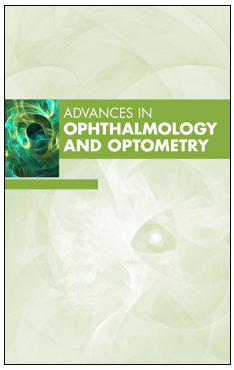

Neuro-ophthalmic complications of COVID-19 infection and vaccination

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Review article

Title

Neuro-ophthalmic complications of COVID-19 infection and vaccination

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Key points:

1. *COVID-19 infection and vaccination have been associated with neuro-ophthalmic complications, but causation has not been firmly established.*
2. *Neuro-ophthalmic manifestations post-COVID-19 infection and vaccination are uncommon and have a good prognosis in most cases.*
3. *Some of the proposed underlying mechanisms of COVID-19 infection-related neuro-ophthalmic complications are molecular mimicry, direct viral infection, hypoxemia, hypercoagulable status, and hyperviscosity.*
4. *Similarly, the proposed underlying mechanisms of COVID-19 vaccine-related neuro-ophthalmic complications are molecular mimicry, autoimmune syndrome associated with vaccine adjuvant, hypercoagulable status, hyperviscosity, thrombosis, and vasculitis.*
5. *No guidelines are established for the management of neuro-ophthalmic associations post-COVID-19 infection and vaccination in the literature. Therefore, treatment should be tailored to the individual patient and follow established guidelines for the treatment of the clinical phenotype.*

Abstract

The COVID-19 pandemic has led to the identification of new disease phenotypes associated with infection by the SARS-CoV-2 virus. This includes multiple neuro-ophthalmological sequelae, which have been associated with COVID-19 infection and administration of COVID-19 vaccines. Some of these associations have a plausible pathophysiological link to the infection or vaccination but true causation has yet to be established. The billions of cases of COVID-19 would wide coupled with the billions of doses of COVID-19 vaccines administered worldwide

means that some of these "rare" neuro-ophthalmic sequelae will happen in temporal association with COVID-19 infection or vaccination due to random chance alone. We review the literature for associations reported between COVID-19 infection or vaccination and neuro-ophthalmic sequelae and review the potential pathophysiological processes which may underly these associations.

Keywords

COVID-19, vaccine, SARS-CoV-2, Severe Acute Respiratory Syndrome, Giant cell arteritis, optic neuritis, neuro-ophthalmology, neuro-myelitis optica, NMO, myelin oligodendrocyte glycoprotein, MOG, Non-Arteritic Anterior Ischemic Optic Neuropathy, NA-AION, NAION, non-arteritic ischemic optic neuropathy, thyroid eye disease, Miller Fisher Syndrome, MFS, myasthenia gravis, TED, idiopathic orbital inflammatory syndrome, papilledema, optic disc edema, idiopathic intracranial hypertension, IIH

Introduction:

Severe Acute Respiratory Syndrome caused by *corona virus 2* (SARS-CoV-2, COVID-19*)*, is the novel viral infection responsible for the devastating and ongoing COVID-19 pandemic. Since the beginning of the pandemic, the World Health Organization (WHO) estimates over a billion confirmed cases of COVID-19 infection, and over 6 million deaths worldwide have occurred. (1) This devastating disease has had implications for all aspects of medicine with new disease phenotypes emerging, including in ophthalmology.

The scale of this pandemic has led to an unprecedented rapid creation of vaccines against COVID-19. Since becoming available to the public at the end of 2020, over 12 billion COVID-19 vaccine doses have been administered worldwide. This has led to a marked reduction in the rate of infections, transmissions, hospitalizations, and death from COVID-19 infection and,

hopefully, will lead to the end of this pandemic. (2–4) However, new presentations of autoimmune conditions have been associated with COVID-19 vaccination. (5)The post-infection and post-vaccine manifestations of the COVID-19 pandemic are still emerging. Reports have demonstrated that SARS-CoV-2 infection and vaccination can affect multiple organ systems including the eyes, resulting in a spectrum of ocular manifestations such as conjunctivitis, episcleritis, uveitis, vascular occlusions, and retinitis. Also, neuro-ophthalmic manifestations exist, ranging from a simple headache to irreversible blindness from optic neuritis (ON) or giant cell arteritis (GCA).

