MSJ Experimental Translational Clinical

Case Report

High fever in myelin oligodendrocyte glycoprotein-associated disorder (MOGAD): A diagnostic challenge

Multiple Sclerosis Journal—Experimental, Translational and Clinical

January–March 2023, 1–5

DOI: 10.1177/20552173221148911

Chadi Azar, Grace Akiki, Sara F Haddad, Anthony Kerbage, Fady Haddad and Gabrielle Macaron

Abstract

The phenotypic spectrum of myelin oligodendrocyte glycoprotein (MOG)-IgG associated disorders (MOGAD) has broadened in the past few years, and atypical phenotypes are increasingly recognized. Febrile meningoencephalitis has rarely been reported as a feature of MOGAD and represents a diagnostic challenge. We report the case of 24-year-old women with high-grade fever, meningoencephalomyelitis, and persistently positive MOG-IgG, for whom an extensive infectious work-up was negative and who responded to high-dose intravenous methylprednisolone. The full clinical spectrum of MOGAD is yet to be completely elucidated. In patients presenting with febrile meningoencephalitis, MOG-IgG testing should be considered particularly if infectious work-up is negative.

Keywords: MOG-IgG associated disorders, demyelinating disease, fever, rhombencephalitis encephalomyelitis

Date received: 29 August 2022; accepted 16 December 2022

Introduction

Myelin oligodendrocyte glycoprotein (MOG)-IgG associated disorders (MOGAD) represent a unique phenotypic spectrum of demyelinating inflammatory autoimmune disorders of the central nervous system (CNS) which has broadened considerably in the past few years. Typical presentations include optic neuritis (in up to 80% of patients) often bilateral and severe (in around 40% of patients), longitudinally extensive transverse myelitis often confined to the grey matter and/or involving the conus (in up to 50% of patients), and acute disseminated encephalomyelitis (ADEM) (in about 5% of adults and 20% of children with MOGAD).[1] Other rarer phenotypes include seizures and focal cerebral edema (FLAMES),[2] imaging-negative myelitis,[3] brainstem and area postrema syndromes[4] among others, for which MOGAD is more likely to be overlooked. The presence of high fever and meningeal signs in the context of ADEM is not a classical finding of MOGAD and represents a diagnostic challenge, as infectious causes are to be ruled out first and appropriate treatment can be delayed. We report the case of a patient who developed severe MOGAD-related ADEM with high-fever and meningeal signs mimicking infectious meningoencephalomyelitis.

Case presentation

A previously healthy 24-year-old woman presented to the emergency department with a one-week history of severe headache followed by fever (38.5–39 °C) which rapidly worsened 48 h prior to presentation with mild right-sided brachiofacial paresthesia, phonophobia, photophobia, and urinary retention. She reported the consumption of unpasteurized cheese and watery diarrhea two months ago. Physical examination at presentation showed nuchal rigidity, horizontal nystagmus with right gaze, saddle hypoesthesia, and hyperreflexic deep tendon but downgoing plantar reflexes. Initial brain MRI showed subtle abnormalities in the pons and brainstem (Figure 1A). Paraclinical workup is shown in Table 1. A chest, abdomen, and pelvis CT was normal. Intravenous vancomycin, ceftriaxone, and acyclovir were started empirically. Within the next 12 h, she developed persistent high-grade fever

Correspondence to:
Gabrielle Macaron,
Hotel Dieu de France Hospital, Alfred Naccache Boulevard, Ashrafieh, Beirut, Lebanon, PO box: 166830.
gabrielle.macaron@hdf.usj.edu.lb

Chadi Azar,
Department of Internal Medicine and Clinical Immunology, Hotel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon

Grace Akiki,
Department of Psychiatry, Hotel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon

Sara F Haddad, Anthony Kerbage,
Department of Internal Medicine, Hotel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon

Fady Haddad,
Department of Internal Medicine and Clinical Immunology, Hotel Dieu de France Hospital, Saint Joseph

