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

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Section 1

An 11-year-old girl with no relevant 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 examination included expressive aphasia, right lower facial droop, and right-sided hemiparesis. Noncontrast 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, the patient was afebrile without meningismus, and her neurologic examination 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?

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Section 2

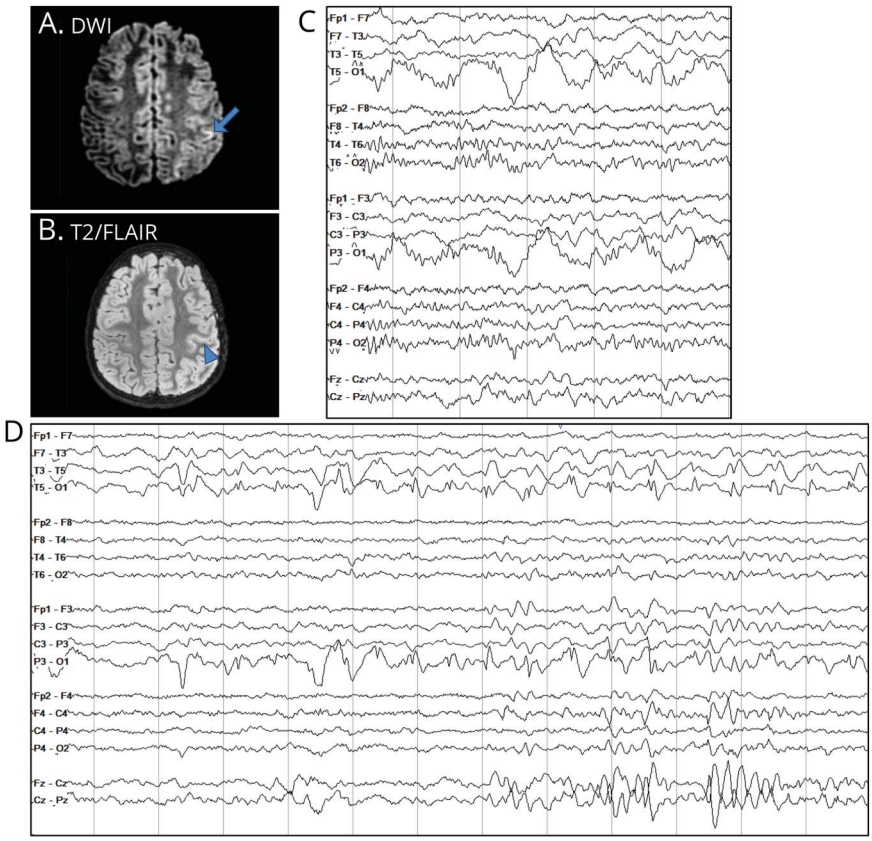
MRI/magnetic resonance angiography brain demonstrated left parietal and perirolandic cortical edema with some reduced diffusion but no abnormal enhancement, overt ischemia, or structural abnormalities (figure 1). Magnetic resonance spectroscopy over the involved area was normal. An EEG showed left posterior 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 postictal Todd paralysis.[1] The focal tonic features were thought to represent spread to the left frontal lobe.[1] The patient was started on levetiracetam (60 mg/kg/d). Because she was initially afebrile without meningismus, and because her CSF studies (below) did not suggest bacterial or herpes simplex virus (HSV) meningoencephalitis, she was not empirically given antimicrobials.

On the 5th day of admission, the patient 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).

Serum infectious studies were negative. A serum autoimmune encephalopathy panel was negative. Antinuclear antibodies (ANAs) were positive with a nucleolar pattern and a titer of 1:320, but erythrocyte sedimentation rate, C-reactive protein, dsDNA, rheumatoid factor, 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 immunoglobulin G (IgG) index were unremarkable and there were zero oligoclonal bands. A CSF autoimmune encephalopathy panel was negative. CSF HSV, varicella-zoster virus, 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 believed to be a contaminant, particularly in an immunocompetent host. Repeat CSF metagenomic testing was negative. CSF cytology demonstrated lymphocytosis but no atypical cells.