Some of these new vaccines use novel technology and long-term data on potential side effects is still pending. The WHO recommendation for reporting possible vaccine side effects is the presence of a temporal association between the administration of the vaccine and the onset of symptoms, with a suggested cut off of 28 days between vaccination and symptoms. The exclusion exists of other triggers for the disease manifestation and the presence of published literature with an established possible relationship between the vaccination and disease onset or exacerbation. (6)

This review aims to focus on, and summarize, the current state of knowledge of neuro-ophthalmic complications of COVID-19 infection and vaccination.

Methodology

The EMBASE, Ovid MEDLINE, and Cochrane central library were searched by a medical librarian from January 1, 2019, until September 28, 2022, using keywords to cover ocular and neuro-ophthalmological complications of COVID-19 infection and vaccination. Manual selection was used to identify articles of interest. The search was restricted to English language.

Discussion

Afferent neuro-ophthalmic complications:

Optic neuritis

Post COVID-19 infection:

Generally, most cases of optic neuritis (ON) associated with COVID-19 infection have a remarkable improvement in vision after treatment with steroids, with only a few reported cases of irreversible vision loss. (7,8) Most of the cases were unilateral with variable onset ranging between (1 to 45 days) post-infection.(9–11) All cases received 1g/day of intravenous methylprednisolone (IVMP) followed by oral prednisone taper. (7) Additionally, myelin oligodendrocyte glycoprotein (MOG)-related optic neuritis was found to have a favorable visual outcome following IVMP with vision better than 20/200 in all cases.(11) In a systematic review, only 3 cases of neuro-myelitis optica (NMO) Aquaporin 4 IgG positive ON were identified. (12) Two were men, 70 and 25 years old, and one in a 7.5 years-old girl. They all presented within a month of their COVID-19 infection. Treatment with steroids, IVIG, PLEX, and rituximab were administered, and gradual improvement was observed in 2 of the patients. Whereas the 70-year-old was treated only with antibiotics, fluids and electrolytes, and eventually the patient died from systemic complications of COVID-19. (12)

Post COVID-19 vaccination:

Optic neuritis post-covid-19 vaccination is the most common reported neuro-ophthalmic association, (13) with fifty-five individual case reports published in the literature. Of these two thirds were vaccinated with the Oxford/AstraZeneca ChAdOx1, followed by BioNTech/Pfizer mRNA-vaccine BNT162b2 vaccine (26%) and Sinovac (7%). The onset of vision loss was within three weeks from the administration of the vaccine in most patients. This is one week after the

antibodies from the vaccine are thought to be formed, which occurs on average at 2 weeks. Most cases were reported in Caucasians (44/55) women (38/55) with a median age of 45 years, which is higher than the typical cases of pre-pandemic ON. Unilateral involvement was more common than bilateral. MOG positive ON were reported in 14 cases, followed by 7 cases of multiple sclerosis (MS) associated ON. This contrasts with the existing literature where MS-ON accounts for the majority (57%) of cases. (14,15) Unlike, typical ON almost half of the patients presented with optic disc swelling (27/55). The treatment of choice was high-dose intravenous steroids in most cases, and a few cases received high doses of oral steroids, while 7 cases did not receive any steroids. Plasma exchange (PLEX) was used in 6 cases either with or after the course of steroids. Median vision after treatment was 20/20. However, 5 cases occurred with vision worse than 20/200.

