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Frequency and Characteristics of MRI-Negative Myelitis Associated with MOG Autoantibodies

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Abstract

Background: Myelitis accompanied by a negative spinal cord MRI may lead to diagnostic uncertainty.

Objective and Methods: We retrospectively investigated the frequency of MRI-negative myelitis (performed <6 weeks from onset) in Mayo Clinic patients with myelin oligodendrocyte glycoprotein (MOG)-IgG-associated myelitis (2000-2019).

Results: The initial spinal cord MRI was negative in 7/73 (10%) patients, despite severe acute disability (median EDSS, 7 [range, 4.5-8]); myelitis symptoms/signs were frequent (paraparesis, neurogenic bladder, sensory level, Lhermitte's phenomenon). Myelitis lesions became overt at follow-up MRI in 3 patients.

Conclusions: A negative spinal cord MRI should not dissuade from MOG-IgG testing in patients with acute/subacute myelitis.

Keywords

Demyelination; MRI; Neuromyelitis optica (NMO); T2 lesions; Myelin oligodendrocyte glycoprotein; Acute transverse myelitis

Introduction

Myelitis is a common manifestation of myelin oligodendrocyte glycoprotein (MOG)-IgG-associated disorder (MOGAD) that typically results in acute severe disability, although

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Ethical approval

The study was approved by the Institutional Review Board of the Mayo Clinic.

Informed consent

All patients consented to the use of their medical records for research.

recovery is often favorable with prompt immunotherapy.(1) Spinal cord MRI may show T2-hyperintense longitudinally-extensive (3 vertebral-body segments), “short” lesions, or both, that are sometimes gray matter-restricted in a linear configuration on sagittal images and/or “H”-shaped axially.(1) However, MOG-IgG-associated myelitis with negative spinal cord MRI has been reported, which could lead to diagnostic uncertainty and treatment delay.(2, 3) In this paper we investigated the frequency and characteristics of patients with MRI-negative myelitis associated to MOG-IgG.

Methods

Patients

We retrospectively identified MOGAD patients seen at Mayo Clinic (January 1, 2000-August 31, 2019) with: 1) First clinical myelitis; 2) spine MRI obtained acutely (6 weeks from myelitis onset); and 2) no documented spinal cord T2-abnormalities on radiology reports. MOG-IgG positivity was confirmed by fluorescence-activated-cell-sorting live cell-based-assay, as previously reported.(1) We excluded four patients with unavailable MRI and one patient with concomitant MRI brainstem abnormalities. Forty-nine patients were previously reported.(1)

MRI-negative myelitis

Two neurologists (E.S.; E.P.F.) reviewed medical records to confirm symptoms/signs exclusively explainable by myelopathy in MRI-negative patients; consensus was reached after discussion in case of disagreement.

Statistics

Wilcoxon-rank-sum and Fisher’s exact tests were used for comparisons as appropriate (JMP Pro 14.1.0).

Results

Among 73 MOGAD patients at first myelitis episode, the initial spinal cord MRI was interpreted as normal in 7 (10%). When comparing these patients to those with abnormal MRI, there was no statistically significant difference in the percentage of patients treated with immunotherapy prior to MRI between the two groups (2/7 [29%] vs 10/65 [15%]; $p=0.3$), while the interval (days) from myelitis onset to the first spine MRI was longer in those with normal MRI (median [range]: 10 [5-30] vs 4.5 [0-28]; $p=0.01$).

Patients’ characteristics

The clinical presentations of the seven patients with MRI-negative myelitis are summarized in Table 1. All tested negative for aquaporin-4-IgG.

