Myelin Oligodendrocyte Glycoprotein Antibody–Associated Optic Neuritis and Myelitis in COVID-19

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The outbreak of the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), was first reported in late December 2019 in Wuhan, China, (1) and has since transformed into a rapidly evolving global pandemic. As the number of infections grows, so does our knowledge of possible clinical symptoms, signs, and manifestations. The coronavirus family of viruses, including SARS coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV), is most well known for causing respiratory syndromes, with severe cases leading to acute respiratory distress syndrome (ARDS). There is an ever-growing body of literature describing other organs as sites of damage caused by this family of viruses, including cardiac (2), gastrointestinal (3), neurological (4–11), and ophthalmic (12–14) involvement. The neuroinvasive potential of SARS-CoV-1, MERS-CoV, and other coronaviruses has been described, and it has been hypothesized that SARS-CoV-2 may be able to directly access the central nervous system (CNS) through a transsynaptic route given considerable sequence homology, and that this may be a mechanism of respiratory failure in COVID-19 (5). Moreover, a recent report of SARS-CoV-2 preceding antiphospholipid antibody syndrome (9) leading to thrombus formation underscores the potential for this infectious agent to trigger autoantibody production. Additional reports of COVID-19 presenting as Miller Fisher syndrome (10), Guillain–Barré syndrome (11), and Kawasaki syndrome (13) offer specific examples of this virus's ability to dysregulate the immune system. Herein, we describe a case of a young man presenting with bilateral severe optic neuritis and myelitis, determined to be simultaneously SARS-CoV-2 and myelin oligodendrocyte glycoprotein (MOG) IgG antibody positive. We believe this is a unique neuro-ophthalmic manifestation of SARS-CoV-2 and the first such case to be reported in the literature.

This report adheres to the tenets of the Declaration of Helsinki. Patient data were obtained through inpatient and outpatient encounters and medical records at Keck Medical Center, University of Southern California. Informed consent was obtained verbally as well as part of the patient agreement for use of clinical information and photographs for educational purposes.

A 26-year-old Hispanic man presented for evaluation of bilateral, subacute, sequential vision loss first affecting the left eye, then the right eye 3 days later. Pain with eye movements preceded the vision symptoms in each eye. An ophthalmologist noted disc edema and urgently referred him to our practice for further evaluation.

On review of systems, he reported a few days of progressive dry cough before the onset of eye pain and vision loss. He also endorsed numbness on the soles of his feet and neck discomfort with forward flexion but denied shooting, electric-like pain. He denied fevers, chills, sweats, shortness of breath, rhinorrhea, chest pain, or changes in taste or smell. There were no recent headaches, weakness, imbalance, bowel or bladder dysfunction, and cognitive or mood changes. He further denied personal or family history of demyelinating or autoimmune disorders. He had 4 dogs at home and denied cat exposure. He denied recent travel or sick contacts.

Our examination revealed hand motion vision in the right eye and 20/250 in the left eye, with a right relative afferent pupillary defect. Ocular motor and remaining cranial nerve examinations were normal. Dilated fundus examination revealed bilateral disc edema and venous congestion, with retinal perivenous hemorrhages in the right eye (Fig. 1).

His clinical picture of severe sequential bilateral optic neuritis with disc edema was highly suspicious for MOG antibody disease, but the broader differential diagnosis also included infectious, inflammatory, and infiltrative processes. Our initial workup included testing for QuantiFERON-TB

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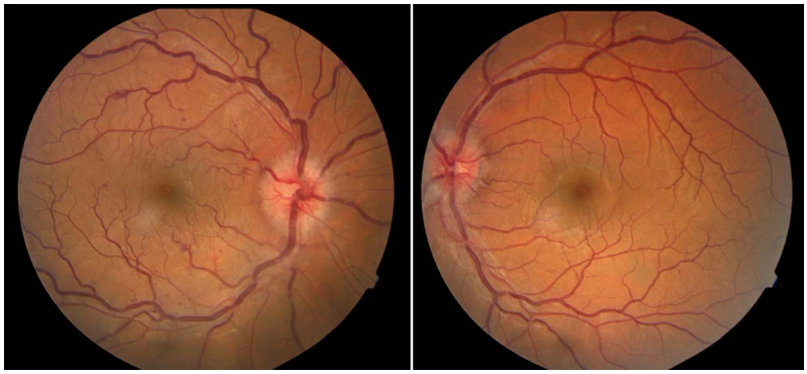

FIG. 1. Color fundus photographs revealing bilateral disc edema and venous congestion, with retinal perivenous hemorrhages of the right eye, indicating severe axoplasmic and venous stasis at the level of the congested right optic nerve head.

Gold Plus, rapid plasma reagin, fluorescent treponemal antibody absorption test, anti-nuclear antibody, anti-neutrophil cytoplasmic antibodies, and aquaporin-4 (AQP4) and MOG-IgG cell-based assays. Given our evolving understanding of the heterogenous clinical presentations of this novel pathogen, and the potential for this presentation to be the result of a secondary immune response, we felt that SARS-CoV-2 polymerase chain reaction (PCR) testing was justified, despite our patient demonstrating only one well-described clinical symptom of COVID-19 (dry cough).