In a separate study of fourteen cases of idiopathic ON post-COVID-19 vaccination (16–23) again, most cases were in women (10 cases) half with unilateral involvement, and age ranged from 19- 67 years. Vision changes were reported from hours to 3 weeks after BioNTech/Pfizer mRNA-vaccine BNT162b2, AstraZeneca ChAdOx1, Janssen (Johnson & Johnson), Covisheild, CoronaVac-Sinovac Life, and Moderna mRNA-1273 vaccines. Optic disc swelling was noted in 8 cases on examination, and the presenting visual acuity of < 20/200 was noted in 4 cases. Universally there appears to be a good visual prognosis after receiving steroids. PLEX for 7 days was given only to 1 patient who failed to improve on IVMP, and had a vision of counting fingers in both eyes. (23)

MOG-ON was reported to comprise approximately 5% of ON cases pre-pandemic, (15) with an increased rate of MOG-ON since the start of the pandemic.(5,13,24–27) There are 10 case

reports of post-COVID-19 vaccine associated MOG-ON in the literature. Most have been in men (7 cases) between the ages 28-66 years with most (7 cases) having unilateral involvement. Half had a visual acuity of <20/200 at presentation and the onset of vision loss was reported between 14 and 21 days and after the AstraZeneca ChAdOx1 vaccine. The treatment of choice was IVMP for 3-5 days, followed by oral steroids. In 4 cases, presenting with poor vision or bilateral involvement, PLEX was initiated. Only one case had a spontaneous resolution of vision with no intervention.

NMO-ON was reported in (3%) of patients pre-pandemic, and it remained an uncommon cause of ON post-vaccination. (15) Case reports of NMO-ON post-vaccination exists and include cases after mRNA vaccination. A 43-year-old and 31-year-old woman, both with unilateral involvement, one with complete recovery of her vision after receiving IVMP 1g/d for 10 days, and the other with no visual recovery after receiving IVMP (1g/d) for 5 days followed by 5 sessions of PLEX. (28,29)

Giant cell arteritis

Post COVID-19 infection:

A noticeable increase in giant cell arteritis (GCA) cases occurred during the COVID-19 pandemic, a report by Lecler et al, observed an increase of 70% from pre-pandemic. (30) Subsequently, higher rates of ocular involvement were seen with GCA during the pandemic. (31,32) This supports the notion of the role of viral infections as an underlying trigger for GCA. In the era of the pandemic, diagnosing GCA is challenging due to the similarities between COVID-19 infection manifestations and GCA. A study by Mehta et al, found that they both share the clinical features of headache, fever, elevated CRP, and cough. Clinical manifestations

that can aid in the differentiation of GCA would be jaw claudication, visual loss, platelet count, and lymphocyte count. (33)

Post COVID-19 vaccination:

Three case reports exist of GCA presenting with arteritic anterior ischemic optic neuropathy (AAION) after COVID-19 vaccination. (34–36) Two in 87 and 79-year-old women, and one in a 68-year-old man. Two cases were after BioNTech/Pfizer mRNA-vaccine BNT162b2 vaccine and one after the AstraZeneca ChAdOx1 vaccine. They all presented within 5 days of receiving the vaccine and all had bilateral involvement. The visual acuity was <20/200 in at least one eye at the time of the presentation. Some had other symptoms of GCA including amaurosis fugax, headache, jaw claudication, scalp tenderness, and lethargy. At least one of the inflammatory markers was high, ESR in 2 cases and C-reactive protein (CRP) in all three cases. A temporal artery biopsy was positive in two of the patients, and for one patient no information was provided about the biopsy. All cases were treated with high-dose IVMP (1g/d x 3-4 days) followed by oral prednisolone (34–36), one patient subsequently received tocilizumab (TCZ) following a relapse 3 months after initial presentation. (34)

In both post-COVID and post-vaccination cases no proved causation exists and the time lapse for the post-vaccination cases theoretically is too soon for the body to have mounted an immune response. Given the number of vaccinations administered to date, some overlap with GCA would be expected.

Non-Arteritic Anterior Ischemic Optic Neuropathy (NA-AION)

Post COVID-19 infection:

The relationship of COVID-19 and NA-AION is unknown. (37) NA-AION has been described in six case reports in association with COVID-19 infection. (38–42) Patients in these reports

were above 40 years old and presented with acute painless unilateral or bilateral (2/6) altitudinal vision loss, which mainly was noted upon awakening (4/6 patients). The onset of visual symptoms ranged from one to four weeks after COVID-19 infection except in one patient where visual symptoms preceded COVID-19 symptoms. (41) All cases demonstrated visual field defect on confrontational testing and Humphrey's visual field analysis. (38,39)

Post COVID-19 vaccination:

NA-AION post-COVID-19 vaccination has rarely been reported. (43–48) All patients shared the clinical presentation of painless sudden vision changes either described as a blurring of vision or a visual field defect and all had unilateral involvement. The onset of visual symptoms was within 15 days from the vaccination, (1-15 days). Most of the patients were older than 50 and had one or more risk factors for developing NAION; small cup-to-disc ratio, hypertension, diabetes or dyslipidemia.