University, Beirut, Lebanon

Gabrielle Macaron,
Department of Neurology, Hotel Dieu de France Hospital, Saint Joseph University, Beirut, Lebanon
Mellen Center for Multiple Sclerosis Treatment and Research, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA

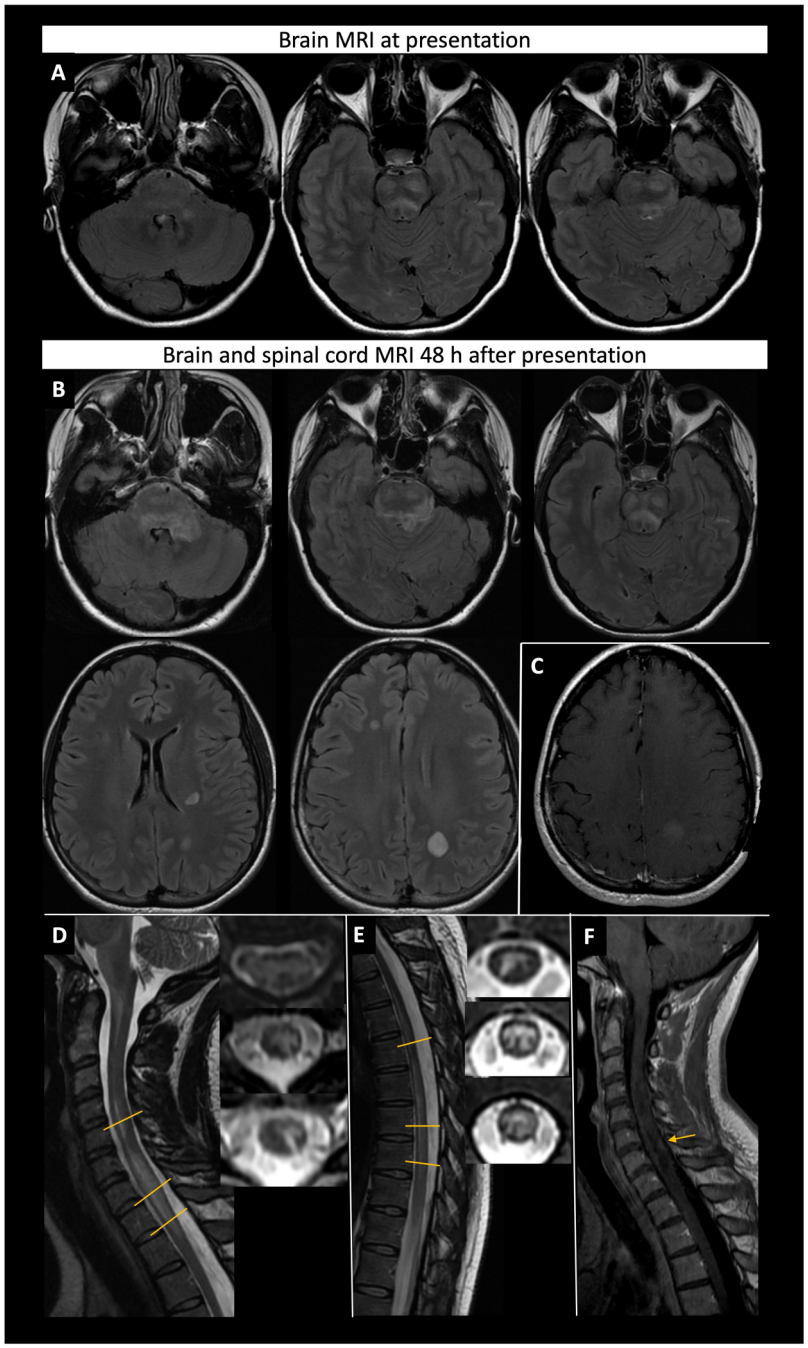

Figure 1. Brain and spinal cord MRIs at presentation. (A) Axial FLAIR sequences of first brain MRI at presentation, 3 days after symptom onset, showing subtle non-enhancing ill-demarcated abnormalities in the left middle cerebellar peduncle and the pons. No other abnormalities were identified on this MRI. (B) Axial FLAIR sequences of brain MRI 48 h after presentation, 5 days after symptom onset, showing worsening of abnormalities in the pons, bilateral cerebellar peduncles, and 3 new round white matter abnormalities in bilateral cerebral hemispheres suggestive of inflammatory demyelination with (C) enhancement of one of the lesions in the left parietal lobe on axial T1 sequences with gadolinium. Sagittal and axial T2 sequences of (D) cervical and (E) dorsal cord MRIs showing longitudinally extensive myelitis extending from C1 to T12, mainly confined to the grey matter, with (F) a focal faint nodular enhancement at the C7 level and prominent T1 hypointensity throughout the cord on axial T1 sequences with gadolinium.

Table 1. Serum and cerebrospinal fluid work-up. CSF studies were performed at day 1 and 3 (prior to obtaining MOG-IgG antibody results).

	Test	Results
Serum	CBC, CMP	Normal except for high WBC 13,200/μL (N: 4–9 10^9/l)
	CRP, Procalcitonin, ESR	Negative
	MOG-IgG	Positive, titer 1:160 (N < 1:10)
	AQP-4 IgG	Negative
	HIV 1/2, HSV 1/2, CMV, *Listeria monocytogenes*, Brucella, *Mycoplasma pneumoniae* serologies	Negative
