Case Report

Connecting the Dots Between the Eyes, the Brain, and COVID-19

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Received 26 September 2023; Accepted 6 March 2025
https://doi.org/10.23886/ejki.13.493.90

Abstract

COVID-19 is a viral infection that affects not only the respiratory system but also other organs of the body. Ocular manifestations due to COVID-19 infection and its vaccination have been reported, including cases of neuro-ophthalmology. This may be due to the neurotropic and neuroinvasive characteristics of the virus. This case series aims to investigate the characteristics of neuro-ophthalmology cases that may function as a guideline and warning to the examiner. We found ten COVID-19 infection cases, consisting of five optic neuritis cases with two pediatric patients, two patients with cavernous sinus thrombosis (CST), two patients presenting with visual field defects, and one patient with sixth nerve palsy. Vaccine-related-wise, we found two patients presenting with optic neuritis, one patient with CST and one with visual field defect, all with a history of getting vector virus vaccine. The majority of the patients in this report were male, with two pediatric patients in total. The most common neuro-ophthalmology manifestations related to COVID-19 infection were optic neuritis, followed by CST, visual field defect, and cranial nerve palsy. Optic neuritis was also the most common case pertaining to vaccination, followed by CST and visual field defect.
Keywords*: COVID-19, COVID vaccine, neuro-ophthalmology.*

Keterkaitan antara Mata, Otak, dan COVID-19

Abstrak

COVID-19 merupakan infeksi virus yang tidak hanya menyerang saluran napas, namun juga organ tubuh lainnya. Manifestasi okular akibat infeksi COVID-19 dan vaksinasinya telah dilaporkan, termasuk kasus neuro-oftalmologi. Hal tersebut mungkin disebabkan oleh karakteristik virus yang neurotropik dan neuroinvasif. Serial kasus ini bertujuan untuk meneliti karakteristik kasus neuro-oftalmologi yang dapat berfungsi sebagai panduan dan peringatan bagi pemeriksa. Kami menemukan 10 kasus terkait infeksi COVID-19, terdiri atas lima kasus neuritis optik dengan dua pasien anak-anak diantaranya, dua pasien dengan trombosis sinus kavernosus (CST), dua pasien dengan gangguan lapang pandang, dan satu pasien dengan kelumpuhan saraf kranialis keenam. Ditemukan juga kasus terkait vaksinasi yaitu dua pasien dengan neuritis optik, satu pasien dengan CST, dan satu pasien dengan gangguan lapang pandang. Seluruh kasus tersebut memiliki riwayat vaksin virus vektor. Mayoritas pasien dalam laporan kasus ini adalah laki-laki, dengan dua pasien anak-anak. Manifestasi neuro-oftalmologi yang paling umum terkait infeksi COVID-19 adalah neuritis optik, diikuti oleh CST, gangguan lapang pandang, dan palsi saraf kranial. Neuritis optik juga sering ditemukan terkait vaksinasi, diikuti oleh CST dan gangguan lapang pandang.
Kata kunci: *COVID-19, vaksin COVID, neuro-oftalmologi.*

Introduction

Coronavirus is an important pathogen for humans and animals. At the end of 2019, a new mutation was discovered as the cause of a number of pneumonia cases in the city of Wuhan, Hubei province, China which later spread and eventually became a global pandemic.[1] The majority of research on SARS-CoV-2 focuses on respiratory tract manifestations, but the number of reported cases with ocular manifestations is growing. Reported manifestations are varied, such as dry eyes, foreign body sensations in the eyes, itching, blurry vision, conjunctivitis, chemosis, as well as photophobia.[2,3] Neuro-ophthalmological manifestations are one of the ocular manifestations that are often reported, thought of as a result of the nature of the coronaviruses that are neurotrophic and neuroinvasive in humans. The coronavirus disease-19 (COVID-19) pandemic itself has caused an acceleration of vaccination research and development to reduce morbidity and mortality due to COVID-19. Ocular adverse events following immunization (AEFI) have been reported in various countries with a mechanism that is still unclear.[4] This study was conducted to determine the characteristics of patients with neuroophthalmological manifestations in cases related to COVID-19, either due to viral infection or post-vaccination.