Within 24 hours, SARS-CoV-2 testing from nasal and oropharyngeal swabs processed by the Roche Cobas 6800 SARS-CoV-2 real-time RT-PCR system (Roche Molecular 66 Systems, Branchburg, NJ) returned positive. He was admitted to Keck Hospital for completion of the workup, multidisciplinary management, and careful clinical monitoring. MRI of the brain and orbits with and without contrast revealed avid, uniform enhancement and thickening of both optic nerves extending from the globe to their intracranial prechiasmal segments, without overt involvement of the chiasm (Fig. 2). One small nonenhancing, nonspecific periventricular T2 hyperintensity was present, adjacent to the occipital horn of the right lateral ventricle. MRI of the spine with and without contrast was notable for patchy T2 hyperintensities in the lower cervical and upper thoracic spinal cord associated with mild central thickening and gadolinium enhancement (Fig. 3). Lumbar puncture revealed a normal opening pressure of 12.7 cm, cerebrospinal fluid (CSF) protein 31, and glucose 57 (within normal limits). CSF white blood cells were elevated at 55 cells/μL (normal < 5) with 100% mononuclear cells. Identical oligoclonal bands were present in both serum and CSF, but none were unique to the CSF, consistent with a systemic inflammatory response. CSF bacterial cultures and SARS-CoV-2 RNA PCR were negative. Serum AQP4 antibodies were not detected; however, MOG-IgG was highly positive at a titer of 1:1,000 (Mayo Clinical Laboratories, Mayo, Rochester, MN).

Immediately after the lumbar puncture, one gram of intravenous methylprednisolone was administered daily for 5 days, followed by an oral prednisone taper. Visual acuity improved rapidly and incrementally to the level of 20/50 in each eye by the time of discharge on the seventh day after admission. His vitals and pulmonary function remained completely normal throughout his hospital course, and he displayed no additional signs or symptoms of COVID-19. The remainder of his infectious and inflammatory bloodwork returned unremarkable. Outpatient follow-up 3 weeks later revealed 20/30 vision in both eyes and complete resolution of disc edema and retinal findings.

Our case of a young Hispanic man with severe bilateral sequential vision loss associated with optic disc edema, retinal venous congestion, long-segment bilateral optic neuritis, and myelitis is fairly classic for MOG-IgG–mediated demyelinating disease (15).

MOG-IgG antibodies target the MOG uniquely expressed on oligodendrocytes. It is thought to serve as a cellular receptor, adhesion molecule, or regulator of

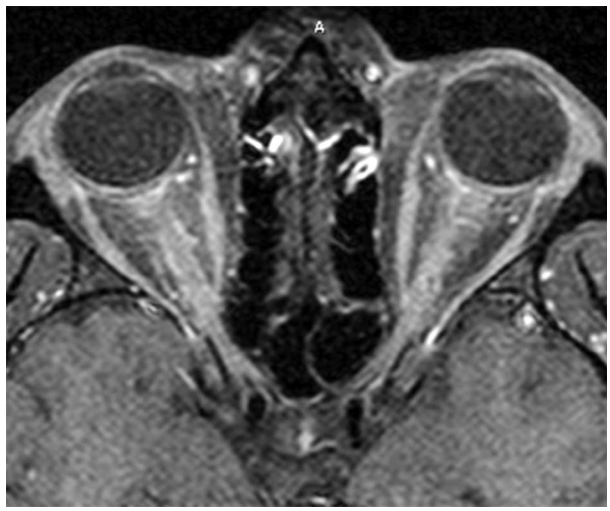

FIG. 2. Postcontrast T1-weighted axial fat-suppressed MRI of orbits reveals thickening and avid uniform enhancement of both optic nerves, extending contiguously from each globe through to the intracranial prechiasmal segments, without overt involvement of the chiasm itself.

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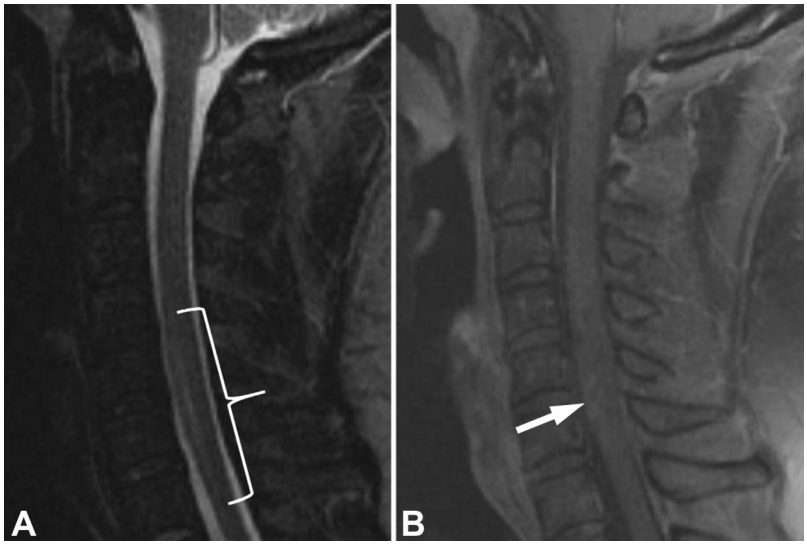

