

MRI-Negative Myelitis Associated With Myelin Oligodendrocyte Glycoprotein Antibody Spectrum Demyelinating Disease

Carlos A. Pérez, MD¹ , Stephanie Garcia-Tarodo, MD¹, and Regina Troxell, MD¹

Abstract

Myelin oligodendrocyte glycoprotein is expressed in the central nervous system on the surface of oligodendrocytes and is associated with a broad range of adult and pediatric demyelinating phenotypes. The entire spectrum of clinical and radiologic features of myelin oligodendrocyte glycoprotein antibody spectrum disorder remains to be fully elucidated. We describe the case of a 9-year-old boy with immune-mediated myelitis undetectable by conventional magnetic resonance imaging in the context of relapsing anti-myelin oligodendrocyte glycoprotein spectrum disorder. Despite the severe clinical presentation, his symptoms improved significantly following treatment with corticosteroids. Because timely diagnosis and treatment is imperative to prevent disease recurrence and reduce long-term morbidity, serum anti-myelin oligodendrocyte glycoprotein antibody testing should be considered in all children with acute demyelinating syndromes and unusual clinical presentations—including seizures—both at presentation and at follow-up.

Keywords

myelin oligodendrocyte glycoprotein antibody, children, seizures, relapsing, myelitis, acute demyelinating syndrome

Received November 27, 2018. Received revised January 20, 2019. Accepted for publication January 21, 2019.

The reported incidence of pediatric acquired demyelinating syndromes is widely variable, ranging from 0.66 to 1.66 per 100 000 children per year according to population-based studies.^{1,2} Serum anti-myelin oligodendrocyte glycoprotein antibodies are present in up to 50% of children with an acquired demyelinating syndrome³ and have been described in association with a range of phenotypic presentations, including acute disseminated encephalomyelitis, optic neuritis, and transverse myelitis.^{3,4} The initial assumption that myelin oligodendrocyte glycoprotein-associated disease typically follows a monophasic course with an excellent prognosis has been recently challenged by a number of reports that a significant number of patients continue to experience clinical relapses years after a first attack.⁴ This raises important questions regarding the need for long-term immunosuppressive therapy in this unique subgroup of patients. The spectrum of acquired demyelinating syndrome subtypes in patients with anti-myelin oligodendrocyte glycoprotein antibodies is characterized by a range of phenotypic central nervous system demyelinating syndromes, including acute disseminated encephalomyelitis, optic neuritis, and transverse myelitis.³ Because conventional imaging has

assumed a central role in the evaluation of these inflammatory disorders, it is a common error to equate the lack of magnetic resonance imaging (MRI) signal changes with lack of clinical disease or need for treatment.⁵ Therapeutic decision-making can be particularly cumbersome in patients with unusual clinical or radiological presentations.

Case Report

The patient first presented at the age of 7 years with a 1-month history of headaches and 2 days of worsening blurry vision with no known preceding infection. His neurologic examination was unremarkable with the exception of bilateral papilledema noted

¹ Division of Child and Adolescent Neurology, Department of Pediatrics, University of Texas Health Science Center at Houston, Houston, TX, USA

Corresponding Author:

Carlos A. Pérez, MD, Division of Child and Adolescent Neurology, Department of Pediatrics, University of Texas Health Science Center at Houston, 6410 Fannin Street, Suite 732, Houston, TX, USA.
Email: carlos.a.perez@uth.tmc.edu



on funduscopy and a visual acuity of less than 20/400 in both eyes. An MRI of the brain and orbits showed bilateral T2 hyperintense signals along the optic nerves that enhanced with contrast. The spine MRI and cerebral spinal fluid studies were negative. He was treated for optic neuritis with intravenous methylprednisolone 30 mg/kg daily for 5 days, after which he recovered fully.

