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Post - COVID – 19 ophthalmic syndromes, Neuro-ophthalmic Manifestations.

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Abstract: Coronavirus disease (COVID – 19) was one of the most severe pandemics that the world has ever experienced. The infection can range from asymptomatic, mild to life threatening respiratory distress. It can affect almost every organ of the body including the organ of vision. This review was carried out to facilitate the diagnostics and initiation of comprehensive therapy of neuro-ophthalmic manifestations that occur as a complication of coronavirus disease. Ophthalmic manifestations may be present in the clinical manifestation of COVID-19 infection or they may develop later in rehabilitation period or following the recovery. Ophthalmologists should be aware of the possible associations of ocular diseases with SARS-CoV-2 in order to look for specific signs, advise appropriate tests, diagnose and initiate early treatment for life and vision threatening complications.

The coronavirus global pandemic has caused significant negative effect on lives of millions with diversity of clinical features and life and sight – threatening consequences. The full spectrum of the disease is yet to be unraveled. A simple search of 'COVID-19 Ophthalmic manifestation ' in search engines throws up over 100 publications. We believe it is important for ophthalmologists to have knowledge about the ophthalmic manifestations of the novel viral infection in order to suspect, diagnose, refer and treat the conditions with skills, machinery, and drugs that we already possess. This article gives an overview of the ophthalmic conditions that have been associated with the virus, directly or indirectly. We have also tried to categorize the manifestations into the phase of the coronavirus disease-19 (COVID-19) when they are most likely to present.

Methods

Literature search was performed in PubMed for 'COVID-19 Neuro-ophthalmic Manifestations'. Articles in the English language, published between January 1, 2020 to January 31, 2020, were included to formulate the description of the current understanding of the ophthalmic manifestations of SAR-CoV-2 virus. Severity of COVID-19 disease was considered as per the description in the article, if mentioned, or based on the symptoms and management described. All the cases were diagnosed as COVID-19 based on nasopharyngeal or oropharyngeal swabs or antibody titers.

Neuro-ophthalmic involvement has varied manifestation and are actually vascular, inflammatory, and neuronal changes triggered by the viral infection but not specific to COVID-19. The literature review showed that the mean age of the patients was 47.4 ± 14.8 (median 50, 17-75) years. The median duration between appearance of ophthalmic symptoms and the COVID-19

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symptoms /diagnosis was 12 (17.6 ± 13.1, 4–55) days. About 50% (14/23) were male and eight had no associated systemic comorbidity. [Table 1]

Table 1 Review of literature of posterior segment manifestations of COVID-19

Study	Type	Location	Age (years)	Sex	Duration between COVID-19 symptoms/ diagnosis and ophthalmic symptoms (days)	Covid illness	Signs	Diagnosis	Management	Outcome
Invernizzi *et al.* [1]	Case	Italy	54	F	9	Mild	OD Va 20/40, RAPD, retinal hemorrhages, venular tortuosity, diffuse fern like retinal whitening	Impending CRVO	Oral prednisolone in tapering doses	1 weekcomplete resolution
Walinjkar *et al.* [2]	Case	India	17	F	21	Mild	OD 6/24, disc edema, splinter hemorrhages, flame shaped, blot hemorrhages in all quadrants	CRVO	Intravitreal ranibizumab x 3 doses	3 months, vision improved 6/12
Sheth *et al.*[3]	Case	India	52	M	10	Moderate-severe	6/60, inferior hemiretinal vein occlusion with SN BRVO, macular edema	Vasculitic RVO	Intravitreal ranibizumab biosimilar, oral steroids	1 month- 6/9, resolution of macular edema, SMD. Resolving DRIL, Loss of EZ and ELM.
Gaba *et al.*[4]	Case	UAE	40	M	4	Severe	OD 6/9, OS 6/18. OU dilated tortuous retinal veins, cotton wool spots, dot blot intraretinal hemorrhages, optic disc edema	Bilateral CRVO	LMWH, rivaroxaban	2 weeksrecovered
Acharya *et al.* [5]	Case	USA	60	M	12	Severe	Optic disc- indistinct margin, cherry	CRAO		