Case Description

Based on the patient registry of the Neuro ophthalmology Outpatient Clinic of the Ophthalmology Department of Cipto Mangunkusumo Hospital and Ophthalmology Emergency Room during the period of February 2020–December 2021, there were 14 patients with a history of COVID-19 or COVID-19 vaccination with neuroophthalmological manifestations in our hospital. The characteristics of patients with neuroophthalmological manifestations related to COVID-19 infection and vaccination is presented in Table 1. The prevalence of men is higher than that of women, which is 64.2%. The median age of the patient was 45.5 years, ranging from 13 to 69 years. Seven cases were new patients from the Emergency Room, and the other seven cases were patients in Neuro-ophthalmology Clinic at our hospital. This study found ten cases of COVID-19 infection and four post-vaccination related cases. Four cases were patients with active infections and six patients came with history of COVID-19 infection. Half of the total cases of this study were cases of optic neuritis, followed by three cases of cavernous sinus thrombosis (CST), three cases of visual field defect, and one case of sixth nerve palsy.

Table 1. Demographic Characteristics of Patients with Neuro-ophthalmic Manifestation Following COVID-19 Infection and Vaccination between February 2020—December 2021

Variable	n
Gender	
Male	9
Female	5
Mean Age; range	45.5; 13—69
Vaccine Related	3
Admission	
Emergency unit	7
Outpatient clinic	7
COVID-19	
Previous history	6
Active	4
Vaccinated	4
Cases	
Optic neuritis	7
Cavernous sinus thrombosis	3
Visual field defect	3
N. VII Paresis	1

Table 2 shows details of neuroophthalmological manifestations in cases related to COVID-19 infection. There were 10 cases related to COVID-19 infection with five cases of optic neuritis, consisting of three cases with active infections at the onset, as well as two cases of neuroophthalmological manifestation with history of COVID-19, with the onset ranging from three to four weeks after infection. The patients consist of four men and one woman, with age ranging from 13 years to 50 years. One patient had complaints in one eye, and the other four patients had manifestations in both eyes. Visual acuity of these patients varied from light perception (LP) to 6/12 with corrections. Four patients had papillary edema of both eyes, while one patient with retrobulbar neuritis had normal posterior segment, but relative afferent pupillary defect (RAPD) and visual field defect were found. There were also two patients diagnosed with CST in cases related to COVID-19 infection. Both patients were male, age 35- and 46-year-old. One patient had an active COVID-19 infection and the other patient had a history of COVID-19 infection three weeks

before the onset. Both patients had visual acuity of no light perception (NLP). Ocular examinations found the palpebral spasm with edema and ptosis, as well as uvea prolapse in the cornea. This patient was diagnosed with CST due to mucormycosis. Two patients with a history of COVID-19 infection had neuroophthalmological manifestations presented as visual field defects. Both patients were men aged 59 and 69, with a four- and one-week history of COVID-19 infection, respectively. No ocular abnormalities were found in both the anterior and posterior segments. Patient number 10 came with cranial nerve palsy with complaints of the left eye unable to glance to the temporal side. This patient was a 43-year-old female with a history of COVID-19 four weeks before the ocular symptoms started.

Table 3 shows details of neuroophthalmological manifestations in cases related to COVID-19 vaccination. There were two patients with optic neuritis with a history of COVID-19 vaccination. One patient was a 43-year-old woman with a history of viral vector type vaccine, AZD1222, with an onset of 7 weeks after the first dose of vaccination. Patient number 3 was a 50-year-old female patient who came in with CST with a history of AZD1222 vaccination two weeks before onset of symptoms. There was also one patient with a visual field defect, a 50-year-old female with a history of AZD1222 vaccination.

Discussion

From a total of 14 patients who presented with neuroophthalmological manifestations related to COVID-19 infection and vaccination, seven of them were cases of optic neuritis, with a total of five infection-related cases and two post-vaccination related cases. Visual acuity ranged from LP to 6/12. Cases of optic neuritis related to COVID-19 infection have been reported several in case reports, one of which is by Zhou et al.[5] The case is a 26-year-old male who experienced blurring of both eyes with a visual acuity of 1/300 and 6/60, right eye and left eye respectively. Papillary edema was found in both eyes. From laboratory examinations, positive SARS-CoV-2 and myelin oligodendrocyte glycoprotein (MOG) antibodies were found. The MRI result indicated the presence of a thickening of both optic nerves. Meanwhile in this case series, MOG examination was not performed due to financial issues, since the examination is not covered by national health insurance. Until now, it is still unclear whether SARS-CoV-2 can directly infect the optic nerve or not. Singh et al.[6] performed examination in mouse models and isolated the CoV variant of viral hepatitis-A59 (MHV-A59) from paralyzed mice. It was found that MHV-A59 can cause extensive demyelination and encephalomyelitis. The virus can infect glia cells, astrocytes, oligodendrocytes, and microglia. This type of virus is used to induce optic neuritis due to viral infections, which comes from the hypothesis that inflammation resulting from viral infections is the etiology of multiple sclerosis (MS).

