Since the onset of the COVID-19 pandemic, possible association of retinal vascular occlusions and COVID-19 that have been reported.\(^{1-7}\) Suggested associations between the infection itself as well as vaccination for COVID have been reported. Proposed hypotheses include endothelial insult following COVID-19 infection that follows a tendency for vasculitis, along with a thromboembolic-hyercagulability tendency.\(^1\) Direct affliction of endothelial cells has been noted in post-mortem eyes (2). On autopsy, diffuse small vessel thrombosis due to complement-mediated microvascular injury and platelet-fibrin microthrombi have been noted.\(^7\) Elevated Prothrombin time, D-Dimer levels and inflammatory cytokines have been reported in preliminary analysis in support of this hypothesis.\(^7\) Both retinal arterial and venous occlusions have been reported. The ocular management chosen in reported cases in the literature has not been very different from any other case of retinal vascular occlusion apart from the additional management of COVID itself.

**Retinal artery occlusion:** Multiple cases of CRAO have been reported. The reported time duration varies from early phase following COVID infection to weeks of COVID.\(^{1-4}\) It has been seen in both hospitalized patients on multiple drugs for COVID with ICU support, as well as those with mild disease being managed at home. A report by Bapaye et al described bilateral simultaneous CRAO as well.\(^3\) Interestingly some of these patients had pre-existing systemic disease while some did not have any. Not surprisingly cases with arterial obstruction of the cranial vasculature have also been noted simultaneously with retinal arterial occlusions.\(^1\) As per previous reports, these have been noted in almost half of the cases of CRAO reported following COVID. We highlight below a few cases seen by us in our experience.
Case 1: A 31-year-old male presented to our clinic with sudden painless loss of vision in his left eye for one day. He reported having high grade fever for 3 days and tested positive for COVID-19 on RT-PCR. This patient however also had a history of low platelet counts after developing fever. Fundus examination showed cherry red spot with box-caring of retinal arteries suggesting a diagnosis of CRAO in the left eye. The retinal perfusion was absent on examination and hence an urgent paracentesis was performed (Fig 1). He was investigated thoroughly for any systemic risk factors, including hypertension, blood sugar fasting and post-prandial, serum lipid profile, serum homocysteine, carotid doppler, 2D echo, which were either normal or negative. Nine months after the disease the vision remained stable with no improvement (as informed on telephonic consultation).

![Fundus picture of left eye showing CRAO. Pale retinal edema, cherry red spot, non-perfused vessels and box-caring are appreciable.](image)

**Fig 1: Legend:** Fundus picture of left eye showing CRAO. Pale retinal edema, cherry red spot, non-perfused vessels and box-caring are appreciable.

**Retinal Vein Occlusion:** In general, venous thrombosis has been noted in up to 25% of patients in ICU due to COVID, and central venous thrombosis is also known.\(^5\) Cases of RVO have also been noted following COVID-19 infection. These have been reported in young patients without any systemic risk factors, as well with pre-existing risk factors.\(^5-7\) All manifestations including BRVO, HRVO and CRVO have been reported (5-10). Literature suggests RVOs involving all individuals such as asymptomatic family
members of COVID infected individuals, those with mild symptoms, as well others who required hospitalization for COVID. The onset of RVO have been variable, some during active infections, whereas others noted after it. Authors have proposed e venous occlusion secondary to both direct vasculitis as well as thrombotic tendency secondary to increased inflammatory cytokines.

Case 2 represents images of a 46-year-old-male who developed vision loss 2 days following covid vaccination in left eye. Fundus photographs taken at referring centre showed BRAO in the left eye with tortuous vessels and OCT confirmed the nerve fibre layer stasis (Fig 2). An urgent paracentesis had been done. Next day we noted worsening with increase in vascular tortuosity and development of retinal haemorrhages in all quadrants suggesting development of RVO. OCT showed increase in the SRF and macular edema. No active therapy was given and two weeks later the edema has subsided significantly with reduction in retinal haemorrhages, vascular tortuosity and retinal edema. The patient also reported a subjective improvement in vision though quantitatively it was 20/25.

Fig 2A: BRAO with corresponding nerve fibre layer edema on OCT
Fig 2B: first follow up after paracentesis shows development of RVO with macular edema and SRF on OCT. Cotton wool spots, retinal haemorrhages and tortuous vessels are appreciable.

Fig 2C: After 2 weeks resolution of macular edema, haemorrhages and reduction of nerve fibre layer edema were noted.

Case 3 represents images of a 58-year-old male who had multiple risk factors for retinal vascular occlusions including diabetes mellitus (DM), hypertension (HTN), and coronary artery disease (CAD). 7 months prior he had developed COVID for which he was hospitalized for 2 days and managed with oral HCQ. At that time eye evaluation had revealed retinal haemorrhages and patient had not noted vision loss. No therapy was advised. He received COVID vaccination 1 month prior following which he developed
visual field loss. The patient described this as occurrence of black lines in visual field with loss of vision. On examination, he had a visual acuity of 20/40 in left eye, retinal hemorrhages in the inferior half of the retina suggesting inferior HRVO and macular edema (Fig 3A). He received an intravitreal injection of anti VEGF agent, following which vision improved to 20/30, improvement in the central scotoma. Also retinal haemorrhages diminished significantly and macular edema resolved (Fig 3B). The patient is yet to return for next follow up.

Fig 3A: Hemiretinal vein occlusion with macular edema, Inferior retinal haemorrhages are seen and OCT shows CME and SRF.

Fig 3B: At month after intravitreal injection. Resolution of retinal vein occlusion along with reduction in macular edema is noted. The retinal thickness is normalized.
The 3 cases discussed by us and literature cited resonate with a possible tendency for development of retinal vascular occlusion following COVID or COVID vaccination. At this point of time, evidence lacks understandably to provide a stronger cause-effect relation.

**Stress, Steroid and SARS COVID-19: Post pandemic blooming of central serous chorioretinopathy**

Systemic steroids are used as life-saving measure in the management of SARS-COVID-19 infection especially when there is lowering oxygen saturation and worsening of the chest imaging, to fight, against the cytokine storm and proinflammatory state of the body.\(^{[10]}\) We report here three cases of central serous chorioretinopathy (CSCR) who were treated with oral corticosteroids for SARS-COVID-19 related pneumonia.

Case 1: A 34-year-old male presented with sudden onset scotoma in his right eye (RE) for 4 days. Medical records revealed prior treatment with tablet methylprednisolone (16mg/day) orally for 10 days for SARS-COVID-19 related pneumonia a month ago. He did not report any other physical or emotional stress apart from COVID-19 related hospitalization. The best corrected visual acuity (BCVA) was 20/60 in RE and 20/20 in LE respectively. Fundus examination revealed a 3DD sub-retinal fluid with fibrin centred at the fovea in RE whereas, LE was unremarkable. Optical coherence tomography (OCT) showed a neurosensory detachment, subretinal hyperreflective material, a serous pigment epithelial detachment with micro-break at its apex suggestive of CSCR. [Figure 4 A&B]
Figure 4: Colour fundus photograph (A) of right eye shows large neurosensory detachment with subretinal fibrin at macula; corresponding optical coherence (B) tomography image shows neurosensory detachment, subretinal hyperreflective material, a serous pigment epithelial detachment with a possible micro-rip at its apex.

Case 2: A 32-year-old male presented to our casualty with sudden onset scotoma bilaterally for 2 days. He was diagnosed and treated with oral methylprednisolone (16mg/day x 1 week) for SARS-2 COVID-19 related pneumonia 2 weeks prior. Though the BCVA was 20/20, fundus evaluation revealed sub-retinal fluid with fibrin in both eyes which, was confirmed by OCT. Patient also attributed his psychological distress to the current illness.

Case 3: A 28-year-old student was referred to us with complaints of sudden onset metamorphopsia for 24hrs in both eyes. He was recently diagnosed and underwent treatment with oral methylprednisolone (16mg/day x 1 weeks) for SARS-COVID-19 related pneumonia 10 days ago. Similar to previous cases, bilateral CSCR was documented in fundus and OCT. Psychological stress owing to the hampering of his academic and daily activities along with hospital admission and economic burden in view of COVID-19 was also noticed. Considering this being the first episode and that the inciting agent was stopped, we decided to observe these cases with abstinence from steroids as possible. [Table 1]

Proposed pathophysiology of steroid induced CSCR:
Systemic corticosteroids precipitate choroidal vascular vasoconstriction leading to ischemia and stimulation of hypoxic WBCs resulting in inflammation and breakdown of outer blood retinal barrier. Exogenous steroids and factors raising endogenous
cortisol, such as stress, cause CSCR by altering the choroidal permeability along with increased capillary fragility leading to leakage of fluid into sub-retinal space.\textsuperscript{[13]} In addition, cortisol causes suppression of fibroblastic activity and damage to the RPE cells/tight junctions, reversal of polarity of the RPE cell, leading to pumping of fluid into the sub-retinal space. Although association between the duration and dose of systemic steroid use with the risk of CSCR development has not been documented;\textsuperscript{[14]} Wakakura et al reported a prolonged latency of >6 months of CSCR onset in patients taking <20 mg daily dose of prednisolone, which doesn’t hold true in our series possibly pointing towards the cumulative impact of psychological stress.\textsuperscript{[15]} Exogenous corticosteroids along with stress induced increase in endogenous cortisol levels could have acted as a trigger for the occurrence of CSCR.

