Anti-Aquaporin 4 related optic neuritis and myelitis post-COVID-19 Infection

Running title: NMO post-COVID-19 Infection

Author Names: Pouriska B. Kivanany, PhD¹, Subahari Raviskanthan MBBS², Peter W. Mortensen MD², Andrew G. Lee MD²,³,⁴,⁵,⁶,⁷

Institutions:

¹Texas A and M College of Medicine, Bryan, Texas, USA
²Department of Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, Houston, TX, USA
³Departments of Ophthalmology, Neurology, and Neurosurgery, Weill Cornell Medicine, New York, New York, USA
⁴Department of Ophthalmology, University of Texas Medical Branch, Galveston, Texas
⁵University of Texas MD Anderson Cancer Center, Houston, Texas, USA
⁶Department of Ophthalmology, The University of Iowa Hospitals and Clinics, Iowa City, Iowa

Corresponding author

Andrew G. Lee, MD
Chair, Department of Ophthalmology - Blanton Eye Institute
Houston Methodist Hospital
6560 Fannin St. Ste 450 Houston, TX 77030
Phone: (713)-441-8823
Email: aglee@houstonmethodist.org
Publication Originality Statement. We confirm this publication is original.

Funding. There was no funding

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Keywords: COVID-19, NMO, Optic Neuritis

Disclosures: Pouriska B. Kivanany, Subahari Raviskanthan, Peter W. Mortensen, and Andrew G. Lee declare that they have no conflict of interest.
Coronavirus disease 2019 (COVID-19) causes severe acute respiratory syndrome (SARS-CoV-2) and is a novel disease first reported in December 2019. Common symptoms associated with COVID-19 are cough, fatigue, dyspnea, and fever. Over the last year, multiple post infectious sequelae have been reported, with multi-system involvement. Similar to other coronaviruses, it is speculated that COVID-19 may enter the central nervous system (CNS) via transsynaptic pathways causing neurologic manifestations, such as neuromyelitis optica (NMO). To date, there have only been two cases of anti-aquaporin 4 (AQP4) associated transverse myelitis in a presumed COVID-19 patient. We report a case of anti-AQP4 related optic neuritis post-COVID infection; to our knowledge, this is the only such case in the English language ophthalmic literature.

A 35-year-old Hispanic female presented to the Emergency Department (ED) with progressive headaches, fevers, neck stiffness, nausea, vomiting and binocular diplopia. Her headaches were not positional. She had no respiratory symptoms or vision loss. Her past medical history was significant for COVID-19 infection 6 weeks prior, confirmed with polymerase chain reaction (PCR). Her only medication was aspirin/paracetamol/caffeine tablets as needed. She had 3-4 standard alcoholic drinks weekly and denied tobacco and drug use. Her body mass index was 29.4kg/m².

Her vital signs were within normal limits, and she was afebrile. Neurological examination at this time was significant for esotropia in primary gaze. The ductions and versions were consistent with a left abducens nerve palsy. Saccadic velocities were not documented. Laboratory investigations were significant for white blood count of 13.46k/µL (normal 4.50-
11.00k/μL) with immature granulocytes on blood film. Sedimentation rate and C-reactive protein were within normal limits. Magnetic resonance imaging (MRI) of the brain and orbits with contrast and venogram showed empty sella and bilateral papilledema (Figure 1). There was no venous sinus thrombosis. Lumbar puncture (LP) revealed a white blood cell (WBC) count of 171/CMM (normal 0-5/CMM) with 94% lymphocytes. Cerebrospinal protein, glucose, Gram stain, bacterial and fungal culture, and viral workup were negative. The opening pressure was 31 cm H2O, and oligoclonal bands were not detected. The patient reported symptomatic improvement in the headache post-LP, and her abducens nerve palsy resolved.

The patient was empirically treated with intravenous acyclovir, cefepime, and vancomycin, as well as acetazolamide 500mg PO BID for intracranial hypertension in the setting of aseptic meningitis until the Gram stain and viral CSF results returned negative. She was discharged home after 4 days.

She represented 10 days later due to worsening headaches, and new vision loss in the right eye (OD) and painful eye movements. On neuro-ophthalmic examination, her visual acuity was light perception OD and 20/40 in the left eye (OS). Her pupils were isocoric with a relative afferent pupillary defect OD. Motility was full in both eyes (OU). Slit lamp biomicroscopy and intraocular pressures were normal. Dilated fundus exam revealed Grade 3 disc edema OD and Grade 2 OS. Upper limb neurological examination revealed a left Hoffman’s sign, bilateral hyperreflexia at brachioradialis reflexes, with no motor or sensory abnormalities. In the lower limbs, she had normal tone, with non-sustained clonus bilaterally, and hyperreflexic ankle jerks bilaterally. She had a sensory level at T12. There was no bowel or bladder involvement. In
retrospect, she reported unsteady gait and lower limb weakness at the time of her initial emergency department presentation. MRI showed right optic nerve enhancement, as well as non-enhancing central cord abnormality at T4 extending to T7-T8 (Figure 2). AQP4 antibodies subsequently returned positive with a titer of 1:1000, consistent with a diagnosis of NMO. The patient was treated with 5 days intravenous methylprednisolone and 5 cycles of plasma exchange subsequently without significant vision improvement. She is currently being worked up for ongoing immunosuppression.