Some of the cases underwent investigations to rule out GCA, along with brain and orbit imaging to rule out optic neuritis. IV or PO steroids were administered in some cases, either for the suspicion of optic neuritis or giant cell arteritis. Some tried steroids as an intervention when the visual acuity was poor as a treatment of last resort to improve vision, and it was deemed successful in 1 case where vision improved from count fingers (CF) to 20/100-1 eccentrically after 6 weeks. (48) This case report doesn't demonstrate causation or bestow a treatment effect from steroids as up to a third of NAION cases will report some improvement in vision, especially once the disc edema resolves.

Papilledema

Post COVID-19 infection:

Headache is a prominent symptom of both elevated intracranial pressure (ICP) and COVID-19. In a cross-sectional study of 56 patients with COVID-19 infection 13 had a new persistent headache prompting further clinical evaluation including lumbar puncture. (49) Of those 85% (11/13) were found to have high opening pressure (> 200mmH2O), and over half (7/13) were above (250mmH2O) with normal composition and were diagnosed with IIH. Imaging of the brain was not significant except in one patient who had typical imaging features of increased intracranial pressure. All patients had normal fundoscopic examinations except for 2 who showed papilledema. Interestingly, blurred vision was reported by only three patients.

Cerebral venous sinus thrombosis is a serious complication post COVID-19 infection. Nearly all reported cases of papilledema related to CVST in the setting of COVID-19 had a favorable visual outcome except the case described by Omari et al. of a morbidly obese woman who presented with a bilateral progressive visual loss associated with severe headache and tinnitus. The patient recently was admitted to the hospital for bilateral pulmonary embolism and deep venous thrombosis, possibly due to COVID-19 infection. (50) CSF workup was remarkable only for an elevated opening pressure of more than (600 mmH2O). Despite maximum treatment, with acetazolamide and heparin, bilateral optic nerve sheath fenestration (ONSF), and endovascular transverse sinus thrombectomy, her vision deteriorated to no light perception (NLP).

Post COVID-19 vaccination:

There have been 2 published case reports of papilledema in the setting of COVID-19 vaccination-associated IIH. (51,52) Both cases were young male patients with normal body mass index (BMI) and atypical demographics for IIH. One presented 7 days after the AstraZeneca ChAdOx1 vaccine, and the other 12 days after Sputnik V vaccine. Both had other symptoms of

high ICP such as headache, pulsatile tinnitus, dizziness and blurring of vision. MRI/MRV were normal except for signs of high ICP. Lumbar puncture with high opening pressure of (620mmH2O and 390mmH2O). One was treated with acetazolamide 750mg twice daily and torsemide 5mg once daily, and the other was given pulse IVMP 500mg daily for 5 days and oral acetazolamide 250mg three times a day. After three months the symptoms and papilledema had completely resolved in both cases. (51,52)

The above-mentioned cases did not involve CVST. However, coagulation problems that result in CVST have been reported post-COVID-19 vaccination, presenting with intracranial hypertension and papilledema. Other associated symptoms are headache, focal neurological deficit, seizures, and venous hemorrhage. Symptoms appear to happen approximately (10 days) from the day of the vaccination. Most cases were reported with the AstraZeneca ChAdOx1 vaccine. (53,54) The group most at risk was women under 60 years of age. (54) It is thought that CVST post-COVID-19 vaccine is secondary to vaccine-induced thrombotic thrombocytopenia (VITT), which is similar to heparin-induced thrombocytopenia (HIT). (53) In one meta-analysis of 144 patients up to 80% had an accompanying thrombocytopenia and hypofibrinogenemia with a positive PF4 antibodies. (54) Most patients present to the emergency department and are treated with non-heparin anticoagulants. The mortality rate from CVST is as high as 40%, therefore, timely diagnosis is key. (53)

Efferent neuro-ophthalmic complications:

Ocular motility disorders:

Diplopia is one of the more common symptoms reported post-COVID-19 infection and vaccination. Underlying pathologies vary from cranial nerve palsy and Miller Fisher Syndrome

(MFS) to neuromuscular junction disorders like myasthenia gravis (MG), and muscular pathologies like thyroid eye disease (TED) and idiopathic orbital inflammatory syndrome (IOIS).