Median age at myelitis was 45 years (range, 35-80), 3 (43%) were female, and all were Caucasian. The myelitis occurred at MOGAD presentation in all. Myelitis symptoms/signs included: sensory disturbances, 7; bowel/bladder dysfunction, 7 (requiring catheterization in 5); weakness, 6; upper motor neuron signs (spasticity, hyperreflexia, or positive Babinski),

4; trunk sensory level, 3; and Lhermitte's phenomenon, 3. One patient had an isolated myelitis while six had other neurologic manifestations (optic neuritis, 4; headache, 4; encephalopathy, 2). Three had viral-like prodromes. Median expanded disability status scale (EDSS)-score at nadir was 7 (range, 4.5-8). Median MOG-IgG titer was 100 (range, 100-10,000). Cerebrospinal fluid analysis, available in six, revealed pleocytosis (5/6; median white cell count, 70/ μ L [range, 28-161]) and absence of oligoclonal bands (6/6). Somatosensory evoked potentials were obtained in two patients revealing conduction delay localizable to the spinal cord in both. Two patients had normal nerve conduction/electromyography while one had conduction block and denervation changes concomitant with a spastic paraparesis confirming a myelo-neuropathy.

On MRI re-review (E.S.; K.N.K.; E.P.F.), one patient showed a subtle focal area of T2-hyperintensity on axial image (Figure 1-A). Six patients underwent spine MRI with gadolinium but none had abnormal enhancement. Myelitis lesions became overt in 3 of 6 patients who underwent follow-up MRI after a median of 6 days (range, 6-26; Figure 1-D). Brain MRI, available in five, showed concomitant abnormalities in one (Figure 1-E).

All patients received acute immunotherapy (corticosteroids, 7; intravenous immunoglobulin, 2; plasmapheresis, 2) with improvement. Initial diagnoses assigned in the setting of MRI-negative myelitis included: bacterial/viral encephalitis, 2; Guillain-Barre syndrome, 1; and amyotrophic lateral sclerosis, 1. Four patients had typical MOGAD relapses including optic neuritis, encephalitis and myelitis.

Discussion

In this study of MOGAD patients at first episode of clinical myelitis, the initial spinal cord MRI was interpreted as negative in 10%, despite severe myelitis manifestations. A negative acute MRI should not dissuade from MOG-IgG testing with a subacute myelopathy.

A prior study reported a negative MRI in 1 of 28 patients (4%) with MOG-IgG-associated myelitis, not focusing on the first myelitis episode.(4) Although typically not expected with other well-defined acute/sub-acute myelitis (e.g., aquaporin-4-IgG-associated myelitis), an initially negative MRI may occur in idiopathic transverse myelitis (5%),(5) acute flaccid myelitis (5%),(6) and paraneoplastic myelopathies (35%).(7) It is also common with glycine receptor and glutamic acid decarboxylase-65 antibodies but the exact frequency is unknown. (8) Faint T2-hyperintensity is typical of glial fibrillary acidic protein (GFAP)-IgG-associated myelitis and generally has accompanying brain abnormalities (e.g. radial perivascular enhancement).(9) Lastly, an initially negative MRI is seen in up to 24% of cases of spinal cord infarction.(10) Spinal cord infarct would usually have a more hyperacute presentation (nadir <4-12 hours), absence of cerebrospinal fluid pleocytosis, lack of brain/optic nerve involvement, and no viral-like prodrome.(1, 10)

The reason why some patients with MOGAD myelitis have negative MRI is uncertain but could relate to imaging timing (late imaging missing a transient lesion or early imaging missing an evolving lesion),(11) insensitivity of MRI to the detection of MOG-IgG-associated inflammation, a spinal meningitis without myelitis, or a functional disturbance

mediated by MOG-IgG binding. The longer time to MRI in the imaging-negative group could be explained by those patients having a more slowly evolving clinical course or statistical chance in the setting of small numbers.

Patients with MOGAD myelitis may show questionable T2-hyperintensities on MRI that are in contrast to the severity of myelitis symptoms or can be interpreted as physiological variants (e.g., a faint linear T2-hyperintense on sagittal images may be difficult to discern from a prominent central canal). In uncertain cases, careful evaluation of axial images or repeat MRI after days/weeks may confirm the myelitis (Figure 1). Somatosensory evoked potentials may also help confirm the spinal cord localization, further justifying MOG-IgG testing. The abnormal electromyographic findings in one patient coexisting with a spastic paraparesis suggested a myeloradiculitis which is recognized to occur with MOGAD.(12)

Our study is limited by the retrospective nature and potential referral bias (atypical cases might be over-represented at our tertiary care center). One patient had clinical/MRI-evidence of brain involvement that could have contributed to their symptoms. However, the constellation of clinical findings (e.g., urinary retention, lower limb numbness, weakness, and spasticity/hyperreflexia), and sparing of the brainstem on brain MRI strongly supported a myelopathy.