Six months later, he presented after 2 episodes of generalized tonic-clonic seizures. There were no neurologic deficits at presentation. A head computed tomography and routine blood work were normal, and he was discharged home. An outpatient MRI of the brain and orbits with and without contrast and a prolonged electroencephalogram evaluation were both unremarkable and no antiepileptics were initiated. The patient returned to baseline without any interventions and experienced no further seizures. Up to this point, serum anti-myelin oligodendrocyte glycoprotein antibody testing was not performed due to a lack of widely available commercial testing and a general lack of knowledge regarding its clinical significance.

At his most recent admission 1 year later, he returned with a 2-month history of worsening fatigue, gait disturbance, lower extremity paresthesias, back pain, bladder incontinence, frequent headaches, and intermittent blurry vision. There was no preceding trauma or illness. Neurologic examination revealed 4/5 strength on left ankle inversion and dorsiflexion with left foot drop, bilateral lower extremity hyperreflexia, and bilateral non-sustained ankle clonus. There was no clear sensory level and his visual acuity was normal. Table 1 summarizes remarkable diagnostic data obtained, including a normal brain and entire spine MRI and positive for anti-myelin oligodendrocyte glycoprotein antibodies. All blood samples were collected prior to treatment.

A diagnosis of immune-mediated myelitis was considered based on clinical findings and evidence of spinal cord inflammation as demonstrated by cerebral spinal fluid pleocytosis. The patient was treated with a 5-day course of intravenous methylprednisolone 30 mg/kg daily followed by an 8-week tapering dose of oral steroids. Given his history of bilateral optic neuritis and seizures, rituximab therapy was initiated to prevent future attacks in the context of previous acute demyelinating events consistent with recurrent myelin oligodendrocyte glycoprotein antibody spectrum disease.

A brain and whole-spine MRI with and without contrast repeated 6 weeks later remained normal. At his 3-month clinic follow-up, repeat serum anti-myelin oligodendrocyte glycoprotein antibody titers were unchanged (1:100) but became negative at his 6- and 12-month follow-up visits and he has remained asymptomatic. Figure 1 summarizes a time line of clinical events, diagnostic workup, and working diagnosis at the time of each hospitalization.

Discussion

We describe the case of a 9-year-old boy with immune-mediated myelitis undetectable by conventional MRI in the context of relapsing anti-myelin oligodendrocyte glycoprotein antibody spectrum disorder. Rapid resolution of symptoms was

Table 1. Diagnostic Evaluation Obtained During the Patient's Most Recent Hospitalization.^a

Laboratory Studies	Value	Reference Range
Serum		
White blood cell (WBC) count, K/ μ L	8.3	4.5-13.5
Segmented neutrophils, %	60.8	34-64
Lymphocytes, %	26.9	27-47
Red blood cell (RBC) count, M/ μ L	4.87	4.20-5.40
Erythrocyte sedimentation rate (ESR), mm/h	19	0-10
Antinuclear antibodies (ANA) titer	1:40	Negative
Epstein-Barr virus (EBV) IgG, Antibody Index (AI)	>1.10 (positive)	Negative
Epstein-Barr virus (EBV) IgM, Antibody Index (AI)	Negative	Negative
Aquaporin-4 (AQP4) antibodies, ^b titer	Negative	Negative
Anti-MOG antibodies,^c titer	1:100	Negative
Cerebrospinal fluid (CSF)		
Protein, mg/dL	97	45-80
Glucose, mg/dL	24	15-45
RBC/ μ L	0	0
WBC/μL	7	0-5
Lymphocytes, %	93	40-80
Myelin basic protein, ng/mL	2.3	0-1.2
Oligoclonal bands	Negative	Negative
JC virus PCR	Negative	Negative
Other		
Test Name	Result	
Brain/orbits MRI ^d	Unremarkable	
Entire spine MRI ^d	Unremarkable	
Visual evoked potentials	Unremarkable	

Abbreviations: MRI, magnetic resonance imaging; MOG, myelin oligodendrocyte glycoprotein; RBC, red blood cell; WBC, white blood cell.