Figure 1 MRI and EEG findings at initial presentation



(A, B) Initial MRI brain at the onset of symptoms demonstrates reduced diffusion in in the left supramarginal gyrus (A; arrow), as well as cortical edema in the left perirolandic cortex (B; arrowhead). (C, D) EEG, shown in a longitudinal bipolar montage, 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. DWI = diffusion-weighted imaging; FLAIR = fluid-attenuated inversion recovery.

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

	Values
Autoimmune/inflammatory	
Serum	
ESR[a]	35 mm/h
CRP	<0.02
ANA[a]	1:320
dsDNA	<10
Rheumatoid factor	<40
SSA/SSB	<5
Anti-Smith	16.2
Anti-RNP	<10.0
pANCA/cANCA	<10
ACE	46
Ribosomal antibody	<1
Lysozyme	4.6 μg/mL
anti-TPO[a]	1:200
TSI	101
Thyroglobulin	<2 IU/mL
Antiphospholipid antibody panel	Negative
Autoimmune encephalopathy panel	Negative
Anti-NMO/AQP4	Negative
Anti-MOG[a]	1:1,000
Ferritin	48 μg/L
Fibrinogen[a]	498 mg/dL
Soluble IL-2	970
Functional NK cells	6 LU30
Lymphocyte subsets	WNL
CSF	
Autoimmune encephalopathy panel	Negative
Infectious	
Serum	
EBV PCR	Negative
West Nile virus IgG	Negative
West Nile virus IgM	Negative
Quantiferon	Negative
Histoplasma	Negative
Chlamydia psittacosis	Negative
CSF	
HSV PCR	Negative
VZV PCR	Negative
Enterovirus	Negative
EBV PCR	Negative
West Nile virus IgM	Negative
West Nile virus IgG	Negative
β-d-glucan	<60 pg/mL
Cryptococcal antigen	Negative
Fungal culture	Negative
Bacterial culture	Negative
Urine histoplasma	Negative
Metabolic	
Serum	
Ammonia	17 μmol/L
Lactate	1.3 mmol/L
Pyruvate	1.1 mg/dL
Amino acids	WNL
Free carnitine	44.7 μmol/L
Total carnitine	58.2 μmol/L
Acyl/free carnitine ratio	0.3
Acylcarnitine profile	WNL
CSF	
Lactate	1.4 mmol/L
Pyruvate	1.7 mg/dL
Urine	
Organic acids	WNL
Endocrine	
Serum	
TSH	0.39 mIU/L
Free T4	14 pmol/L
T3	2.8 pg/mL
Neoplastic CSF cytology	Negative

Abbreviations: ACE = angiotensin-converting enzyme; ANA = antinuclear antibodies; cANCA = cytoplasmic antineutrophil cytoplasmic antibodies; CRP = C-reactive protein; EBV = Epstein-Barr virus; ESR = erythrocyte sedimentation rate; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; IL = interleukin; MOG = myelin oligodendrocyte glycoprotein; NK = natural killer; NMO = neuromyelitis optica; pANCA = perinuclear antineutrophil cytoplasmic antibodies; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone; TSI = thyroid stimulating immunoglobulin; VZV = varicella-zoster virus; WNL = within normal limits.
[a] Abnormal values.

Questions for consideration:

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

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Section 3

Based on the patient's 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/d) and discharged on a prednisone taper with a plan to continue management as an outpatient.