Cranial neuropathies

Post COVID-19 infection:

In a systematic review, 56 patients with cranial neuropathy associated with COVID-19 were analyzed. Generally, COVID-19 infection was found associated with neuropathies of all cranial nerves (CN) with a predilection for CN VII, VI, and III. (55) Isolated cranial neuropathies were more prevalent than multiple cranial neuropathies. Unilateral involvement is more common than bilateral involvement, though bilateral involvement may be a sign of Guillain-Barré syndrome. Treatment included steroids, IVIG, acyclovir/valacyclovir, and rarely PLEX. Complete recovery was seen in 21 patients and partial recovery in 30 patients at discharge or last follow-up.

Post COVID-19 vaccination:

After the facial nerve, dysfunction of the abducens nerve is the most common reported neuropathy post-vaccination from any vaccine, followed by the oculomotor and the trochlear nerves. A similar pattern was observed with COVID-19 vaccines. Several reports exist of patients presenting with new onset sixth and third nerve palsy. (56–64) The onset of diplopia usually was from 1-7 days. It has been reported post BioNTech/Pfizer mRNA-vaccine BNT162b2, Moderna mRNA-1273, Covishield, AstraZeneca ChAdOx1 and Sinopharm. Age ranged from 23-88 years, with no obvious gender predominance. Almost all cases had unilateral involvement (8/9) and normal brain imaging (7/9), with one showing focal enlargement of the root exit zone and the cisternal portion of the left sixth nerve with post-gadolinium enhancement, and the other showing enhancement of both CN6. (63) Two thirds had full spontaneous recovery of symptoms after 2 months, including those with brain imaging abnormalities. Steroids were

used in 2/9 patients; one had no response and the other showed complete recovery after 5 days on low-dose steroids.

Multiple cranial neuropathies also have been reported post-COVID vaccination. One case reported by Manea et al. was of a 29-year-old man with left III, V, VI and VII cranial nerve palsies 6 days after having his first dose of the Pfizer vaccine. (65) Another case by Shalabi et al. was a 41-year-old man with right IV, VI, VII, VIII and X, associated with cervical lymphadenopathy 7 days after receiving his mRNA vaccine. (66) In both cases, an extensive workup was done, including brain imaging with contrast, infectious and inflammatory lab workup, a lumbar puncture to check for infections and malignant cells and even a full body computed tomography to rule out systemic malignancy were performed. In both cases, an enhancement occurred in post-gadolinium brain imaging of some of the involved cranial nerves, and a short-course of intravenous steroids was administered with subsequent clinical improvement. (65,66). As with NA-AION, improvement after steroids doesn't necessarily confirm a treatment affect as the natural history of isolated nerve palsies is for them to improve spontaneously.

Miller Fisher syndrome

Post COVID-19 infection:

MFS is variant of Guillain-**Barré** syndrome, which is characterized by a triad of ophthalmoplegia, loss of tendon reflexes, and acute onset of ataxia. MFS has been reported after COVID-19 infection and vaccination. Although the number of MFS cases in the context of COVID-19 infection is still increasing, no long-term sequelae were documented. (67–69) A proposed mechanism by which MFS develops is through an immune-mediated post infectious

process.(70) This is supported by the incubation period, the positive response to IVIG, and the presence of anti-ganglioside antibodies in 20% of reported cases.(67,70)

Post COVID-19 vaccination:

