Diagnostic and treatment challenges in MRI-negative myelitis associated with MOG antibody: A case report and literature review

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ABSTRACT

Background:
MRI negative cases of MOG associated inflammatory myelopathy, optic neuritis, and encephalitis have been reported in the literature. Negative MRI can lead to diagnostic uncertainties and treatment delay.

Objectives:
We report the case of a patient presenting with a subacute myelopathy and negative spinal MRI who tested positive for serum MOG antibodies and showed improvement with immunotherapy.

Conclusion:
MOGAD may present with atypical patterns or negative MRIs, leading to diagnostic uncertainties. A negative spinal cord MRI in patients with a history and examination consistent with an inflammatory myelopathy should not preclude investigation of MOG antibodies and initiation of early empirical immunotherapy.

Introduction

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a spectrum of autoimmune-mediated syndromes presenting as monophasic or relapsing inflammatory attacks of the CNS. It typically manifests as optic neuritis and/or myelitis in the adult population, but clinical phenotypes also include acute disseminated encephalomyelitis (ADEM); cerebral cortical encephalitis (CCE); and brainstem syndromes.[1,2]

When the spinal cord is affected, as with any myelitis, patients may experience weakness, a sensory level, bladder/bowel dysfunction, and spasticity. A minority can present with an acute flaccid myelitis instead of the more common upper motor neuron syndrome. In contrast to enterovirus D68–associated acute flaccid myelitis, MOG-associated cases often responded well to short-term immunotherapy.[3]

A viral prodrome is more commonly in MOG-associated myelitis than with other CNS demyelinating diseases. Characteristic imaging features can also be suggestive of this condition. MRI may reveal longitudinally extensive lesions (three or more spinal segments) and/or short segment lesions.[1,2] The absence of gadolinium enhancement and the restriction of lesions to gray matter are typical, distinguishing it from multiple sclerosis (MS) or AQP4-positive neuromyelitis optica spectrum disorder (NMOSD).[3] It can affect the spinal cord anywhere from the medulla to the conus medullaris. In fact, involvement of the conus medullaris is more common in MOGAD than in other inflammatory disorders.[3]

Patients who have MOG attacks typically recover well. It is not unusual for a patient with MOGAD to present with complete paralysis due to thoracic myelitis and return to the clinic 3 to 6 months later with the ability to walk again, often without assistance.[1] Nevertheless, among all MOG-associated disorder phenotypes, myelitis is the most likely to cause permanent disability.[3]

Recovery from myelitis often leads to the normalization of the spinal cord, making it difficult to visualize old lesions on subsequent scans. This has led to the notion that MOGAD may be a cause of "MRI negative myelitis".[1,4] However, cases of MOGAD without evidence of signal abnormalities on MRI have also been reported during early stages of this condition, which has led to diagnostic uncertainties and treatment delay.[5,6]

The recommended MOG antibody test is a cell-based assay, and since 2018, its use has become widespread. However, like other techniques for assessing this antibody (e.g., ELISA), it has a high rate of false-positive results. In some laboratories, only IgG1 antibodies to MOG are considered positive, whereas in others, IgG is deemed positive if it exceeds a specific titer, increasing its specificity.[1] More frequently than not, lower MOG antibody levels should prompt consideration of other conditions.

This report describes a patient with a clinical presentation of an inflammatory myelopathy with negative MRI results in the acute and subacute setting, yet positive serology for MOG-IgG antibodies at a low titer, illustrating the diagnostic challenges in MOGAD and the potential for low titers to represent true positives in the right clinical scenario.

Case Report

Written consent was obtained from our patient for this case report. A 47-year-old female with a medical history of thyroid cancer in remission (post resection) and a prior gastric sleeve surgery (2 years prior) presented to our institution with a 10-day history of subacute asymmetric bilateral lower extremity paresthesia and weakness with urinary retention and saddle anesthesia. At another hospital on day 5 of symptoms, MRIs of the **cervical** and **thoracic spine** were reportedly **negative**, and she was treated with 500 mg of IV **methylprednisolone** for three doses, but the steroid course was **terminated early** due to an "inconclusive" workup. She was discharged with a

suspected diagnosis of **functional neurologic disorder (FND).**

Over the next 5 days, her deficits progressively worsened, eventually leading to **flaccid paraplegia.** At presentation to our institution, her physical exam revealed **paraplegia** with **loss of all sensory modalities** below the T11 dermatome and increased reflexes in her lower extremities. The patient had received her first dose of the **Pfizer-BioNTech COVID-19 vaccine 14 days prior** to symptom onset.

