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Life-Threatening MOG Antibody-Associated Hemorrhagic ADEM With Elevated CSF IL-6

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Abstract

Acute disseminated encephalomyelitis (ADEM) is one characteristic manifestation of myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD). A previously healthy man presented with retro-orbital headache and urinary retention 14 days after Tdap vaccination. Brain and spine MRI suggested a CNS demyelinating process. Despite treatment with IV steroids, he deteriorated, manifesting hemiparesis and later impaired consciousness, requiring intubation. A repeat brain MRI demonstrated new bilateral supratentorial lesions associated with venous sinus thrombosis, hemorrhage, and midline shift. Anti-MOG antibody was present at a high titer. CSF IL-6 protein was >2,000 times above the upper limits of normal. He improved after plasma exchange, then began monthly treatment alone with anti-IL-6 receptor antibody, tocilizumab, and has remained stable. This case highlights how adult-onset MOGAD, like childhood ADEM, can rapidly become life-threatening. The markedly elevated CSF IL-6 observed here supports consideration for evaluating CSF cytokines more broadly in patients with acute MOGAD.

Case Presentation

A previously healthy 35-year-old man presented to an urgent care with 9 days of retro-orbital headache. Two weeks before symptom onset, he received tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccination. He was diagnosed with migraine but returned to care 3 days later with persistent headache and new-onset urinary retention, visual disturbance (blurred vision in the left eye), and vertigo. MRI with contrast demonstrated an enhancing white matter T2/FLAIR hyperintense lesion in the anterior right lateral aspect of the pons with additional subcortical white matter lesions in the posterior right frontal lobe (Figure 1). There were anterior central T2 hyperintense lesions in the thoracic cord that enhanced with gadolinium. CSF analysis demonstrated a lymphocytic predominant pleocytosis (214 cells/μL) and elevated protein (61 mg/dL). There were no CSF-specific oligoclonal bands. He was treated with IV methylprednisolone (IVMP) 1,000 mg daily for 3 days and started intermittent bladder catheterization. Three days after IVMP, he returned to the emergency department with lower extremity weakness and difficulty with walking and urination. Despite additional IVMP followed by oral prednisone, his symptoms persisted, and he also developed lower extremity paresthesia.

At an outpatient neurology appointment 10 days later, his examination was notable for hyperreflexic patellar stretch and extensor plantar responses. Blood was drawn for a comprehensive serologic evaluation (eTable 1), and he remained on prednisone 60 mg daily. Over the next few days, he developed worsened lower extremity weakness, altered mental status, and language disturbance. He was hospitalized because of alertness and required intubation. Brain

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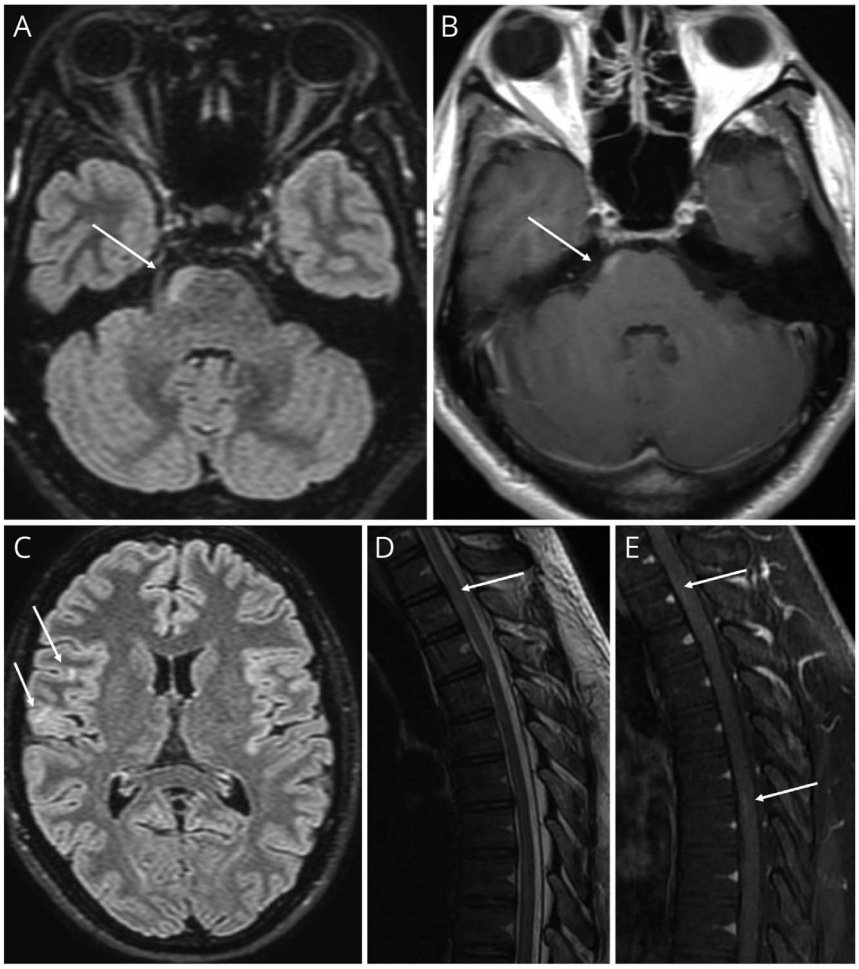
Glossary

