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Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease and Transverse Myelitis Probably Associated With SARS-CoV-2 mRNA Vaccines: Two Case Reports

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Abstract

Post-vaccination CNS demyelinating syndromes have been reported with a variety of vaccines including the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines. We report a case of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) probably associated with the mRNA-1273 (by Moderna) SARS-CoV-2 mRNA vaccine, and a case of acute transverse myelitis (ATM) probably associated with the BNT162b2 (by Pfizer-BioNTech) SARS-CoV-2 mRNA vaccine. A 38-year-old man developed left blurry vision, lower extremity weakness/paresthesia, and bowel/bladder dysfunction three days after receiving the Moderna vaccine. He was diagnosed with left optic neuritis and longitudinally extensive transverse myelitis; he tested positive for the myelin oligodendrocyte glycoprotein antibody. A 39-year-old woman presented with progressive lower extremity weakness/numbness 7 days after receiving the Pfizer vaccine. She was diagnosed with ATM. Both patients improved with intravenous corticosteroids. The association between CNS demyelinating syndromes and vaccination has been reported for many years. We describe two cases of acute CNS demyelinating events probably associated with both mRNA variations of the SARS-CoV-2 vaccines. While the risk of CNS demyelinating events is non-negligible, the incidence is very low and the overall benefits of vaccination outweigh the marginal risk. However, providers should be aware of this potential neurological complication of the SARS-CoV-2 mRNA vaccines.

Keywords

demyelinating diseases, optic neuritis, transverse myelitis, autoimmune diseases of the nervous system, COVID-19 vaccine

Introduction

Post-vaccination CNS demyelinating syndromes have been reported with different vaccines, most notably the influenza and human papilloma vaccines (HPV).[1] Though these events are rare, they remain a concern with the development of new vaccines. A variety of vaccines have been newly developed against the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) and there have been several reports of post-vaccination CNS demyelinating syndromes. The AZD1222 (Oxford-AstraZeneca) vaccine was possibly associated with a case of longitudinally extensive transverse myelitis and probably associated with a case of focal myelitis.[2,3] A case of acute disseminated encephalomyelitis was probably associated with the inactivated SARS-CoV-2 vaccine (Vero cell).[4] Two cases of new-onset multiple sclerosis (MS) and a case of new-onset neuromyelitis optica (NMO) probably associated with the BNT162b2 (Pfizer-BioNTech) SARS-CoV-2 mRNA vaccine have been reported.[5,6] One case of new-onset relapsing-remitting MS was probably associated with the mRNA-1273 (Moderna) SARS-CoV-2 mRNA vaccine.[6] We report a case of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) probably associated with the Moderna vaccine, and a case of acute transverse myelitis (ATM) probably associated with the Pfizer vaccine.

Case Report

Case 1

A 38-year-old man with no past medical history presented to our hospital in April 2021 with left blurred vision, lower

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extremity (LE) weakness/paresthesia and bowel/bladder dysfunction starting three days after receiving the first dose of the Moderna vaccine. He had no other vaccine associated side effects. His symptoms started acutely and worsened for a week prior to admission. Neurological exam revealed left color desaturation with relative afferent pupillary defect, mild bilateral LE weakness, and sensory deficit to light touch, vibration, and temperature with pin sensory level at T10. Visual acuity was 20/20 in the right eye and 20/30 in the left eye. Fundoscopy exam was normal.

Laboratory data reveled leukocytosis at 17.88 K/uL, negative SARS-COV-2 nasopharyngeal PCR and infection screen. MRI of the orbits revealed enhancement involving the intraorbital segment of the left optic nerve (Figure 1; A-B). MRI of the cervical and thoracic spine revealed multifocal longitudinal areas of T2 hyperintense signal associated with gadolinium enhancement (Figure 1; C-F). CSF analysis revealed elevated protein (52 mg/dL) and WBC (215 cells/uL, 78% lymphocytes with no oligoclonal bands). Serum myelin oligodendrocyte glycoprotein (MOG) antibody was positive with a titer of 1:1000 (performed through fluorescence-activated cell sorting assay) while aquaporin-4 (AQP-4) antibody test was negative (Table 1). He had no family history of autoimmune disorders.