When inoculated intracranially in a mouse model, MHV-A59 gave rise to meningitis, focal acute encephalitis, and optic neuritis. Inflammation of the optic nerve occurs within three days after inoculation with its peak occurrence occurring within five days. The loss of axons was characterized by a significant decrease in axon staining when compared with the optical nerve in the control group 30 days after inoculation.[6] Four out of seven patients with optic neuritis in this study had positive ANA results on laboratory examination. This is in accordance with the theory that viral pathogens are one of the exogenous triggers that most often give rise to autoimmunity.[7] Antibodies to the SARS-CoV-2 infection virus protein that occurs in susceptible individuals appear as a potential trigger for autoimmune conditions due to cross-reactivity with autoimmune target proteins. Research conducted by Peker et al[7] found that out of 50 patients with active COVID-19 pneumonia, there were nine patients (18%) with positive ANA results. Pascolini et al[8] found that the positive ANA result was significantly more prevalent in cases with poor prognosis with higher mortality rates. Trahtemberg et al[9] found that the percentage of patients treated with COVID-19 in the Intensive Care Unit (ICU) with a positive ANA reached 64%. However, in contrast to the previous study, Peker et al[7] found no association between disease severity and ANA detection patterns in patients with COVID pneumonia.[5]

Table 2. Clinical and Supporting Examination Characteristics of Patient with a History of COVID-19 Infection Presenting Neuro-ophthalmic Manifestation

No	Gender/ Age	Status	Onset	Visual Acuity		Diagnosis	Ocular Examination	Imaging	Lab
1	M/37	Post COVID-19	3 weeks	6/12	0.5/60	Bilateral atypical optic neuritis	Bilateral papil edema	CT-scan within normal limit	TG: 207/LDL: 190/D-dimer: 530/ ESR: 28/total cholesterol: 266/ANA (+)
2	M/14	Active		LPWP	2/60	Bilateral atypical optic neuritis	Bilateral papil edema	CT-scan within normal limit	ESR: 29/ANA (+)
3	M/45	Active			1/300GP	Retrobulbar neuritis of left eye, DM	RAPD (+) LE	CT-scan within normal limit	ESR: 80/HbA1c: 5.9/ D-dimer: 14.410/ ANA (+)
4	M/50	Post COVID-19	weeks	6/12	6/12	Bilateral atypical optic neuritis, DM, HT	Bilateral papil edema	-	TG: 157/fibrinogen: 755/ HbA1c: 9.3/ RBG: 259/ ESR: 96/ANA (+)
5	F/13	Active		1/300GP	1/300GP	Bilateral atypical optic neuritis	Bilateral papil edema	CT scan and MRI within normal limit	ESR: 25
6	M/35	Post COVID-19	3 weeks	NLP		CST of RE, DM	IOP 37 mmHg, ptosis, 2mm lagophthalmos, chemotic	MRI: minor thrombus on the medial cavernous sinus	L: 17.160/SGOT/SGPT: 150/209/CRP: 21/ RBG: 144/ ESR: 85/fibrinogen: 476/ D-dimer: 900
7	M/46	Active			NLP	Mucormycosis, CST of RE, DM, HT	Ptosis, necrotic conjunctiva, prolapse of the uvea in the infero-nasal cornea	CT-scan: thrombus in the left cavernous sinus, endophthalmitis of LE	L: 16.000/ CRP: 111/ ESR: 134/HbA1c: 12.6/fibrinogen: 830/D-dimer: 1740
8	M/59	Post COVID-19	weeks	6/6	6/6	Visual field defect susp intracranial, DM, ischemic stroke	Hazy lens	MRI: subacute infarct of left occipital lobe	HbA1c: 8.5
9	M/69	Post COVID-19	1 week	2/60	6/60	Hemianopia homonymous sinistra, DM, ischemic stroke	Hazy lens	-	Increased thrombocyte aggregation
10	F/43	Post COVID-19	4 weeks		3/60	N.VI paresis of left eye, viral keratitis of left eye	Corneal infiltrate (+)	CT-scan: follow up	

M= male, F=female, NLP = no light perception, GP=good perception, IOP = intraocular pressure, ET = esotropia, CT= computed tomography, MRI = magnetic resonance imaging, TG = triglyceride, LDL=low-density lipoprotein, ESR = erythrocyte sedimentation rate, ANA = anti-nuclear antibody, RBG = random blood glucose, L=leukocyte, SGOT= serum glutamic oxaloacetic transaminase, SGPT = serum glutamic pyruvic transaminase, CRP= c-reactive protein, DM = diabetes mellitus, HT = hypertension