CSF	**On admission**	
	WBC	103 cells/mm3 (5% neutrophils, 71% lymphocytes, 24% mononuclear cells) (N: 0–5)
	RBC	37 cells/mm^3 (N: 0–5)
	Protein	1.05 g/L (N: 0.12–0.6)
	Glucose	2 mmol/L (N: 2.2–3.9)
	Gram staining	Negative
	IgG index	0.63 (N < 0.70)
	Viral[a] and bacterial[b] PCR panels	Negative
	Cryptococcus neoformans and *gattii, Mycobacterium tuberculosis, and* Brucella PCRs	Negative
	Bacterial and fungal cultures	Negative
	Toxocara Canii serology	Negative
	48 h after admission	
	WBC	131 cells/mm^3 (3% neutrophils, 87% lymphocytes, 10% mononuclear cells) (N: 0–5)
	RBC	6 cells/mm^3 (N: 0–5)
	Protein levels	0.41 g/L (N: 0.12–0.6)
	Glucose	3 mmol/L (N: 2.2–3.9)
	V.D.R.L	Negative
	Mycotic culture	Negative
Other	RT-PCR SARS-CoV-2 (nasal swab)	Negative (repeated 3 times)

AQP-4: aquaporin-4; CBC: complete blood count; CMP: complete metabolic panel; CMV: cytomegalovirus; CRP: C-reactive protein; CSF: cerebrospinal fluid; EBV: Epstein–Barr virus; ESR: erythrocyte sedimentation rate; HIV: human immunodeficiency virus; HSV: herpes simplex virus; MOG: myelin oligodendrocyte glycoprotein; N: normal; PCR: polymerase chain reaction; RBC: red blood cells; RT-PCR : reverse transcription PCR; SARS-Cov-2: severe acute respiratory syndrome coronavirus 2; VDRL: Venereal Disease Research Laboratory; WBC: white blood cells.
[a]Viral PCR panel in CSF included HSV1, HSV2, VZV, EBV, CMV, HHV6, HHV7, HHV8, human parechovirus, human enterovirus, mumps, and measles.
[b]Bacterial PCR panel in CSF included (Neisseria meningitides, Listeria monocytogenes, Haemophilus influenzae, Streptococcus agalactiae and pneumonia, Escherichia coli, Staphylococcus aureus, Borrelia burgdoferi and miyamotoi.

