ISSN: 3032-3134 (ONLINE)
InaJBCS Indonesian Journal of Biomedicine and Clinical Sciences

# Neuro-ophthalmologic manifestations of COVID-19: a review

**Indra Tri Mahayana*, Stefani Melisa Karina, Nyssa Alexandra Tedjonegoro**

Department of Ophthalmology, Neuro-Ophthalmology Division, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta, Indonesia

https://doi.org/10.22146/inajbcs.v56i4.16836

Submitted: 2023-01-04
Accepted : 2023-08-16

## ABSTRACT

Several mechanisms for the pathogenesis of COVID-19 have been proposed. These are direct viral toxicity, endothelial cell damage and thromboinflammation, dysregulated immune response, and renin-angiotensin-aldosterone system (RAAS) dysregulation. The ophthalmic manifestations of COVID-19 vary, affecting the anterior, posterior, and neuro-ophthalmic components. However, the relationship between COVID-19 and neuro-ophthalmologic presentations is limited. This literature review focuses on discussing these manifestations. A manual search was performed using the following keywords “neuro-ophthalmology”, “ocular”, “manifestations”, COVID-19, and coronavirus. The searches were conducted in PubMed and Google Scholar, where any study type and online publications were included. The most common ocular manifestation found in COVID-19 patients is conjunctival involvement. Some reported neuro-ophthalmic manifestations of COVID-19 are papillophlebitis, optic neuritis, cranial nerve palsies, Miller Fisher syndrome, Tolosa-Hunt syndrome, Adie’s tonic pupil, and internuclear ophthalmoplegia. A physician should examine the presence of diplopia, pain during eye movement, declining vision, or any other neurological symptoms. Therefore, it is essential to perform a comprehensive eye examination which includes visual acuity, pupillary response, ocular motility, ptosis, and optic disc examination. Additional tests such as neuroimaging or angiography might be performed to detect cerebral infarction or any other abnormalities when necessary. It is vital to be vigilant and consider COVID-19 as one of the possible causes of disease during this pandemic.

***Keywords***:
COVID-19;
coronavirus;
neuro-ophthalmology;
manifestations;
ocular

## ABSTRAK

Beberapa mekanisme terkait patogenesis COVID-19 diusulkan. Mekanisme tersebut adalah toksisitas virus langsung, kerusakan endotel dan tromboinflamasi, disregulasi respon imun, dan disregulasi sistem renin-angiotensin-aldosterone (RAAS). Manifestasi oftalmik COVID-19 sangat bervariasi, tidak hanya mempengaruhi segmen anterior tapi juga segmen posterior dan komponen neuro-oftalmologi. Namun demikian, masih sedikit yang diketahui tentang hubungan COVID-19 dan manifestasi neuro-oftalmologis. Tinjauan literatur ini fokus membahas manifestasi tersebut. Pencarian pustakan dilakukan secara manual menggunakan kata kunci “neuro-oftalmologi“, “okular“, “manifestasi“, “COVID-19“, dan/atau “coronavirus“. Pencarian dilakukan di database PubMed dan Google Scholar di mana semua jenis studi dan publikasi *online* dimasukkan. Keterlibatan konjungtiva merupakan manifestasi okular yang paling sering ditemukan pada pasien COVID-19. Beberapa manifestasi neuro-oftalmik COVID-19 yang dilaporkan termasuk papillophlebitis, neuritis optik, kelumpuhan saraf kranial, sindrom Miller Fisher, sindrom Tolosa-Hunt, Adie’s tonic pupil dan internuclear ophthalmoplegia. Dokter harus memperhatikan gejala diplopia, nyeri pada gerakan bola mata, penurunan tajam penglihatan, atau gejala neurologis lainnya. Pemeriksaan mata yang komprehensif yang meliputi ketajaman visual, respon pupil, motilitas okular, ptosis, dan diskus optikus harus dilakukan. Jika ada indikasi, lakukan pemeriksaan neuroimaging atau angiografi untuk mendeteksi kelainan atau infark serebral. Sangat penting mewaspadai dan mempertimbangkan COVID-19 sebagai salah satu penyebab penyakit selama pandemi ini.

*corresponding author: tri.mahayana@gmail.com, indra.tri.m@mail.ugm.ac.id

## INTRODUCTION

Coronaviridae is a family of enveloped positive-strand RNA virus which infects vertebrates.[1-2] Currently, this family consists of 2 subfamilies, 5 genera, 26 subgenera, and 46 species.[1] The emergence of a novel coronavirus, namely the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused the coronavirus disease (COVID-19), was one of the most significant medical outbreaks in the last three years. The first COVID-19 case was identified in Wuhan, the capital city of Hubei Province in China, and manifested as pneumonia with unknown etiology.[2-3] COVID-19 has various clinical manifestations, ranging from asymptomatic to fever, cough, runny nose, headache, and myalgia to acute respiratory failure and multiorgan dysfunction.[1] Based on WHO, by 23rd August 2022, the total of confirmed COVID-19 cases worldwide was 594,367,247, including 6,451,016 deaths. In Indonesia alone, a total of 6,323,715 confirmed COVID-19 cases, including 157,420 deaths, have been recorded by today.[4]

The ophthalmic clinical manifestations of COVID-19 have not been widely explained, yet, presumably due to several reasons, such as technical issues, examiners' safety issues, and the tendency to ignore eye complaints compared to life-threatening complaints. Based on several studies, COVID-19 has various ophthalmologic manifestations affecting the eyelids, ocular surface, anterior and posterior segments, orbital, and neuro-ophthalmology.[5] The neuro-ophthalmologic manifestations vary from papillophlebitis, optic neuritis, Adie's tonic pupil, and ocular motor cranial nerve palsies.

The neurotropic and neuroinvasive abilities of coronavirus have been described in humans. It is suspected that the coronavirus could infect the central nervous system via hematogenic and lymphatic pathways, where the infected leucocytes serve as reservoirs and vectors for central nervous system infection and retrograde trans-neuronal transmission post-nasal and olfactory bulb infection. The human host cell infection pathway is mediated by angiotensin-converting enzyme receptor 2 for SARS-CoV-1 and SARS-CoV-2. This finding was proven through demonstration in the aqueous humor.[1] Other than that, COVID-19 patients experienced elevated D dimer levels, thrombocytopenia, and prolonged prothrombin time or international normalized ratio. Hence, a similar mechanism has been suspected in some neuro-ophthalmologic manifestations, such as cranial neuropathies.[6] This literature review was written to summarize and broaden the understanding of the ophthalmic clinical manifestation of COVID-19, especially in neuro-ophthalmology.

## MATERIAL AND METHODS

This was a literature review with a manual search using the following keywords "neuro-ophthalmology", "ocular", "manifestations", "COVID-19", and "coronavirus". The searches were conducted in PubMed and Google Scholar, where any study type and online publications written in English were included. This literature review was undertaken in August-October 2022.