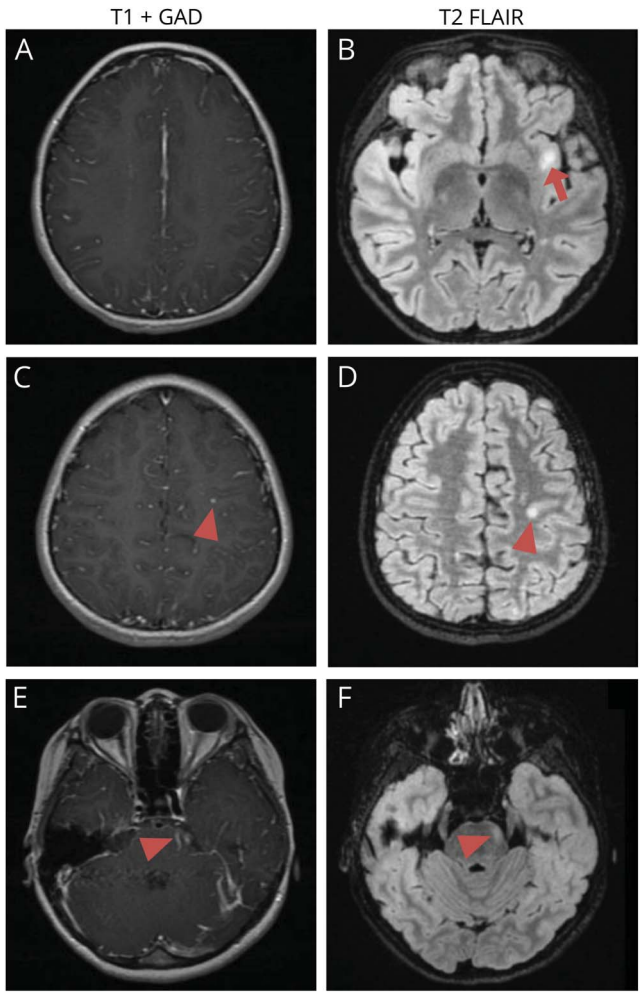
In the interval, the patient had no further fevers or seizures. She had near-complete return to baseline with only subtle acalculia and dysgraphia. When an outpatient surveillance MRI demonstrated new enhancing lesions in the left frontal and insular subcortical white matter (figure 2), she was readmitted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

While inpatient, the patient was again febrile with temperatures as high as 39.5°C and had 2 seizures with acute confusion and aphasia. EEG again demonstrated a left posterior quadrant origin. Lacosamide (5 mg/kg/d) 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). Autoinflammatory diseases and 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 examination was normal. Interval imaging demonstrated new areas of left-sided linear intraparenchymal enhancement, cortical and subcortical fluid-attenuated inversion recovery (FLAIR) hyperintensity, and leptomeningeal enhancement, in addition to evolution of the prior findings (figure 2). MRI spine was normal.

Figure 2 Repeat MRI findings



Subsequent MRI during the second admission demonstrates multiple foci of subcortical fluid-attenuated inversion recovery (FLAIR) hyperintensity with associated punctate and linear enhancement (arrowheads A–F), cortical thickening and FLAIR hyperintensity (arrow, B), and leptomeningeal enhancement (arrowhead, C). Of note, the pontine lesion (F) surrounds a linear area of enhancement (E), which may reflect an engorged vessel.

Questions for consideration:

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

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Section 4

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 1:1,000. The presentation was consistent with a newly described MOG-antibody-associated phenotype called FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures (FLAMES).[4] The patient was restarted on 5 days of methylprednisolone (30 mg/kg/d) followed by an 8-week prednisone taper, and she received a single dose of rituximab (750 mg/m^2). Given that her symptoms were not highly debilitating, we opted for steroids over IV immunoglobulin or plasmapheresis, following an accepted approach to pediatric anti-MOG-associated disease.[5]

After discontinuing prednisone, the patient returned with left optic neuritis. MRI brain demonstrated no other new lesions. Lymphocyte subsets demonstrated persistent B-cell depletion after rituximab. The patient repeated 5 days of pulse-dose steroids with visual improvement and was discharged on a prolonged course of prednisone (60 mg daily) and a plan to follow up in the 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 vs 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; 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 seizures[4,9–12] or 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 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 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 20 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] Although 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 exist 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 (>1:1,280) are most at risk by 24 months.[14]

The exact pathogenic mechanism of anti-MOG antibodies in human disease is unclear.[8] Our patient had no 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.

Questions about FLAMES include 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.

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Appendix Authors

Name	Location	Contribution
Jeffrey B. Russ, MD, PhD	University of California San Francisco	Designed and conceptualized study, participated in patient care, analyzed data, drafted and revised the manuscript
Clare M. Timbie, MD, PhD	University of California San Francisco	Designed and conceptualized study, participated in patient care, analyzed data, drafted and revised the manuscript
Yi Li, MD	University of California San Francisco	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, CA	Designed and conceptualized study, participated in patient care, analyzed data, compiled EEG results, drafted and revised the manuscript

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