^aRemarkable studies are shown in bold.

^bIndirect immunofluorescence assay.

^cLive cell-based assay.

^dAll MRI studies were performed with and without contrast on a 3.0-T magnet. The brain MRI sequences obtained include axial fluid-attenuated inversion recovery (FLAIR); axial, coronal, and sagittal T1 and T2; axial diffusion-weighted imaging (DWI), and axial susceptibility-weighted imaging (SWI). The spinal cord MRI sequences obtained include sagittal and axial T2, as well as sagittal T1.

observed following corticosteroid therapy and long-term immunosuppression was initiated. As our period of follow-up is short, we cannot ascertain that a relapse will not occur in the future. However, the present case illustrates a few important radiological and clinical issues.

Detection of central nervous system white matter lesions continues to be a key supportive criterion for the diagnosis of acute demyelinating syndromes.^{6,7} Radiologic analyses of qualitative MRI features in patients with anti-myelin oligodendrocyte glycoprotein spectrum disease have shown a bimodal distribution of findings by age of onset, with younger children having a high prevalence of widespread

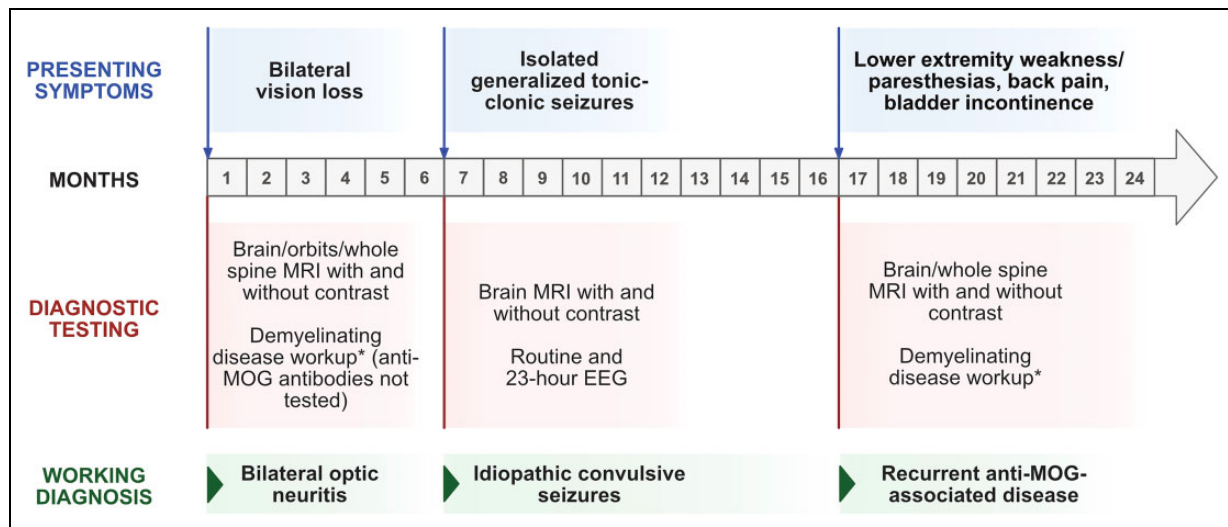


Figure 1. Time line of clinical events, diagnostic workup, and working diagnosis at the time of each hospitalization. Demyelinating disease workup: serum studies (vitamin B12 and folate levels, antinuclear antibody [ANA], erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), Lyme disease panel, thyroid function panel, anticardiolipin antibody testing, angiotensin converting (ACE), and anti-MOG antibody; CSF studies: glucose, protein, WBC and RBC counts, IgG index and oligoclonal bands, as well as aquaporin-4 antibodies.