Table 1: Patient profile and details about steroid intake and probable cause of psychological distress

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age in years /gender</th>
<th>Form of steroid intake (Dose: mg/day)</th>
<th>Duration of intake (days)</th>
<th>Latent period of onset of symptom (days)</th>
<th>Laterality of CSCR</th>
<th>Probable cause of psychological distress</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34/Male</td>
<td>Methylprednisolone (16)</td>
<td>10</td>
<td>14</td>
<td>Unilateral</td>
<td>Hospital admission and ongoing illness</td>
</tr>
<tr>
<td>2</td>
<td>32/Male</td>
<td>Methylprednisolone (16)</td>
<td>7</td>
<td>14</td>
<td>Bilateral</td>
<td>Hospital admission and ongoing illness</td>
</tr>
<tr>
<td>3</td>
<td>28/Male</td>
<td>Methylprednisolone (16)</td>
<td>7</td>
<td>10</td>
<td>Bilateral</td>
<td>Hospital admission, hampered academic and daily life activities</td>
</tr>
</tbody>
</table>
Infected Endophthalmitis

COVID-19 though starts with pulmonary involvement, it can progress to a fatal multi-organ system affection and death in older individuals with existing co-morbidities.\cite{16,17} In hospitalised patients systemic bacterial and fungal infections have been reported, the incidence of which increased with duration of hospital and intensive care unit admission.\cite{18} The reported ophthalmic infectious manifestations included conjunctivitis, keratoconjunctivitis, episcleritis, neuroretinitis, dacryoadenitis and orbital cellulitis.\cite{19,23} There are few reports of intraocular infection, such as endophthalmitis, in patients hospitalized and treated for COVID-19 (Fig 5).\cite{24,26}

![Baseline, 1 Month, 6 Months](image)

Figure 5: A case of post covid endogenous fungal endophthalmitis managed with vitrectomy and intravitreal antibiotics. The patient had multiple foci of subretinal infiltrate with a large macular abscess apart from vitritis and subretinal haemorrhage at presentation. Over the course of therapy, the vitritis and haemorrhage diminished, and the exudates organized to form a scar at 6 months.

There are at least four distinct types of posterior segment infection one may see in COVID-19 patients (unpublished author’s data yet).

The first variety is multifocal retino-choroiditis sparsely distributed in posterior pole, and or beyond arcade and equator. They manifest as small irregular discrete areas of yellowish coloured retino-choroiditis or choroiditis patches. This type of lesion responds well to systemic broad-spectrum antibiotic and antifungals. Most patients with these types of lesions are systemically stable.

The second variety is a focal endogenous endophthalmitis characterised by single pre-retinal exudate on the posterior pole protruding towards the vitreous cavity with associated overlying vitritis.
The **third type is multifocal endogenous endophthalmitis** where you can see multiple small pre-retinal exudates protruding towards the vitreous with overlying vitritis, this is very similar to the second variety. Vitreous biopsy and multiple intravitreal antifungal injections is required to save the eye ball and the vision to some extent. It responds well to above treatment, but the final visual acuity depends on the amount of scarring.

The **fourth variety is diffuse endogenous endophthalmitis**, it involves the entire vitreous cavity and most part of retina. This requires an urgent pars plana vitrectomy followed by multiple intravitreal antibiotics. This variety may lead to retinal detachment and poor visual recovery. Silicone oil injection may be required if retina is necrosed and detachment is anticipated. The diffuse variety is often associated with poor systemic conditions and death. Poor prognostic factors are delayed presentation, diffuse involvement, non-compliance to treatment, infrequent intraocular anti-fungal infections, delayed vitrectomy, etc. Significant number of culture positive endogenous endophthalmitis in COVID-19 patients are due to fungal pathogen of which candida species is the commonest organism, other organisms are Aspergillus species and Mucorales.

The intraocular antifungal used commonly is amphotericin B which has a half-life of 7 days in presence of endophthalmitis, after vitrectomy the half-life is reduced to 4.5 days so twice weekly dose of intravitreal amphotericin B injection is recommended. The other drug that can be used is intravitreal voriconazole, however, half-life of voriconazole is only 2.5 hours so frequent dosing is required with hospital admission. The systemic treatment depends on presence of candidemia and invasive aspergillosis. In life threatening candidemia intravenous injection of lyophilised amphotericin B is preferred drug. In non-life threatening candidemia Posaconazole is used 300 mg twice daily and then 300 mg once daily intravenous or oral route. In absence of invasive systemic fungal infection systemic antifungals have limited role in endogenous endophthalmitis.

**Relation with COVID-19 infection:**

The duration of eye manifestation and COVID symptoms has varied from 1-10 weeks. These patients often reveal hospitalisation and ICU admission for COVID care. Most common systemic co morbidity is diabetes. These patients usually give history of receiving systemic steroids and anti-viral medications.
Three classes of drugs used to treat the patients with COVID 19 infection can increase the risk of endogenous endophthalmitis. These drugs are systemic corticosteroids, broad-spectrum antibiotics, and IL-6 inhibitors (tocilizumab). Corticosteroids are known to cause immunosuppression and increases the risk of bacterial/ fungal infection. Broad-spectrum antibiotics kill the bacteria and allow growth and multiplication of the commensals, including the yeasts. The IL-6 inhibitors (such as Tocilizumab) impair the function of neutrophil, macrophage, and T cells, thus increasing the risk of fungal infection. During COVID care these patients often shows raised inflammatory markers, anaemia, thrombocytopenia.

Endophthalmitis is not uncommon in hospitalised COVID-19 patients, a routine eye examination may be useful in hospitalised and debilitated COVID-19 patients for early detection and appropriate eye care.

**Inflammatory disorders**

COVID-19 patients are known to have lymphopenia along with decreased lymphocyte function, and low CD4+, CD8+ T cell numbers, B cells, and natural killer (NK) cells. Cell markers of immunosuppression and T-cell exhaustion have also been documented in patients with COVID-19. Other biological and clinical markers of acquired immunosuppression such as eosinopenia, and multiorgan failure are also known, resulting in dysfunctional immune responses. Different stages of the infection include an elevated number of macrophages, hyperactivation of T cells and the release of increased plasma levels of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNFα), leading to what is termed as “a cytokine storm” and cytokine release syndrome. This immune dysregulation as a result of COVID-19 infection has been associated with increased incidence of co-infections and secondary infections.

In line with this discussion, Providencia et al had reported a case of reactivation of serpiginous choroiditis following COVID-19. Gupta et al also reported a case of viral retinitis in a patient with SARS-Cov-2 infection. However, this patient also had a past history of undergoing chemotherapy for diffuse large B cell Lymphoma and the viral infection could have added to the immunosuppressed state thus leading to reactivation of the VZV virus in their case. Occurrence of all kinds of uveitis, anterior, intermediate and posterior, has been noted in literature. Goyal et al. have reported multifocal choroiditis 1 week after COVID vaccination in a previously healthy young
subject. The use of immune-modulator therapy in patients of uveitis also needs to be addressed carefully in presence of COVID-19.\textsuperscript{[36]}

Case: Herein we discuss a patient who had past-history of Acute Retinal Necrosis (ARN) in 2016 and had been under regular reviews. The disease was quiescent and the patient was maintaining a visual acuity of 20/20. The patient reported in December 2020 with complaints of floaters and a decrease in vision to 20/40 in his right eye. Examination revealed the presence of retinitis lesions in periphery which were characteristic of a reactivation of ARN. The patient gave a history of an episode of COVID-19 infection 1 month prior to the onset of ocular complaints (Fig 6,7).

![Fundus picture of RE with laser marks in periphery and no active retinitis lesion in 2016.](image)

Figure 6: Fundus picture of RE with laser marks in periphery and no active retinitis lesion in 2016.
Figure 7: Fundus image of RE with areas of active retinitis at the time of presentation in after 4 years during pandemic

Prior to this patient, we have described two patients who had recovered from COVID 19 and presented with a typical clinical picture of ARN with dense vitritis and necrotising retinitis. The vitreous samples from both the patients tested positive for HSV-1 by RT-PCR. This report supported that COVID 19 can result in an immune dysregulated state thereby leading to reactivation of Herpes viruses and subsequently leading to ARN.[35] COVID-19 can therefore lead a state of immune-dysregulation which can result in reactivation of viruses. It is therefore important for clinicians to be aware of the possibility of viral reactivations and secondary infections in such patients.

While we, along with other authors of the cited publications, have noted these retinal and uveal manifestations in the eye, it must be remembered that it is very difficult to directly implicate COVID or its vaccination for these disorders. We should wait for evidence to build up, before we contemplate a change in clinical approach to these disorders in the era of the current pandemic.

**Contributor Statement:**

Dr SKP: CSCR, Dr BT: RVO, Dr MT: Inflammatory disorders, Dr SN: Infective endophthalmitis
References


COVID ASSOCIATED MUCORMYCOSIS: RISK FACTORS, CLINICAL PRESENTATION AND MANAGEMENT OUTCOMES

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Conflict of Interest: None
I. Introduction
Mucormycosis is an aggressive, debilitating and potentially life-threatening opportunistic fungal infection caused by fungi of the order *Mucorales*. The overall prevalence of mucormycosis worldwide before COVID-19 pandemic was 0.005–1.7 per million.\(^1\) Uncontrolled diabetes mellitus is the most common underlying risk factor for the development of mucormycosis. India ranks second in the number of diabetics globally\(^2\) and has seen the highest burden of mucormycosis, nearly 80 times that in other parts of the world, with a prevalence of 0.14 per 1000.\(^3-5\) During the COVID-19 pandemic, a surge in mucormycosis has been reported globally with maximum numbers of cases reported from India. Infact India accounted for more than 50% of reported cases, particularly among patients with uncontrolled diabetes. While mucormycosis can affect the nose, sinus, orbit, CNS, lung, gastrointestinal tract and skin, the rhino-orbital-cerebral (ROCM) is the most common presentation.