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Declaration of Conflicting Interests

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Figure 1 - Representative examples of negative spinal cord MRI in patients with MOG-IgG-associated myelitis

The left part of the figure shows cervical (top rows) and thoracic (bottom rows) T2-weighted spinal cord MRI images in four patients with MRI-negative MOG-IgG associated myelitis. In the first patient (A), despite a normal aspect of spinal cord parenchyma on sagittal images (A1, A3), a subtle focal area of T2-hyperintensity can be noted on axial images in the cervical spinal cord (A2, arrowhead), that was likely considered insufficient to justify symptoms severity (EDSS: 4.5) during the initial MRI review. In the second (B) and third (C) examples, spinal cord MRIs appear normal despite an EDSS of 7 and 4.5, respectively. In the fourth patient (D) with encephalomyelitis, the first (D1-D4) and second (not shown) spinal cord MRI were negative despite an EDSS of 7.5. The patient was empirically started on intravenous methylprednisolone and plasma exchange with improvement and a third MRI obtained 22 days later showed diffuse T2-hyperintense lesions in the spinal cord on both

sagittal (D5, D7; arrows) and axial (D6, D8) images. In the right part of the figure (E), axial brain MRI images of the patient in B with fluid attenuated inversion recovery abnormalities in the corona radiata (E1), and mesial left thalamus (E2) that are unlikely to contribute to the myelopathic symptoms/signs.

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Table 1 –

Clinical presentations in 7 patients with MRI-negative myelitis

N – Age/Sex	MOGAD clinical presentation with MRI-negative myelitis
1 – 35/F	<ul style="list-style-type: none"> • Subacute onset of mild bilateral visual deficit and retro-ocular pain. • About 1-2 weeks after developed urinary retention that reached maximum severity in 4 days requiring catheterization. She also complained of diffuse dysesthesia with allodynia and Lhermitte's phenomenon. EDSS at nadir: 4.5. • One week after was admitted for worsening of the retro-ocular headache. • Brain and spinal cord MRI were reported as unremarkable (Figure 1; A). • CSF: protein, 100 mg/dL; white blood cell count, 48/μL; no abnormal oligoclonal bands. • Serum MOG-IgG was positive and was started on intravenous methylprednisolone 1g/day for 5 days with improvement of vision and myelitis.
2 – 38/F	<ul style="list-style-type: none"> • New-onset low-back pain and pain with eye-movements. • Two weeks after developed acute urinary retention requiring catheterization, followed by headache, visual disturbances, and worsening weakness and numbness over lower back and legs. A Lhermitte's phenomenon was also present. Was hospitalized for trouble ambulating. EDSS at nadir: 6. • Brain and spine MRI were initially unremarkable, although abnormalities were noted on follow-up spine MRI, 6 days later). EMG/NCS was normal. • CSF: protein, 82 mg/dL; white blood cell count 48/μL; no abnormal oligoclonal bands. • Empirically started on IVIG (x5 days) with a working diagnosis of Guillain-Barre' syndrome with improvement of symptoms. • Serum MOG-IgG was later found to be positive.
3 – 45/F	<ul style="list-style-type: none"> • Admitted after 10 days of urinary retention (requiring catheterization) and constipation along with low-back pain, progressive lower extremities numbness and weakness, reduced appetite, nausea/vomiting, headache, and short-memory impairment. He was wheelchair-bound at nadir. EDSS at nadir: 7. • Spinal cord MRI was unremarkable (Figure 1; B). Brain MRI 3 days later showed multifocal T2-hyperintensities involving the left thalamus, temporal pole, and corona radiata (Figure 1; E). • CSF study reported to be consistent with bacterial meningitis (exact results not available). He was treated with both antibiotics and IVIG with minimal improvement, but with rehabilitation he was eventually able to walk without a gait aid two months later. • MOG-IgG were found to be positive on serum during subsequent relapses.
4 – 47/M	<ul style="list-style-type: none"> • Admitted for presumed viral meningoencephalitis after 10 days of worsening headache and urinary retention requiring indwelling catheterization. • CSF: protein, 81 mg/dL; white blood cell count 200/μL; no abnormal oligoclonal bands. • After two days, he developed confusion and bilateral leg weakness, culminating in paraplegia in <48 hours. A mid-thoracic sensory-level was present on examination. EDSS at nadir: 7.5. Brain and spinal cord MRI were negative. • Two days later he showed worsening mental status and overnight fever. Repeat brain and spinal cord MRI remained negative. • Further MRI imaging 6 days after onset revealed brain and spinal cord T2-abnormalities. MOG-IgG was positive on serum. • The patient was treated with intravenous methylprednisolone and PLEX with benefit.
5 – 46/M	<ul style="list-style-type: none"> • Woke up with bilateral visual disturbances (complete vision loss in one eye) and orbital pain a few days after a non-specific upper respiratory illness. Over 48 hours he developed bladder and bowel dysfunction with progressive bilateral lower limb numbness, pain, weakness and gait imbalance. EDSS at nadir: 4.5. • CSF: protein, 52 mg/dL; white blood cell count 161/μL; no abnormal oligoclonal bands. • Brain MRI revealed swelling of both optic nerves with enhancement, more prominent on the left. • Two weeks after symptom onset he was treated with intravenous methylprednisolone (x5 days) with improvement of both vision and myelopathic features. Cervical and thoracic spinal cord MRI obtained during steroid treatment was unremarkable (Figure 1; C) and repeat spinal cord MRI two weeks later was also normal. • MOG-IgG was subsequently found to be positive in serum.