## RESULTS

Studies discussing the neuro-ophthalmic manifestation of COVID-19 are presented in TABLE 1. Since neuro-ophthalmic manifestations are not commonly found, therefore the authors' main sources are isolated case reports.

TABLE 1. Neuro-ophthalmologic manifestations of COVID-19 articles

| Authors | Main findings |
|---|---|
| Insausti-García *et al.*[11] | A Caucasian adult patient with COVID-19 had decreasing unilateral eye sensitivity. Optical coherence tomography (OCT) shows papilledema without any macula edema. The patient was treated with acetylsalicylic acid and bromfenac. |
| Ahmed *et al.*[13] | A 67-y.o. male was reported with unilateral optic neuritis and COVID-19 infection. Brain imaging revealed right optic nerve thickening. |
| Sawalha *et al.*[14] | A patient had bilateral optic neuritis within a week of COVID-19 infection and was administered intravenous methylprednisolone for 5 d. |
| Zhou *et al.*[15] | A patient had bilateral optic neuritis within a few days of COVID-19 symptoms. Head imaging with contrast showed optic nerve thickening. The patient was prescribed intravenous methylprednisolone and oral prednisone. |
| Quijano-Nieto & Córdoba-Ortega[17] | A 36-y.o. female patient developed painless blurred vision, bilateral pupil dilatation, and symptoms of COVID-19 infection. Both pupils constrict on pilocarpine examination. |
| Ortiz-Seller *et al.*[18] | Two days after the onset of COVID-19, a patient complained of retro-ocular pain and decreasing visual acuity. Administration of pilocarpine eye drops constricts the pupils leading to Adie's tonic pupil. The patient was treated with oral prednisone. |
| Gopal *et al.*[21] | A 37-y.o. female suffered from a painful right brow and blurry right eye three weeks after COVID-19 infection. Her right pupil constricts on pilocarpine examination. |
| Dinkin *et al.*[22] | Two cases of COVID-19 with cranial neuropathies were discussed in this study. The first is a 71-y.o. woman with painless diplopia who could not abduct her right eye. The patient was treated with hydroxychloroquine. The second case is a patient with multiple cranial nerve paresis and Miller Fisher syndrome. The patient was treated with intravenous immunoglobulin and hydroxychloroquine. |
| Belghmaidi *et al.*[23] | A COVID-19 patient was presented with isolated oculomotor nerve paresis, diplopia, and strabismus. The patient was prescribed chloroquine, azithromycin, vitamin C, and zinc. |
| Tan *et al.*[24] | A total of 11 patients with oculomotor nerve palsy were analyzed. 55% of patients did not have any past illness. The longest interval between eye and COVID-19 symptoms was 16 d. |
| Falcone *et al.*[25] | A 32-y.o. man suffered from acute binocular, horizontal diplopia, and upper respiratory symptoms. MRI examination showed left lateral rectus muscle atrophy on T1 and hyperintense T2. |

TABLE 1. Cont.

| Authors | Main findings |
|---|---|
| Greer *et al.*[26] | Two cases of COVID-19 infection with isolated sixth nerve palsy were reported. Both patients had a history of well-controlled hypertension. |
| Reyes-Bueno *et al.*[28] | A 51-y.o. woman developed binocular diplopia and muscle weakness two weeks after experiencing respiratory symptoms. She was treated with intravenous immunoglobulin and gabapentin. |
| Gogu *et al.*[29] | A 45-y.o. man with diabetes mellitus suffered from Tolosa-Hunt syndrome and COVID-19 infection. His brain and orbits imaging showed an inflammation in the left cavernous sinus and orbital apex. The patient was prescribed intravenous methylprednisolone and oral prednisone. |
| Hajjar *et al.*[30] | A patient diagnosed with the Tolosa-Hunt syndrome triad had spontaneous clinical improvement after three months. The patient's pupils were reactive in the fifth month. |
| Fathy *et al.*[32] | A 4-y.o. female patient presented with unilateral internuclear ophthalmoplegia and arrested hydrocephalus. She was prescribed ceftriaxone and acyclovir. |
| Vasanthpuram & Badakere[33] | A case of COVID-19 patient with sudden onset of binocular diplopia was reported. The patient was treated with vitamin B12, vitamin C, doxycycline, and ivermectin. |

## DISCUSSION

### Pathophysiology of COVID-19

SARS-CoV-2 uses a similar mechanism to identify a receptor as SARS-CoV, an earlier virulent coronavirus responsible for the SARS epidemic 2003. The coronavirus protein spike facilitates viral entry into the target cell. The spike in SARS-CoV and SARS-CoV-2 subunits involves the angiotensin-converting enzyme 2 (ACE2) as the entry receptor. Cell entry requires spike protein priming by the cellular serine protease TMPRSS2 or other proteases. Co-expression on the ACE2 cell surface and TMPRSS is necessary to complete this entry process. The viral efficiency by binding with ACE2 is the primary determinant of transmission. Recent studies have shown a higher affinity for SARS-CoV-2 to ACE2 compared to SARS-CoV to ACE2, which may explain the increased transmissibility of SARS-CoV-2. The mechanisms responsible for the pathophysiology of multi-organ damage secondary to SARS-CoV-2 infection include direct viral toxicity, endothelial cell damage and thromboinflammation, dysregulated immune response, and renin-angiotensin-aldosterone system (RAAS) dysregulation (FIGURE 1).[7]

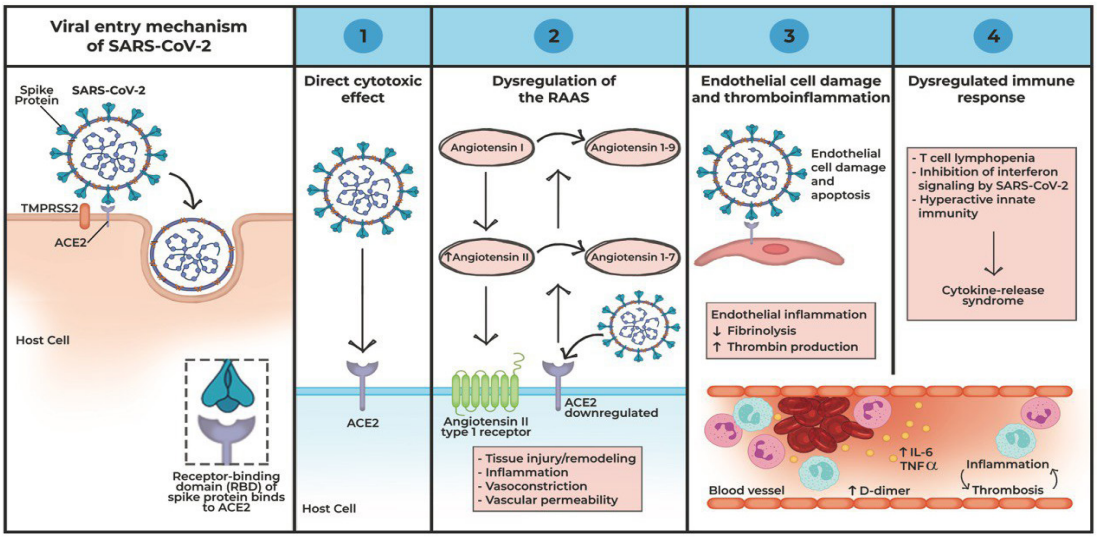


FIGURE 1. Pathophysiology of COVID-19.[7]

Direct viral toxicity, defined as a direct viral invasion into the nerve parenchyma, aids in gaining viral access to the central nervous system through the nasal mucosa, lamina cribrosa, and olfactory bulb or by retrograde axonal transport.[7] Endothelial cell damage, thromboinflammation, immune response-RAAS dysregulation due to ACE2-mediated entry of the SARS-CoV-2 virus with subsequent inflammation and formation of a prothrombotic environment which might directly affect the optic nerve bundles.