II. Risk factors for the development of ROCM
While COVID-19 infection has been the most common risk factor for developing mucormycosis, other risk factors include the following:\(^6,7\)
- Uncontrolled diabetes and diabetic ketoacidosis
- Patients on immunosuppressive therapy
- Hematological malignancy
- Post organ transplant
- Primary or secondary immunodeficiency
- Iron overload
- Prolonged Intravenous antibiotic use
- Human immunodeficiency virus (HIV) infection
- Renal failure
- Liver diseases
- Chronic alcoholism
- Chronic kidney disease
- Pulmonary tuberculosis
- Malnutrition and low birth weight in the pediatric population.
III. Routes of spread:

i) Direct spread

Direct spread can occur through following pathways (Figure 1):[8]

a. Paranasal sinuses → Orbit and the brain
b. Pterygopalatine fossa → Infratemporal fossa, orbit via the inferior orbital fissure, nasal cavity via sphenopalatine foramen, middle cranial fossa via foramen rotundum and the oral cavity
c. Sphenoid sinus → Cavernous sinus, brain and skull base
d. Maxillary sinus → Facial and retroantral soft tissues and along Nasolacrimal duct
e. Intraorbital disease → Orbital apex → Cavernous sinus

ii) Angioinvasion

Mucorales are capable of extensive angioinvasion with resultant thrombosis and tissue necrosis. This ability also allows Mucorales to disseminate via the hematogenous route from the original site of infection to other target organs.

IV. Classification system for ROCM

Based on the presence of predisposing factors, typical signs and symptoms and supportive diagnostic evidence, ROCM can be classified as possible, probable and proven ROCM (table 1). Several classification systems have been proposed for ROCM based on the clinic-radiological criteria with an intent to guide the physician to make a management plan and have a prognostic value.9,10 However, an assumption is made that progression occurs from one stage to the next while there have been a number of cases where presentation in the highest stage does not necessarily imply that all other anatomical structures are involved; thus, these staging systems need improvisation in suggesting the involvement of anatomical structures per se. This may lead to an alteration in the ordinal nature of staging but will pinpoint the relevant pathology. Additionally, there are situations where the concordance between clinical findings and radiology is poor and hence the management is largely guided by the imaging features, especially the loss of contrast enhancement that suggests presence of necrotic tissue.
V. Clinical features of ROCM

Symptoms:
   a) Nasal block/stuffiness
   b) Nasal discharge
   c) Epistaxis
   d) Orbital/facial pain
   e) Headache
   f) Orbital/facial edema
   g) Orbital/facial discoloration
   h) Ptosis
   i) Proptosis
   j) Loss of vision
   k) Diplopia
   l) Toothache
   m) Loose teeth
   n) Facial deviation

Signs:
   a) Nasal discharge (Fig 2 D)
   b) Nasal eschar/ulcer (Fig 2 D)
   c) Periocular/facial edema (Fig 2 A)
   d) Periocular/facial discoloration (Fig 2 D)
   e) Periocular hypesthesia
   f) Ptosis (Fig 2 B)
   g) Proptosis (Fig 2 C)
   h) Loss of vision
   i) Diplopia/ restricted extra-ocular movements
   j) Oral/palatal ulcer/eschar (Fig 2 D)
   k) Facial palsy (Fig 2 A)
   l) Altered sensorium
   m) Fundus exam: Disc edema (Fig 3 A) and/or cherry red spot (Fig 3 B)
VI. Diagnostic pathways
To confirm the diagnosis, a thorough clinical and radiological evaluation supported by Laboratory tests are required. The available diagnostic tests are as follows:

A. Diagnostic nasal endoscopy:

i) When to perform:
Endoscopic nasal evaluation is done in all suspected cases of ROCM (Fig. 4). It provides direct visualization of the pathological areas and helps to take appropriate and adequate samples from the active sites. Diagnostic swabs (nasal endoscopy guided) are collected from the nasal cavity for microbiology or histopathology evaluation.

ii) Nasal endoscopy:
2.7mm, 0 or 30-degree rigid telescope is used for diagnostic nasal endoscopy. 2 sprays of Co-phenylcaine spray (5% lignocaine with 0.5% phenylephrine) are applied into each nasal cavity for adequate anesthetic and decongestive effect prior to the procedure. Endoscopy can be performed bedside, in clinics or in operating rooms under topical or general anesthesia with the patient in supine and 45 degrees of head elevation and face towards the examiner. A standard 3-pass technique is followed. The first pass traverses the floor of the nose, the second pass the osteo-meatal complex and the third pass is made along the septum and the post part of the middle turbinate.

iii) Specific signs:
Discoloration (Black or grey: Necrosis, White: Ischemia), granulation and ulceration of the nasal mucosa over the middle turbinate, middle meatus and septum are common. Discharge at areas beyond the necrosis or underneath a black eschar should be looked for. Nasal swabs or tissue samples should be collected from clinically active parts of the lesion and not from grossly necrotic tissue to improve the diagnostic yield. Care must be taken not to touch the anterior parts of the nose while obtaining the swabs to avoid contamination.
iv. Sterilization of the endoscope:
Cetrimide and Chlorhexidine gluconate solution (Savlon™) are used to clean the endoscope and use as an anti-fogging solution. The endoscope is cleaned with Sterilium within about 30 minutes of the procedure and not allowed to dry.

B. Microbiologic work-up for mucormycosis:
In clinical practice, laboratory diagnosis of mucormycosis includes histopathology, direct examination of wet mounts and culture. Microscopy (Direct or histopathology) and culture of clinical specimens help in establishing the diagnosis of a probable case to a proven case of ROCM. (11,12)

i. Direct Microscopy:
- Nasal swabs, para nasal sinus mucosa and orbital tissues are subjected to direct microscopy using KOH mount and calcofluor white. It provides a rapid presumptive diagnosis and has sensitivity of about 90%.
- Hyphae of mucorales are typically broad, irregular, ribbon-like, non-septate or pauci-septate with variable width (6-25 μm) and non-dichotomous (> 45-90 degrees) branching. In contrast the hyphae of non-mucorales (Aspergillus) are thin 3-5μm wide, regularly septate with dichotomous branching at 45 degrees. (Fig 5a & c)

ii. Cultures:
- Most fungal culture media (Sabouraud dextrose agar and potato dextrose agar) grow mucorales in 3-7 days when incubated at 30 to 37°C.
- The mucor colonies appear fluffy white, gray or black cotton candy-like. (Fig 5d) Lactophenol cotton blue mount helps in studying the morphology of sprongiophores which appear coarse and dotted with brown or black sporangia. (Fig 5b)
- Culture helps in genus and species identification and antifungal susceptibility testing but cannot distinguish the genera based on colony morphology for which molecular methods are required.
• The fungal hyphae being fragile in nature often get damaged during tissue manipulation, thus having only 50% chance of organism growth on culture even if detected on smear. It is recommended to avoid excessive tissue homogenization during processing for better yield. (10,11)

•

iii) Serology:
• Enzyme linked immunosorbent assays (ELISA), immunoblots, immunodiffusion tests & Enzyme linked immunospot (ELISpot) assay, D-glucan and Galactomannan detection are useful to detect mucorales specific T cells in the blood or serum. (10,11,12)
• These tests act as surrogate diagnostic markers and needs further validation. (11)

iv. Molecular methods:
• Molecular assays like conventional PCR, quantitative PCR (q PCR), semi nested PCR with high-resolution melt analysis and real-time PCR, FISH and MALDI-TOF MS have been validated in the detection of Mucorales. (9-13)
• These techniques target the internal transcribed spacer (ITS), 18S r RNA or 28S r DNA genes.
• These assays can be done on fresh tissue samples, formalin-fixed or paraffin-embedded (FFPE) samples, on blood or serum. The sensitivity varies from 97-100% in fresh samples and 56-80% in FFPE samples in detecting mucor DNA
• These tests require minimal sample preparation, are faster and complement the conventional microbiological tests.

C. Histopathology of Mucormycosis:
• Mucorales demonstrate tissue invasion on tissue sections stained with Haematoxylin-eosin, Periodic acid schiff stain (Fig 6a, b) and Grocott-Gomori’s methenamine silver stain (Fig 6c)
• The characteristic morphology of hyphae (Fig 6d) is diagnostic in 80% cases and often due to folding of tissues over itself during processing; the hyphae of mucorales may show pseudo-septate. (11)
• Acute or invasive lesions: demonstrate hemorrhagic infraction angioinvasion, coagulation necrosis, neutrophil infiltration and perineural invasion. Chronic lesions show pyogranulomatous inflammation with presence of giant cells.\(^{(10)}\)

**D. Imaging in ROCM:**
Imaging forms an important component in the evaluation and management of patients with ROCM. Computed Tomography (CT) and Magnetic resonance Imaging (MRI) are the commonly used; *contrast enhanced MRI is the preferred imaging modality.*\(^{(8)}\)

**i. Role of CT Scan:**
CT scan is widely available, relatively inexpensive, more feasible, has a shorter acquisition time and minimal motion related artifacts.\(^{(8)}\) It is helpful for sick, uncooperative patients, patients with metallic dental fixtures, artificial pacemakers and heart valves.\(^{(8)}\) Staging the disease and planning of navigation guided surgery is done with CT images. CT findings in invasive fungal rhinosinusitis include non-specific acute or chronic rhinosinusitis with thickening of the nasal and paranasal mucosa, air/fluid levels in the sinuses, periantral fat infiltration and bony erosion.\(^{(8)}\)

**ii. Role of MRI Scan:**
• MRI is a multiplanar imaging modality with excellent soft tissue resolution with lesser radiation exposure. It is useful for prognosticating the disease and to monitor disease resolution.\(^{(8)}\)
• Axial and coronal images of 2mm slice thickness in the following sequences are acquired.
• T1 and T2 weighted images:
• Short tau inversion recovery (STIR) / Fat saturated T2W images: Most sensitive sequences to demonstrate pathology
• Fat saturated T1W images with contrast: Best for delineating the extent of pathology and areas of necrosis
• MR angiogram: Best in cases with cavernous sinus involvement to look for angioinvasion
• Diffusion Imaging: To detect areas of cerebral and optic nerve infarction

**iii) Evaluation of Paranasal sinuses:**

• In invasive fungal sinusitis, there is thickening of the nasal and paranasal sinus mucosa with variable hyperintensities and irregular patchy enhancement on post contrast T1 W images. There may be complete or partial opacification of one or more sinuses. *(Fig 7a)*

• Ischemia and non-enhancement of turbinates: This is an early sentinel sign of angioinvasion, and is also referred to as the *Black Turbinate Sign* *(Fig 7c, yellow asterisk)*

• Bone destruction with enhancement is suggestive of extrasinus extension into the orbit, masticator space, palate, pterygopalatine fossa and the cavernous sinus.

