Neuro-Ophthalmic Manifestations of COVID-19 Infection and Vaccination

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Abstract

We describe cases of visual snow syndrome, optic neuritis, cranial nerve palsies and ocular myasthenia gravis newly diagnosed in the setting of a recent coronavirus disease 2019 (COVID-19) infection or vaccination with Pfizer-BioNTech. We also report the ocular exam findings, workup and treatment of the eight patients with these neuro-ophthalmic manifestations. Recognition of these conditions as possible early manifestation of the infection would result in decreased viral transmission and better diagnosis. Further investigation is recommended to depict the pathogenesis of COVID-19 infection or vaccination and these neuro-ophthalmic manifestations.

Introduction:

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a single-stranded, highly pathogenic RNA virus accountable for the coronavirus disease 2019 (COVID-19) global pandemic. The infection can range from asymptomatic manifestations to severe respiratory failure with fever, cough, shortness of breath, myalgias and arthralgias as the most common findings.[1] Initially reported neurologic manifestations range from nonspecific symptoms (headache, dizziness) to acute cerebrovascular disease.[2] Subtle post- and para-infectious neurologic and ophthalmologic manifestations may have been underreported. We hereby present a series of four neuro-ophthalmic conditions concomitant with a COVID-19 infection: visual snow syndrome, optic neuritis, cranial nerves palsy and ocular myasthenia gravis and a case of optic neuritis manifesting after the 2nd dose of the Pfizer-BioNTech COVID-19 vaccine.

All patients consented to sharing their exam findings with the scientific community.

Observation

Visual Snow Syndrome

Case 1

A 38-year-old man was referred to our clinic for positive visual disturbances of 3 months duration which started after being diagnosed with COVID-19 infection by nasopharyngeal polymerase chain reaction (PCR). He described small white dots over the entire visual field, more prominent when looking at a dark-colored background. He also reported palinopsia (both afterimages and trailing moving objects), photophobia, as well as enhanced entopic phenomena, portrayed as excessive floaters and spontaneous photopsia. He later developed tinnitus and severe headache which prompted evaluation by an otolaryngologist. An attempt to diagnose and treat labrynthitis with vestibular rehabilitation therapy failed.

Case 2

A 16-year-old male patient complained of white flashing dots in his visual field that he described as “constant out-of-signal TV screen superimposing my vision” which started after he tested positive for COVID-19 around 5 months earlier. He also reported bright flashing lights and trailing images of moving cars.

Case 3

A 27-year-old female known to have inflammatory bowel disease- associated uveitis maintained on ustekinumab injection every 2 months was referred to the neuro-ophthalmic clinic for worsening floaters, flashes, afterimages of static objects and trailing of moving object during the

past year. To note that the patient has recovered from a COVID-19 infection as her symptoms appeared. She also recently developed tinnitus and headaches.

In all three previously described cases, the COVID-19 infection did not require hospitalization nor medication. Also, Magnetic Resonance Imaging and Venogram (MRI and MRV respectively) as well as our detailed ophthalmic exam were unremarkable. Patients were diagnosed with visual snow syndrome (VSS) according to Puledda et al's criteria.[3] All patients reported improvement on tricyclic antidepressant.

Optic Neuritis

Case 1

A healthy 25-year-old female presented complaining of blurry vision in the left eye with pain exacerbated by eye movement for the past week. Two weeks prior to presentation, she tested positive for COVID-19 infection with uncomplicated course. She denied any family history of neurological or immunological diseases.

Ophthalmic exam was significant for visual acuity of 20/60, decreased color vision, central scotoma, and optic nerve edema in the left eye (Figure 1). She also had a left relative afferent pupillary defect (RAPD).

In view of the typical optic neuritis signs and symptoms, MRI brain and orbit with and without gadolinium was performed and the patient was started on intravenous steroids for four days followed by an-eleven-day course of oral prednisolone tapering. Imaging was significant for left optic nerve enhancement. No T2 enhancing lesions were noted in the brain. On follow-up exam ten days later, best corrected visual acuity (BCVA) improved to 20/20 and the patient could identify 24 plates on Ishihara colored test. IgG and IgM COVID-19 serologies were positive.