ADEM = acute disseminated encephalomyelitis; **CVST** = cerebral venous sinus thrombosis; **IVMP** = IV methylprednisolone; **MOGAD** = myelin oligodendrocyte glycoprotein antibody–associated disease; **PLEX** = plasma exchanges; **TT** = Tetanus toxoid.

MRI with contrast demonstrated new multifocal T2/FLAIR hyperintensities in the supratentorial white matter, corpus callosum, and basal ganglia with peripheral enhancement and extensive intralesional blood products. Hemorrhagic T2/FLAIR hyperintensities of the bilateral thalami were noted with evidence of thrombosis of the bilateral internal cerebral veins, straight sinus, transverse sinus, and right sigmoid sinus (Figure 2). No lesions were noted on the spinal MRI at this time. CSF analysis showed RBC of 105 cells/μL, WBC of 87 cells/μL (85% polys), and 89 mg/dL protein.

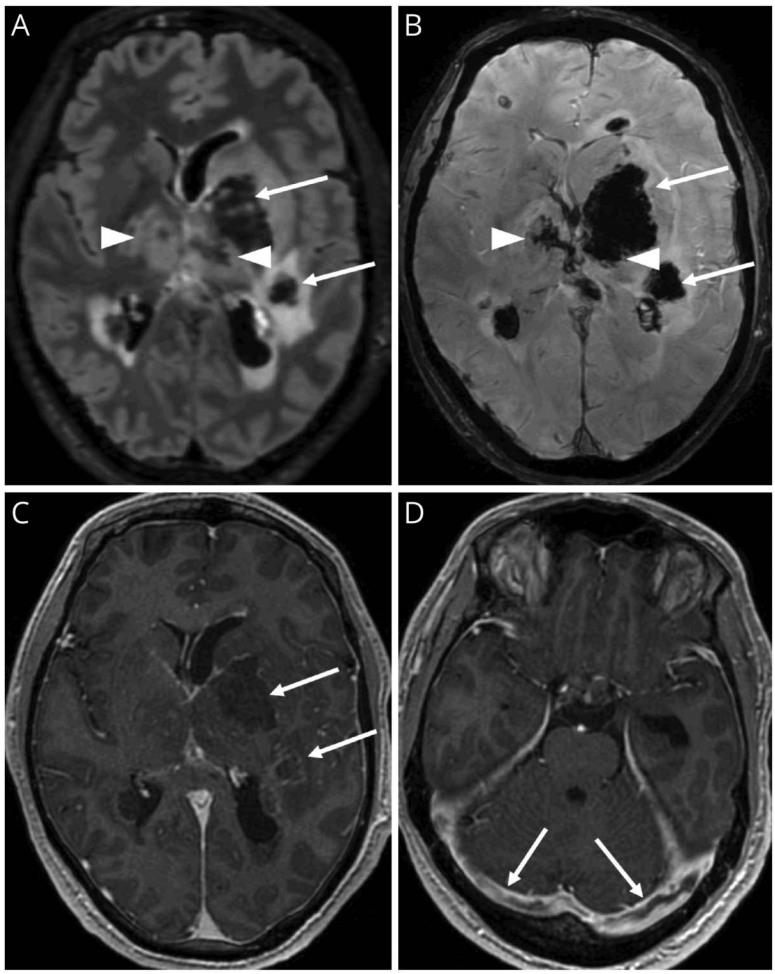
He was transferred to a tertiary care center for further management. Serum MOG-IgG that had been drawn at his outpatient neurology appointment returned positive at a titer level of 1:1,000 by cell-based assay (eTable). CSF interleukin-6 (IL-6) level was elevated at 17,904.6 pg/mL (normal level ≤7.5 pg/mL) (Table). Given his worsening despite IV steroid treatment, he underwent 5 sessions of plasma exchange (PLEX), and the cerebral venous sinus thrombosis (CVST), presumed secondary to inflammation from MOGAD, was treated with anticoagulation. He improved clinically, and this was attributed to PLEX treatment. Interval imaging showed decreased enhancement and a marked decrease in vasogenic edema surrounding numerous hemorrhagic lesions in the supratentorial brain (Figure 3). After his inpatient hospitalization, he was transferred to a rehabilitation hospital. Given the elevated CSF IL-6 level, he was started on the IL-6R antagonist tocilizumab 8 mg/kg every 4 weeks, which he has continued for more than one year. He

Figure 1 Brain and Spinal Cord Imaging at the Time of Clinical Presentation



Brain MRI at presentation demonstrates small T2-FLAIR hyperintense lesions of the right frontal subcortical white matter and right lateral pons (A, C, arrows) with mild enhancement (B, arrow). Thoracic spine MRI demonstrates T2 hyperintensity at T2-3 (D, arrow) and enhancement involving the ventral cord at T2-3 and T6-7 (E, arrows).