**iv. Evaluation of Orbit:**

Orbital involvement occurs through pathways of least resistance such as the lamina papyracea, nasolacrimal duct, ethmoid foramina, vascular perforations of the medial orbital wall, by destruction of the bony orbital walls.

• Thickening of the medial rectus and formation of medial orbital abscess: it is an early sign of orbit involvement *(fig 7c,d)*

• Increased intensity along the optic nerve with increased caliber of the nerve is a feature of invasion of the optic nerve. *(fig 7d)*

• Severe proptosis, stretching of the optic nerve and tenting of globe at the posterior pole of the eyeball with edema of the retrobulbar fat indicates severe inflammation. *(fig 7e)*

• Diffuse thickening and enhancement of the ocular coats is seen if globe is affected.

• Orbital apex involvement appears as enhancing soft tissue at the orbital apex extending into the optic canal and superior orbital fissure with patchy enhancement.

• Cavernous sinus thrombosis may appear as bulkiness with loss of normal concavity of the lateral walls of the sinus with filling defects in post contrast.
images. Dilated superior ophthalmic vein and narrowing of internal carotid artery with filling defects are seen in case of thrombosis.

**v. Evaluation of Central Nervous system:** (3,4)
- Intracranial involvement commonly occurs by direct spread across the cribriform plate, walls of the ethmoid and frontal sinuses, pterygopalatine fossa, along the internal carotid artery and perineural spread from the cavernous sinus along the trigeminal nerve.
- Hyperintense meninges with uniform enhancement suggest meningeal involvement (fig 8a). Well-defined areas of central hyperintensity with variable rim enhancement suggest intra cerebral abscess (fig 8B & C).

**vi. Imaging as guide to organ salvage:** (8)
- Enhancement is the key feature in imaging and is a guide for surgical resection
- *Areas with enhancement in the orbit have intact vascularity and can be preserved and treated with on iv antifungals or supplemented with transcutaneous retrobulbar amphotericin-b injections.* Non-enhancing areas are nidus for fungal growth, and needs extensive orbital and sinus debridement or orbital exenteration.

**VII. Treatment algorithm**
The treatment begins with prompt reversal of immunosuppression and a strict glycemic control in all suspected or proven cases of ROCM. The further management depends on the type of ROCM

- **Possible ROCM:** In patients with predisposing factors such as uncontrolled diabetes mellitus and a history of COVID-19 infection within 6 weeks, a diagnostic nasal endoscopy and a close follow up for development of signs and symptoms of ROCM are mandated. A CT or MRI with contrast may be considered in high-risk individual as imaging signs of ROCM may develop before clinical signs and symptoms.

- **Probable & Proven ROCM:** In patients with signs and symptoms of ROCM, supported by nasal endoscopy and MRI orbit with contrast i.e., probable ROCM
or in patients with microbiological confirmation i.e., proven ROCM, the treatment begins with (i) prompt reversal of systemic immunosuppression, (ii) strict glycemic control, (iii) systemic antifungals and (iv) early and complete sinus debridement with clear margins. Orbital interventions in such cases depends on the type and extent of orbital involvement.

- **Orbital intervention in ROCM:** For cases with localized extraconal orbital involvement contagious to ethmoid sinus involvement an endoscopic endonasal medial wall decompression with orbital debridement can be performed. Following guidelines may be considered for managing these patients
  a) For cases with localized extraconal orbital involvement with contrast enhancement present (CE+) the disease can be left to heal with the systemic liposomal amphotericin B (LAMB) or can be treated with additional transcutaneous retrobulbar amphotericin B (TRAMB) *(fig 9a).*
  b) For diffuse intra and extraconal disease, orbital apex involvement and perineural involvement, when contrast enhancement is present, TRAMB can be considered. In this subset of cases when there is evidence of necrotic tissue in the orbit i.e. CE is absent, debridement needs to be considered *(fig 9b).*
  c) For patients with diffuse areas of loss of CE in the orbit, exenteration needs to be performed *(fig 9c).* *Figure 10* gives an outline of the treatment algorithm.

**VIII. Systemic antifungals**
Mucorales exhibit inherent quality of resistance to most of the available antifungals with limited choice for selection of the drugs. The medication of choice for Mucormycosis falls largely under polyene and triazole group of antifungals.

**Polyene antifungals:**
1) Amphotericin-B (AMB)
A polyene anti-fungal, AMB, is considered as the first line of treatment for mucormycosis. With the introduction of lipid formulations {Liposomal Amphotericin-B (LAmB), Amphotericin-B lipid complex (ABLC), Amphotericin-B colloidal dispersion (ABCD)}, the incidence of nephrotoxicity and other adverse
effects have reduced significantly leading to replacement of the conventional formulations [Amphotericin-B deoxycholate (ABD)].

A. Mechanism of action:

- **Ergosterol binding:** Amphotericin-B binds to ergosterol, the most important component of the fungal cell wall that maintains structural integrity. It leads to increased cell membrane permeability, thereby, allowing leakage of intracellular contents and cell death.

- **Oxidative damage of fungal cell wall:** Mucorales exhibit minimum inhibitory concentration (MIC) of > 6 mg/ml and are likely to respond only with higher doses of anti-fungals. Thus, the therapeutic dosage of LAmB for Rhinocerebral Mucormycosis ranges from 5–10 mg/kg per day for intravenous infusion. In case of CNS involvement, a high dose of 10 mg/kg per day is recommended.\(^{14-16}\)

(2) **Triazoles.**

A. Isavuconazole and Posaconazole are the only newer second generation triazoles with considerable activity against the invasive Mucormycosis.

B. **Mechanism of action:** It acts by inhibiting 14-α-sterol demethylase leading to suppression of ergosterol synthesis there by altering cell membrane permeability.

i. **Posaconazole:** It is a broad-spectrum azole, considered as salvage or second line therapy for invasive mucormycosis. Mucorales exhibit minimum inhibitory concentration (MIC) ranging from 1-4 mg/ml. It is available in different formulations: oral suspension, tablet form and intravenous infusions. The therapeutic dosage of posaconazole for ROCM is 200 mg (6th hourly) for oral suspension; 300 mg (12th hourly) for day 1 followed by 300 mg/day for tablet form.\(^{14,17-19}\)

ii. **Isavuconazole:** It is the newer triazole with extended spectrum activity and the only azole validated for the first line therapy of Invasive Mucormycosis. The prodrug form of this drug is Isavuconazole sulfate, which metabolises to its active form instantly by serum butyrlcholinesterase. When compared to the other azoles, the
drug interaction and toxicity are less with excellent oral bioavailability. Mucorales exhibit wide range of minimum inhibitory concentration (MIC) and the lower ranges are comparable to posocanzole and Amphotericin-B. The therapeutic dosage of Isavuconazole for ROCM is 200 mg (8th hourly) for 6 doses followed by 200 mg/day for intravenous infusion or as oral tablets. (17-21)

**IX. Local Antifungals: Transcutaneous Retrobulbar Amphotericin-B (TRAMB)**

TRAMB is a minimally invasive procedure that helps salvage the orbital anatomy in patients that have orbital mucormycosis with focal involvement and presence of CE in the orbit.

A. Indications:
   1. Focal orbital involvement with presence of CE
   2. Salvageable vision or globe
   3. Post orbital debridement or exenteration with positive margins for local disease control

B. Drugs used:
   1. First line: Liposomal amphotericin B is advisable on account of its minimal tissue inflammation. (20)

   2. Second line: When liposomal formulations are not available, deoxycholate Amphotericin-B can be used as second line of treatment for TRAMB. Deoxy cholate amphotericin B is associated with severe orbital tissue inflammation leading to periorcular swelling, chemosis and decreased vision. (22, 23)

C. Dose:
The preferred regimen of TRAMB for Orbital Mucormycosis is 3.5mg/ml/ day for 3 consecutive days.

D. Procedure:
   1. Affected quadrant is anesthetized with 1-2 ml of lignocaine to minimize injection related pain.
   2. After 5 minutes, 1 ml of 3.5 mg/ml of Amphotericin-B is injected into the retrobulbar space in the involved quadrant with 24G needle, most commonly in the inferomedial orbit.
   3. Apply gentle pressure and monitor the patient for 5 minutes.
E. Complications:
Orbital inflammation and orbital compartment syndrome might occur requiring a lateral canthotomy and cantholysis.
F. Follow-up: Assess response with repeat imaging after 2-3 weeks, further injections can be given depending on the clinical response. In case of progression consider orbital debridement or exenteration.²⁴

X. Orbital debridement in ROCM
Certain cases of orbital involvement may not improve despite treatment with intravenous antifungals and sinus debridement. The vascular invasion due to mucormycosis results in thrombosis causing infarction and necrosis of the involved tissues leading to decreased tissue penetration of systemic antifungal therapy and local TRAMB injections. Treatment thus usually consists of systemic antifungals together with aggressive surgical debridement of infected tissue.