Neuro-ophthalmic manifestations related to COVID-19 include optic neuritis (some of which are myelin oligodendrocyte glycoprotein (MOG) associated), cranial nerve palsies, visual snow, and visual field defects (1). NMO, whilst not previously reported with optic neuritis, can be precipitated by viral infections, including COVID-19 (3). To be diagnosed with NMO, patients must have both optic neuritis and acute myelitis, and 2/3 of either: contiguous cord MRI lesion in 3 vertebral segments, brain MRI not meeting criteria for multiple sclerosis (MS), or AQP4-IgG seropositive (4). Our patient met all of these criteria.

It is known that COVID-19 binds to angiotensin-converting enzyme-2 (ACE2) receptors to access host cells (3). COVID-19 may be able to penetrate through the blood-brain barrier cellular architecture by utilizing these ACE2 receptors, and priming the CNS for developing NMO (3). There have been recent reports of patients developing optic neuritis as a sequela of COVID-19, with some having associated MOG antibodies (1). There are no reported cases of AQP4-IgG associated optic neuritis, however, there are two cases of COVID-19 associated transverse myelitis, which presumably occurs via a similar mechanism (2, 3).
Post infectious NMO has been reported in the literature, with herpes zoster being the most common associated infection. A case control study of 19 patients with NMO screening for acute infections at the time of initial presentation / flare of symptoms found that 47% of the patients had associated evidence of acute infection, of which most were viral infections, compared to 15% of the control group (5). Given this potential association, as well as the strong immune response that COVID-19 often produces, we suspect that secondary autoantibody production is the mechanism in which our patient’s NMO occurred. The 7 week delay between the COVID symptoms and her subsequent presentation could also be explained by a form of immune constitution reconstitution syndrome which has been hypothesized for delayed autoimmune manifestations after COVID-19, explained by an unregulated immune response after recovery from the triggering illness causing new autoimmune phenomena (6).

As the spectrum of COVID 19 related complications keeps expanding, new associations will continue to be identified. Whilst it is not possible to prove direct correlation between COVID-19 and out patient’s NMO or the temporal relationship, other COVID-19 and post-infectious NMO reports make it important to consider. To our knowledge, this is the first presentation of anti-AQP4 related optic neuritis and myelitis post-COVID-19. Clinicians should remain aware of post-infectious manifestations of COVID-19 and continue screening and workup of patients as the presence of antibodies may change the patient’s visual prognosis and requirement for continued immunosuppression.
References:


6. Cañas CA. The triggering of post-COVID-19 autoimmunity phenomena could be associated with both transient immunosuppression and an inappropriate form of immune reconstitution in susceptible individuals. Med Hypotheses. 2020
Figure 1: Magnetic resonance imaging of the brain and orbits at initial presentation. (A) T1 sagittal image showing empty sella (arrow). (B) T2 axial image showing flattening of the globe and optic disc edema in both eyes (arrow).
Figure 2: Magnetic resonance imaging during patient’s representation. T1 fat saturated post contrast showing right optic nerve enhancement in axial (A) and coronal (B) sequences. Sagittal Short T1 inversion recovery sequence (C) showing hyperintense lesion T4 – T8.
Statement of Authorship

Category 1:
a) Conception and design
Pouriska Kivanany, Subahari Raviskanthan, Peter W Mortensen, Andrew G Lee

b) Acquisition of data
Pouriska Kivanany, Subahari Raviskanthan, Peter W Mortensen, Andrew G Lee

c) Analysis and interpretation of data
Pouriska Kivanany, Subahari Raviskanthan, Peter W Mortensen, Andrew G Lee

Category 2:
a) Drafting the manuscript
Pouriska Kivanany, Subahari Raviskanthan, Peter W Mortensen, Andrew G Lee

b) Revising it for intellectual content
Pouriska Kivanany, Subahari Raviskanthan, Peter W Mortensen, Andrew G Lee

Category 3:
a) Final approval of the completed manuscript
Pouriska Kivanany, Subahari Raviskanthan, Peter W Mortensen, Andrew G Lee