He was treated with IV methylprednisolone 1000 mg for 5 days. Due to minimal response on the third day of steroids, he was started on plasmapheresis for five sessions. He had modest improvement in his symptoms. He was discharged on an oral prednisone taper. In follow up visit two months later, he reported residual LE weakness and bladder dysfunction.

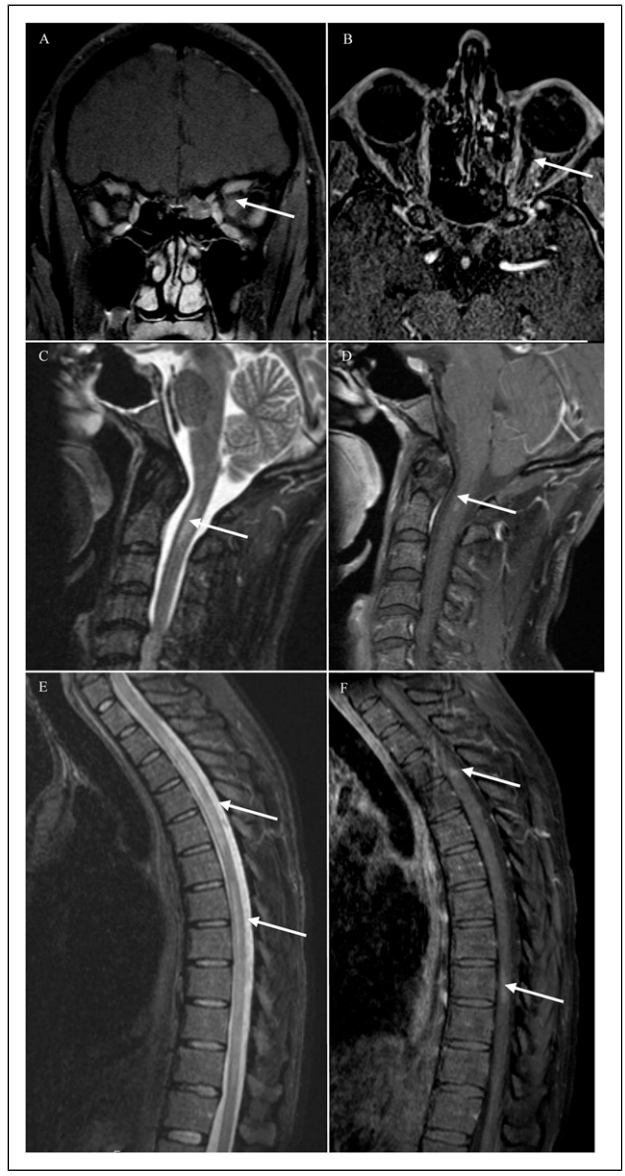

Figure 1. Legend: A and B) MRI of the orbits. T1-weighted post gadolinium sequences demonstrating gadolinium uptake in the left optic nerve consistent with optic neuritis (arrows) on coronal (A) and axial (B) sequences. C and D) MRI of the cervical spine. T2-weighted sagittal sequence (C) demonstrating increased T2 signal in the upper spinal cord (arrow) associated with gadolinium uptake (arrow) as demonstrated on T1-weighted post gadolinium sagittal sequence (D). E and F) MRI of the thoracic spine. T2-weighted sagittal sequence demonstrating multifocal patchy T2 signal abnormalities extending from T2-T5 level (arrow) and another from T7-T11 level (arrow) (E) associated with abnormal patchy contrast enhancement most pronounced at T9 (arrow) on T1-weighted post gadolinium sagittal sequence (F).