acute disseminated encephalomyelitis–like lesions and longitudinally extensive transverse myelitis, and older patients presenting more frequently with optic neuritis and short transverse myelitis.⁸ Although myelopathy with normal conventional imaging is not uncommon,⁹ recent reports have drawn attention to the diagnostic conundrum of MRI-negative autoimmune diseases.¹⁰

Although conventional MRI biomarkers are integral parts of current diagnostic criteria for acquired demyelinating syndrome, the clinical manifestations and MRI findings can be dissociated in a small proportion of patients.¹⁰ Awareness of this clinico-radiological paradox should be extended across the entire spectrum of acquired demyelinating syndromes, including anti-myelin oligodendrocyte glycoprotein antibody spectrum disorder, and should be carefully considered as its clinical and radiologic features continue to be defined.

Because MRI interpretation requires analysis in the clinical context and knowledge of the timing of the scan,⁹ it is possible that the timing of image acquisition relative to the onset of symptoms in our patient may explain the lack of visible spinal cord pathology. Alternatively, or perhaps co-contributory, our patient may have experienced a clinical relapse due to a diffuse underlying process not visible on conventional MRI. Although repeat spinal cord imaging after 1 to 3 weeks may reveal intramedullary lesions in some cases of acute myelitis,⁹ there is little evidence at this time to suggest that follow-up imaging in the subacute phase of the illness would be abnormal, but this should be further elucidated, especially in cases of anti-myelin oligodendrocyte glycoprotein antibody spectrum disorder. Because the risks associated with sedation and general anesthesia did not outweigh the benefits of repeat imaging at the time of our patient's hospitalization, no repeat imaging was obtained at the time of hospitalization.

Newer advanced MRI techniques such as diffusion tensor imaging have been demonstrated to provide more sensitive detection of microscopic changes in normal-appearing white matter in patients with multiple sclerosis (MS) and neuromyelitis optica spectrum disorder.^{5,10-12} Similarly, large prospective studies should assess the clinical utility of nonconventional MRI sequencing in myelin oligodendrocyte glycoprotein antibody spectrum disease, to determine whether occult normal-appearing white matter is also present in this subgroup of patients.

From a clinical standpoint, the relationship between anti-myelin oligodendrocyte glycoprotein antibody titers and clinical disease activity remains an area of active investigation. Although persisting reactivity to anti-myelin oligodendrocyte glycoprotein antibody is associated with a recurrent non-MS disease course,^{3,4} the clinical relevance of anti-myelin oligodendrocyte glycoprotein titers based on current literature remains unclear. In addition, seizures have been increasingly described in patients with anti-myelin oligodendrocyte glycoprotein syndromes,⁴ which suggests that seizures may be a clinical manifestation of myelin oligodendrocyte glycoprotein-associated disease in addition to the commonly described acquired demyelinating syndromes.¹³ Therefore, it is possible that testing for anti-myelin oligodendrocyte glycoprotein antibodies at the time of our patient's seizure may have yielded diagnostic results and prompted earlier initiation of treatment. Nonetheless, this assumption is purely speculative and will require validation in future studies. In the present case, the decision to initiate immunotherapy was based on the clinical and molecular diagnosis of immune-mediated myelitis and anti-myelin oligodendrocyte glycoprotein antibody spectrum disease, which highlights the need for refinement of current diagnostic criteria for acquired demyelinating syndrome phenotypes.

The timing of conventional MRI evaluations in relation to the onset of symptoms, as well as the significance of unusual radiologic phenotypes, should be considered in future imaging diagnostic criteria for myelin oligodendrocyte glycoprotein antibody spectrum disease. Furthermore, the diagnostic utility of advanced MRI sequencing, myelin oligodendrocyte glycoprotein antibody titers, and myelin oligodendrocyte glycoprotein antibody testing as part of the routine clinical assessment of children presenting with an acquired demyelinating syndrome, especially in patients with new-onset seizures in the context of a prior acquired demyelinating syndrome without a clear etiology, should be investigated in future studies, as this may have implications for timely recognition of patients at risk for a relapse who would benefit from immune-modulating therapy.

