
Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000010655

Clinical Reasoning: An 11-year-old girl with focal seizures, fevers, and unilateral, enhancing cortical lesions

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Search Terms: myelin oligodendrocyte glycoprotein, MOG, FLAMES, unilateral, autoimmune encephalitis

Publication History: None

Submission Type: *Neurology* Resident and Fellow Section, Clinical Reasoning

Title Character Count: 81

Number of Tables: 1

Number of Figures: 2

References: 15

Word Count: 1614

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

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Study funding: No targeted funding reported.

Disclosures:

J. Russ is a member of the *Neurology* Resident & Fellow Section Editorial Team.
C. Timbie, Y. Li, and E. Gonzalez-Giraldo report no disclosures relevant to the manuscript.

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Section 1:

An 11-year-old Asian American girl with no past medical history experienced acute-onset confusion and speech arrest without loss of consciousness, eye deviation, tonic stiffening, or convulsion. At an outside Emergency Department, her exam included expressive aphasia, right lower facial droop, and right-sided hemiparesis. Non-contrast head CT was negative for acute intracranial pathology, CT angiogram showed patent vasculature, and CT perfusion showed no areas of perfusion mismatch. The patient was transferred to our institution for further management.

On arrival, she was afebrile without meningismus, and her neurologic exam had improved substantially with mild expressive aphasia, slight right nasolabial fold flattening, and distal right upper extremity weakness. Over the next day, she had recurrent paroxysmal episodes of confusion, aphasia, right arm tonic stiffening and subsequent right hemiparesis.

Questions for Consideration:

1. What is the differential for pediatric patients with acute-onset aphasia and hemiparesis?
2. If the episodes were seizures, what lateralization/localization would you suspect for their onset based on semiology?

Go to Section 2

Section 2:

MRI/MRA brain demonstrated left parietal and perirolandic cortical edema with some reduced diffusion but no abnormal enhancement, overt ischemia, or structural abnormalities (Figure 1). MR spectroscopy over the involved area was normal. An EEG showed left posterior quadrant slowing with occasional left posterior temporal sharp waves, and multiple electrographic seizures originating from the left posterior quadrant (Figure 1), consistent with her aphasic seizures and post-ictal Todd's paralysis.¹ The focal tonic features were thought to represent spread to the left frontal lobe.¹ She was started on levetiracetam (60 mg/kg/day). Since she was initially afebrile without meningismus, and since her CSF studies (below) did not suggest bacterial or HSV meningoencephalitis, she was not empirically given antimicrobials.

On the fifth day of admission, she became intermittently febrile with temperatures up to 39.4°C. At this time, the differential for her acute-onset focal seizures was broad and included infectious, autoimmune, neoplastic, and metabolic possibilities (Table 1).

Serum infectious studies were negative. A serum autoimmune encephalopathy panel was negative. Her ANA was positive with a nucleolar pattern and a titer of 1:320, but her ESR, CRP, dsDNA, RF, and SSA/SSB were unremarkable. Serum metabolic studies, including ammonia, lactate, pyruvate, amino acids, free and total carnitine, and acylcarnitine profile, were normal. Urine organic acids were normal.

Lumbar puncture demonstrated a mixed pleocytosis: 35 white blood cells with 40% neutrophils, 47% lymphocytes, and 13% monocytes. CSF glucose, protein, lactate, pyruvate and IgG index were unremarkable and there were zero oligoclonal bands. A CSF autoimmune encephalopathy panel was negative. CSF HSV, VZV, enterovirus, West Nile virus, and bacterial culture were negative. Metagenomic next-generation sequencing for organisms was performed and resulted in a subthreshold positive result for *Candida glabrata*, which was felt to be a contaminant, particularly in an immunocompetent host. Repeat CSF metagenomic testing was negative. CSF cytology demonstrated lymphocytosis but no atypical cells.

Questions for Consideration:

1. Based on these results, how would you prioritize the differential diagnosis?
2. Would you start any empiric therapies?

Go to Section 3

Section 3:

Based on her elevated ANA, mixed CSF pleocytosis, and unrevealing infectious, metabolic, and neoplastic workup, an inflammatory/autoimmune process was favored. She was started on empiric high-dose methylprednisolone (30 mg/kg/day) and discharged on a prednisone taper with a plan to continue management as an outpatient.

