Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease Presenting as Recurrent and Migrating Focal Cortical Encephalitis

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Abstract
Although pediatric myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease is increasingly well-recognized, its full clinical spectrum is still being defined. Cortical encephalitis is emerging as a distinct clinico-radiologic syndrome of adult MOG antibody-associated disease. We describe a 12-year-old girl who presented with new onset seizures and left-sided hemiparesis. Brain MRI showed edema of the right temporal-parietal-occipital cortex with associated focal leptomeningeal enhancement. Patient received high-dose corticosteroids and 21 days of acyclovir despite negative infectious work-up due to the focal nature of encephalitis. Patient remained seizure-free for 20 months before presenting with new right hemiclonic seizures with right-sided hemiparesis and edema of the left temporal-parietal cortex with associated leptomeningeal enhancement. Patient’s MOG antibody titer was 1:40. She completed high-dose corticosteroids and intravenous immunoglobulin. Our patient highlights the importance of MOG antibody testing in pediatric focal cortical encephalitis to avoid unnecessary anti-viral agents and provide more appropriate immunotherapy and a more informed prognosis.

Keywords
Myelin oligodendrocyte glycoprotein (MOG), autoimmune encephalitis, neuroimmunology, pediatric neurology, seizures

Introduction
Although pediatric myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease is increasingly well-recognized, the full clinical spectrum of the disease is still being defined. Acute disseminated encephalomyelitis (ADEM), optic neuritis, and transverse myelitis have been the most commonly described MOG antibody-associated demyelinating syndromes in the pediatric population.¹,²

Recently, encephalitis of the cerebral cortex without significant subcortical white matter involvement has emerged as a distinct type of MOG antibody-associated encephalitis and is often accompanied by seizures.³⁻⁵ A 2020 prospective observational study of 116 pediatric patients with MOG antibody-associated disorders found that encephalitis other than ADEM occurred in 19% of the cohort and was the second most common presenting syndrome after ADEM, which occurred in 68% of the cohort.³ Among the patients with encephalitis other than ADEM, 18% (n = 4) had isolated cortical or cortical-subcortical single lesions.³ A 2019 case report and systematic review of literature identified 20 patients with unilateral cortical FLAIR-hyperintense lesions in MOG antibody-associated encephalitis: 80% of these patients had seizures, and 65% had more typical antecedent or subsequent demyelinating syndromes such as ADEM and optic neuritis.⁴ While cortical lesions are not uncommonly found in MOG antibody-associated disease, encephalitis restricted to the cortex without significant subcortical white matter involvement has been primarily described in adults.⁵⁻¹¹
Here we describe one of the first pediatric patients who presented with recurrent and migrating focal cortical encephalitis associated with epilepsy.

**Case**

A 12-year-old girl with history of asthma presented to the emergency department (ED) with new onset seizures. The first seizure was characterized by rhythmic jerking of bilateral upper extremities with upward eye rolling that lasted for 1 minute and followed by postictal emesis and somnolence. Upon arrival to the ED, patient was witnessed to have a second seizure characterized by motor arrest, unresponsiveness, and lateral nystagmus of unreported direction. Seizure activity resolved with administration of lorazepam. Her neurologic exam several hours following the seizure was normal. Head CT without contrast was normal. Electroencephalogram (EEG) showed right posterior temporal, parietal and occipital slowing with very frequent epileptiform discharges in the right posterior temporal-parietal region. The discharges appeared to wax and wane in frequency without consistent periodicity. She was diagnosed with idiopathic focal epilepsy and started on levetiracetam with plans for an outpatient brain MRI. A week later, she re-presented to the ED following a cluster of 3 seizures within 10 minutes, all described as rhythmic jerking of all 4 extremities with upward eye rolling each lasting a few seconds. After the seizures resolved, she developed left hemiparesis and mild encephalopathy with impaired attention and concentration. Brain MRI with and without gadolinium showed T2/FLAIR hyperintensity and restricted diffusion involving the cortex in the right posterior temporal and parieto-occipital lobes with associated focal leptomeningeal enhancement as well as a non-enhancing bilateral thalamic T2/FLAIR hyperintense lesions (Figure 1). Initial lumbar puncture showed cerebrospinal fluid (CSF) WBC 7, RBC 2642, protein 24; repeat lumbar puncture 2 days later showed WBC 11, RBC 2736, protein 291. CSF herpes simplex virus (HSV) polymerase chain reaction (PCR) tests from both CSF samples were negative. Other CSF studies, including HSV IgM, West Nile virus (WNV) IgM and IgG, varicella zoster virus (VZV) PCR, mycoplasma pneumoniae PCR, cytomegalovirus PCR, Epstein-Barr virus (EBV) PCR, Mayo autoimmune encephalopathy panel, culture, and cytology, were all negative. Serologies for EBV, WNV, VZV, CMV, and arboviruses did not show acute infection. Serum enterovirus PCR and ANA screen were negative. Viral nasopharyngeal respiratory panel was negative. Despite the negative HSV testing, she completed a 21-day course of acyclovir due to the focal nature of her encephalitis and...
absence of a more likely etiology. She was started on levetiracetam and completed 5 days of high-dose corticosteroids followed by a 6-week oral steroid taper. Patient’s left hemiparesis and encephalopathy fully resolved, and she continued to do well in school. Her repeat MRI brain 3 months later showed no new lesions and showed significant improvement in the T2/FLAIR hyperintensities of the right posterior hemispheric and right thalamic lesions and resolution of diffusion restriction and leptomeningeal enhancement. Repeat EEG 6 months later showed mild right central-temporal, parietal, and occipital slowing. Patient remained seizure-free at 1 year following discharge, and levetiracetam was discontinued at that time.