AC: anterior chamber, AMN: acute macular neuroretinopathy, ARN: acute retinal necrosis, CRAO: central retinal artery occlusion, CRVO: Central retinal vein occlusion, DRIL: disorganization of retinal inner layers, ELM: external limiting membrane, EZ: ellipsoid zone, F: female, FC: finger counting, INL: inner nuclear layer, IT: inferotemporal, IVMP: intravenous methylprednisolone, IZ: interdigitation zone, KP: keratic precipitates, LMWH: low molecular weight heparin, LTA: lower temporal arcade, M: male, OAO: ophthalmic artery occlusion, OCT: optical coherence tomography, OD: Right eye, OPL: outer plexiform layer, ONL: outer nuclear layer, OS: Left eye, OU: bilateral, PAMM: paracentral acute middle maculopathy, RAPD: relative afferent pupillary defect, RPE: retinal pigment epithelium, SMD: serous macular detachment, SN: superonasal, SRF: subretinal fluid, UTA: upper temporal arcade, Va: visual acuity, VZV: varicella zoster virus

Table 1. Review of literature of posterior segment manifestations of COVID-19

Papillophlebitis

Papillophlebitis is an uncommon condition seen in healthy, young adults and one such case has been reported in a COVID-19 patient. There is painless, unilateral, slight diminution of vision. Visual fields show an enlarged blind spot. Ophthalmic findings include dilated, tortuous retinal vessels, disc edema, superficial retinal hemorrhages, cotton wool spot with or without macular edema. FA shows discrete venous staining and leakage, late staining of optic disc but no evidence of ischemia or peripheral vasculitis. [Fig. 1javascript:void(0)] While the final visual prognosis is quite favorable, about 30% of the cases develop vision-threatening ischemic venous occlusion with consequent neovascular glaucoma and macular edema. Systemic evaluation for hypercoagulable state, vasculitis syndromes, hyperviscosity, and vascular inflammatory disorders should be done to determine the possible etiology that could result in inflammation of retinal vasculature and capillaries of the disc. The role of COVID-19 as a possible cause comes in view of its association with coagulopathy and disproportionate inflammatory response or cytokine storm.[6]

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Optic neuritis

In humans, neurological manifestations have been documented in almost 36% of the cases.[7] These were anosmia, headache, dizziness, hypogeusia, Guillain-Barré syndrome (GBS), and ischemic stroke. Ischemic stroke has been particularly noted in the younger adults similar to the average age of the reported patients with neuro-ophthalmic features.[8] The SARS-CoV-2 virus has been shown to cause optic neuritis is animal models. Neurotropism of the virus has been proposed as one of the mechanisms for the neurological and neuro-ophthalmic manifestations. [Fig.2javascript:void(0)] shows a case of bilateral optic neuritis in a healthy young female two weeks after a mild COVID-19 infection. In a case report by Sawalha *et al.*, bilateral optic neuritis followed within a week of COVID-19 symptoms.[9] Similarly, another case of optic neuritis developing within a few days of COVID-19 was reported by Zhou *et al.*[9] Patients presented with painful vision loss, relative afferent pupillary defect (RAPD) in the more severely affected eye with visual field defects and optic nerve enhancement on magnetic resonance imaging (MRI). Both cases had anti-myelin oligodendrocyte glycoprotein (MOG) antibodies. Cerebrospinal fluid (CSF) examination, immunological profile, viral panel and MRI brain did not reveal any other underlying etiology. Treatment was on the same lines as a typical case of optic neuritis with intravenous methylprednisolone (IVMP) followed by oral prednisolone leading to visual recovery and resolution of disc edema. MOG-antibody associated optic neuritis in the setting of COVID-19 is a parainfectious demyelinating syndrome with a viral prodrome. The virus has not been isolated from the CSF of the patients indicating that the virus may not be directly involved, rather it may be an immune-mediated insult. It is possible that in future, a spike in demyelinating neurological conditions may be seen, triggered by the viral infection.[10]