A. Indications
1. Focal orbital involvement with absence of CE
2. Salvageable vision or globe
3. Post orbital exenteration with residual apical disease

B. Surgical technique
1. Since the commonest quadrant of involvement is the medial orbital compartment, minimally invasive incisions such as the medial transcaruncular and the inferior transconjunctival incisions can be used for debridement of the inferomedial orbital tissues. Similarly the region of the inferior orbital fissure can be debrided using the inferior transconjunctival incision. Superior orbital quadrant can be approached via the sub-brow or the eyelid crease incision.
2. Along with soft tissue debridement, bony debridement may be necessary in patients with osteomyelitis secondary to mucormycosis.
3. The surgical debridement continues till all the necrotic tissues are excised and there is fresh bleeding from the surrounding structures. Care is taken to prevent damage to the extra-ocular muscles, globe and the optic nerve.

C. Complications
1. Decreased vision
2. Diplopia
3. Ptosis
4. Increased orbital inflammation
5. Orbital compartment syndrome

XI. Orbital exenteration in ROCM

A. Indications

1. Orbital exenteration is typically recommended in patients who show progression of disease in spite of medical and surgical treatments.\textsuperscript{[24,25]}
2. Other indications for orbital exenteration have included ophthalmoplegia, proptosis, cranial involvement and ocular involvement.\textsuperscript{[26-31]}
3. Some have even reported that exenteration could increase patients’ survival in the presence of intracranial spread and rapid progression.\textsuperscript{[28]} At the same time, it has also been reported that orbital exenteration, by itself, does not affect the patients’ survival in ROCM.\textsuperscript{[24]} The possible explanation being that orbital exenteration is typically performed for patients in the end-stage disease.\textsuperscript{[29]} Hence, it was noted that no standard of care currently exists to guide physicians on when exenteration may benefit a mucormycosis patient.\textsuperscript{[32]} In summary, there are no clear guidelines for the effective management of the orbital component in ROCM.\textsuperscript{[31]}

B. Surgical technique

1. In most cases an eyelid sparing exenteration may be possible. However, when the disease is severe and involves the eyelid skin, a total exenteration may be warranted. In several cases of mucormycosis, an extended exenteration with removal of the paranasal sinuses or skull base with a craniotomy may be combined. The steps of an eyelid sparing exenteration are described below.
2. General anaesthesia should be employed. In exceptional situations local retrobulbar, infraorbital, and periorbital nerve blocks may be used if general anaesthesia is absolutely contraindicated.
3. A 4-0 black silk suture is passed through the skin, orbicularis muscle and superficial tarsus of the upper and lower lids and tied together to close the eyelids and to provide traction during the procedure.
4. A skin incision is outlined 4 mm above the upper and lower lash line and extended at the canthi to meet in an ellipse (Fig. 11a).
5. A skin and orbicularis oculi muscle incision is placed with a blade or the monopolar tip of a radiofrequency device. Sub-orbicularis dissection is carried out superiorly and inferiorly until the periosteum just outside the orbital rim is exposed for 360° (Fig. 11b, c and d).
6. An incision is then made through the periosteum for 360° about 4 mm outside of the orbital rim to expose the underlying bone (Fig. 11e). The supero-medial neurovascular bundles are cauterised.
7. Medially the medial canthal tendon is dis-inserted from the orbital rim.
8. A periosteal elevator is used to free the periosteum for 360° around the bony orbital margin and into the orbital cavity (Fig. 11e and f). The medial orbit is approached in the end since it is highly vascular. Care must be taken when using the periosteal elevator nasally to prevent fracturing the thin lamina papyracea of the ethmoid bone. The infraorbital, zygomatico-facial, zygomatico-temporal and ethmoid neuro-vascular bundles are cauterised (Fig. 11f). The nasolacrimal duct is cut at the junction of the sac and the duct in then lacrimal sac fossa (Fig. 11g).
9. When the periosteum is free posteriorly, the enucleation scissors are inserted between the periosteum and bone inferotemporally and gently advanced to the orbital apex (Fig. 11h).
10. The tissues are then cut as near to the orbital apex as possible, and the orbital contents are removed by continued traction on the silk sutures in the eyelids while cutting the residual adhesions in the posterior orbit.
11. The socket is immediately packed with a gauze and indirect pressure applied to achieve hemostasis. The gauze is then removed and the orbital apex inspected. Residual soft tissue at the orbital apex is removed piecemeal, and bipolar cautery and repeat packing are used until there is no further bleeding. Absorbable gelatin sponges dipped in tramadol or an absorbable hemostat such as SURGICEL may be used to control hemostasis (Fig. 11i)
12. A rubber drain may be placed in the socket after complete hemostasis, and the skin of the upper and lower eyelids are sutured together in 2 layers. The orbicularis is suture with 6-0 vicryl and the skin with 4-0 prolene continuous interlocking sutures. (Fig. 11j and k).

13. This leaves the residual orbital cavity filled with air that is aspirated with syringe prior to patching the socket (Fig. 11l). One skin suture is tied to the drain if placed and the drain removed after a week. Alternately, the exenterated socket is aspirated daily for collection of blood within the socket until the aspirate is less than 4 cc in volume. An orbital prosthesis can be fabricated and dispensed after 6 weeks.

C. Complications

1. Communication between the orbit and nasal cavity due to infected necrotic bone or previous endoscopic endonasal decompression.
2. CSF leak
3. Postoperative infection
4. Discharging fistula
5. Wound gape
6. Extensive bleeding necessitating a blood transfusion

XII. Tackling osteomyelitis

Osteomyelitis is defined as inflammation of the medullary cavities, haversian system and adjacent cortex of bone. (fig 12) Fungal osteomyelitis is very rarely seen but is documented in the maxillofacial area. Despite multimodal aggressive treatment of ROCM certain patients may end up with osteomyelitis of the orbital and adjacent bones. (33) The commonest manifestation of osteomyelitis is persistent overlying soft tissue inflammation. The management of osteomyelitis revolves around debridement or excision of the infected bones while continuing appropriate intravenous antifungal therapy and debridement of the sinus and orbit as appropriate with prompt reversal of the immunocompromised status. (33) The bony defect can later be corrected with autologous bone grafting and of needed soft tissue reconstruction over it.
XIII. Prosthetic rehabilitation

Orbital prostheses are manufactured by anaplastologists. Silicone followed by polymethyl methacrylate and polyurethane remain the most popular materials for the fabrication of these prosthesis. Several other materials have been used for prostheses, such as, silver, porcelain, gelatin, latex and acrylic. PMMA prosthesis is usually dispensed as a spectacle retained prosthesis. Silicone provides a light weight, soft and flexible prosthesis that can be coloured in a wide range. It can be dispensed as an adhesive retention or an osseo integrated prosthesis. However the main disadvantage of the silicone prosthesis is the discoloration that requires renewing the prosthesis every 18–24 months.\(^{(35,36)}\) The prosthesis can be shaped using silicone or polyvinyl mold, 3D printer technology with laser scanning.\(^{(37)}\) Orbital prostheses are usually delivered with an opened artificial eye with satisfactory cosmetic outcomes in static position.

XIV. Prognosis

ROCM is a rapidly progressive disease, with 30–90% mortality rate in cases with cerebral involvement.\(^{(38,39)}\) For cases associated with COVID-19, the overall mortality has been estimated to be 31%.\(^{(40)}\) The median time before succumbing to the disease was 75 days.\(^{(39)}\)
References:


**Legends:**

![Legends Image]

**Figure 1:**

Pathways of spread in rhino-orbital-cerebral mucormycosis by direct spread. From the ethmoid and maxillary sinuses into the orbit or intracranial compartment (a). Pterygopalatine fossa is a crossroads at the skull base, where nasal pathology may spread into the infratemporal fossa and cavernous sinus (b). Sphenoid sinus disease may extend into the cavernous sinus, brain, and skull base (c). Maxillary sinus disease may extend into the facial and retroantral soft tissue and along the nasolacrimal duct (d). Intraorbital disease may spread into the orbital apex and cavernous sinus (e)

Figure 2:
(A) Left sided periocular, facial edema with facial palsy, (B) Left eye ptosis, (C) Right eye proptosis, (D) Nasal discharge with left periorbital and facial discoloration with palatal eschar.
**Figure 3:**
Fundus findings in ROCM: (A) Disc edema with peripapillary hemorrhage, (B) Cherry red spot

**Figure 4:**
(a) A possible ROCM with left side affection, (b) CT imaging shows only PNS involvement on nasal endoscopy, (c) Ischemic black appearing middle turbinate on endoscopic evaluation (white arrow), (d) discharge surrounding the necrotic area (black arrow).
**Figure 5:**
(a) KOH-CFW mount of nasal swab showing typical broad ribbon shaped hyphae of Mucorales, (b) Sporangiophore of mucor on LPCB mount, (c) KOH-CFW mount of nasal swab showing thin septate hyphae of non-mucorales, (d) Fluffy grey-black cotton candy colonies of mucorales on blood agar.
Figure 6:
(a) PAS-stained section showing mucor in the nasal mucosa (Original magnification x30), (b) PAS stained section showing extensive scleral necrosis (Original magnification x30), (c) GMS stained section showing angioinvasion in the nasal mucosa (Original magnification x30)

Figure 7:
MRI features of rhino-orbital mucormycosis
(a) Opacification of maxillary sinuses in T1W images, (b) Hyperintensity of left ethmoid mucosa in T1 W Fat saturated image with thickened and hyperintense EOM, (c) Non enhancement of the nasal mucosa on post-contrast T1W (Black turbinates sign, yellow asterisk) with right orbital extraconal involvement with an area of loss of CE (yellow arrow), (d) Localized medial orbital involvement without
CE (yellow asterisk) with contiguous ethmoid sinus involvement, (e) Left orbital peri-neural involvement (Yellow arrow), (f) Left orbital involvement with a large area of loss of CE and tenting (dotted line) of the globe.
EOM: extraocular muscles, CE: contrast enhancement.