The onset of symptoms in MFS post-vaccination ranged from 7-18 days. It has been reported after Moderna vaccine, Oxford/AstraZeneca ChAdOx1, BioNTech/Pfizer mRNA-vaccine BNT162b2, tozinameran BNT162b2 mRNA, and CoronaVac-Sinovac Life. Different patterns of ophthalmoplegia were seen in these case reports. (71–78) In 5/7 cases, evidence existed of albuminocytological dissociation in the cerebrospinal fluid sample analysis, which is defined as elevated proteins without pleocytosis. In 3/7 anti-ganglioside antibodies such as anti-GQ1b antibody were positive.(74,78) Patients were treated with IVIG with recovery taking from weeks to months. One patient received physiotherapy only with reported full spontaneous recovery at 10-weeks follow-up. (75)

Myasthenia gravis

Post COVID-19 infection:

Neuromuscular complications of COVID-19 pose a unique challenge for physicians worldwide. New onset ocular MG has been reported in patients with proven COVID-19 infection.(79–83) The incidence of MG was found to be marginally higher in patients with COVID-19 infection compared to general population (0.087% and 0.07% respectively). (84) Age has ranged from (6 to 65 years old). Patients complained mostly of diplopia and fatigable ptosis with limitations of ocular motility noted on exam. Treatment comprised of standard dose of pyridostigmine, prednisone, and in some case IVIG. Some of the reported cases had a favorable outcome with complete recovery of their ocular MG, while others had only partial recovery. (79,83) All patients had elevated titers of anti-acetylcholine receptor antibodies. Two cases occurred following a complicated admission with multisystem inflammatory syndrome in children, which

recently has been recognized by Centers for Disease Control and Prevention (CDC) as a COVID-19 sequela.(80,81)

Post COVID-19 vaccination:

New onset or exacerbation of ocular or generalized MG has been reported after BioNTech/Pfizer mRNA-vaccine BNT162b2, Moderna mRNA-1273, and AstraZeneca ChAdOx1 vaccines. (85,86) The age and gender of those patients mostly followed the demographic of the second peak of MG disease, which is commonly seen in men who are above 60 years of age(87–94). Exacerbation of pre-existing MG post-vaccine is thought to be from 1-15%. (87) Ocular MG cases presented with intermittent fatigable ptosis and diplopia. (88,90,92,94) In some of the cases, associated symptoms occurred such as fatigue and weakness, myalgia, dysarthria, dysphagia, and head drop. (87,89,91,93) In 8 of the 11 patients acetylcholine receptors (AchR) antibodies was positive, but none were positive for anti-muscle-specific kinase (MuSK) antibodies. (85,87,88,90,91) Electromyography was positive in 5 cases, showing either single-fiber electromyography (SFEMG) test of the orbicularis oculi identified with abnormal jitter or repetitive nerve stimulation providing diagnostic confirmatory for a postsynaptic neuromuscular junction disorder. (85,93,94) Computed tomography of the chest was negative except for one patient with mild thymic hyperplasia; interestingly, this case was double seronegative. (93) The treatment of choice was pyridostigmine alone (85,87,93,94) or combined with steroids (85,87–89,91,92) with complete or partial improvement of bulbomotor symptoms in most cases. PLEX was used for 5 days in a patient who showed no signs of improvement. The patient improved clinically after the second round of PLEX and was placed on azathioprine for maintenance(85).

Thyroid eye disease

TED is an autoimmune disease manifesting with enlargement of the extraocular muscles, proptosis, and eyelid retraction. It commonly is associated with Graves disease (GD). No case reports exist of TED related to COVID-19 infection.

Post COVID-19 vaccination:

In a study by Jafarzadeh et al, subacute thyroiditis was found to be the most prevalent thyroid dysfunction after COVID-19 vaccination, followed by GD. TED was reported to be in 1.2% only. (95) TED post-COVID-19 vaccination was documented after BioNTech/Pfizer mRNA-vaccine BNT162b2 and Moderna mRNA-1273 vaccine, two were new onset, and two were reactivation. (96,97) Patients were middle-aged women with no history of smoking. Two were previously treated GD patients, one was a treated Hashimoto's thyroiditis patient, and one had no history of underlying thyroid dysfunction. (96,97) Patients presented with different ocular manifestations of the TED as soon as 1 day and as far as 3 weeks from vaccine administration. Their ocular manifestations ranged from periorbital swelling, chemosis, proptosis, lid retraction, extraocular muscle restriction, and diplopia. Luckily none had any afferent issues on the exam like compressive optic neuropathy. All showed evidence of thyroid dysfunction on laboratory workup except in one case. (96,97) A CT or MRI scan of the brain and orbit demonstrated enlargement of the EOM's in all of the individuals. Patients responded well to the treatment with Tepezza (Teprotumumab). Spontaneous improvement of symptoms after 4 months was noted in one patient. (97)