Case 2

A 43-year-old female presented for continuity of care, three weeks after suffering from left eye blurry vision and pain on ocular movement. Her initial exam, performed on outside basis, was significant for decreased visual acuity, dyschromatopsia and optic nerve swelling of the left eye. It also revealed prolonged latency and decrease amplitude on pattern visual evoked potential, nasal visual field defect in the left eye on Humphrey visual field and no demyelinating lesions on brain MRI. To note that the patient received her 2nd dose of the Pfizer-BioNTech COVID-19 vaccine three days prior to the onset of these symptoms. Patient presented to our center with no complaints. On exam, her visual acuity was 20/30 in the left eye with minimal dyschromatopsia, absence of RAPD and no optic nerve swelling. Repeat Humphrey visual test showed marked improvement. The likely diagnosis was vaccine-induced left optic neuritis. No further investigations or treatments were recommended as symptoms self-resolved and patient had no history of neuro-inflammation.

Cranial Nerve Palsy

Case 1

A 34-year-old male patient presented with acute binocular horizontal diplopia, when looking to far, of 5 days duration. The onset of diplopia coincided with the onset of fever and loss of taste. Patient serologically tested positive for acute COVID-19 infection.

He denied headaches, tinnitus, transient visual obscurations, nausea, vomiting, motor abnormalities or any recent trauma. Ocular history was relevant for angioid streaks in both eyes and a history of choroidal neo-vessel in the left eye in 2012.

BCVA was unchanged from previous exam, anterior segment exam was within normal limit and no RAPD was noted. Fundus exam was significant for angioid streaks around the optic disc in both eyes with atrophy at the macula in the left eye.

Ocular motility examination revealed esotropia of 4 Prism Diopters (PD) in primary gaze at near and 6PD at distance, 4 PD on right gaze and 12 PD on left gaze. He also had -1 limitation in abduction of the left eye and slower saccadic velocity on left side gaze. He was thus diagnosed with left cranial nerve six palsy. Brain MRI was normal. Two weeks later, the patient had complete resolution of diplopia and no signs of left abducens nerve palsy on exam.

Case 2

A 28-year-old man complained of horizontal binocular diplopia a month after his positive COVID-19 molecular testing. Patient denied ptosis, dysphagia or dysarthria.

BCVA was 20/20 in both eyes. Worth 4 Dot testing was positive for fusion at near and double Maddox Rod suggested a 2.5 PD excyclotorsion in the right eye. Ocular motility examination revealed esotropia of 10 PD to far and 6PD to near. This esotropia was worse on left gaze (18 PD) with associated mild abduction deficit on same gaze consistent with a diagnosis of left CN6 palsy. Exam was also relevant for right hypertropia (2PD) worse on opposite gaze (10PD) and same head tilt (3PD) with limited depression of the right eye on adduction consistent with a diagnosis of right superior oblique palsy.

Acetylcholine receptor antibodies, thyroid stimulating hormone and its autoantibodies as well as MRI of the brain were unremarkable. On follow-up exam 1 month later, ocular motility exam improved with resolution of diplopia.

Ocular Myasthenia Gravis (OMG)

A 34-year-old man presented to our clinic with a two-week history of bilateral ptosis coinciding with his mild COVID-19 infection. His medical history was significant for congenital hydrocephalus treated with ventriculoperitoneal shunt and type 1 neurofibromatosis. Ocular exam revealed a fatigable asymmetrical ptosis improving on ice-pack test (Figure 2). Motility examination revealed bilateral symmetrical ophthalmoparesis with -4 deficit in all gazes. Neurologic exam was significant for new onset upper extremity weakness.

We recommended pyridostigmine 60mg three times daily and assessment of acetylcholine receptor antibodies (AChR-Abs) levels. On follow-up visit two weeks later, AchR-Abs came out positive, and patient reported improvement in his symptoms (Figure 3). Follow-up exam was significant for improvement of both the ophthalmoparesis (now -2 in all gazes) and the ptosis measurements with a marginal reflex distance (MRD1) improving from -1 to +1 in both eyes. Chest imaging was negative for thymoma and patient was referred to neurology clinic for a full assessment. On follow-up exams, ptosis resolved but weakness worsened in the upper extremities and progressed to affect the neck extensors. Repeat electromyography was positive for severe decrement upon repetitive nerve stimulation in the right median and accessory nerve. Since the patient was already on pyridostigmine 60mg three times daily and failed a previous trial of steroids, decision was made to start mycophenolic acid 1000 mg twice daily with monthly IVIG. Two weeks later, significant improvement was noted.