Figure 8:
Orbital presentations of ROCM
(a) T1W post contrast MRI demonstrating right localized extraconal orbital involvement with fat stranding appearing as a lacy white shadow in the medial and inferior extraconal compartment, (b) T1W post contrast MRI demonstrating left orbital involvement with proptosis and a large area of hyperintensity lateral to the eyeball with a necrotic area within (yellow asterisks), (c) T1W post contrast MRI demonstrating left extensive orbital involvement with a large necrotic area filling the entire orbit (yellow asterisks)

Figure 9:
Cerebral involvement in ROCM
Figure 10:
Treatment algorithm for orbital component of Invasive Rhino-orbital Mucormycosis. TRAMB: Transcutaneous Retrobulbar Amphotericin-B. (A) T1W post contrast MRI demonstrating left temporal lobe leptomeningeal enhancement, (B) T1W post contrast MRI demonstrating right temporal lobe involvement with an hyperintense rim and a isointense core, (C) T1W post contrast MRI demonstrating right frontal lobe involvement with an hyperintense rim and a hypointense core.
Figure 11:
From top left: (a) skin marking 4 mm from the eye margin, (b) skin incision taken with the monopolar tip of a radiofrequency machine, (c) sub-orbicularis dissection done, (d) medial canthal tendon incised close to the orbital rim, (e) orbital rim exposed all 360°, (f) neuro-vascular bundles cauterised, (g) nasolacrimal duct cut, (h) enucleation scissors used to dissect orbital contents out at the posterior orbit, (i) hemostasis achieved, (j) orbicularis closed with 6-0 vicryl, (k) skin closed with 4-0 prolene, (l) air from the socket aspirated.

Figure 12:
Clinical and imaging findings of a patient with left zygomatic and maxillary osteomyelitis
(a) clinical photograph with left premaxillary fullness, (b) 3D reconstructed image demonstrating bone destruction in the left maxilla and zygoma, (c) coronal CT image demonstrating bone destruction and marrow involvement in the zygoma.
**Table 1:**
Classification of ROCM

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Possible ROCM</strong></td>
<td>Predisposing factors with typical signs and symptoms of ROCM</td>
</tr>
<tr>
<td><strong>Probable ROCM</strong></td>
<td>Signs and symptoms + Diagnostic nasal endoscopic findings and/or diagnostic radiological findings</td>
</tr>
<tr>
<td><strong>Proven ROCM</strong></td>
<td>Clinico-radiological features + Microbiology evidence on direct microscopy and/or culture and/or histopathological evidence with special stains</td>
</tr>
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</table>

ROCM: Rhino-orbital-cerebral mucormycosis
Table 2: Systemic antifungal therapy for ROCM

<table>
<thead>
<tr>
<th>Systemic management protocol for ROCM</th>
</tr>
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<tbody>
<tr>
<td>1. Prompt reversal of immunosuppression</td>
</tr>
<tr>
<td>2. Strict glycaemic control</td>
</tr>
<tr>
<td>3. Complete debridement of paranasal sinuses and involved bones when possible</td>
</tr>
<tr>
<td>4. iv antifungals as below; opt for option 1 over whenever feasible</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Status of disease</th>
<th>Option 1</th>
<th>Option 2</th>
<th>Option 3</th>
<th>Option 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable disease</td>
<td>Start with Liposomal Amphotericin-B 5 mg/kg per day</td>
<td>IV Isavuconazole 200 mg q8H for 6 doses followed by 200 mg qDay or IV Posaconazole 300 mg iv BD on day 1 followed by 300 mg qDay</td>
<td>Change to oral treatment Tab Posaconazole 300 mg daily or Tab Isavuconazole 200 mg daily</td>
<td>Start with IV Amphotericin B deoxycholate 0.3 to 0.5 mg/kg qDay</td>
</tr>
<tr>
<td>Progressive disease or Intracranial involvement</td>
<td>Start with Liposomal Amphotericin-B 10 mg/kg per day</td>
<td>IV Isavuconazole 200 mg q8H for 6 doses followed by 200 mg qDay or IV Posaconazole 300 mg iv BD on day 1 followed by 300 mg qDay</td>
<td>Combination of Liposomal Amphotericin-B with oral Posaconazole or isavuconazole</td>
<td>Start with Amphotericin B deoxycholate 1 to 1.5 mg/kg qDay</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>Shift to Isavuconazole</td>
<td>Shift to Posaconazole</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Duration of treatment:
- Induction treatment: Liposomal Amphotericin B 5 to 10 mg/kg/day for 4 - 6 weeks followed by
- Maintenance treatment: Oral Posaconazole (300mg daily) or Isavuconazole (200 mg daily) for 3 – 6 months
NEURO-OPHTHALMOLOGICAL MANIFESTATIONS OF COVID-19: COMMON MANIFESTATIONS AND PATHOPHYSIOLOGY

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**Introduction**

Many neurological and neuro-ophthalmological manifestations of severe acute respiratory syndrome-2 coronavirus disease 19 (SARS-2 COVID-19) infection have been reported. Prior reports from China suggest that up to one-third of the patients had neurological symptoms including headaches, myalgias but also definite neuro-ophthalmological symptoms such as vision loss.1 These include optic neuritis, optic perineuritis, cranial nerve palsies, stroke, Adie pupil, cerebral sinus venous thrombosis, etc.2-11 Although many associations do remain speculative, some of these associations do have well defined basis. In this chapter, we shall describe these associations, proposed mechanisms neuro-ophthalmological involvement as per the reported literature and also briefly share our experience.

**Pathophysiology and CNS spread:**

Reported literature suggests that infection of the human cells is mediated by the angiotensin-converting enzyme 2 (ACE2) receptor for SARS-CoV-1 and SARS-CoV -2.12 These receptors have been identified in various parts of the central nervous system (CNS) which possibly explains the predilection of the central nervous system and many neurological manifestations.13

The reported ways of spread to the CNS include direct spread via the respiratory route and hematogenous spread, with the leucocytes acting as the reservoir of viral transmission.14-18

Although not completely understood, the following general pathogenetic mechanism have been proposed for the various neuro-ophthalmological manifestations associated with COVID-19 (table 1):

1. **Cytotoxic effect of the direct invasion of the CNS:** Access to the CNS is thought to be through retrograde transsynaptic neuronal dissemination via the olfactory bulb.17,18 Following direct invasion of the central nervous system, a transfection of the nerves is believed to be responsible for CNS abnormalities.14-17
Further proposed mechanisms include: a post-viral inflammatory syndrome, sequelae of a proinflammatory state with hypercoagulability and cytokines storm and the result of systemic abnormalities including hypoxia and severe hypertension.

2. **Post-viral inflammatory syndrome** is similar to the hyperactivation of the immune system observed following any other infection such as viral illness. This mechanism is believed to be responsible for manifestations such as demyelinating optic neuritis, perineuritis, Guillain-Barre syndrome, cranial nerve palsies, activation /precipitation of myasthenia, etc. It might be acute onset or might take a few weeks to manifest.

3. **The hypercoagulable state** results from the prothrombotic state resulting from the activation of coagulation pathways. This results in thrombosis and vascular complications resulting in acute infarcts, resulting in cerebrovascular accidents and venous sinus thrombosis.

**Table 1: Summary of the proposed mechanisms of the CNS manifestations of COVID-19**

<table>
<thead>
<tr>
<th>S. No</th>
<th>Proposed mechanism</th>
<th>Likely manifestation</th>
<th>Time from active infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Direct Invasion</td>
<td>Adie’s Tonic Pupil, Cranial nerve palsies</td>
<td>Acute phase</td>
</tr>
<tr>
<td>2</td>
<td>Post-viral inflammatory syndrome</td>
<td>Optic neuritis, Guillain-Barre Syndrome</td>
<td>Variable, may take up to a few weeks</td>
</tr>
<tr>
<td>3</td>
<td>Hyper-coagulable state</td>
<td>Strokes, CSVT</td>
<td>1-2 weeks; cytokine storm</td>
</tr>
</tbody>
</table>
As the understanding of the disease and more robust literature grows, understanding of these mechanisms and implicated pathophysiology might become clearer.

In this section, we describe in brief important reported neuro-ophthalmological manifestations, their pathophysiology, and outcomes in setting of COVID-19.

**Optic neuritis:**

Demyelinating disorders associated with SARS-CoV-2 infection, including Guillain-Barre syndrome and Miller-Fisher syndrome have been reported in literature. Animal models infected with coronavirus have been reported to develop optic neuritis. In humans, optic neuritis associated with coronavirus is more commonly thought to be an autoimmune or inflammatory process rather than direct invasion of the nerve. At present various proposed etiologies include increased production of antibodies following COVID-19 infection, and activation of multisystem inflammatory syndrome. COVID-19 infection is believed to act as a trigger that activates the immune response similar to other viral infections. There is also a proposed role of inflammatory cytokines especially IL-6 and IL-17 that might play a role in CNS demyelination.