COVID-19 patients experienced elevated D-dimer levels, thrombocytopenia, and prolonged prothrombin time or international normalized ratio. A similar mechanism has been suspected in some neuro-ophthalmologic manifestations, such as cranial neuropathies, which often occur in the context of ischemia.[6] Aside from that, an article mentioned the possibility of neuro-ophthalmological symptoms resulting from hypoxia, severe hypertension, toxic metabolic processes, ischemic and hemorrhagic strokes, along with para-infectious and post-infectious inflammatory processes.[8]

## Ophthalmic clinical manifestations of COVID-19

COVID-19 has various ocular clinical manifestations. Based on several published case reports, the visual manifestation can be divided into four based on the anatomical areas. The following sections are the ocular surface and anterior segment, the posterior segment, the orbit, and neuro-ophthalmology (TABLE 2).[5] The neuro-ophthalmic complications of COVID-19 are further distinguished into afferent and efferent. The afferent manifestations include papillophlebitis, papilledema, and optic neuritis, while the efferent manifestations are Adie's tonic pupil, cranial neuropathies, Miller Fisher syndrome, and other eye movement disorders.[9] Little is known about the relationship between COVID-19 and neuro-ophthalmologic presentations. Hence, this literature review focuses on discussing these manifestations.

TABLE 2. Ocular manifestations of COVID-19[5]

| Ocular surface and anterior segment | Posterior segment | The orbit | Neuro-ophthalmology |
|---|---|---|---|
| Follicular conjunctivitis | Central retinal vein occlusion (CRVO) | Dacryoadenitis | Papillophlebitis |
| Viral keratoconjunctivitis | Central retinal artery occlusion (CRAO) | Retroorbital pain | Optic neuritis |
| Hemorrhagic conjunctivitis and pseudo-membrane | Acute macular neuro-retinopathy (AMN) | Orbit cellulitis and sinusitis | Adie's tonic pupil |
| Episcleritis | Paracentral acute middle maculopathy (PAMM) | Mucormycosis | Cranial nerves paresis:<br>• Oculomotor nerve paresis<br>• Abducens nerve paresis<br>• Multiple cranial nerve paresis and Miller Fisher syndrome<br>• Tolosa-Hunt syndrome |
| | Vitritis and outer retinal abnormality | | Internuclear ophthalmoplegia |
| | Acute retinal necrosis (ARN) | | |
| | Serpiginous choroiditis | | |

**Neuro-ophthalmologic clinical manifestations of COVID-19**

*Papillophlebitis*

Papillophlebitis is a rare condition seen in healthy young adults. It is characterized by unilateral optic disc swelling without optic nerve function abnormalities or a central retinal vein occlusion (CRVO).[10] A case report discusses papillophlebitis in a Caucasian adult patient with COVID-19. Six weeks before experiencing any eye complaint, the patient complained of having fever, myalgia, and cough for two weeks. Ocular manifestations include a unilateral decrease in sensitivity, with visual acuity preserved at 6/6 on both eyes, without pain and relative afferent pupillary defect (RAPD).[11]

Funduscopic examination revealed severe optic disc inflammation, dilated and tortuous retinal vessels, superficial retinal hemorrhages in all four quadrants, and cotton wool spots. Perimetry examination shows blind spot expansion. Fluorescein angiography revealed venous staining and leakage, late staining of the optic disc without ischemia, or peripheral vasculitis. Optical coherence tomography (OCT) shows papilledema without the involvement of macula edema (FIGURE 2). The patient was given acetylsalicylic acid 100 mg orally daily, and bromfenac 0.9 mg/dL eye drops twice daily.[11]

A week after diagnosis, the patient's vision had decreased to 6/60 due to macular edema. The patient was then given a sustained-release dexamethasone intravitreal implant. After two weeks, the patient's vision improved to 6/12, and the macular and papillary edema were reduced (FIGURE 3).[11]

Differential diagnoses of papillophlebitis include central retinal vein occlusion (CRVO), non-arteritic ischemic optic neuropathy, diabetic papillopathy, infectious papillitis,

hypertensive retinopathy, and orbital compressive lesions. The patient's age, presence or absence of RAPD, cardiovascular risk factors, and other investigations may be distinguished from clinical manifestations.[11]

The visual prognosis of papillophlebitis is generally good, without permanent visual impairment, and often a spontaneous improvement. Approximately 30% of patients develop complications such as ischemic venous occlusion, leading to neovascular glaucoma and macular edema.[11]