Figure 2 Brain Imaging at the Time of Clinical Deterioration



Brain MRI at the time of clinical deterioration demonstrates new supratentorial T2-FLAIR hyperintense lesions involving the white matter and left globus pallidus (A, arrows) with extensive hemorrhage (B, arrows) and peripheral enhancement (C, arrows). Bilateral thalamic T2-FLAIR hyperintensity (A, arrowheads) with hemorrhage (B, arrowheads) and bilateral transverse sinus thrombosis (D, arrows). Internal cerebral vein thrombosis not shown.

completed a slow oral prednisone taper 10 months later. His serum MOG-IgG level remains positive at 1:1,000. Currently, he ambulates without assistance but struggles with neurocognitive deficits. He has not been able to return to work.

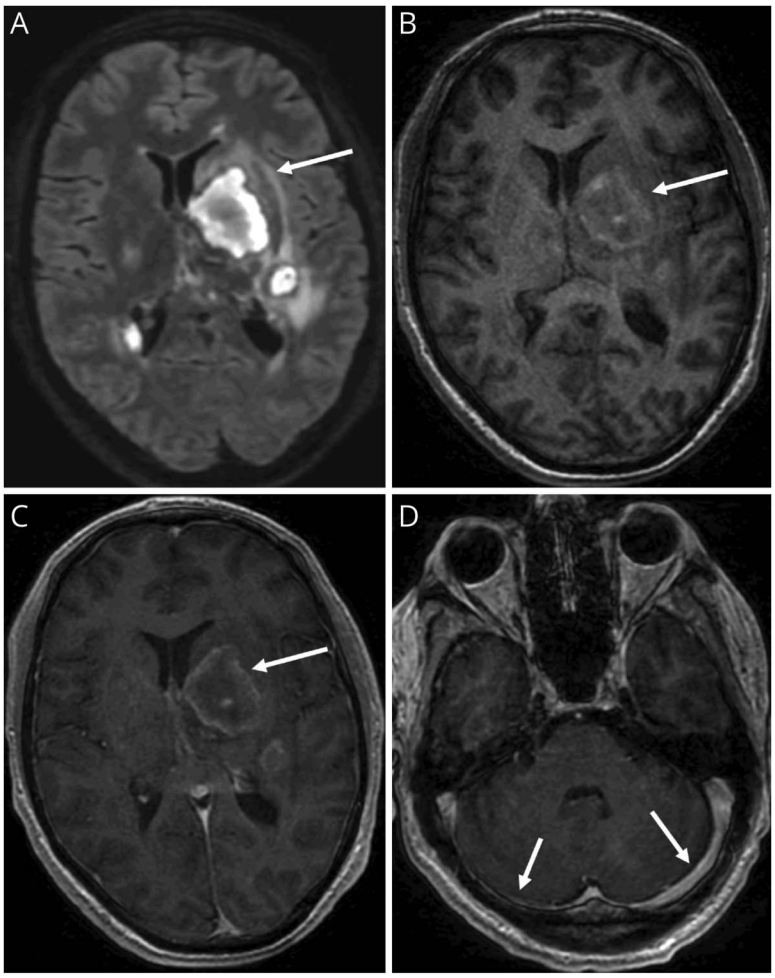
Discussion

MOGAD is a recently recognized CNS demyelinating disorder that can affect both children and adults.[1,2] The MOG-specific antibodies in patients with MOGAD are predominantly IgG1, a T-cell–dependent Ig subclass.[1,3] In this report, we present a 35-year-old man who exhibited a distinct clinical phenotype subsequent to Tdap vaccination leading to the diagnosis of MOGAD. Our patient manifested optic-spinal involvement with a notably rapid progression in severity. Severe ADEM, as we observed in this case, is more common in children than adults.[2,4,5] Our patient had multifocal T2/FLAIR hyperintensities within the supratentorial white matter, corpus callosum, basal ganglia, and spinal cord, which are characteristic of MOGAD.[2,6,7] Notably, the