In the interval, she had no further fevers or seizures. She had near-complete return to baseline with only subtle acalculia and dysgraphia. When an outpatient surveillance MRI demonstrated new enhancing lesions in the left frontal and insular subcortical white matter (Figure 2), she was readmitted for expedited evaluation.

While inpatient, she was again febrile with temperatures as high as 39.5°C and had two seizures with acute confusion and aphasia. EEG again demonstrated a left posterior quadrant origin. Lacosamide (5 mg/kg/day) prevented further seizures.

In consultation with our Infectious Disease and Rheumatology colleagues, additional studies were sent to further consider infectious, autoimmune, endocrine, and neoplastic etiologies (Table 1). Autoinflammatory diseases, genetic disorders of the innate immune system with heterogeneous CNS manifestations,² were considered, but the time course and absence of typically associated non-neurologic inflammatory symptoms suggested an acquired autoimmune disorder.

Repeat lumbar puncture demonstrated a mixed pleocytosis (41 white blood cells with 55% lymphocytes, 28% neutrophils, 16% monocytes, and 1% eosinophils) with an unremarkable glucose and protein. CSF IgG index was 0.7 and there were zero oligoclonal bands. Ophthalmologic exam was normal. Interval imaging demonstrated new areas of left-sided linear intraparenchymal enhancement, cortical and subcortical FLAIR hyperintensity, and leptomeningeal enhancement, in addition to evolution of the prior findings (Figure 2). MRI spine was normal.

Questions for Consideration:

1. Does the differential diagnosis change with these findings?
2. Is there targeted testing you would send to confirm a diagnosis?

Go to Section 4

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Section 4:

At this time, anti-myelin oligodendrocyte glycoprotein (MOG) IgG, tested at Mayo Laboratories via a cell-based assay employing full-length MOG antigen,³ returned positive with a titer of 1:1000. Her presentation was consistent with a newly described MOG-antibody-associated phenotype called FLAIR-hyperintense Lesions in Anti-MOG-associated Encephalitis with Seizures (FLAMES).⁴ She was restarted on 5 days of methylprednisolone (30 mg/kg/day) followed by an 8-week prednisone taper, and she received a single dose of rituximab (750 mg/m²). Given that her symptoms were not highly debilitating, we opted for steroids over IVIG or plasmapheresis, following an accepted approach to pediatric anti-MOG-associated disease.⁵

Unfortunately, after discontinuing prednisone, she returned with left optic neuritis. MRI brain demonstrated no other new lesions (not shown). Lymphocyte subsets demonstrated persistent B-cell depletion after rituximab. The patient repeated five days of pulse-dose steroids with visual improvement and was discharged on a prolonged course of prednisone (60mg daily) and a plan to follow up in Neuroimmunology Clinic.

Discussion:

Since its detection in children with autoimmune neuroinflammatory disorders,⁶ anti-MOG antibody has identified a phenotypically diverse subpopulation of patients with autoimmune CNS disorders. Pediatric anti-MOG-associated disease is prevalent; a recent prospective study found that 22% of pediatric patients diagnosed with encephalitis or acquired demyelinating disease were positive for anti-MOG antibody.⁷

Various case series have described the presentations of pediatric versus adult anti-MOG-associated disorders, revealing some general themes: patients with anti-MOG antibodies tend to be younger than patients with neuromyelitis optica (NMO) or multiple sclerosis (MS); they rarely meet MS diagnostic criteria; they often present with optic neuritis, myelitis, or acute disseminated encephalomyelitis (ADEM); they often have radiographic involvement of supratentorial white matter, brainstem, or spinal cord; and they are rarely simultaneously positive for anti-NMO antibodies.^{4,8-10} To avoid “overdiagnosis,” an international panel published a consensus guideline for testing and diagnosis, suggesting that criteria for anti-MOG-encephalomyelitis include: 1) monophasic or recurrent optic neuritis, myelitis, encephalitis, or a combination thereof; 2) radiographic or electrophysiologic evidence of demyelination; and 3) MOG-IgG seropositivity via a cell-based assay that uses full-length human MOG antigen.¹¹