FIG. 3. A. Sagittal STIR MRI of the cervical spine demonstrating 3 contiguous segments of central cord hyperintensity and mild intrinsic thickening (bracketed area). **B**. Postcontrast T1-weighted sagittal image demonstrating patchy faint gadolinium enhancement of the same area (*arrow*), consistent with active inflammation. STIR, short inversion-time inversion recovery.

microtubule stability (16,17). MOG antibodies can circulate freely but do not exhibit a pathologic effect, unless they gain access to the CNS through disruption of the blood–brain barrier, typically as a result of inflammation or infection (18). Once access to the CNS is gained, pathology is mediated by T cells and complement-fixing antibodies, leading to the varied clinical features associated with MOG antibody–mediated CNS disease, including optic neuritis, transverse myelitis, encephalitis, and acute disseminated encephalomyelitis (ADEM) (15–17).

An etiologic link between parainfectious or postinfectious demyelinating syndromes and a prodromal viral illness has long been considered and is now well established. The earliest such report may be from 1790 describing a 23-year-old woman with weakness and bladder dysfunction occurring 1 week after a measles rash (19). Leake et al. (20) noted that 93% of patients with ADEM in their series had a history of viral illness within 21 days of the onset of neurological symptoms. The prevailing mechanism of injury is felt to involve molecular mimicry, where a variety of potential viral antigens trigger an immune response directed toward endogenous CNS myelin proteins, including MOG (21). Recent literature has focused on the considerable phenotypic, epidemiologic, and immunologic overlap between ADEM and MOG-IgG–mediated CNS disease. As many as 50% of patients with ADEM have been reported to test positive for serum MOG antibodies, and this proportion may be even higher in ADEM patients with recurrent polyphasic disease (22). Hence, there is a large body of established literature linking viral pathogens and the development of ADEM and MOG antibody–mediated CNS injury (23–26). Pertinent to the ongoing COVID-19 pandemic, in 2004, Yeh et al. (27) described a patient with ADEM associated with a human coronavirus (HCoV-OC43) detected in his serum and CSF samples, and murine hepatitis coronavirus has been implicated in CNS demyelinating disease for over 2 decades (28).

SARS-CoV-2 has demonstrated its ability to incite a profound host immune response. The most established immunological manifestation is ARDS, occurring in up to 29% of cases (29). Multiple groups have begun to characterize its complex immunological basis, involving a variety of cytokines and inflammatory markers including C-reactive protein, D-dimer, IL-2, IL-6, IL-7, IL-10, granulocyte colony stimulating factor, IP10, MCP1, MIP1A, and TNFα, particularly in patients with more severe COVID-19 disease. Our report, along with the aforementioned recent reports of antiphospholipid antibody, Kawasaki, Miller Fisher, and Guillain–Barré syndromes in association with SARS-CoV-2, highlights the potential for this infectious agent to trigger autoantibody production, which could have a broad array of clinical manifestations depending on the target organ of the autoantibodies. Interestingly, our patient did not have ARDS or some other manifestation of severe COVID-19 clinically, suggesting that novel autoantibody syndromes may need to be considered in the differential diagnosis of mild COVID-19 when clinically appropriate.

We recognize that CSF SARS-CoV-2 PCR testing has not been validated, and its sensitivity and specificity in clinical settings are not currently known. As such, the negative CSF SARS-CoV-2 PCR result does not rule out direct CNS infection in this case. Although neurotropism is certainly plausible, we believe a secondary, immune-based pathogenesis triggered by SARS-CoV-2 is far more likely in this case. The clinical symptoms and signs, serum and CSF results,

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radiological findings, and dramatic treatment response to steroids all firmly support an inflammatory disorder and are quite characteristic of MOG-IgG–mediated CNS disease. The established connection between a viral prodrome and MOG antibody disease, taken together with the clear temporal sequence between our patient's SARS-CoV-2 infection, neuroimmunological presentation, and MOG-IgG seropositivity, provides robust evidence supporting a causal link between SARS-CoV-2 infection and MOG-IgG–mediated CNS demyelination.

To the best of our knowledge, this is the first reported case to establish concurrent SARS-CoV-2 infection and MOG-IgG antibody–mediated CNS disease. As a global community, we continue to learn in real time about the myriad of possible clinical manifestations comprising COVID-19. SARS-CoV-2 infection should be considered in any patient presenting with new neuroimmunological manifestations potentially consistent with MOG-IgG–mediated disease. Failure to recognize this potential connection and immunological basis for devastating vision loss in this context may lead to a number of adverse outcomes. These include delayed diagnosis of the underlying SARS-CoV-2 infection, systemic compromise after treatment with high-dose corticosteroids (30) in the presence of an unrecognized SARS-CoV-2 infection, or a potential delay in initiation or withholding of high-dose corticosteroids, if the secondary autoantibody response is unrecognized and the clinical presentation is presumed secondary to direct viral injury.

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