Authors' Note

The manuscript has been approved by all authors and represents valid work; neither this manuscript nor one with substantially similar content under my authorship has been published or is being considered for publication elsewhere. We certify that we are the sole authors of this article and hereby take public responsibility for the entire content of the manuscript.

Author Contributions

CAP drafted the manuscript and undertook the literature review. SGT and RT contributed equally to this work, critically reviewed the manuscript, and approved the final version.


Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Carlos A. Pérez, MD  <https://orcid.org/0000-0002-1818-9353>

Ethical Approval

Because this case report does not contain identifying or protected health information, ethical approval was not obtained.

References

- Langer-Gould A, Zhang JL, Chung J, Yeung Y, Waubant E, Yao J. Incidence of acquired CNS demyelinating syndromes in a multiethnic cohort of children. *Neurology*. 2011;77(12):1143-1148.
- de Mol CL, Wong YYM, van Pelt ED, et al. Incidence and outcome of acquired demyelinating syndromes in Dutch children: update of a nationwide and prospective study. *J Neurol*. 2018; 265(6):1310-1319. doi:10.1007/s00415-018-8835-6.
- Hacohen Y, Wong YY, Lechner C, et al. Disease course and treatment responses in children with relapsing myelin oligodendrocyte glycoprotein antibody-associated disease. *JAMA Neurol*. 2018;75(4):478-487. doi:10.1001/jamaneurol.2017.4601.
- Di Pauli F, Reindl M, Berger T. New clinical implications of anti-myelin oligodendrocyte glycoprotein antibodies in children with CNS demyelinating diseases. *Mult Scler Relat Disord*. 2018; 22(2018):35-37. doi:10.1016/j.msard.2018.02.023.
- Takewaki D, Lin Y, Sato W, et al. Normal brain imaging accompanies neuroimmunologically justified, autoimmune encephalomyelitis. *Neurol Neuroimmunol Neuroinflammation*. 2018;5: e456. doi:10.1212/NXI.0000000000000456.
- Hacohen Y, Chong WK, Barkhof F, et al. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. *Neurology*. 2017;89:1-10. doi:10.1212/WNL.0000000000004117.
- Rostasy K, Bajer-Kornek B, Venkateswaran S, Hemingway C, Tardieu M. Differential diagnosis and evaluation in pediatric inflammatory demyelinating disorders. *Neurology*. 2016;87(9): S28-S37. doi:10.1212/WNL.0000000000002878.
- Fernandez-Carbonell C, Vargas-Lowy D, Musallam A, et al. Clinical and MRI phenotype of children with MOG antibodies. *Mult Scler J*. 2016;22(2):174-184.
- Absoud M, Greenberg BM, Lim M, Lotze T, Thomas T, Deiva K. Pediatric transverse myelitis. *Neurology*. 2016;87(9):S46-S52. doi:10.1212/WNL.0000000000002820.
- Finke C. Diagnosing MRI-negative autoimmune diseases. *Neurol Neuroimmunol Neuroinflammation*. 2018;5(3):e457. doi:10.1212/NXI.0000000000000457.
- Jeong IH, Choi JY, Kim S-H, et al. Normal-appearing white matter demyelination in neuromyelitis optica spectrum disorder. *Eur J Neurol*. 2017;24(4):5-7. doi:10.1111/ene.13266.
- Kim S-H, Kwak K, Hyun J-W, et al. Diffusion tensor imaging of normal-appearing white matter in patients with neuromyelitis optica spectrum disorder and multiple sclerosis. *Eur J Neurol*. 2017;24(7):966-973. doi:10.1111/ene.13321.
- Gutman JM, Kupersmith M, Galetta S, Kister I. Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in patients with optic neuritis and seizures. *J Neurol Sci*. 2018;387(2018): 170-173. doi:10.1016/j.jns.2018.01.042.