(40 °C) over the next 48 h, altered mental status, dysarthria, diplopia, facial diplegia, and severe weakness in bilateral lower extremities. Physical examination was prominent for ophthalmoplegia secondary to bilateral cranial nerve 6 palsy, multidirectional nystagmus, facial diplegia, left pronator drift, decreased strength in left (2/5 proximally, 1/5 distally) and right (3/5 proximally, 4/5 distally) lower extremities, hyperreflexia in all four limbs, bilateral extensor plantar reflexes, and bilateral dysmetria in upper extremities, more prominent on the left. Repeat brain and spinal cord MRI 48 h after presentation showed several lesions in the

brainstem, pons, left middle cerebellar peduncles, supratentorial regions, and longitudinally extensive myelitis (Figure 1B–F). Antibiotic therapy was empirically broadened to intravenous ampicillin, ceftriaxone, gentamycin, acyclovir, and oral doxycycline and rifampin. Intravenous methylprednisolone (1 g/day for 8 days) was started 24 h after antimicrobial treatment initiation. MOG-IgG testing using a fixed cell-based assay (MVZ Labor Dr. Limbach and colleagues, Breitspiel, Heidelberg) was positive (titer of 1:160). Antibiotics were discontinued after negative infectious work-up. Progressive clinical improvement was noted 6 days after methylprednisolone initiation. Repeat MRI 10 days after initial imaging showed significant improvement to near resolution of most lesions. Physical examination 45 days after discharge showed complete recovery of strength and cranial nerve function, with persistent obstructive urinary symptoms and subtle spasticity in the left lower extremity.

She was treated with an oral prednisone tapered over five months. Repeat Anti-MOG IgG remained positive six months after initial presentation with a titer of 1:160.

Discussion

The full spectrum of MOGAD continues to broaden as new and atypical presentations are reported in the literature. Diagnostic criteria for MOGAD have been proposed in 2018 by an expert consensus.[5] None of the clinical and neuroimaging findings are highly specific for MOGAD and anti-MOG-IgG testing using cell-based assays is necessary for appropriate diagnosis. After the exclusion of alternate diagnoses, MOGAD is diagnosed based on the presence of a compatible clinical presentation, neuroimaging findings compatible with demyelinating CNS lesions and positive MOG-IgG detected by cell-based assay.[5] Post-infectious MOG-IgG formation has been described, indicating a possible infectious trigger for MOG-autoimmunity.[6]

We report an atypical presentation of MOGAD mimicking severe infectious encephalomyelitis. Our patient developed high-grade fever (40 °C), meningeal signs, and encephalomyelitis, particularly a rhombencephalitis presentation on initial MRI. Her history misled us to the possibility of an infectious etiology. CSF analysis showed lymphocytic pleocytosis with hypoglycorrhachia and increased protein. Our differential diagnoses were listeriosis, brucellosis, tuberculosis, and a viral infection, for which broad-spectrum antibiotics and acyclovir were initiated.

Fever is considered a major red flag for the diagnosis of autoimmune CNS disorders and warrants the exclusion of CNS infections. However, a couple of recent papers reports the presence of fever in MOGAD in a significant proportion of patients and concomitant to neurological symptom onset.[7] In a recent review of 146 MOGAD case reports, fever was described in 39%, although not reported in larger descriptive cohorts and review papers.[8]

Fever seems to be more frequent in children with MOGAD compared to adults.[7, 8] Even in rare severe complications that may occur in MOGAD-related ADEM such as status epilepticus, increased intracranial pressure, and respiratory failure requiring ventilatory support, fever is not mentioned as a key clinical feature.[9] The reason why fever develops in some patient is unclear, but may be explained by CNS infiltration of immune cells with subsequent inflammatory cascades and production of pro-inflammatory cytokines, increased vascular permeability and blood-brain barrier disruption, as well as direct lesions involving the midbrain.[10]