A case of acute hypokinetic rigid syndrome with transient opsoclonus was reported in a patient admitted for severe COVID-19 infection. In this case as well, a parainfectious immune-mediated midbrain affliction was the suggested mechanism.[11]

Adie's tonic pupil

Adie's tonic pupil can result from systemic conditions like diabetes or other viral infections. Development of tonic pupil in the patient after COVID-19 onset made the authors consider the association. The patient was a health care worker who gave a history of retro-ocular pain and reading difficulty two days after the onset of systemic COVID-19 symptoms. Pupillary hypersensitivity to 0.1% pilocarpine confirmed the diagnosis of Adie's tonic pupil. The short duration between COVID-19 symptoms and ocular features points towards the direct role of the virus itself on the nerves.[12] The functional receptor for the virus, ACE-2 receptor, has been identified in both brain and the basal layer of nasal epithelium. It has been suggested that the virus can enter the brain from the nasal epithelium via the olfactory bulb. Countering this theory, others have suggested that olfactory sensory neuron does not contain ACE-2 receptor and transmembrane protease serine 2 (TMPRSS2). However, radiological changes have been shown in the olfactory bulb and gyri recti.[13] The patient also had bilateral chorioretinopathy. The systemic evaluation for autoimmune and infectious causes were all negative. The etiology of spectrum of white dot syndrome remains unknown though it follows autoimmune diseases and viral infections. Systemic oral steroids led to full anatomical and functional recovery, further favoring the role of autoimmune factors mediated by COVID-19 in the development of both chorioretinopathy and Adie's tonic pupil.

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Miller Fisher Syndrome (MFS) and cranial nerve palsy

MFS with acute onset ataxia, loss of tendon reflexes, and ophthalmoplegia and cases of cranial nerve palsies have been reported in several patients recently diagnosed with COVID-19.[14] Patients give history of acute onset of diplopia as the ocular complaint. 6th nerve was most commonly involved followed by oculomotor nerve [Fig 3javascript:void(0)]. A case of right-sided facial nerve palsy has been reported in a child with agammaglobulinaemia and hyper IgM syndrome, asthma, and obstructive sleep apnoea in the USA.[15] RT-PCR was positive for SARS-CoV-2 but not for HSV and VZV. Cases of MFS responded well to intravenous immunoglobulin (IVIG) while cranial nerve palsies resolved spontaneously in most cases in 2-6 weeks. In these cases, again a misdirected immune system triggered by the viral infection is believed to be at fault.

Neurogenic ptosis

Acute onset of bilateral ptosis with other neurological signs of GBS was reported by Assini *et al.* from Italy.[16] Symptoms developed almost 20 days after severe COVID-19 infection. CSF examination showed oligoclonal bands with increased IgG/albumin ratio. No SARS-CoV-2 virus was detected in the CSF. GBS with cranial nerve involvement can thus be a late manifestation of severe COVID-19 infection. Good response to immunoglobulin supports the immune-mediated pathogenesis.

Delayed onset of ocular myasthenia gravis was reported by Huber *et al.* in a 21-year-old healthy woman.[17] She gave history of mild flu-like symptoms a month ago. Her antibody titers were suggestive of past infection with SARS-CoV-2. Acetylcholine receptor antibodies were positive. In view of rapid worsening of symptoms, she was treated with IVIG with gradually increasing dose of pyridostigmine. It is likely that COVID-19 infection can potentially trigger or exacerbate autoimmune diseases.