Upon admission, her **CSF analysis** showed: **23 WBC/uL** (normal <5), **10,752 RBC/uL** (none), **48 mg/dl protein** (normal 15-45), and **62 mg/dl glucose** (normal 40-75). **Oligoclonal bands (OCBs)** were not tested initially, but a follow-up lumbar puncture (3 months later) showed no elevation of **free kappa light chains** (0.016, range <0.1000).

Extensive **infectious workup** (syphilis, HIV, hepatitis, COVID-19, bacterial and fungal CSF cultures, CSF viral PCR [enterovirus, herpes simplex virus, West Nile]) were all negative. Metabolic labs, including vitamin B12 (1369 pg/ml, normal range 180-914), folate (13.4 ng/ml, normal range >3.9), vitamin E (10 mg/L, normal range 5.5-17), and copper (1.09 mcg/ml, normal range 0.75-1.45) were within normal limits. **Rheumatologic labs** (ANA, anti-SSA/SSB, rheumatoid factor, aquaporin-4 antibodies, etc.) were also negative. Sedimentation rate (5 mm/hr [range 0-20]) and C-reactive protein (0.04 mg/dl [range <1.0]) were not elevated.

The exception to her negative workup was a positive serum MOG IgG antibody (Myelin Oligodendrocyte Glycoprotein (MOG-IgG1) Fluorescence-Activated Cell Sorting (FACS) Assay, Serum, Mayo Clinic Laboratories) with a titer of 1:40 (reference range <1:20).

Initial **MRI of the cervical, thoracic, and lumbar spine** (Day 10 since the onset of symptoms) was **normal. Brain MRI** showed **non-specific FLAIR hyperintensities** in the **bifrontal cortex** (Figure 1). A **spinal angiogram** was normal ruling out a vascular etiology. **Electromyography (EMG)** showed normal motor and sensory peripheral nerve function. A repeat cervicothoracic MRI was unrevealing. She had no previous history consistent with optic neuritis, thus evoked potentials of the optic nerves and optical coherence tomography were not performed. A **second CSF analysis** (Day 16 since the onset of symptoms) showed **1 WBC/uL, 31 mg/dl protein**, and **55 mg/dl glucose.**

Despite the diagnostic uncertainty, the patient was started on **1000 mg IV methylprednisolone** daily for five days. Due to the severity of her symptoms, she also underwent **five cycles of plasmapheresis** with minimal improvement by the time of hospital dismissal to inpatient rehabilitation.

At her two-week outpatient follow-up, she showed **mild improvement** in her motor and sensory deficits. Follow-up MOG-IgG a month later **remained positive** at a titer of 1:20. **Two months later**, the patient developed **left arm weakness** and worsening **left leg weakness**, prompting further treatment with **IV methylprednisolone** and **intravenous immunoglobulin (IVIG).** MRIs of the cervical and thoracic spinal cord were again unrevealing. She was further treated with two doses of rituximab followed by monthly IVIG for maintenance immunotherapy. At the **six-month follow-up**, she was able to walk with a **walker** and had resolved sensory and urinary symptoms. A **one-year follow-up MRI** continued to show no spinal cord lesions.

Fourteen months post-presentation, she was ambulatory without assistance but had mild residual **left leg weakness** (4/5 strength in left knee flexion, dorsiflexion, and plantar flexion). The patient moved out of town and was evaluated at a different institution for a suspected **myelopathy relapse** a month later. A **thoracic spine MRI** reported a **long-segment T2 hyperintensity** spanning **5 levels (T7-T11)** with **questionable patchy enhancement**, though these images were not available for our review.

Discussion

We present a case of MOG antibody-associated myelitis with MRI-negative findings in both the acute and subacute phases, along with a low positive antibody titer, both of which pose significant diagnostic and therapeutic challenges.

While MRI is an essential diagnostic tool in the workup of inflammatory CNS conditions, our case highlights the growing recognition of **MRI-negative MOGAD**, a phenomenon reported in the literature. A retrospective study at Mayo Clinic found that 10% (7 out of 73 patients) of patients with myelitis associated with MOG antibody had normal MRIs within six weeks of symptom onset. Three out of 7 patients developed myelitic lesions when MRIs were repeated after 6 to 26 days. The MOG-IgG titer in these patients ranged from 100-10,000.[4] In our patient, normal MRIs of the spinal cord were seen on follow up scans up to 1 year from her initial presentation and her MOG titers did not exceed 1:40.