Table 3. Clinical and Supporting Examination Characteristics of Patient with a History of COVID-19 Vaccination Presenting Neuro-ophthalmic Manifestation

No	Gender / Age	COVID-19 Status	Onset	Visual Acuity		Diagnosis	Ocular Examination	Imaging	Lab
1	F/48	Post vaccine AZD 1222 1st dose	7 weeks	0.5/60	0.5/60	Bilateral optic neuritis	Bilateral papil edema	CT-scan: thickening of the right optic nerve	ESR: 30/ Increased thrombocyte aggregation
2	F/18	Post vaccine AZD 1222 1st dose	1 day	2/60	6/24	Bilateral optic neuritis, LHON	Bilateral papil edema	-	Mutation T14484C on ND6 gene by LHON mutation
3	F/50	Post vaccine AZD 1222 1st dose	2 weeks	NLP	6/15	Bilateral CST, Grave's ophthalmopathy, hyperthyroid	RE: Lagophthalmos 7mm with corneal exposure 2mm, chemotic all quadrants, RAPD (+), papil edema LE: lagophthalmos 8mm with corneal exposure 1mm, chemotic all quadrants, subconjunctival bleeding, RAPD (+), papil edema	MRI: -Thickening of conjunctiva, slight right proptosis dd/ inflammation -Enhancement of right papil oculi, right posterior sclera oculi to part of the bilateral proximal optic nerve sheath, and thickening of optic nerve calibre left and right with DWI restriction in right optic nerve, optic neuritis. -Susp. CST especially right	Fibrinogen: 446.3/ PT: 24.7 (11.6)/ APTT: 48.3 (31)
4	F/50	Post vaccine AZD 1222 1st dose	1 day	6/6	6/6	Hemianopia homonymous LE, ischemic stroke, DM, HT	Hazy lens	MRI: Acute infarct on right occipital lobe, minimal subacute infarct left periventricle	FBG: 230/ HbA1c: 11.3 Total cholesterol: 227/ LDL: 145

LHON = Leber hereditary optic neuropathy, CST = cavernous sinus thrombosis, RE = right eye, LE = left eye, RAPD = relative afferent pupillary defect, DWI = diffuse weighted imaging, PT= prothrombin time, APTT= activated partial thromboplastin time, FBG = fasting blood glucose

There were two CST patients associated with COVID-19 infection and one patient with a history of vaccination. The cavernous sinus is a venous dural sinus located laterally from the sella tursica, between two layers of the dura in the middle of the cranial fossa. The cavernous sinus is the pathway of the cranial nerve III, IV, and VI, as well as the ophthalmic and maxillary branches of the trigeminal nerve. CST mortality reached 100% before the antibiotic era because of sepsis or central nervous system infection. With the current aggressive management, the mortality rate can be reduced to 30%.[10,11] CST has symptoms similar to other eye diseases such as orbital cellulitis and orbital apex syndrome. Common symptoms include ptosis, proptosis, chemosis, ophthalmoplegia (paresis of III, IV, and VI cranial nerve), and loss of sensation from the ophthalmic and maxillary branches of the trigeminal nervus. Visual acuity can decrease as a result of several etiologies such as optic nerve ischemia or ischemia of the retina.[10] COVID-19 itself is known to increase the risk of venous thromboembolism through several mechanisms such as excessive inflammation, platelet activation, endothelial dysfunction, and stasis. The Angiotensin-converting-enzyme-2 (ACE 2) receptor facilitates the expression of SARS-CoV-2 on the mucosal surfaces of several organs such as the lungs, liver, kidneys, and skin. ACE 2 is also expressed in arterial and venous endothelial cells as well as smooth muscle arteries. SARS-CoV-2 infection induces endothelitis in organs as a direct consequence of the virus and the inflammatory response of the host. Along with cytokine abnormalities, these factors contribute to the process of vasoconstriction, inflammation, ischemia, and hypercoagulability conditions.[12,13]