Nevertheless, uncommon, heterogeneous features of anti-MOG-associated disease have been described, including patients with seizures,^{4,9-12} or patients with cortical or leptomeningeal findings on imaging,^{4,10,12} suggestive of a novel anti-MOG-associated syndrome. First described in adults by Ogawa et al.,¹³ this syndrome has been named FLAIR-hyperintense Lesions in Anti-MOG-associated Encephalitis with Seizures (FLAMES).⁴ Patients with FLAMES often present with focal or generalized seizures as an early symptom.^{4,13} In a case review of 20 patients with FLAMES, 85% had seizures, 70% had headache, 65% had fevers, and 55% had a focal deficit that corresponded to the unilateral area of cortex involved on imaging.⁴ The presence of fever is noteworthy, as this can make it harder to rule out infectious causes and delay immunosuppression.

Typical features of autoimmune demyelinating diseases, such as optic neuritis or myelitis, can still precede, co-occur with, or succeed the FLAMES symptoms,^{4,13} and thus patients may meet diagnostic criteria only over an extended time.¹¹

On imaging, patients with FLAMES characteristically present with unilateral cortical T2-hyperintensity,^{4,13} and may not initially meet the second diagnostic criterion requiring radiologic evidence of demyelination.¹¹ Subcortical involvement, sometimes with enhancement, can evolve later, as seen in our patient.^{4,13} Findings can be bihemispheric, but are commonly unilateral.^{4,13} Six out of twenty patients described in Budhram et al.⁴ also demonstrated leptomeningeal enhancement.

Our patient responded to high-dose steroids, which was successful in all 24 previously reported FLAMES cases,^{4,13} and is a mainstay of acute therapy for anti-MOG-associated disease.⁵ While there is no standard approach to maintenance therapy for MOG-associated illness, the prominent suspected role of antibody production in the pathophysiology of this disorder makes rituximab, which depletes B-cell precursors, a common choice.⁵ Though minimal specific data exists on the risk of relapse in FLAMES, a study of MOG-antibody-positive children suggests that relapse occurs in roughly one-third of patients, and that older school-aged children (median age of 10 years) with higher initial antibody titers (>1:1280) are most at risk by 24 months.¹⁴

Finally, the exact pathogenic mechanism of anti-MOG antibodies in human disease is unclear.⁸ Our patient had zero CSF oligoclonal bands, which has been observed in

FLAMES and other MOG-associated disorders, suggesting that anti-MOG disease may have a different neuroinflammatory mechanism than other demyelinating disorders.^{4,15} Anti-MOG antibodies may bind to myelin, activate complement, and directly precipitate oligodendrocyte death.⁸ Alternatively, they may act more indirectly via antigen-presenting-cell uptake leading to T-cell activation and cerebral inflammation.⁸ A third possibility is that anti-MOG antibodies are an epiphenomenon of a parallel neuroinflammatory process and are merely a convenient biomarker.^{4,8} Human pathology specimens from anti-MOG-positive patients demonstrate antibody and complement deposition, demyelination, and loss of MOG expression by oligodendrocytes,^{8,15} supporting at least some directly pathogenic role in anti-MOG-associated disease.

Outstanding questions about FLAMES are why gray matter rather than white matter is initially involved, and why neuroimaging findings are unilaterally restricted. As FLAMES becomes more widely recognized, our understanding of the unique risk factors, clinical trajectory, radiographic profile, pathophysiology, and therapeutic options for this unusual condition will be clarified.

Appendix 1: Authors

Name	Location	Contribution
Jeffrey Russ, MD, PhD	University of California San Francisco, California	Designed and conceptualized study, participated in patient care, analyzed data, drafted and revised the manuscript
Clare Timbie, MD, PhD	University of California San Francisco, California	Designed and conceptualized study, participated in patient care, analyzed data, drafted and revised the manuscript
Yi Li, MD	University of California San Francisco, California	Designed and conceptualized study, participated in patient care, analyzed data, compiled imaging, drafted and revised the manuscript
Ernesto Gonzalez-Giraldo, MD	University of California San Francisco, California	Designed and conceptualized study, participated in patient care, analyzed data, compiled EEG results, drafted and revised the manuscript

Data Availability: De-identified patient information from this case will be made available to other clinicians and researchers upon written request to the Corresponding Author.