Case 2

A 39-year-old woman with a history of obstructive sleep apnea and diabetes type 2 presented to our hospital in April 2021 with progressive LE weakness and numbness up to the mid-thoracic region that started about 7 days after receiving the first dose of the Pfizer vaccine. She noted early vaccine associated side effects of dizziness within 5 minutes of receiving her vaccine. Her weakness and numbness slowly progressed. She received her second vaccination three weeks later and her symptoms acutely worsened, prompting her to come to the hospital. Neurological examination revealed pin sensory level at T4 and mild bilateral LE weakness. MRI of the spine showed an expansile enhancing lesion extending from T2-T3 associated with gadolinium enhancement consistent with ATM (Figure 2; G, H). MRI of the brain with and without contrast was normal. CSF analysis revealed elevated protein (53 mg/dL), WBC 21 cells/uL (96% lymphocytes) and was positive for unique oligoclonal bands. Serum testing for MOG and AQP-4 antibodies were negative. She had no family history of autoimmune disorders (Table 1).

She was treated with IV methylprednisolone 1000 mg for 5 days and reported improvement in strength with mild residual sensory symptoms. She returned a month later with acute onset right sided numbness, diplopia, and vertigo. Repeat brain MRI showed a questionable punctate focus of contrast enhancement in the right posterior midbrain. This lesion was not a typical MS lesion. There was no

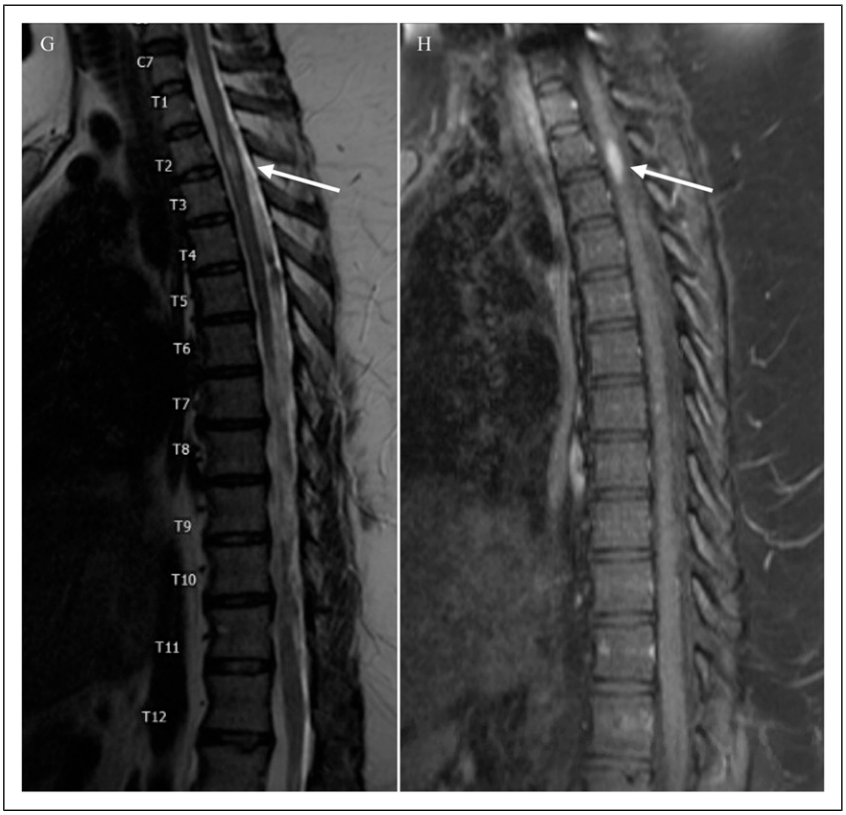

Figure 2. Legend: G and H) MRI of the thoracic spine. T2-weighted sagittal sequence demonstrating focal expansile area of T2 signal abnormality at T2-T3 level (G) associated with gadolinium enhancement (arrow) on T1-weighted post gadolinium sagittal sequence (H).

enhancement in the white matter of the brain and spinal imaging was stable. She received another course of IV methylprednisolone and her symptoms improved. Due to an unclear etiology of this event, she was not given a diagnosis of MS.