Optic neuritis following coronavirus infection has been reported to present as post-infectious or para-infectious demyelinating disease with a prodromal viral illness. Its association with demyelinating central nervous system (CNS) disorder like multiple sclerosis and acute disseminated encephalomyelitis (ADEM) has also been reported. However, there are also reports that describe occurrence of optic neuritis in patients with prior episodes of neuromyelitis optica spectrum disorder (NMOSD), and myelin-oligodendrocyte glycoprotein associated demyelination (MOGAD). These are thought be secondary to activation of the autoimmune cascade following COVID-19 infection. Although there are few reports that these patients might be double seronegative for NMO and MOG antibodies.

In our limited unpublished experience, we saw 11 cases of optic neuritis in setting of recent COVID19 infection and post vaccination. 6 were males and 5 were females. Of
these seven tested positive for COVID 19 by RT-PCR and rest were negative/ suspected cases. 7 had papillitis, 2 each had retrobulbar neuritis and 2 had optic disc pallor. Only one patient tested positive for NMO antibodies. 9 patients showed T2 hyperintensities of involved segments of optic nerve with enhancement on contrast but none showed any other signs of CNS involvement. Visual outcome was good in 6 patients at 1-month follow up post treatment with intravenous methylprednisolone 1g/day for 3-5 days, followed by tapering doses of oral steroids (Fig 1a-d). As of now, limited experience does suggest that these patients do show good recovery of visual function and prognosis is similar to optic neuritis in various demyelinating conditions in general.

Although there are concerns about increased occurrence of optic neuritis following COVID-19 infection, our experience and personal communication from various Neuro-Ophthalmology colleagues across India, does not suggest an increased risk of optic neuritis.

There are some reports suggesting onset of optic perineuritis following COVID-19 infection and optic neuritis following COVID-19 vaccination though more conclusive evidence needs to be understood. Helmechen et al recently reported the occurrence of bilateral optic neuritis/chiasm neuritis with longitudinal extensive transverse myelitis in a patient with prior longitudinal stable multiple sclerosis 2-weeks following vector-based vaccination against the SARS-COV-2 infection. Similarly, there are few reports that suggest transverse myelitis might be an uncommon occurrence following COVID-19 vaccination.

There are also concerns about immediate and long-term treatment of patients with immunomodulators to prevent recurrences. Although not completely understood, in a recent review Helmchen et al suggested that it is reasonably safe to patients with most of the agents except methotrexate, rituximab and cyclophosphamide which might increase the risk of opportunistic infections. However, azathioprine and mycophenolate mofetil do remain reasonably safe. These guidelines might help us
understand the choice but the potential benefits of treatment should be weighed in a given patient.

Figure 1 a-d:
Representative case of 37-year-old-man with atypical optic neuritis 1 week following onset of COVID-19 symptoms, showing papillitis in the right eye (a) and MRI showing hyperintensities and enhancement [in axial (c)and coronal (d) sections] along the right optic nerve.

Stroke and cerebral sinus venous thrombosis, (CSVT):
Cerebrovascular accident (CVA) or stroke is a serious complication of SARS-2 COV-19 infection.\textsuperscript{28,47} Although the reported occurrence of COVID-19 is relatively low and ranges from 1.6\% to 2.5\%, this is in general believed to be an underestimate due to lesser
number of patients especially those with mild to moderate symptoms, seeking medical attention.\textsuperscript{9,10} Prior reports suggest that majority of the patients are elderly but stroke can also be the first manifestation in young patients (less than 50 years of age).\textsuperscript{47} Ghannam et al reported that majority of the patients have ischemic strokes (87.5%), while remaining patients had venous thrombosis (5%), intraparenchymal hemorrhage in 5% and another 2.5% had subarachnoid haemorrhage.\textsuperscript{48} In most series, large vessel occlusion was the most common presentation.\textsuperscript{450} Figure 2 describes a patient with acute onset stroke following COVID-19 infection.

Reported presentations is usually within three weeks of SARS-2 Cov19 infection with acute vision loss or visual field defect. Median reported time is 10 days after the onset of respiratory symptoms.\textsuperscript{50} Other reported manifestations of CNS strokes could include diplopia due to cranial nerve palsies, or inter-nuclear ophthalmoplegia.\textsuperscript{49} Few novel cases of simultagnosia (Balint syndrome) and hallucinatory palinopsia have been reported in cases of parieto-occipital lobe involvement.\textsuperscript{51-53}

Some distinctive features of the stroke in COVID-19 are: large vessel strokes, strokes involving multiple territories (reported in about 26%),\textsuperscript{54} involvements of otherwise uncommonly affected vessels. [e.g., occlusion of the pericallosal artery or the presence of multiple focal stenoses in the V4 segment of the vertebral artery, and concurrent deep vein thrombosis and pulmonary embolism.\textsuperscript{55} Few authors report also the occurrence of a vasculitis like pattern with thrombosis at multiple sites and vessel wall enhancement.\textsuperscript{54}

The pathogenesis of the stroke in patients with stroke includes activation of the \textit{Virchow’s tria}: Endothelial injury resulting from the effect of the virus binding on endothelial cells, hyper viscosity syndrome and also hypercoagulable state. It is proposed endothelial injury occurs following binding to angiotensin-converting enzyme-2 (ACE-2) receptors on the cells by the virus. This is followed by increased activation of ACE-1 receptor activity, resulting in the release of prothrombotic risk
factors. Further, increased fibrinogen levels and release of inflammatory interleukins lead to blood stasis and hypercoagulable state, initiating the coagulation cascade.\textsuperscript{47,50}

There may be signs of CNS dysfunction including hemiparesis, hemiplegia, speech or cognitive defects. As increased coagulopathy can also result in hepatic and renal dysfunction, non-contrast CT scan of the brain is the initial investigation of choice.\textsuperscript{50} In these patients, angiography should be avoided unless necessary as there might be concomitant hepatic and renal dysfunction.\textsuperscript{50} Most studies report that affected patients have elevated D-dimer, fibrinogen, LDH and CRP levels at the time of acute stroke.\textsuperscript{47,48,50,54-56}

Although likelihood of other co-existing systemic risk factors is negative in most cases, most authorities still recommend that laboratory work up for systemic risk factors, is mandatory in all cases.

Treatment mainly includes initiation of low molecular weight heparin or administration of tissue plasminogen activator (tPA). Another novel approach involves use of exogenous ACE2 using Human recombinant soluble ACE2 which acts by acting as a competitive antagonist against SARS spike protein. This shall counter the depletion of ACE2 receptors when injected in coronavirus infected patients.\textsuperscript{47,57}

Reported prognosis of patients with strokes in patients with COVID-19 are variable. However, in general the prognosis is believed to be worse than stroke in patients without COVID-19.\textsuperscript{58,59}

Older age at presentation with raised D-dimer levels, blood glucose, serum creatinine and higher National Institutes of Health Stroke Scale (NIHSS) score are known to be poor prognostic factors.\textsuperscript{47,48,50,53-59}

There have also been reports of SARS-2 COV-19 causing cerebral sinus venous thrombosis.\textsuperscript{60-63} The pathogenesis is believed to be secondary to a hypercoagulable state resulting in the activation of coagulation cascade, although virus induced endothelial injury and inflammatory reaction have also been speculated.\textsuperscript{53,60,62} The presenting
symptom is usually headache, but since headache may be present in viral infections in general, it may be a diagnostic challenge to identify this life threatening condition with COVID-19 early. MRI brain with MR venography (MRV) should be done in all suspected cases and immediate treatment to reduce the intracranial pressure along with anti-coagulants needs to be instituted in patients. 

**Figure 2:**
Representative case of a 76-year-old male with sudden loss of vision 2 days following COVID-19 infection. MRI Brain revealed acute stroke involving both occipital lobes (yellow arrows) and multiple small lacunar infarcts in the bilateral frontal lobes (white arrow). The erythrocyte sedimentation rate (ESR) was 90 mm, C-reactive protein (CRP) was 27.12 mg/L and D-dimer levels were raised (1.2 mg/L).

**Ophthalmoplegia:**

Ophthalmoplegia due to central and peripheral nervous system involvement associated with SARS-CoV-2 infection has been widely reported. Most of them have a short
period of latency between the onset of respiratory symptoms and development of neurological disease, suggestive of a para-infectious etiology.7

Miller-fisher syndrome with features of gait ataxia, hyporeflexia, paraesthesia and ophthalmoplegia is reported to occur within days of coronavirus infection.3,4 There may be symptoms of anosmia and ageusia.2 Ophthalmoplegia may present as horizontal or vertical diplopia with associated ptosis, pupillary abnormalities or adduction limitation with abducting nystagmus, suggestive of internuclear ophthalmoplegia.49 MRI may show enhancement and enlargement along the involved nerve, suggestive of a pro-inflammatory cause.4 However, a few cases have shown an acute infarct in the mid-brain and pons on MRI, suggestive of a prothrombotic etiology. Most reports show partial to good recovery with immunosuppressants.3

Guillain-Barre syndrome, presenting with features of ascending polyneuropathy, areflexia, ageusia and ophthalmoplegia have also been described.64,65 It is also known to be associated with cranial neuropathy.25,64,65 It is believed to occur secondary to hyper-activation of the immune response secondary to molecular mimicry from the Covid spike protein is suspected.25,53

Another important cause of ophthalmoparesis following COVID-19 infection can be orbital or cavernous sinus involvement secondary to the mucormycosis. This has been discussed in detail in the prior section on Mucormycosis.