Cerebrovascular accident (CVA) with vision loss

Acute vision loss following CVA can also result from the procoagulant state in COVID-19 infection. Pre-existing endothelial dysfunction may make patients more susceptible. In the two cases reported, one had diabetes mellitus and the other patient had SLE with end-stage kidney disease and COPD with a prior history of CVA. Acute onset of bilateral, painless vision loss should prompt the treating physicians to advise an urgent imaging of the brain with angiography.[18] Yang *et al.* described the development of bilateral supranuclear gaze palsy with right branch retinal artery occlusion in a 60-year old patient with a history of atrial fibrillation, COPD, bladder carcinoma on chemotherapy and bacterial endocarditis. Diffusion-weighted MRI revealed an infarct in left paramedian midbrain. In this case as well, COVID-19 possibly aggravated the procoagulant state of the patient.[19]

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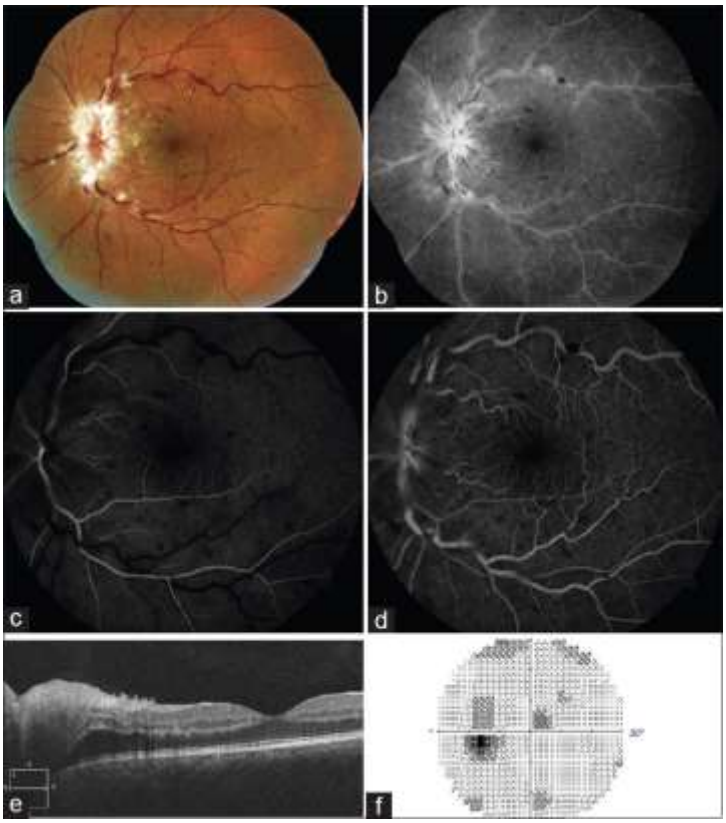

Figure 1. Papillophlebitis as a manifestation of COVID-19: A 40-year-old patient developed diminution of vision in left eye 6 weeks after a mild COVID-19 infection. (a) Fundus photograph and (b) red free retinography showing inflammation of the optic disc, retinal venous vasodilatation and tortuosity, and superficial hemorrhages in all four quadrants. (c) Early and (d) late arteriovenous phase FA showing discrete venous staining and leakage, in addition to leakage and late staining from the optic disc. (e) OCT showing optic disc edema without macular edema. (f) Visual field with slight central scotoma and a slight to moderate increase in the blind spot. (Reproduced with permission from Insausti-García A, Reche-Sainz JA, Ruiz-Arranz C, Vázquez ÁL, Ferro-Osuna M. Papillophlebitis in a COVID-19 patient: Inflammation and hypercoagulable state. Eur J Ophthalmol 2020 Jul 30.)