Acknowledgements: The authors would like to thank Kendall Nash, MD; Sharon Wietstock, MD; Carla Francisco, MD; William Soulsby, MD; Susan Kim, MD, MMSc; Greta Peng, MD; and Manjiree Vikas Karandikar, MD for their assistance with clinical management of this patient. The authors would also like to thank Daniel Lachance from the Mayo Clinic for providing information on the anti-MOG-antibody assay.

Figure 1: The patient's MRI and EEG findings at initial presentation. Patient's initial MRI brain (A,B) at the onset of symptoms, demonstrating reduced diffusion in the left supramarginal gyrus (A; arrow), as well as cortical edema in the left perirolandic cortex (B; arrowhead). Patient's EEG (C,D), shown in a longitudinal bipolar montage, which demonstrates marked interhemispheric asymmetry with focal slowing maximal in the left posterior quadrant (C), and the onset of an electrographic seizure with emergence of rhythmic left posterior spikes with evolution in frequency and morphology

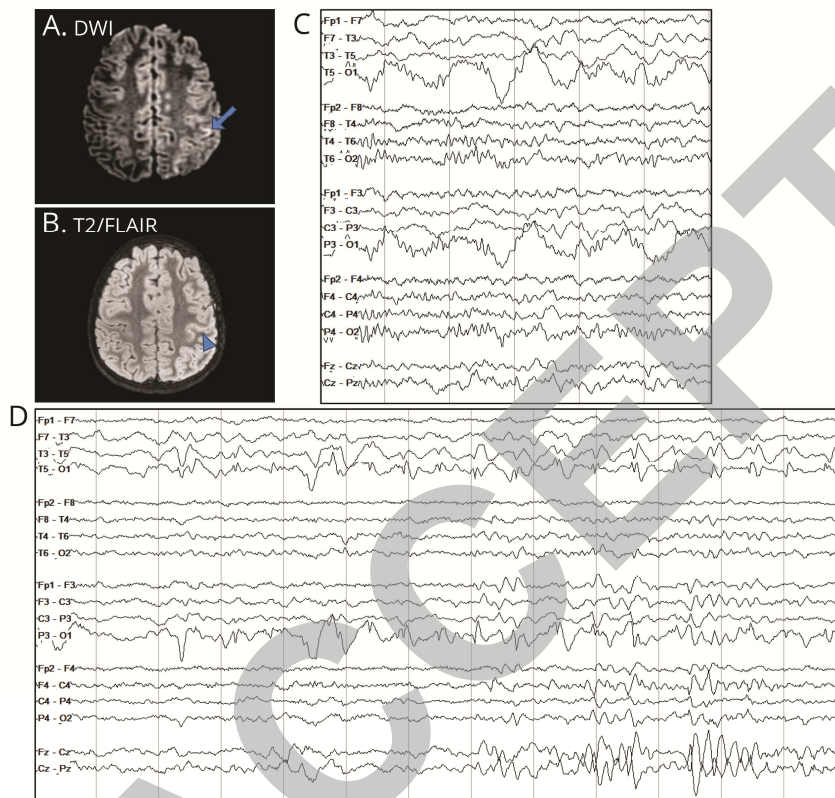


Figure 2: The patient's repeat MRI findings. Patient's subsequent MRI during her second admission, which demonstrates multiple foci of subcortical FLAIR hyperintensity with associated punctate and linear enhancement (arrowheads **A-F**), cortical thickening and FLAIR hyperintensity (arrow, **B**), and leptomeningeal enhancement (dashed arrow, **C**). Of note, the pontine lesion (**F**) surrounds a linear area of enhancement (**E**), which may reflect an engorged vessel.