Discussion

We describe two cases of acute CNS demyelinating syndromes probably associated with both variations of the SARS-CoV-2 mRNA vaccines. In both cases, the onset of acute neurological symptoms occurred within 1 week of receiving the first dose of the vaccine. There was improvement with corticosteroid therapy, but the patients still had residual symptoms. The temporal association of CNS inflammatory syndromes after the administration of vaccines is not unique to SARS-CoV-2 vaccines. In a review of post-vaccination CNS demyelinating syndromes, the influenza and HPV vaccines were most commonly involved and the mean onset of symptoms was 14.2 days after vaccination.[1] Our patients developed symptoms in an earlier time frame, potentially due to prior SARS-CoV-2 exposure. Nonetheless, our cases fit well within the usual time frame (<6 weeks from vaccination to onset of adverse event) to fit a causality label as "probable".[7]

Interestingly, a high proportion of the previously reported cases from the Influenza and HPV vaccines had either optic neuritis or transverse myelitis, similar to our patients. Over half of reported demyelinating events after vaccines are optic neuritis.[1] The proposed pathogenesis of CNS demyelinating syndromes after vaccines includes molecular mimicry, epitope spreading, bystander activation, polyclonal activation, effects of adjuvants, and depends on vaccine-related factors like type, dose, and route of administration.[6,8] The adjuvanticity of SARS-CoV-2 vaccines are novel in that they involve Toll-like Receptor (TLR) 7 and 9 agonism. Several immune-mediated disorders have been linked to altered nucleic acid metabolism and processing that have stimulated TLR-7/9 experimentally. This mechanism of vaccine induced stimulation of the immune system is different from prior vaccines and represents a new vaccine strategy for diseases, however, it also uses a common pathogenic pathway that could cause immune mediated disorders.[5]

Additionally, we report a patient who developed MOGAD after the Moderna vaccine. MOGAD has been reported in a few post-vaccination cases,[9] but not, to the best of our knowledge, from SARS-CoV-2 vaccines yet. There are multiple reports of new onset MOGAD occurring in close temporal association with the SARS-CoV-2 infection and includes cases of optic neuritis, myelitis, vasculopathy, and

Table 1. Summary of demographic and clinical data from two subjects with CNS demyelinating events probably associated with SARS-CoV-2 mRNA vaccines.

	Case 1	Case 2
Patient profile	38-year-old man	39-year-old woman
Diagnosis	MOGAD after Moderna SARS-CoV-2 vaccine	Transverse myelitis after Pfizer SARS-CoV-2 vaccine
Clinical Presentation	Left eye blurred vision, lower extremity weakness and paresthesia, bowel/urinary dysfunction	Lower extremity weakness and numbness below the mid-thoracic region
Symptom onset	3 days after vaccination	7 days after vaccination
CSF Results	WBC: 215 cells/uL (78% lymphocytes, 12% eosinophils, 7% monocytes, and 3% basophils) Protein: 52 mg/dL Glucose: 72 mg/dL RBC: 3 cells/uL Oligoclonal bands: absent IgG Index: 0.49	WBC: 21 cells/uL (96% lymphocytes, 4% monocytes) Protein: 53 mg/dL Glucose: 86 mg/dL RBC: 18 cells/uL Oligoclonal bands: present IgG Index: 2.74
MOG and aqp-4 test (serum)	MOG ab: positive, titer 1:1000 aqp-4 ab: negative	MOG ab: negative aqp-4 ab: negative
Negative studies	Serum: ANA multiplex screen, fungitell assay, HIV 1 and 2 antibodies, syphilis IgG/IgM antibodies, blood cultures CSF: Culture and direct smear, acid fast culture, fungus culture, VDRL, angiotensin converting enzyme, meningitis/ encephalitis panel, aquaporin-4 antibody, cytology (1.4 cc)	Serum: ANA multiplex screen, angiotensin-converting enzyme, Lyme antibody, vitamin B12, folate CSF: meningitis/encephalitis panel, autoimmune encephalopathy panel, culture, direct smear, cytology (8 cc)
Response to treatment	Improvement with high dose steroids and plasma exchange but did not return to baseline.	Improvement with two rounds of high dose steroids but did not return to baseline.