IOIS can mimic the presentation of TED, and one case was reported after COVID-19 vaccination. Presenting with diplopia, periorbital erythema, pain and proptosis. Proper

investigations and management are prompted in these cases to exclude other causes of orbital inflammation. (98) It is unclear if the association of TED and IOIS with COVID-19 vaccination is due to random chance alone, although it is interesting that most of the cases of TED were in patients who had an underlying predisposition for the disease including two reactivations of TED.

Pupillary defects:

Adie's Tonic pupil

Post COVID-19 infection:

Adie's pupil also has been identified as a potential long-term sequelae of COVID-19 infection. Only two cases are identified in the literature with long-term pupillary abnormalities following COVID-19 infection.(99,100) Both cases experienced visual dysfunction with evidence of anisocoria three weeks following COVID-19 infection, proven by a positive RT-PCR test or high titer of SARS-CoV-2 IgG antibodies. One patient had findings consistent with right trochlear nerve palsy including right hypertropia on an alternate cover test and right excyclotorsion.(99) Brain imaging using CT and MRI with contrast was unremarkable in both patients. The diagnosis of tonic pupil was confirmed in both cases using a diluted 0.125% pilocarpine test. Treatment consisted of oral corticosteroids, remdesivir, IV antibiotics, dexamethasone, and deriphylline. However, the tonic pupil remained with difficulty focusing near objects despite medical therapy.(100)

Post COVID-19 vaccination:

Only one case series exists of Adie's tonic pupil associated post-COVID-19 vaccination. Gönültas et al described two cases, one was a 27-year-old woman, and another was a 48 years old man, 10 and 12 days after receiving the Pfizer vaccine. , (101) Both responded to the pharmacological testing using dilute pilocarpine 0.1% with positive constriction of the affected

pupil. One had absent deep tendon reflexes and, subsequently, was diagnosed with Holmes-Adie-syndrome. (101)

Horner syndrome:

One report exists of a transient isolated Horner syndrome (HS) in a 65-years-old woman 3 days after being infected with COVID-19.(102) The patient had a normal workup including CT/CTA head, neck, and brain MRI with and without gadolinium. Complete resolution of her ptosis and miosis after 8 days of symptoms onset.(102) HS has not been reported yet in association with COVID-19 vaccination.

Proposed mechanisms of neuro-ophthalmic complications post COVID-19 infection:

While the pathophysiology in the course of COVID-19 infection is not fully understood, several mechanisms have been proposed to explain neuro-ophthalmic manifestations from COVID-19 infection, most favoring an immune-mediated background. The SARS-CoV-2 virus may be implicated through molecular mimicry, inducing an autoimmune response, and causing disorders such as ON and MG.(9,10,82,103,104)

The SARS-CoV-2 virus also has been reported to have a neurotoxic effect through binding to the angiotensin enzyme 2 (ACE2) receptor which is an important entry receptor for the virus to vital organs like the brain. Direct viral infection could explain some of the autoimmune disorders occurring in patients post COVID-19 infection such as optic neuritis, cranial neuropathies, and Adie's tonic pupils(8,55,105,106) Retrograde transport of the virus particles to the central nervous system is thought to underlie some of these disorders and is supported by a post-mortem case series that found that SARS-CoV-2 viral proteins in the cranial nerves of (53%) of the

investigated patients.(107) Also, viral particles are thought to travel from the lungs to the autonomic center in the brain stem causing disorders like Horner syndrome (HS).(102) Moreover, in cases like GCA, the virus is thought to have an affinity to the vascular endothelium causing direct damage. (31,108) The SARS-CoV-2 virus can cause a disruption the blood-brain barrier by pro-inflammatory cytokines and result in increased permeability of the blood-brain barrier, which gives access for antibodies such as myelin oligodendrocyte glycoprotein (MOG) antibodies to the central nervous system. (109)