In our patient, in light of a negative comprehensive infectious work-up along with a non-response to initial broad-spectrum antibiotic and antiviral treatment and the ADEM-like lesions on brain and spinal cord MRI, post-infectious ADEM, neuromyelitis optica spectrum disorders, and MOGAD were suggested. The presence of fever argued against a classic ADEM, as it represents an exclusionary feature for this diagnosis. She responded within 24 h after initiation of high dose IV solumedrol (1 g per day for 8 days), and continued to improve steadily on a slow oral prednisone taper over the next month. MOG-IgG were positive with persistent positivity at month 6 after oral prednisone discontinuation, confirming the diagnosis of MOGAD. MRI lesions showed significant improvement with near-resolution of most lesions on follow-up scan, further corroborating the diagnosis.

This case highlights that MOGAD should be in the differential diagnosis of adult patients with febrile encephalomyelitis, specifically if the initial infectious work-up is negative, to avoid treatment delay and consequently, worse outcomes.

Acknowledgements

The authors thank the patient for providing consent to publish his case.

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: GM served on advisory boards for Genentech-Roche, Novartis, Mercks, and Biologix, received speaker fees from Biologix, Mercks, and Novartis, and participated in educational activities for Neurology Live and John Hopkin's e-Litterature Review.

Ethical considerations

Consent was obtained from the patient for publishing this case report.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Chadi Azar https://orcid.org/0000-0001-6431-0727
Sara F Haddad https://orcid.org/0000-0002-7262-028X
Anthony Kerbage https://orcid.org/0000-0003-3824-9859
Gabrielle Macaron https://orcid.org/0000-0002-7303-2332

References

1. Marignier R, Hacohen Y, Cobo-Calvo A, et al. Myelin-oligodendrocyte glycoprotein antibody-associated disease. *Lancet Neurol* 2021; 20: 762–772. 2021/08/22.
2. Jain K, Cherian A KPD, et al. FLAMES: a novel burning entity in MOG IgG associated disease. *Mult Scler Relat Disord* 2021; 49: 102759. 2021/01/29.
3. Macaron G and Ontaneda D. MOG-related disorders: a new cause of imaging-negative myelitis? *Mult Scler* 2020; 26: 511–515. 2019/04/02.
4. Jarius S, Kleiter I, Ruprecht K, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 3: brainstem involvement - frequency, presentation and outcome. *J Neuroinflammation* 2016; 13: 281. 2016/11/03.
5. Jarius S, Paul F, Aktas O, et al. MOG Encephalomyelitis: international recommendations on diagnosis and antibody testing. *J Neuroinflammation* 2018; 15: 134. 2018/05/05.
6. Sato R, Okanari K, Maeda T, et al. Postinfectious acute disseminated encephalomyelitis associated with anti-myelin oligodendrocyte glycoprotein antibody. *Child Neurol Open* 2020; 7: 2329048x20942442. 2020/07/25.
7. Udani V, Badheka R and Desai N. Prolonged fever: an atypical presentation in MOG antibody-associated disorders. *Pediatr Neurol* 2021; 122: 1–6. 2021/07/02.
8. Lampros A, De Broucker T and Bonnan M. Fever is a common onset feature of MOG-IgG associated disorders (MOGAD). *Mult Scler Relat Disord* 2021; 49: 102748. 2021/01/22.
9. Zhao-Fleming HH, Valencia Sanchez C, Sechi E, et al. CNS Demyelinating attacks requiring ventilatory support with myelin oligodendrocyte glycoprotein or aquaporin-4 antibodies. *Neurology* 2021; 97: e1351–e1358. 2021/08/15.
10. Massa S, Fracchiolla A, Neglia C, et al. Update on acute disseminated encephalomyelitis in children and adolescents. *Children (Basel)* 2021. 8 2021/05/01. DOI: 10.3390/children8040280.