Table CSF Cytokine Analysis Performed in the Intensive Care Unit

CSF interleukins	Results	Flag	Units	Reference range
Interferon gamma	9.8	High	pg/mL	≤4.2
Interleukin 10	64.8	High	pg/mL	≤12.7
Interleukin 12	<1.9	Normal	pg/mL	≤1.9
Interleukin 13	30.8	High	pg/mL	≤7.3
Interleukin 17	<1.4	Normal	pg/mL	≤4.6
Interleukin 1 beta	36.8	High	pg/mL	≤6.5
Interleukin 2	2.3	High	pg/mL	≤2.1
Interleukin 2 receptor, soluble	33.5	High	pg/mL	≤26.8
Interleukin 4	<2.2	Normal	pg/mL	≤5.2
Interleukin 5	8.8	High	pg/mL	≤2.1
Interleukin 6	17,904.6	High	pg/mL	≤7.5

Figure 3 Brain Imaging After Plasma Exchange (PLEX)



Brain MRI after treatment with 5 PLEX sessions demonstrates decrease in edema associated with supratentorial T2-FLAIR hyperintense lesions (A, arrow) with intrinsic T1 hyperintensity (B, arrow) and minimal peripheral enhancement (C, arrow). Improvement in previously seen transverse sinus thrombosis (D, arrows).

association with CVST is an unusually prominent feature in this case of MOGAD.[8,9] The rapid progression may have contributed to the CVST and subsequent hemorrhage, possibly due to elevated venous pressure. This patient's rapid response to PLEX emphasizes the potential benefit of PLEX in patients with severe MOGAD who are refractory to IV steroids.

In addition to the presentation of hemorrhagic leukoencephalomyelitis, other features of this case are unusual. In general, one does not routinely perform CSF cytokine protein analysis in clinical practice. The exceptionally high level of CSF IL-6 in association with MOGAD that we observed is uncommon, although one research study identified elevated CSF IL-6 in MOGAD and neuromyelitis optica spectrum disorder.[10] Unfortunately, we did not collect peripheral blood IL-6 simultaneously. IL-6, a pleiotropic cytokine primarily recognized for its proinflammatory activity, is produced by myeloid cells, B cells, and T cells.[11-13] IL-6 is the hallmark cytokine driving Th17 differentiation.[14] In this regard, observational studies suggest benefit of tocilizumab in MOGAD, and satralizumab, another IL-6 receptor antagonist, is currently being tested in a phase III, randomized, double-blind, placebo-controlled MOGAD trial.[5,15,16] Our patient has remained stable on tocilizumab monotherapy suggesting benefit, although his risk of relapse is unclear. Nevertheless, our observation regarding CSF IL-6 elevation provides further support for testing inhibitors of the IL-6 pathway in MOGAD.

Vaccinations against specific bacteria and viruses provide protective immunity for most individuals, yet it is recognized that rare adverse events can occur.[17,18] It is possible that Tdap vaccination before the onset of neurologic symptoms contributed to this patient's development of ADEM and diagnosis of MOGAD. Unfortunately, we do not know whether the patient was MOG IgG seropositive before Tdap vaccination. However, it is known that ADEM and MOGAD can occur weeks after infection and vaccinations,[19,20] and epidemiologic research has shown a statistically significant elevated risk of ADEM after Tdap vaccination.[21] Cases of MOG antibody–associated ADEM have been reported shortly after SARS-CoV-2 vaccination[22] or infection.[23,24] However, our patient had no history of SARS-CoV-2 infection; his most recent SARS-CoV-2 mRNA

vaccination was received 6 months before his clinical deterioration and he tested negative during hospitalization, essentially eliminating a possible association with either SARS-CoV-2 vaccination or SARS-CoV-2 infection in this patient's development of CVST and hemorrhagic ADEM. Of interest, although tetanus toxoid (TT) and MOG are dissimilar proteins, amino acid sequences of 2 known human T-cell epitopes of TT[25] are homologous to sequences of MOG that stimulate MOG-specific T cells in patients with MS and controls (eFigure 1).[26,27] Thus, the TT of Tdap could serve as a molecular mimic of MOG. Tdap also contains alum, an adjuvant that augments the innate and adaptive immune response to vaccination.[28] Nevertheless, although the onset of neurologic symptoms 14 days after Tdap vaccination aligns with the WHO criteria for causality,[29] there are plausible immunologic mechanisms and literature associating Tdap with the onset of ADEM, one cannot conclude with scientific certainty that Tdap vaccination had a causal role in the development of MOGAD in this patient.

In summary, our case highlights an unusual presentation of severe MOGAD, emphasizes the potential benefit of PLEX in severe MOGAD cases refractory to steroid treatment, and demonstrates how assessment of CSF IL-6 may help guide treatment decisions. One may wish to consider testing CSF cytokines in patients with acute manifestations of MOGAD more widely.

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Disclosure

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Emmanuelle Waubant, MD, PhD	UCSF Weill Institute for Neurosciences, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
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