**Cranial nerve palsies:**

There have been several reports of cranial nerve palsies following COVID-19 infection during various stages of recovery.66-71 As described above, when associated with hyporeflexia and paraesthesia, they may be variants of Miller-Fisher syndrome or Guillain-Barre syndrome (GBS).4,5 However, several cases of isolated mononeuropathies have also been reported.66-69,71 The most commonly affected cranial nerve is the olfactory nerve with anosmia being the presenting symptom.72,74 It has been postulated that the entry of the virus into the nervous system is through the olfactory bulb from the
respiratory system through direct invasion,\textsuperscript{14,72-74} which results in an early presentation of the condition.

Further ocular motor deficits presenting with diplopia and ptosis have been reported following the involvement of abducens, trochlear and oculomotor nerve, with abducens being the most commonly involved.\textsuperscript{13} Reports suggest that there may be enhancement of the involved cranial nerve on MRI brain, suggesting an inflammatory process, either following a para-infectious, or an immune-mediated process, which result in a slightly delayed presentation.\textsuperscript{4}

\begin{center}
\textbf{Figure 3:}
\end{center}

Representative case of a 55-year-old male who presented with acute onset horizontal diplopia secondary to left abducens nerve palsy. The clinical presentation was 2 days following COVID-19 infection. The other systemic metabolic parameters and the MRI were within normal limits.

\textit{It is important to recognize that in these patients association with COVID-19 infection remains mainly presumed and a diagnosis of exclusion. Association with a recent history}
of proven COVID infection, or onset following respiratory symptoms, definite temporal profile, lack of other structural lesions along the course of the nerve, and absence of other vasculopathic risk factors suggests probable association with COVID-19 infection. In the presence of concomitant vasculopathic risk factors, but meeting other criteria, the diagnosis of cranial nerve palsy secondary to COVID-19 infection remains probable. Therefore, we recommend further work-up should include neuro-imaging and evaluation for systemic risk factors, especially in multiple nerve involvement.

Also, there are few concerns of acute onset isolated sixth and third cranial nerve palsies following COVID-19 vaccination, but these remain unclear. However, recent literature does describe sequential contralateral facial nerve palsies following COVID-19 vaccination in a 61-year-old man following first and second dose of COVID-19 vaccination, suggesting that similar events might occur with third, fourth and sixth cranial nerves.75

At present we have limited experience with only few reported cases of isolated acute onset cranial nerve palsies following COVID-19 infection or COVID1-9 vaccination, however, a majority of them did have associated vasculopathic risk factors. MRI brain was either normal or showed microvascular ischemic changes. However, majority of the patients did present within 2-3 weeks of the COVID-19 infection. In general, patients with presumed post -infectious cranial nerve palsies recovered well, while post-vaccination sixth nerve palsy had slow recovery.

**Orbital apex syndrome:**

Involvement of the orbital apex, especially in cases of Rhino-orbital mucormycosis (ROCM), has been reported post SARS-CoV-2 infection. This might also occur following other infections such as varicella-zoster infection involving the orbit.76 Although presentation is often within days of infection, with severe ocular pain, profound vision loss, ptosis and complete ophthalmoplegia. There may be early spread to the contralateral side in extensive infection. Other clinical features are proptosis, ptosis, loss
of corneal and facial sensations. The extent of orbital involvement can be accurately diagnosed on neuro-imaging. Management of this condition is already described in detail in the section on mucormycosis. The prognosis in most cases is poor in spite of immediate surgical intervention with persisting vision loss and ophthalmoparesis.

**Ocular myasthenia:**

Viral infections, especially varicella zoster, West Nile virus and Zika virus, have been reported to precipitate myasthenic crisis.\(^{77-79}\) The proposed mechanism has been immune-mediated damage of the acetylcholine receptors in the post synaptic neuromuscular junctions, resulting in ocular myasthenia gravis (OMG).\(^{1,8}\) There have been a few reports of new-onset ocular myasthenia gravis post SARS-Cov-2 infection. Further, COVID-19 infection might also precipitate exacerbation in a patient of ocular myasthenia.\(^{80}\) The proposed mechanism is activation of immune-mediated response due to molecular mimicry of the SARS Cov-2 virus protein with acetylcholine receptors, resulting in their depletion and non-availability.\(^{81-83}\)

Clinical presentation is usually with ptosis and diplopia with history of diurnal variability in symptoms. Fatigue test and ice pack test is positive in most cases. Neostigmine test, serum acetylcholine receptor antibody test and electromyography studies can be done to confirm the diagnosis of suspected OMG. However, laboratory investigations show an increase in the inflammatory markers post SARS-CoV-2 infection, implicating an immune mediated inflammatory response in these cases.\(^{81}\)

Treatment in the form of oral steroids with oral pyridostigmine is usually effective in most cases, with good recovery. However, long term outcomes with chances of recurrences and need for long term immune-suppression is currently not understood. At the same time, reports do suggest that long term immune-modulation may be avoided in these patients especially if they have mild symptoms such as ptosis, mild diplopia and are easily controlled by acute phase treatment.
**Adie tonic pupil:**

Association between viral infection and Adie tonic pupil has been proven in the past.\textsuperscript{84} Unilateral or bilateral Adie tonic pupil is reported following occur post SARS-Cov-2 infection, either in isolation or with other neurological manifestations.\textsuperscript{85-89} The suspected mechanism is a delayed immune-mediated response, affecting the ciliary ganglion and the sphincter pupillae muscle.\textsuperscript{85} Clinical presentation is usually after 3-6 weeks of infection with symptoms of blurring of vision or difficulty in near work. However, presentation can sometimes be within days of viral infection. In these cases, mechanism is suspected to be direct invasion of the virus into the nerve. Vermiform eye movements can be noted on slit lamp. 0.125% pilocarpine test is diagnostic of the condition. MRI brain may reveal hyperintensities in the ciliary ganglion.\textsuperscript{90} Treatment is usually conservative, aimed at improving the visual symptoms with optical near correction or topical 0.1% pilocarpine eye drops.

![Image](https://example.com/image.png)

**Figure 4:**

Representative case of a 32-year-old female with anisocoria due to bilateral Adie tonic pupils 6 weeks following COVID-19 infection. Figure 4a: Increased pupil size in the LE (4 mm; yellow arrow) compared to the RE (2.5 mm; white arrow). Figure 4b: Post instillation of 0.125% pilocarpine eye drop, reduced pupil size was noted in right eye (1 mm; white arrow) as well as in the LE (1.5 mm; yellow arrow).

**Bilateral vision loss:**

Vision loss post coronavirus infection can be due to bilateral optic neuritis, ischemic or haemorrhagic cerebrovascular stroke and orbital apex inflammation. There are also
reports of posterior reversible encephalopathy syndrome (PRES) and acute haemorrhagic necrotic encephalopathy post SARS-CoV-2 infection. It is suspected to be precipitated in cases of acute hypertension, autoimmune disease and immunomodulator use. Of these conditions, PRES is considered to have a transient course and good visual prognosis.

Another cause of acute bilateral severe vision loss is a serious inflammatory condition closely resembling Kawasaki disease has been reported in children called Multisystem inflammatory syndrome (MIS-C). The pathogenesis is suspected inflammation, cytokine storm and endothelial dysfunction due to the viral infection resulting in vasculitis and coronary artery aneurysms. The reported presentation is acute onset vision loss with severe conjunctival hyperemia, uveitis and papilledema with devastating systemic complications. Treatment should be immediate with intravenous immunoglobulins (IVIG) and anti-inflammatory agent (steroids) and anticoagulants, but prognosis is very poor in affected cases.

**Intracranial hypertension:**

Raised intracranial pressure due to primary and secondary causes has been reported in association with SARS-COV-2 infection. Silva et al reported 13 COVID positive patients that underwent lumbar puncture in view of neurological symptoms and new and persistent headache over a period of 2 months. They reported a complete or partial resolution of headache after lumbar puncture in 11 patients with 6 patients having a cerebrospinal fluid (CSF) opening pressure of more than 25 cm of H₂O. All patients need to undergo MRI brain with venography in order to look for secondary causes of raised intracranial pressure including CSVT, which can be life threatening.

In our limited experience, we have really not seen an increased prevalence of new cases or recurrences of IIH in our facilities. However, more robust data needs to be collected.
**Conclusion:**

In summary, many neurological and neuro-ophthalmological complications of COVID-19 infection and vaccination have been reported. These continue to be described, and as evidence accumulates, we shall be able to have more robust data and greater understanding of the mechanism of these manifestations.

However, given these observations described in the chapter, it is very likely that we as ophthalmologists need to be aware of possible manifestations especially optic neuritis, vision loss, ophthalmoparesis, strokes, new onset myasthenia that may be associated with COVID-19. In these patients, we recommend the following:

1. Take a history of COVID-19 infection, or acute respiratory infection preceding the onset of manifestation.
2. Even in absence of these, asymptomatic infection cannot be ruled out. Therefore, in these patients, consider RT-PCR of nasopharyngeal swab in acute manifestations or antibody testing for COVID-19 with delayed presentation.
3. In patients with optic neuritis especially seronegative for NMO and MOG, apart from other work-up, it is possibly more imperative than before to obtain CSF analysis for infectious causes and obtain RT-PCR for COVID-19 as well.
4. In patients with acute onset strokes, a protected pathway protocol\(^7\) (i.e., taking COVID-19 precautions for the care of the patient and care-giver) can be practiced. Further apart from the routine work-up, Contrast administration can be avoided if possible. Also, one should obtain testing for acute phase reactants such as D-Dimer, Serum ferritin, LDH levels which are routinely noted to be elevated in these patients.
5. In all patients with suspected manifestations secondary to COVID-19 or even following vaccination, it is important to look at the temporal profile of the association and exclude other routine causes.
Further large multicentric data will be needed to generate more robust conclusions, about these associations, their manifestations, appropriate workup and management.
References:


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