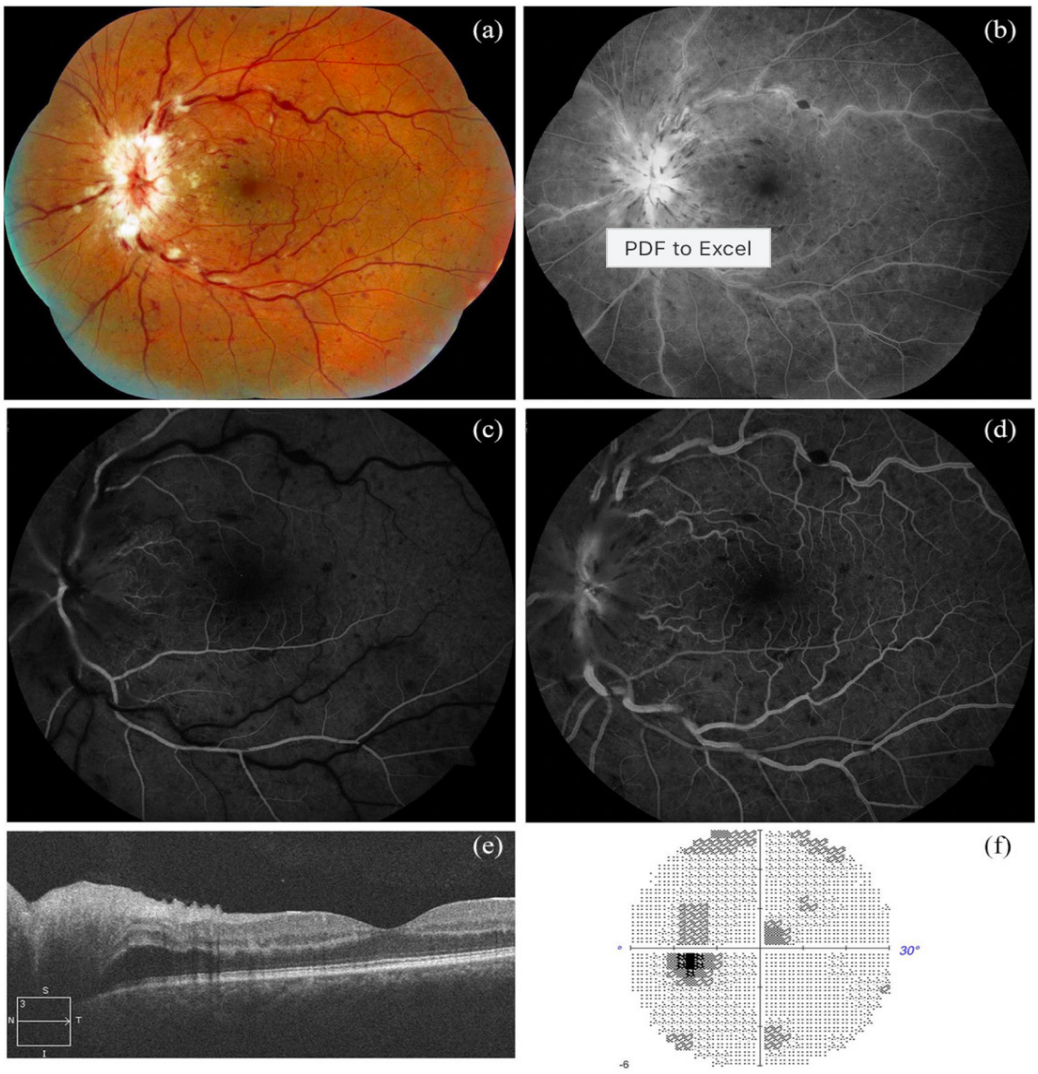


FIGURE 2. Papillophlebitis at early presentation (a) Retinography and (b) red-free retinography show inflamed optic disc, dilated and tortuous retinal vessels, superficial retinal hemorrhage on all four quadrants, (c) FA on early arteriovenous phase (d) FA: stained and vein leakage, late staining of the optic disc (e) OCT: optic disc edema without macula edema (f) HFA: mild central scotoma and blind spot extension.[11]

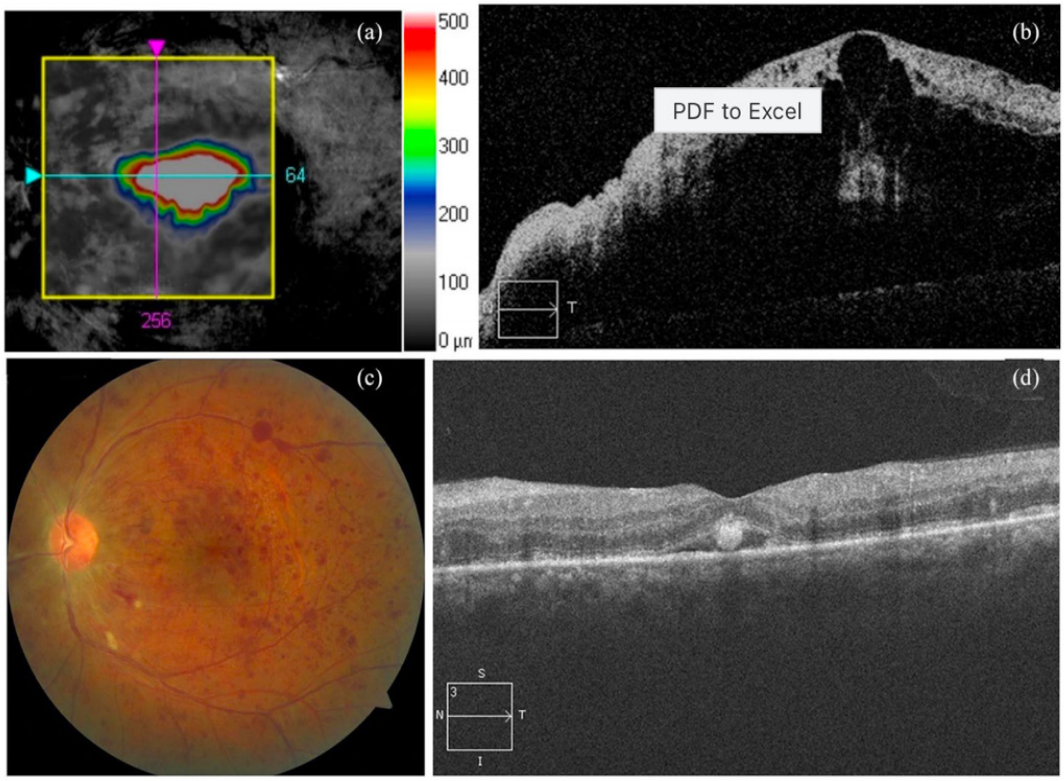


FIGURE 3. Papillophlebitis before and after therapy (a and b) macula OCT shows cystoid macula edema. (c) Retinography and (d) macula OCT after intravitreal dexamethasone sustained-release implant. There was an improvement in optic disc macula edema and vessels.[11]

*Optic neuritis*

Optic neuritis is an inflammation that demyelinates the optic nerve and reduces vision in one or both eyes.[12] The demyelination and swelling of the optic nerve fibers are caused by systemic T-cell activation leading to an immunological antigen-antibody reaction.[13] Optic neuritis is highly associated with multiple sclerosis (MS), and it is the presenting feature in 15 – 20% of these patients and occurs in 50% of them at some time during their illness.[14] Several case reports have reported the association of COVID-19 with the incidence of optic neuritis. The onset of optic neuritis varies; it can occur between a few days, two weeks, or even three weeks after a positive COVID-19 nasopharyngeal polymerase chain reaction (RT-PCR) swab.[13-15]

Optic neuritis may either be unilateral or bilateral. Symptoms include mild (6/9) to severe vision loss (1/300), pain during eye movement, and diplopia.[13-15] A case report by Ahmed *et al.*[13] reported a 67 -y.o. male patient with unilateral optic neuritis three weeks after he was diagnosed with COVID-19. In a case report by Zhou *et al.*,[15] bilateral optic neuritis was found within a few days of COVID-19 symptoms. Similarly, Sawalha *et al.*[14] reported a patient with bilateral optic neuritis within a week of COVID-19 symptoms. On examination, RAPD was found, and perimetry may show a general vision loss and superior arcuate defect.[14] Dyschromatopsia may be found on color sensitivity examination.[13] On funduscopic examination, papilledema with venous congestion and perivenous retinal hemorrhage was found.[15] In all three case reports, the result of Myelin Oligodendrocyte Glycoprotein (MOG) was positive (1:160 to 1:1000).[13-15] A head Magnetic Resonance Imaging

(MRI) examination was performed in these cases. Brain MRI by Ahmed *et al.*[13] suggested mild thickening and T2 hyperintensity of the intracanalicular part of the right optic nerve (~ 5.2 mm) with normal brain parenchyma and left optic nerve. Similarly, a head MRI with contrast by Zhou *et al.*[15] showed enhancement and thickened optic nerve.