Reports also have suggested that COVID-19-induced hypoxemia and hypercoagulability can increase the risk of circulatory insufficiency and NA-AION.(110,111) Also, hypercoagulability and hyperviscosity can lead to venous congestion and Idiopathic intracranial hypertension (IIH) or cerebral venous sinus thrombosis (CVST). (49,54)

Proposed mechanism of neuro-ophthalmic complications post COVID-19 vaccination:

Multiple mechanisms have been proposed for post-vaccine-related complications, some are very similar to those proposed for post COVID-19 infection. One is the molecular mimicry theory, where the vaccine introduces proteins to the host that mimic self-antigens or similar conformational structures. In the case of optic neuritis, the molecular mimicry between the virus and CNS myelin, where they share the same amino acid sequence, leads to the formation of antibodies that attack myelin and cause demyelination. (24)This theory also has been proposed for cranial neuropathies post-vaccination where autoimmune inflammatory demyelinating peripheral neuropathy occurs. (56,57,62) A similar mechanism is well established in Miller-Fisher Syndrome (MFS) where molecular mimicry may induce GQ1b or GT1a ganglioside antibody production and cause a secondary, acute, demyelinating, inflammatory polyneuropathy

affecting the peripheral nervous system.(72,73) Likewise in MG, the host immune system perceives the vaccine antigen as similar to host acetylcholine receptors (AChR) and attacks those receptors.(87,88,90,92,94)

The other theory is the presence of adjuvant material in some of the vaccines, which are added to the vaccine to enhance immune response but may also produce an unwanted exaggerated immune reaction. This material is thought to play a role in the pathogenesis of an autoimmune syndrome associated with adjuvants ASIA that can possibly explain ON, GCA and MG post-vaccination. (22,92,112)

Similarly, the vaccine could work to trigger and unmask the disease in individuals who were genetically predisposed to develop autoimmune diseases such as in patients with ON, GCA, TED and MG. (24,93,96) Especially in those with symptoms occurring within a few days after receiving the vaccine. (113)The presence of the human leukocyte antigen (HLA) DRB1*16:02 genotype in patients with GCA also supports the genetic predisposition theory.

It is thought that endothelial cell dysfunction secondary to neuroinflammation from the vaccine can lead to hypercoagulopathy, hyperviscosity, thrombosis, and venous stasis. Subsequently, this might lead to cranial neuropathies, (64) NA-AION and IIH. (40,51,52).

Conclusion:

To date COVID-19 infection and vaccines have been associated with neuro-ophthalmic complications but causation remains to be proven. At the moment, most of our information comes from case reports and case series yet the literature is still growing with the continuation of the global pandemic and vaccination programs. It's important to remember that these neuro-

ophthalmic conditions still occurred in the absence of COVID-19 and given the billions of cases of COVID-19 infection and vaccines which have been administered worldwide, overlap is inevitable due to random chance alone. It also is important to note that while COVID-19 vaccines may be associated with neuro-ophthalmic sequela, COVID-19 is a deadly disease with its own long term sequela, and the sequela post-vaccination are treatable with almost universally good outcomes if recognized and treated early. Insufficient evidence exists to justify the deferment of vaccination based on these very rare neuro-ophthalmic associations, some of which are highly likely due to random chance alone. Both the SARS-CoV-2 virus and all the vaccines that have been produced to combat this global pandemic may have the potential to cause or exacerbate neuro-ophthalmic conditions, and ophthalmologists should be mindful of this potential and treat accordingly.

Clinics Care Points

- Consider SARS-CoV-2 infection and ask about COVID-19 symptoms when presented with an otherwise unexplained cranial neuropathy.
- Treat patients in accordance with best practices for the clinical neuro-ophthalmic phenotype with which they present irrespective of any COVID-19 association.
- Understand that post-COVID conditions can occur months after the COVID-19 infection.

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