Twenty months after her first episode of encephalitis, patient returned to ED with new right-sided weakness and focal seizures characterized by right-sided extremity jerking and gaze deviation. On exam, she demonstrated mild encephalopathy with impaired concentration. She was noted to have right-sided lower facial droop, 4/5 right bicep and tricep, 3/5 right wrist extension, and 0/5 right grip strength. Remainder of the neurologic exam, including fundoscopic exam, was within normal limits. Patient was started on levetiracetam, antibiotics, and acyclovir. Brain MRI showed complete resolution of previous right hemispheric abnormalities with development of left posterior temporal-parietal T2/FLAIR abnormalities with associated leptomeningeal enhancement (Figure 2). Electroencephalogram showed continuous focal slowing in the right posterior region and left hemisphere, and frequent focal epileptiform spikes in the right centroparietal and temporal head regions. The epileptiform discharges and right posterior slowing were consistent with sequelae from her first episode of encephalitis. The new left hemispheric slowing may represent postictal abnormalities from her seizures approximately 24 hours prior to the EEG, or represent focal cerebral dysfunction related to the new abnormalities demonstrated on MRI. Workup was notable for negative COVID-19 testing; normal CSF cell count, protein, and glucose, negative HSV PCR, meningitis/encephalitis panel, and negative culture. MOG antibody testing by cell-based assay was positive with a titer of 1:40. Aquaporin-4-IgG was negative. Cerebrospinal fluid and serum autoimmune encephalopathy panels were sent to Mayo Clinic Laboratories prior to any administration of intravenous immunoglobulin (IVIg). Antibody titers in the CSF were negative; however, serum autoimmune encephalopathy panel showed elevated antibody titers of glutamic acid decarboxylase (GAD65) (0.03 nmol/L; reference range: ≤ 0.02) and N-type calcium channel binding antibody (0.25 nmol/L; reference range: ≤ 0.03).

Patient received high dose corticosteroids with oral taper and IVIg 2 g/kg. Antibiotics and acyclovir were discontinued after infectious workup returned negative. Patient’s mental status improved, but she continued to exhibit mild difficulty with concentration. Her right-sided weakness fully resolved. She was discharged home with plans for monthly IVIg.

Discussion/Conclusion

Cortical encephalitis without significant subcortical white matter involvement is emerging as a distinct presenting syndrome of MOG antibody-associated disease that has been best characterized in adults. Here we describe one of the first pediatric cases of focal cortical encephalitis associated with epilepsy.

Our patient presented with new onset acute symptomatic focal epilepsy with mild encephalopathy and was found to have focal cortical T2/FLAIR hyperintense and diffusion-restricting lesions in the right temporal-parietal-occipital lobes with associated focal leptomeningeal enhancement as well as a non-enhancing right thalamic lesion. Patient’s presentation was not consistent with ADEM because of the almost-exclusively cortical distribution of lesions, absence of subcortical white matter involvement, and minimal dissemination. Although

Figure 2. During patient’s second attack of MOG cortical encephalitis, MRI brain showed complete resolution of previous right hemispheric abnormalities with development of left posterior temporal-parietal FLAIR abnormalities (A, arrow) with associated leptomeningeal enhancement (B, arrow).
there was no laboratory evidence of viral infection, she completed a full course of acyclovir due to the focal nature of her encephalitis and the lack of a more likely alternative diagnosis at the time. A limited neuroimmunologic work-up was performed at her initial presentation, including negative CSF autoimmune encephalopathy panel; however, MOG antibodies were not tested at that time due to the lack of known association between this clinico-radiologic syndrome and MOG antibody-associated disease. When she relapsed twenty months later with focal cortical encephalitis involving the opposite hemisphere, her clinical course became more concerning for a neuroinflammatory disorder due to the recurrent and episodic nature of her illness.

Patient’s serum Mayo autoimmune encephalopathy panel was mildly positive for GAD65 and N-type calcium channel antibody. Antibodies to GAD65 may be associated with stiff-person syndrome and thyrogastric autoimmune disorders. Voltage-gated calcium channel antibodies often co-exist with other antibodies (e.g. GABA-B receptor antibodies) that are much more specific for autoimmune encephalitis. Elevated voltage-gated calcium channel antibodies have frequently been found in both healthy controls and non-autoimmune conditions, including neurodegenerative conditions, and the voltage-gated calcium channel antibody positivity has been hypothesized to be a downstream effect due to neuronal injury following a non-specific immune activation due to a primary underlying disease process. The co-existence of MOG antibodies and voltage-gated calcium channel antibodies is not well-documented; however because MOG antibodies have been shown to cause similar presentations in adults without the co-existence of voltage-gated calcium channel antibodies, the N-type calcium channel and GAD65 antibodies likely do not represent significant findings in our patient.

The most commonly described demyelinating syndromes of MOG antibody-associated disease in children are ADEM, optic neuritis, and transverse myelitis. Recently, meningoencephalitis has also become increasingly well-recognized, but focal cortical encephalitis characterized by edema of almost-exclusively the cortex with associated focal leptomeningeal enhancement has not been well-described in children. Our patient highlights the importance of testing for MOG antibody titers as a potential cause for pediatric focal cortical encephalitis. Consideration of MOG antibody-associated disease in these patients will provide the opportunity for faster and more appropriate treatment with immunotherapy, decrease the use of unnecessary anti-viral agents, and provide more a informative prognosis for families.

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