Discussion:

The pathophysiology of COVID-19 infection induced neuro-ophthalmic complications has yet to be elicited. Direct viral infiltration of the nervous system and autoimmune inflammatory etiologies have been proposed.[4]

Evidence of neuroinvasion was described with other coronaviruses like SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).[5] Proposed neurotropic mechanisms include hematogenous entry and neuronal retrograde dissemination. One of the main mechanisms by which hematogenous entry occur is through binding of coronaviruses to the ACE2-R present on endothelial cells of the blood brain barrier (BBB) and on leukocytes, which become viral reservoirs allowing dissemination of the infection.[5,6] Another potential route of entry to the nervous system is through retrograde viral spread whereby the virus affects neurons in the periphery and use the cell transport system to gain access to the CNS.[5]

Moreover, mounting evidence suggests an autoimmune pathophysiology to these para- and post-infectious manifestations in the context of new onset auto-immune diseases like Guillain-Barré syndrome (GBS),[7] OMG,[8,9] and optic neuritis[10,11] reported in the setting of a COVID-19 infection . The presence of antibodies: ganglioside GD1b in a patient with Miller Fisher syndrome[7], MOG antibodies in patients with optic neuritis[10,11] and AChR-Abs in patients with OMG[8,9], including our patient, in addition to the clinical improvement with intravenous immunoglobulin (IVIG) in GBS patients support an autoimmune etiology. SARS-CoV-2 might act as a trigger to antibodies formation. GBS, MG and optic neuritis are common manifestations of viral-triggered autoimmune neurologic diseases.[9] In a phenomenon known as molecular mimicry, antibodies produced by SARS-CoV-2 inflammatory response may cross-react with myelin protein, acetylcholine receptor or MOG proteins respectively resulting in GBS,

OMG and optic neuritis. Demonstrated mimicry between SARS-CoV-2 and heat shock proteins 60 and 90, associated with GBS and other autoimmune diseases might affirm the previous statement.[12]

Post-vaccination optic neuritis has been associated with multiple vaccines,[13] including rabies, influenza, measles and zoster with mean onset of 10.8 days post-injection and generally favorable visual prognosis. Molecular mimicry between myelin basic protein and viral proteins, systemic autoimmune process and superantigen activation have been proposed as possible mechanisms. A total of 55 cases of optic neuritis after different available COVID-19 vaccines have been reported from 10 countries in a preprint.[14] Among these, 13 received the Pfizer-BioNTech vaccine and ended up with favorable visual outcome with adequate response to steroids despite delay in treatment initiation. Ideal management remains elusive and ought to be tailored individually without delaying recognition of what seems to be a possible causal association.

Visual snow after viral illnesses including COVID-19 infection has not been reported in the literature. One case report of visual snow-like phenomenon and posterior uveitis was reported recently by Braceros et al.[15] This case showed that the patient had some ocular inflammation but none of our patients with VSS had any signs of uveitis. The reason why COVID-19 could trigger VSS is unclear as we still do not have a good grasp of the pathophysiology of the latter. One theory could be related to the ability of the virus to cause cortical hyperexcitability that might be exacerbated by some level of anxiety accompanying COVID-19 infection.[16]

Conclusion

In conclusion, COVID-19 induced neuro-ophthalmologic complications ought to be recognized as they can represent early manifestation of the infection. This would prevent a delayed diagnosis, a misdiagnosis and avoid transmission, as we would expect similar conditions to manifest with or after a COVID-19 infection. The pathophysiology has yet to be elucidated and it offers the opportunity for a better understanding of the mechanisms of neuro-invasion and autoimmunity.

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Figure Legends:

Figure 1: Left eye fundus photograph showing optic nerve swelling in patient 1 with optic neuritis

Figure 2: (A) Bilateral asymmetric ptosis worse in the right eye as compared to the left in a patient worked-up for ocular myasthenia gravis. (B) In-clinic improvement in ptosis minutes after ice-pack test was performed.

Figure 3: Assessment of response to recommended course of pyridostigmine in a patient with suspected ocular myasthenia gravis. Note the chronological improvement, as compared to (A) baseline; 1, 2, 24 and 36 hours after pyridostigmine initiation as respectively shown in (B), (C), (D) and (E).