The absence of spinal cord abnormalities on MRI in patients who otherwise have a clinical presentation consistent with an inflammatory myelopathy is atypical. The fact that a substantial proportion of patients can have negative CSF findings further complicates this situation, putting this patient population at risk of being misdiagnosed and at risk of treatment delays. This was exemplified by our patient, who, despite the significant deficits, was discharged from an outside facility with a suspected diagnosis of FND. Negative MRIs are also common in patients with other autoimmune conditions such as anti-NMDA receptor autoimmune encephalitis and glutamic acid decarboxylase (GAD) antibody spectrum disorders.[7] Myelopathies with a negative MRI encompass a broad differential diagnosis that should not be ignored (Table 1). Early identification of these etiologies allows a prompt and targeted medical treatment, potentially leading to a better prognosis.

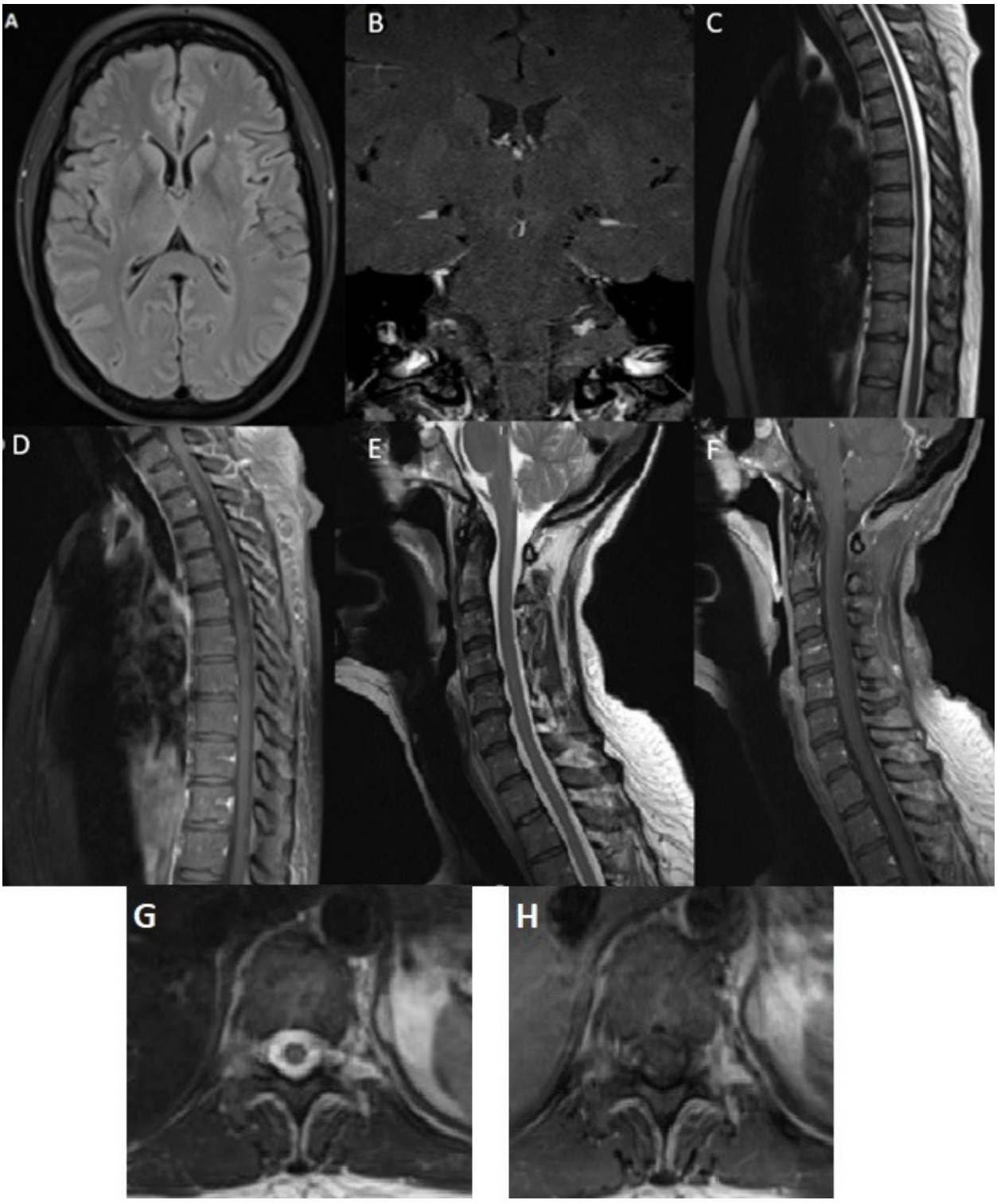

Figure 1. 3T MRIs. A) MRI brain w/wo contrast, T2 FLAIR sequence showing several punctate FLAIR hyperintense subcortical bifrontal white matter foci (blue arrows). B) Coronal T1 post-contrast brain MRI with no enhancing lesions. C and D) (C. Sagittal T2, D. Sagittal T1 post-contrast) MRI of the T-spine without cord signal abnormalities or enhancing lesions. E and F) (E. Sagittal T2 and F. Sagittal T1 post-contrast) MRI of the C-spine without cord signal abnormalities or enhancing lesions. G and H) (G. Axial T2 H. axial T1 post-contrast) Axial MRIs of the T-spine at T11 showing no obvious lesions, corresponding to the sensory level on patient´s neurologic examination.

Table 1. Differential diagnosis in negative-MRI myelopathies.

Myelopathy Subtype
Nutritional
B12 deficiency
Copper deficiency
Vitamin E deficiency
Vascular
Spinal arteriovenous malformation/fistula
Spinal cord infarcts
CNS vasculitis
Infectious
Viral myelitis
Covid-19, Zoster, Epstein-Barr, herpes simplex, cytomegalovirus, adenovirus, enterovirus, coxsackie B virus, AIDS, HIV, HTLV I or II
Fungal Infections
Cryptococcus, aspergillus
Post infectious
Autoimmune
Systemic lupus erythematosus
Sjogren's syndrome
Stiff person syndrome/GAD spectrum disorders
Glial fibrillary acidic protein (GFAP) - related disorders
Anti-glycine receptor-associated myelopathy
MOGAD
Neoplastic
Intravascular B cell lymphoma
Paraneoplastic encephalomyelitis
Anti-hu and anti-CV2/CRMP5
Structural lesions
Parasagittal meningioma
Arnold-Chiari malformation
Tethered Cord