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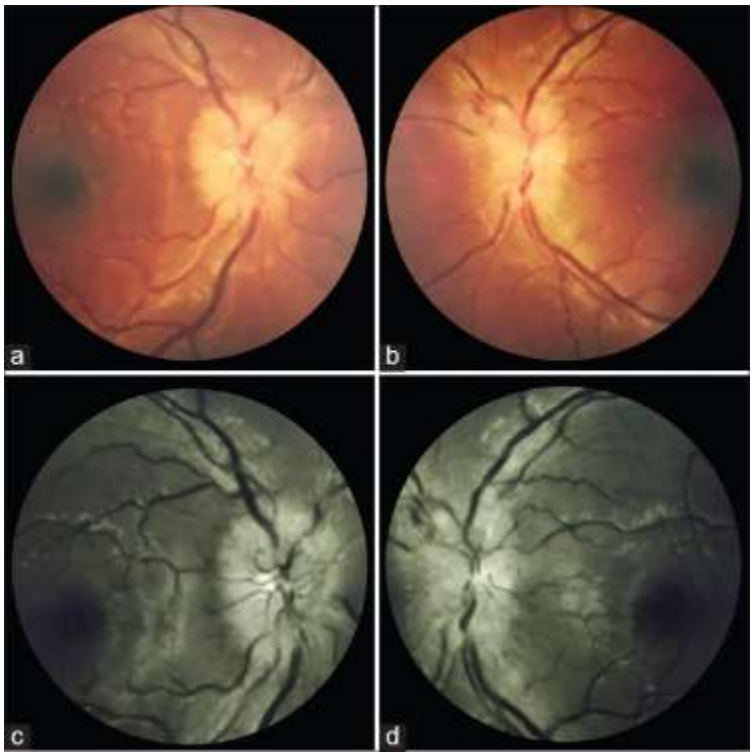

Figure 2. Bilateral atypical optic neuritis after a mild COVID-19 infection: A 34-year-old female presented with complaints of gradual blurring of vision in right eye with pain on eye movements since 1 week and history of a similar episode 3 weeks back in left eye, which improved spontaneously. She had recovered from a mild COVID-19 infection 2 weeks before the onset of ocular symptoms. On examination, her uncorrected visual acuity was 20/200, N24 in right eye, and 20/25, N6 in left eye. Pupil examination revealed a Grade III RAPD in right eye. (a and b) Fundus photograph and (c and d) red-free imaging showing bilateral disc oedema, more in the right eye. (Contributed by Rachna Vinaya Kumar, Paediatric ophthalmology, Neuro ophthalmology and Adult Strabismus Services, Apollo Eye Institute, Apollo Hospitals, Hyderabad, India

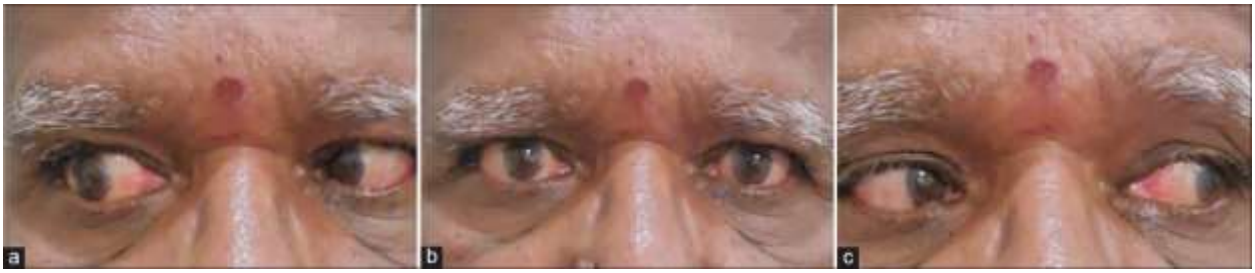

Figure 3. Sixth nerve palsy after COVID-19: A 64-year-old male presented with acute onset diplopia. (a) On examination there was right abduction limitation with (b) orthophoria in primary gaze and (c) normal adduction of right eye. (Contributed by Rachna Vinaya Kumar, Paediatric ophthalmology, Neuro-ophthalmology and Adult Strabismus Services, Apollo Eye Institute, Apollo Hospitals, Hyderabad, India)

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Conclusion

The prevalence of ophthalmic manifestations among COVID-19 patients ranges from 2-32%.[19]. The given complications certainly deteriorate the life quality of individuals with COVID-19 infection. Thus, it is crucial for eye-care specialists to get familiarized with the data provided in fresh researches carried out worldwide as well as in the given literature review as well as to be able to recognize and address them with sophisticated knowledge.

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