Summary of demographic and clinic data from two subjects with CNS demyelinating events probably associated with SARS-CoV-2 mRNA vaccines.

encephalitis.[10] Anti-MOG antibodies may not be pathogenic in the absence of a cell-mediated inflammatory response.[11] Therefore, a proposed mechanism is that vaccinations may enhance the pathogenicity by causing a cell-mediated immune response leading to a demyelinating event.

One patient had the second SARS-CoV-2 vaccine with subsequent acute worsening of symptoms. There are no guidelines on if individuals who have an acute demyelinating event after the vaccine should receive the second vaccination or booster. A recent article reported a survey of 438 participants with NMO, MOG or TM, and 16.7% had new or worsening neurological symptoms after vaccination. The majority had sensory symptoms and only 17.8% of those participants required medical treatment.[12] Due to the relatively low rate of new or worsening symptoms, and with most symptoms being of mild severity, SARS-CoV-2 vaccinations could be considered in these patients. In our case, the patient had worsening weakness and paresthesias. The decision to vaccinate again in cases of demyelination after SARS-CoV-2 vaccines should be decided on a case-by-case basis and discussed with the patient.

Although we cannot prove causality, the temporal relationship between vaccines and demyelinating events has been well documented as mentioned above. Similar autoimmune events after vaccines have been reported regarding a Guillain–Barre Syndrome (GBS) outbreak after the "swine flu" vaccination, ATM after the polio vaccine, and autoimmune thrombocytopenia after the measles–mumps–rubella vaccine. Animal models have additionally shown that autoantibodies can be produced after immunization.[13]

While the occurrence of such events is non-negligible, the overall risk is low and estimated at 0.1%.[1] The most common neurological symptoms after SARS-CoV-2 vaccines include dizziness, headache, muscle spasms, myalgia, and paresthesias.[14] Severe SARS-CoV-2 infection has been associated with demyelinating neurological events with the proposed mechanism of activating toll-like receptors leading to a cytokine storm, along with generating autoantibodies. Several cases of acute demyelinating syndromes have been reported in patients with SARS-CoV-2 infection, and these outnumber the few post-vaccination cases we identified.[15] MOG antibodies have also been associated with various neurological symptoms from SARS-CoV-2 infection, including optic neuritis, myelitis, vasculopathy, and encephalitis.[10] This leads us to conclude that the overall benefits of vaccination outweigh the marginal risk of demyelinating events. However, new onset demyelinating events can still occur, and now both NMO and MOGAD cases have been reported after SARS-CoV-2 mRNA vaccines. New onset demyelinating events may be from the novel adjuvanticity of SARS-CoV-2 vaccines involving TLR 7/9 agonism, that has been linked experimentally to several immune-mediated disorders. These patients may also have an innate predisposition to developing a CNS inflammatory disorder.

Providers should be aware of these potential neurological complications of the SARS-CoV-2 mRNA vaccines. Larger prospective studies are needed to further evaluate the

relationship between SARS-CoV-2 mRNA vaccines and new onset demyelination. Through an increased understanding of the immune response to vaccines, and a better understanding at who may be at risk, safer and potentially more personalized vaccine strategies may be developed in the future.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Gyang has received personal compensation for consultation with Genentech, EMD Serono, and Greenwich Biosciences, Inc.

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Informed Consent

Written informed consent by both patients for their information and images to be published was obtained.

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