The primary treatment for optic neuritis is intravenous methylprednisolone 1 g/d for 3 d, followed by oral prednisone 1 mg/kg/d for 11 d, which will be tapered over 4 d. This treatment course leads to visual recovery in 2 to 3 wk and resolution of disc edema.[14] In a case report by Sawalha *et al.*[14], the patient was administered the same dose for 5 d. Within 48 hr, the patient's vision and eye pain had improved significantly. On the fifth day, his left eye vision was completely restored, and he was discharged from the hospital on a one-month tapering dose of oral prednisone. Similarly, Zhou *et al.*[15] documented increased visual acuity from 1/300 at presentation to 6/9 after 7-d treatment with steroids.

*Adie's tonic pupil*

Adie's tonic pupil is an anisocoria in which the affected pupil is significantly larger than the healthy one.[16] It occurs if the postganglionic parasympathetic neurons are injured, resulting in tonic pupil response to near vision and disappearing photomotor reflex. These neurons are found from the ciliary ganglion to the pupil sphincter and the ciliary muscle.[17] Adie's pupil is caused by systemic diseases such as diabetes or viral infections and is more common in young women.[16] A study suggested that viral infection may lead to denervation of the postganglionic parasympathetic supply to the pupillary sphincter.[18] Several viral infections, such as chicken pox, herpes zoster, influenza, measles, and viral hepatitis, invade the ciliary ganglion directly, causing Adie's pupils.[19-20] In Adie's pupil, the affected pupil is sensitive to low concentrations of pilocarpine; and there is an absence of light reflect on direct and indirect pupil reflex examinations.[18]

A case of bilateral tonic pupil was reported in a 36-y.o. female patient with a positive RT-PCR test for SARS-CoV-2 17 d ago. She had blurred vision without pain during eye movements. Eye examination showed bilateral pupil dilatation of approximately 8 mm in diameter. Her pupils did not react to light but slowly responded to convergence. Both pupils were constricted on a 0.125% diluted pilocarpine examination and were equal in size after 15 min. Aside from an eye examination, she underwent neurological examination, blood tests, and MRI, all of which gave normal results. The patient was diagnosed with bilateral tonic pupil post-SARS-CoV-2 infection.[17]

Ortiz-Seller *et al.*[18] wrote a case of tonic pupils after the onset of COVID-19. The patient was a healthcare worker who had retro-ocular pain and difficulty reading two days after the onset of systemic COVID-19 symptoms. On early presentation, the best corrected visual Acuity (BCVA) was 6/7.5 with a less reactive pupil. Pupil dilatation is more pronounced on bright illumination with light-near dissociation. Examination with 0.1% pilocarpine eye drops on both eyes caused a hypersensitive response with constriction of both pupils leading to Adie's tonic pupil. Inflammatory chorioretinopathy was also found in this patient. Systemic tracing for autoimmune or infectious causes was negative. The patient was then treated with oral prednisone 60 mg/d. A week after therapy, the patient's condition improved anatomically and functionally, and both eyes had BCVA 6/6.[18] The ACE2 receptor, a functional receptor for the virus, has been identified in the brain and the basal layer of the nasal

epithelium. The virus can enter the brain and nasal epithelium via the olfactory bulb. Radiological changes have been demonstrated in the olfactory bulb and gyrirecti.[5]

Similarly, a recent report by Gopal *et al.*[21] describes a 37-y.o. female patient suffering from blurry right eye vision with pain over the right brow. Three weeks ago, she had a high fever, anosmia, and cough, and tested positive for RT-PCR for SARS-CoV-2. Her eye examination revealed a BCVA 6/6 on both eyes with slight pain in bright light. She declined to have any pain on eye movement. On pupil examination, the diameter of the right eye pupil was 5.5 mm while the left eye was 3.5 mm, revealing an anisocoria. The right eye pupil showed diminished reaction to direct light and near response, while the left eye reacted rapidly to both. To support the diagnosis, a 0.1% pilocarpine test was performed. The right pupil constricts directly after instillation of pilocarpine. Other examinations, such as MRI and magnetic resonance angiography (MRA) of the brain and orbit, gave normal results.

**Cranial nerve paresis**

*Oculomotor nerve paresis*

The oculomotor nerve, or the third cranial nerve palsy, may occur with or without pupil involvement and can be isolated or in conjunction with other cranial nerve palsies.[22,23] The oculomotor nerve palsy is distinguished into complete and partial. Complete oculomotor nerve palsy is characterized by severe levator palpebra superior and extraocular muscle weakness, while partial oculomotor nerve palsy is presented with milder muscle weakness. Pupil involvement is defined as the diminishing or absence of pupillary light responses.[24] In a case report of isolated oculomotor nerve paresis, the following clinical manifestations were diplopia and strabismus; neither ptosis nor pupil involvement was found. When performing an eye movement examination, limitations were found in upward, adduction, and downward movement. Diplopia worsens in adduction position (FIGURE 4). The patient was treated with the recommended COVID-19 management, chloroquine 500 mg once daily, azithromycin 500 mg once daily on the first day, followed by 250 mg on the second to the 7$^{th}$ d, vitamin C 1 g twice daily, and zinc 90 mg twice daily for 10 d. On the 6$^{th}$ d, there was a complete improvement in exotropia and diplopia (FIGURE 4).[23]

Tan *et al.*[24] analysed two patients with oculomotor nerve palsy and nine other cases published in other literature. 55% of the patients did not have any past medical history. The patients' age ranged from 2 to 65 y.o. with a median age of 46 y.o. The male-to-female ratio was nearly equal. Based on the study, almost all the patients had eye complaints soon after their COVID-19 symptoms manifested. Sometimes, the oculomotor nerve palsy may occur before or simultaneous with the respiratory symptoms. The longest interval between these symptoms was 16 d. Of 11 patients, five suffered from partial oculomotor nerve palsy, four from complete oculomotor nerve palsy, and the other two were not mentioned in their respective studies. Only four patients (36%) had diminished pupillary light responses (pupillary involvement). The presence of past medical history did not affect the features of oculomotor nerve palsy. All the patients underwent brain imaging examinations, six of which were brain MRIs with intravenous gadolinium, and only one showed significant left oculomotor nerve enhancement and thickening. Another brain MRI scan revealed an enhanced right inferior rectus muscle. To the best of our knowledge, 64% of the patients (7/11) did not receive any pharmacological therapy for their eye symptoms. Regardless, after a week or two, their eyes were restored completely.