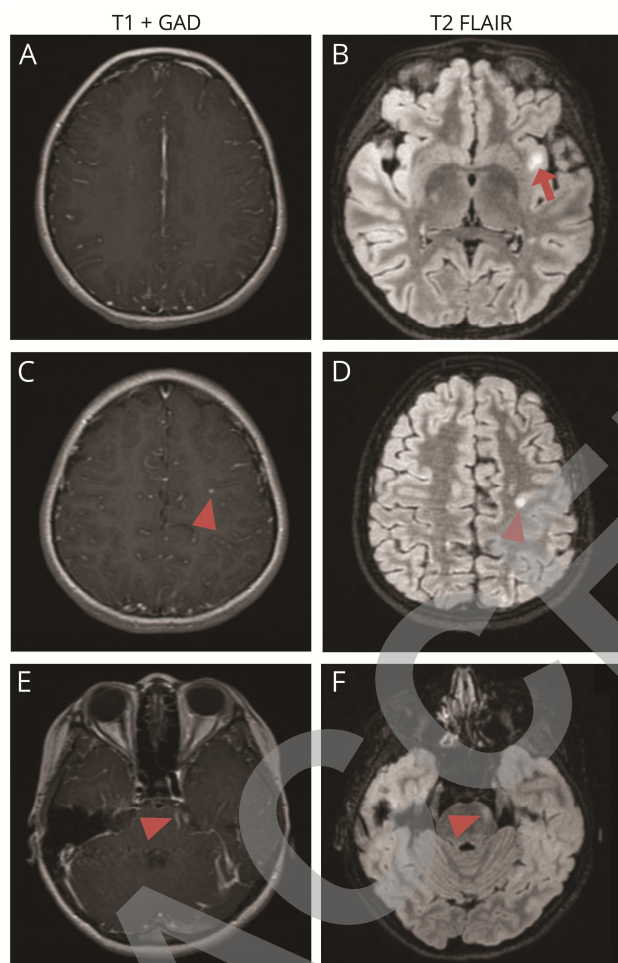


Table 1. Comprehensive summary of the serum, CSF, and urine studies obtained as part of the patient's evaluation.

AUTOIMMUNE/INFLAMMATORY		INFECTIOUS		METABOLIC	
Serum		Serum		Serum	
ESR	35 mm/hr	EBV PCR	Negative	Ammonia	17 umol/L
CRP	<0.02	West Nile Virus IgG	Negative	Lactate	1.3 mmol/L
ANA	1:320	West Nile Virus IgM	Negative	Pyruvate	1.1 mg/dL
dsDNA	<10	Quantiferon	Negative	Amino acids	WNL
Rheumatoid factor	<40	Histoplasma	Negative	Free carnitine	44.7 umol/L
SSA/SSB	<5	C. Psittacosis	Negative	Total carnitine	58.2 umol/L
anti-Smith	16.2			Acyl/free carnitine ratio	0.3
anti-RNP	<10.0	CSF		Acylcarnitine profile	WNL
pANCA/cANCA	<10	HSV PCR	Negative	CSF	
ACE	46	VZV PCR	Negative	Lactate	1.4 mmol/L
Ribosomal antibody	<1	Enterovirus	Negative	Pyruvate	1.7 mg/dL
Lysozyme	4.6 mcg/mL	EBV PCR	Negative	Urine	
anti-TPO	1:200	West Nile Virus IgM	Negative	Organic acids	WNL
TSI	101	West Nile Virus IgG	Negative		
Thyroglobulin	<2 IU/mL	Beta-d-glucan	<60 pg/mL		
Anti-phospholipid antibody panel	Negative	Cryptococcal antigen	Negative		
Autoimmune encephalopathy panel	Negative	Fungal culture	Negative	ENDOCRINE	
anti-NMO/AQP4	Negative	Bacterial culture	Negative	Serum	
anti-MOG	1:1000	Urine		TSH	0.39 mIU/L
Ferritin	48 ug/L	Histoplasma	Negative	Free T4	14 pmol/L
Fibrinogen	498 mg/dL			T3	2.8 pg/mL
Soluble IL-2	970				
Functional NK cells	6 LU30			NEOPLASTIC	
Lymphocyte subsets	WNL			CSF	
CSF				Cytology	Negative
Autoimmune Encephalopathy Panel	Negative				

Table 1. A summary of the serum, CSF, and urine studies that were sent to evaluate for autoimmune/inflammatory, infectious, metabolic, endocrine, and neoplastic etiologies. Abnormal values are in bold font. WNL = within normal limits.

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DOI 10.1212/WNL.0000000000010655

This information is current as of August 14, 2020

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