N – Age/Sex	MOGAD clinical presentation with MRI-negative myelitis
6 – 45/M	<ul style="list-style-type: none"> Presented after 2 weeks of right-sided visual loss (blind within 72 hours), hand and chest numbness (T10 sensory level). Received intravenous methylprednisolone (x3 days) with mild improvement. After one week developed bilateral leg numbness, weakness, and urinary retention requiring catheterization. A Lhermitte's phenomenon was present. Brain MRI showed right optic nerve enhancement. Spinal cord MRI was unremarkable (Figure 1; D). He further worsened over 48 hours until he became paraplegic. EDSS at nadir: 7.5. Repeat spinal cord MRI remained negative. Somatosensory evoked potentials revealed impaired conduction velocity localizing to the spinal cord. EMG/NCS was unremarkable. CSF: protein, 63 mg/dL; white blood cell count 4/μL; no abnormal oligoclonal bands. MOG-IgG was positive in serum. He was treated with intravenous methylprednisolone (x3 days) and PLEX with improvement. Ten days later he relapsed with optic neuritis and myelitis. Spinal cord MRI revealed an enhancing longitudinally-extensive T2-hyperintense lesion that had accompanying gadolinium enhancement. Received PLEX with improvement.
7 – 80/M	<ul style="list-style-type: none"> Presented after 10 days of fluctuating fever, fatigue, urinary urgency and incontinence at night, and progressive spastic weakness in his legs to the point that he was unable to stand. There were no sensory symptoms although altered proprioception and pin-prick sensation was later noted on examination along with hyperreflexia and a unilateral upgoing plantar response. EDSS at nadir: 8. Spinal cord MRI was normal. EMG/NCS study showed conduction block and denervation changes; the possibility of amyotrophic lateral sclerosis was raised. He was empirically treated with oral corticosteroids for one month and subsequently underwent rehabilitation with clinical and EMG improvement. Somatosensory evoked potentials revealed impaired conduction velocity localizing to the spinal cord. MOG-IgG was subsequently found to be positive in serum.

Abbreviations: CSF = cerebrospinal fluid; EDSS = expanded disability status scale-score; EMG/NCS = electromyography/nerve conduction study; IVIG = intravenous immune globulins; MOG = myelin oligodendrocyte glycoprotein; MRI = magnetic resonance imaging; PLEX = plasma exchange.