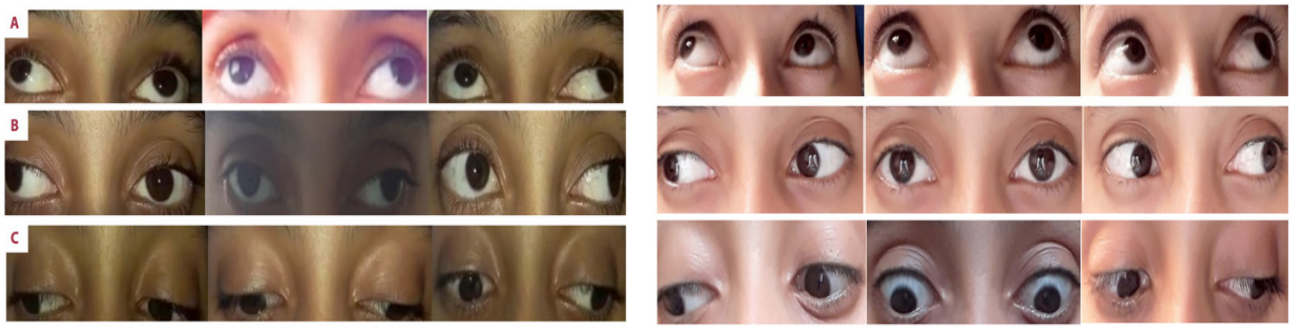


FIGURE 4. Early presentation of isolated oculomotor nerve paresis without pupil involvement, the upward (A), adduction (B), and downward (C) left eye movement was limited (left). Isolated oculomotor nerve paresis without pupil involvement after COVID-19 therapy. There's an improvement in eye movement (right).[9]

*Abducens nerve paresis*

The abducens nerve, the sixth cranial nerve, is responsible for ipsilateral eye abduction. The abducens nerve is the most common cranial nerve involved in COVID-19 infection. The abducens nerve paresis is often associated with microvascular disease in the elderly and viral infections such as Epstein-Barr or enterovirus in pediatrics.[25] Several case reports discuss acute horizontal diplopia that worsens with far vision and abduction towards paresis. The prognosis varies; some report improvement of diplopia along with improvement of systemic COVID-19 symptoms, while others did not show any significant improvement.[22,26]

Dinkin *et al.*,[22] reported a case of a 71-y.o. woman with sudden onset of painless diplopia and inability to abduct her right eye. She had experienced cough and fever beforehand and had a history of hypertension. She was sent to the emergency department (ED), where she was found to be febrile and hypoxemic. Her nasal RT-PCR swab was positive for SARS-CoV-2, and her chest X-ray showed bilateral airspace opacities. MRI examination showed enhancement of optic nerve sheaths and posterior Tenon capsules. She was treated with a 5-d course of hydroxychloroquine. After six days, her abduction palsy showed no significant improvement. However, after two weeks, her diplopia had improved gradually.

Falcone *et al.*,[25] reported a similar case of a 32-y.o. man with acute onset, binocular, horizontal diplopia. Three days before, he had upper respiratory symptoms. He tested positive for COVID-19 and was prescribed hydroxychloroquine for 5 d. Although his respiratory symptoms resolved over the next three weeks, his diplopia persisted until the next five weeks. The patient was completely unable to abduct his left eye. MRI examination showed left lateral rectus muscle atrophy on T1 and hyperintense on T2.

Greer *et al.*,[26] documented two cases of COVID-19 infection with isolated sixth nerve palsy. Both patients had a history of well-controlled systemic hypertension. The first case was a 43-y.o. woman with cough, fatigue, three days of fever, and sudden onset of painless diplopia. She woke up with binocular, horizontal diplopia, which worsened on left lateral gaze and far gaze. The second case was a

52-y.o. man with fever, anosmia, ageusia, myalgia, and fatigue. A day after these symptoms occurred, he had an acute onset of horizontal binocular diplopia, which also worsened in the distance and left gaze. Both patients tested positive on nasal swab for SARS-CoV-2. By his 14th d follow-up, his fever, myalgia, fatigue, and double vision had resolved, but his anosmia and ageusia persisted.

**Multiple cranial nerve paresis and Miller Fisher Syndrome (MFS)**

As a case report on multiple cranial nerve paresis mentioned, the clinical manifestations include diplopia, ptosis, mydriasis, and limited eye movement to downward and adduction, suggesting partial oculomotor nerve paresis. Limited bilateral abduction indicating bilateral abducens nerve paresis, was also stated. In addition, findings leading to MFS, such as ataxia gait with hyporeflexia and hyperesthesia on lower extremities, were found. MRI examination showed T2 hyperintensity and enlargement of the left oculomotor nerve.[22,27] Patients were treated with intravenous immunoglobulin (2 g/kg for three days) for MFS and hydroxychloroquine (1200 mg on the 1st d and 400 mg on the 2nd to 5th d) for COVID-19. Symptoms improve after treatment.[22]

Similarly, a case report by Reyes-Bueno *et al.*[28] discussed a 51-y.o. woman with a cough, sore throat, and diarrhea after recent contact with a COVID-19 patient. Two weeks later, she had binocular diplopia and muscle weakness, which precedes with pain in all four extremities. Soon after, she was unable to walk on her own. Physical examination showed left abducens nerve palsy, global areflexia, and muscle weakness. The patient tested positive for SARS-CoV-2 serum antibodies. She was diagnosed with COVID-19 and MFS, treated with IV immunoglobulin for five days and gabapentin, and her pain, diplopia, and facial and limb paresis improved significantly.

**Tolosa-Hunt Syndrome**

Tolosa-Hunt syndrome is an idiopathic, autoimmune phenomenon in the cavernous sinus. One of the etiology for this syndrome is COVID-19 infection and vaccination. It is suggested that the host's antibodies reacted with the cranial or peripheral nerves instead of the COVID-19 virus, leading to neuronal impairments.[29] The Tolosa-Hunt syndrome Triad includes one or more unilateral orbital pain episodes, isolated or multiple cranial nerve paresis, and granuloma on MRI or biopsy. However, more than 50% of cases reported normal MRI results. Hence, other causes had to be excluded.[30]

Gogu *et al.*[29] documented a case of a 45-y.o. man with diabetes mellitus, presented with Tolosa-Hunt syndrome 23 d after Ad.26.CoV 2-5 vaccine (COVID-10 Vaccine Janssen; manufactured by Johnson & Johnson), and 14 d after COVID-19 infection. He suffered from a severe left-sided headache, left periorbital pain with progressing ptosis, decreasing visual acuity on the left eye, left cranial oculomotor nerves palsies, an afferent pupillary defect, and several painful electric-like shocks episodes on the first two branches of the trigeminal nerve. No more anomalies were found on the rest of his neurological tests. His brain and orbits MRI results revealed inflammation in the left cavernous sinus and orbital apex with perineural enhancement surrounding the left optic nerve sheaths, justifying the presence of a Tolosa-Hunt syndrome. Most Tolosa-Hunt syndrome cases are responsive to corticosteroid treatment. In this case, the patient was prescribed 1 g of intravenous methylprednisolone for three days, followed by slowly tapered oral prednisone. His pain was reduced significantly, along with slight visual

acuity and eye motility improvement.