The MOG antibody cell-based assay is highly specific when the titer is greater than 1:100; lower titers may be associated with false positives.[1] As an aside note, the serum sample for the first MOG ab test in our patient was collected after she had completed five daily doses of 1000 mg of methylprednisolone. Although it may have been too soon, it is unclear whether this could have affected the titer result. Nevertheless, the low antibody titer in this case underscores the need for careful consideration of clinical presentation, disease progression, and patient recovery, rather than relying solely on titers or MRI results for diagnosis. In the presence of a phenotype suggestive of MOGAD, even a low positive titer should prompt consideration of steroids, as this approach represents an overall safe form of acute immunotherapy.

Our patient received the first dose of the Pfizer-BioNTech COVID-19 vaccine 14 days prior to the onset of her neurological symptoms. The number of case reports of inflammatory myelitis following COVID-19 infection is similar to that following COVID-19 vaccination.[8,9] While these cases typically show positive MRI findings, at least 7 cases of an MRI-negative myelopathy associated with COVID-19 infection have been reported.[9,10] To date, no cases of MRI negative myelopathies have been reported in association with a COVID-19 vaccine.

For patients with suspected vaccine-related neurologic complications, it is crucial to select candidates for MOG antibody testing carefully. Testing should be reserved for cases presenting with a well-described MOGAD phenotype to minimize the risk of false positives, particularly because the prevalence of low-titer MOG antibodies in the general healthy population is not well established. The temporal profile of our patient's deficits were typical of an inflammatory myelopathy.

Despite the low positive titer in our patient, the clinical features, the natural course of the disease, the particularly good recovery after her initial attack, and the recurrent attacks after 2 and 15 months of her initial presentation, are strongly suggestive of the titer being a true positive result.

In conclusion, a negative spinal cord MRI in a clinical scenario highly suggestive of an inflammatory myelopathy should not discourage physicians from testing for MOG antibodies and considering early empirical immunotherapy, as prompt treatment may improve the chances of a favorable prognosis. This case highlights the need for further research into the significance of low MOG antibody titers and MRI-negative presentations. More studies are needed to establish clear diagnostic thresholds and treatment protocols for these atypical presentations.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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