There were three patients with visual field defects in this case series, with two patients with a history of COVID-19 and one post-vaccination patient. All three patients had a history of ischemic stroke after COVID-19 infection with the same comorbidities, namely DM and hypertension. COVID-19 patients who have had a stroke are generally elderly, have a history of hypertension and increased D-dimer level. Stroke in COVID patients can occur as a result of several mechanisms, including atherosclerosis, hypertension, and atrial fibrillation. But in COVID-19 patients, the mechanisms of stroke are most likely due to hypercoagulability, vasculitis, and cardiomyopathy.[14] Lee et al[15] reported that 20-55% of patients treated with COVID-19 infection had signs of coagulopathy from laboratory examinations, such as an increase in D-dimer more than twice as normal, an increase in prothrombin time, and mild thrombocytopenia.[15] It is estimated that 8-25% of patients with ischemic stroke may have visual field defect. For homonymous hemianopia defect, stroke is the most frequent cause. Visual field defect of homonymous hemianopia is the most frequent defect found in patients with stroke.[16] One case in this series found a visual field defect in ischemic stroke that occurred after vaccination of the AZD1222 vector. There was a report in Saudi that found a similar case, a 43-year-old man who had an ischemic stroke 3 days after the AZD1222 vaccination. So far, strokes after vaccination have been reported, namely varicella and influenza vaccines, with a mechanism thought to be similar to the nature of the disease itself, causing cerebral angiopathy so that there is a narrowing and occlusion of blood vessels resulting in an ischemic stroke.[17]

There was a 43-year-old female patient with paresis of abducens nerve that occurred four weeks after COVID-19 infection. Cranial nerve paresis in adult patients themselves is generally associated with microvascular disease, with causes such as vasculopathy, tumors, and inflammatory conditions. Based on existing case reports, the most frequent cranial nerve involved is the abducens nerve, which is followed by the oculomotor nerve.[18] These reports correspond to findings of abducens nerve palsy in our center. The mechanism of cranial nerve palsy due to COVID-19 is still unclear. As previously discussed, Bingöl et al[19] found that SARS-CoV-2 uses ACE-2 to invade, and ACE-2 can be found in glial cells and neurons. Therefore, it is concluded that the neurological deficits that occur are the result of neurological damage directly due to the virus invasion or indirectly through neuroinflammatory and autoimmune mechanisms.[19]

Several mechanisms that are previously mentioned, such as vasodilation, increased vascular permeability, endothelial dysfunction, coagulopathy, and direct damage by viruses are possible causes of neurological manifestations of SARS-CoV-2. Studies have shown an increase in pro-inflammatory cytokines in plasma such as IL-2, IL-6, IL-7, IL-10, and alpha TNF that can cause tissue damage. This hypothesis is called a cytokine storm.[20,21] Garvin et al[22] proposed the theory of a bradykinin storm that occurs in COVID-19 patients, in which SARS- CoV-2 causes a decrease in ACE levels in body cells that cause an increase of bradykinin level. This bradykinin storm causes vasodilation and vascular permeability which will then result in edema and inflammation of the surrounding tissues. Endothelial dysfunction and

coagulopathy also play a role in causing neurological symptoms of COVID-19 patients. ACE-2 is the main functional receptor for SARS-CoV-2 and is found in several organs such as the brain, lungs and blood vessels.[22] Another hypothesis is the presence of a direct invasion by the virus, based on the fact that ACE-2 is present in the brain. It is thought that the virus spreads through the blood from infection of the choroid plexus or meninges, or through the olfactory nervus. Anosmia is thought to be a marker of direct invasion of the virus into the nasal mucosa, which then spreads towards the olfactory bulbus.[23] Management of neuro-ophthalmological conditions varies by diagnosis, with optic neuritis often treated with high-dose IV corticosteroids to reduce inflammation and improve vision, cavernous sinus thrombosis requiring urgent broad-spectrum antibiotics or antifungals and sometimes anticoagulation, and sixth nerve palsy managed with corticosteroids, eye patches, or prism glasses.[24-27]

This case series has several limitations. The relatively small number of patients and the lack of literature discussing the relationship of COVID-19 with neuroophthalmological manifestations are the main limitations of this series. Most studies currently available are only individual case reports or case series, but not many have discussed or proved the causal theory. Although it is thought that the patients in this series had ocular symptoms due to COVID-19, it is difficult to establish a definite causal relationship. As the transmission and vaccination of COVID-19 becomes more widespread, patients with neuroophthalmological manifestations that appear coincidentally with a history of COVID-19 infection and vaccination may exists. Some patients had underlying systemic diseases, making it unclear whether these conditions influenced the extent of neuro-ophthalmological damage. Other limitations are the possibility that there are patients with neuroophthalmological complaints whose history of infection or vaccination were not obtained through the history-taking process, or patient who has a history of ocular COVID-19 symptoms but are not confirmed by laboratory examination.

Conclusion

In this case series, the most prevalent neuro-ophthalmological manifestation related to COVID-19 infection is optic neuritis, followed by CST, visual field defects, and cranial nerve palsy. Optic neuritis is also the most common manifestation related to COVID-19 vaccination followed by CST and visual field defect.

Conflict of Interest

The authors report no conflict of interest in this case series.

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