In a case report by Hajjar *et al.*,[30] a patient was presented with periocular pain, complete external ophthalmoplegia, total ptosis, semi-dilated pupils unresponsive to light, mild proptosis (3 mm difference from Hertel examination), and corneal hypoesthesia (FIGURE 5). The patient experienced spontaneous clinical improvement during a three-month follow-up in which ptosis was reduced, and there was a partial improvement in the oculomotor and trochlear nerves. In the 5$^{th}$ mo, the corneal sensation was improved, ptosis was no longer found, and the pupil was reactive. This indicates improvements in the oculomotor, trochlear, and the first branch of the trigeminal nerve paresis (FIGURE 5). The diplopia persisted in the 6$^{th}$ mo follow-up, indicating the presence of the abducens nerve paresis. The patient was planned for strabismus surgery.

**Internuclear Ophthalmoplegia (INO)**

Internuclear ophthalmoplegia is a disorder caused by a lesion in the medial longitudinal fasciculus (MLF) between the third and sixth cranial nerve nuclei. It is marked by ipsilateral eye adduction and nystagmus on the abducting eye.[31-32] INO is mainly caused by multiple sclerosis and infarction, with hydrocephalus being the least common etiology. The enlarged ventricles and increased intracranial pressure on hydrocephalus impairs MLF transmission. Recently, infectious diseases, such as COVID-19, have been assumed to may cause the development of INO.[32]

Fathy *et al.*,[32] published a case report of a 4-y.o. female presented with generalized tonic clonic convulsion two days after suffering upper respiratory tract symptoms. She tested positive for the nasopharyngeal PCR COVID-19 test. After four days, the patient was stable with full consciousness but started experiencing eye complaints. Her right eye was abnormally deviated, while her left eye had abnormal movements. Ophthalmic examination showed equally sized pupils reactive to light, right limited adduction in levoversion with fine nystagmus saccades in the left eye. The afferent pupillary defect was not found. Visual acuity could not be assessed. The presence of papilledema was not reported. The anterior and posterior segments showed normal results. The brain CT scan showed chronic supratentorial hydrocephalic changes with normal cerebellum and upper brain stem. The patient was diagnosed with unilateral INO, arrested hydrocephalus, and treated with ceftriaxone and acyclovir. After several days, her ocular motility improved significantly, and the patient was discharged. However, she did not show up for her follow-up visits.

A case report from India reported a patient who complained of sudden onset of binocular diplopia. On examination, levoversion and vertical diplopia, which worsened on downward gaze, were found. In the primary position, the left eye shows exotropia and hypotropia. The right eye had a -1 adduction and obstructed vertical saccade, while the left eye had nystagmus on abduction, indicative of internuclear ophthalmoplegia. The patient was treated by a general practitioner in the area with an off-label therapy of vitamin B12 once daily, doxycycline 200 mg daily, ivermectin once daily, and vitamin C for 10 d. After a three-week follow-up, there was an absence of diplopia, although adduction remained limited to -1.[33]

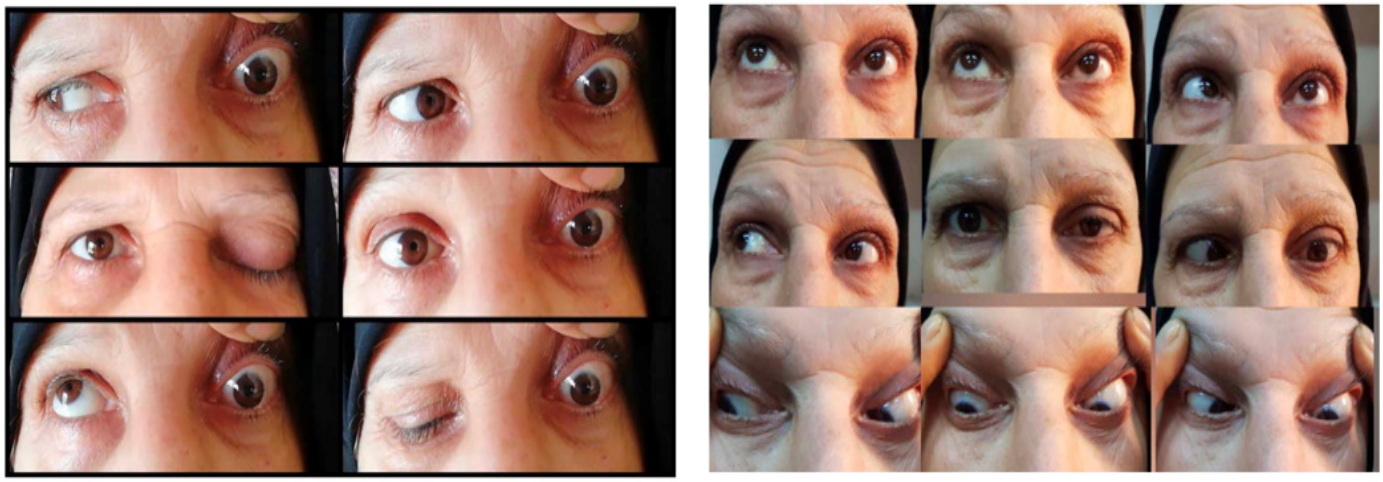

FIGURE 5. Tolosa-Hunt syndrome on presentation, left eye ophthalmoplegia is present (left). Tolosa-Hunt syndrome at 5th mo follow-up. There's an improvement in eye movement except for adduction of the left eye (right).[30]

## CONCLUSION

There are various neuro-ophthalmological manifestations of COVID-19 which are not related to a specific disease. During the pandemic, physicians are given a short time frame to recognize a particular illness, specifically in terms of neuro-ophthalmology. In the future, general physicians and ophthalmologists should take serious consideration when encountering symptoms such as double vision, declining vision, and/or pain upon eye movements.

## ACKNOWLEDGMENTS

The authors declare no conflict of interest in relation to this. This study was funded through RTA (Rekognisi Tugas Akhir) Universitas Gadjah Mada, Indonesia 2024: 5286/UN1.P1/PT.01.03/2024.

## REFERENCES

1. Luís ME, Hipólito-Fernandes D, Mota C, Maleita D, Xavier C, Maio T, *et al.* A review of neuro-ophthalmological manifestations of human coronavirus infection. Eye Brain 2020; 12:129-37. https://doi.org/10.2147/eb.s268828
2. Groß S, Jahn C, Cushman S, Bär C, Thum T. SARS-CoV-2 receptor ACE2-dependent implications on the cardiovascular system: from basic science to clinical implications. J Mol Cell Cardiol 2020; 144:47-53. https://doi.org/10.1016/j.yjmcc.2020.04.031
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223):497-506. https://doi.org/10.1016/s0140-6736(20)30183-5
4. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/.
5. Sen M, Honavar SG, Sharma N, Sachdev MS. COVID-19 and Eye: A review of ophthalmic manifestations of COVID-19. Indian J Ophthalmol 2021; 69(3):488-509. https://doi.org/10.4103/ijo.ijo_297_21

6. Betsch D, Freund PR. Neuro-ophthalmologic manifestations of novel coronavirus. Adv Ophthalmol Optom 2021; 6:275-88. https://doi.org/10.1016/j/yaoo.2021.04.017
7. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, *et al*. Extrapulmonary manifestations of COVID-19. Nat Med 2020; 26(7):1017-32. https://doi.org/10.1038/s41591-020-0968-3
8. Gold DM, Galetta SL. Neuro-ophthalmologic complications of coronavirus disease 2019 (COVID-19). Neurosci Lett 2021; 742:135531. https://doi.org/10.1016/j.neulet.2020.135531
9. Tisdale AK, Dinkin M, Chwalisz BK. Afferent and efferent neuro-ophthalmic complications of coronavirus disease 19. J Neuroophthalmol 2021; 41(2):154-65. https://doi.org/10.1097/WNO.0000000000001276
10. Güngör I, Konuk GE, Süllü Y, Arıtürk N. Papillophlebitis: treatment of vision loss due to subretinal fluid with intravitreal ranibizumab. Neuroophthalmology 2014; 38(6):336-9. https://doi.org/10.3109/01658107.2014.954293
11. 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; 32(1):NP168-72. https://doi.org/10.1177/1120672120947591
12. Guier CP, Stokkermans TJ. Optic neuritis. [Updated 2022 Oct 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
13. Ahmed M, Green SR, Shanmugam L. Unilateral optic neuritis in post COVID-19: a case report. J Clin Diagnos Res 2021; 1-2. https://doi.org/10.7860/JCDR/2021/51880.15595
14. Sawalha K, Adeodokun S. Kamoga G. COVID-19-induced acute bilateral optic neuritis. J Investig Med High Impact Case Rep 2020; 8:232470962097601. https://doi.org/10.1177/2324709620976018
15. Zhou S, Jones-Lopez EC, Soneji DJ, Azevedo CJ, Patel VR. Myelin oligodendrocyte glycoprotein antibody–associated optic neuritis and myelitis in COVID-19. J Neuroophthalmol 2020; 40(3):398-402. https://doi.org/10.1097/wno.0000000000001049
16. Xu SY, Song MM, Li L, Li CX. Adie's pupil: a diagnostic challenge for the physician. Med Sci Monit 2022; 28:e934657. https://doi.org/10.12659/MSM.934657
17. Quijano-Nieto BA, Córdoba-Ortega CM. Tonic pupil after COVID-19 infection. Arch Soc Esp Oftalmol (Engl Ed) 2021; 96(7):353-5. https://doi.org/10.1016/j.oftale.2021.01.001
18. Ortiz-Seller A, Martinez Costa L, Hernández-Pons A, Valls Pascual E, Solves Alemany A, Albert-Fort M. Ophthalmic and neuro-ophthalmic manifestations of coronavirus disease 2019 (COVID-19). Ocul Immunol Inflamm 2020; 28(8):1285-9. https://doi.org/10.1080/09273948.2020.1817497
19. Babu K, Parameswarappa DC, Sudheer B. Tonic pupil in cytomegalovirus anterior uveitis in an immunocompetent adult male - a case report. Ocul Immunol Inflamm 2018; 26(1):104-6. https://doi.org/10.1080/09273948.2017.1376688
20. Karadzic J, Jakovic N, Kovacevic I. Unilateral Adie's tonic pupil and viral hepatitis - report of two cases. Srp Arh Colek Lek 201; 143(7-8):451-4. https://doi.org/10.2298/sarh1508451k
21. Gopal M, Ambika S, Padmalakshmi K. Tonic pupil following COVID-19. J Neuroophthalmol 2021; 41:e764–e766. https://doi.org/10.1097/

WNO.0000000000001221
22. Dinkin M, Gao V, Kahan J, Bobker S, Simoneto M, Wechsler P, *et al*. COVID-19 Presenting with ophthalmoparesis from cranial nerve palsy. Neurology 2020; 95(5):221-3. https://doi.org/10.1212/WNL.0000000000009700
23. Belghmaidi S, Nassih H, Boutgayout S, El Fakiri K, El Qadiry R, Hajji I, *et al*. Third cranial nerve palsy presenting with unilateral diplopia and strabismus in a 24-year-old woman with COVID-19. Am J Case Rep 2020; 21:e925897. https://doi.org/10.12659/ajcr.925897
24. Tan YJ, Ramesh R, Tan YH, Tan SML, Setiawan S. COVID-19 and isolated oculomotor nerve palsy: clinical features and outcomes. Clin Neurol Neurosurg 2023; 225:107601. https://doi.org/10.1016/j.clineuro.2023.107601
25. Falcone MM, Rong AJ, Salazar H, Redick DW, Falcone S, Cavuoto KM. Acute abducens nerve palsy in a patient with the novel coronavirus disease (COVID-19). J AAPOS 2020; 24(4):216-7. https://doi.org/10.1016/j.jaapos.2020.06.001
26. Greer CE, Bhatt JM, Oliveira CA, Dinkin MJ. Isolated cranial nerve 6 palsy in 6 patients with COVID-19 infection. J Neuroophthalmol 2020; 40(4):520-2. https://doi.org/10.1097/wno.0000000000001146
27. Tisdale AK, Chwalisz BK. Neuro-ophthalmic manifestations of coronavirus disease 19. Curr Opin Ophthalmol 2020; 31(6):489-94. https://doi.org/10.1097/icu.0000000000000707
28. Reyes-Bueno JA, García-Trujillo L, Urbaneja P, Ciano-petersen Nl, Postigo-pozo MJ, Martinez-Tomas C, *et al*. Miller-Fisher syndrome after SARS-CoV-2 infection. Eur J Neurol 2020; 27(9):1759-61. https://doi.org/10.1111/ene.14383
29. Gogu AE, Motoc AG, Docu Axelerad A, Stroe AZ, Gogu AA, Jianu DC. Tolosa-Hunt syndrome and hemorrhagic encephalitis presenting in a patient after covid-19 vaccination followed by COVID-19 infection. Brain Sci 2022; 12(7):902. https://doi.org/10.3390/brainsci12070902
30. Hajjar D, Sultan D, Khalaf A, Hesso H, Kayyali A. A case of total ophthalmoplegia associated with a COVID-19 infection: case report. Oxf Med Case Reports 2022; 2022(5):omac050. https://doi.org/10.1093/omcr/omac050
31. Feroze KB, Wang J. Internuclear ophthalmoplegia. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan.
32. Fathy M, Alrashidi S, Hagras SM. COVID-19 provoked internuclear ophthalmoplegia in a child with arrested hydrocephalus. Indian J Ophthalmol 2022; 70(10):3719-21. https://doi.org/10.4103/ijo.IJO_1482_22
33. Vasanthpuram VH, Badakere A. Internuclear ophthalmoplegia as a presenting feature in a COVID-19-positive patient. BMJ Case Rep 2021; 14(4):e241873. https://doi.org/10.1136/bcr-2021-241873