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Clinical Observation

Acute Disseminated Encephalomyelitis (ADEM) and Increased Intracranial Pressure Associated With Anti–Myelin Oligodendrocyte Glycoprotein Antibodies

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ABSTRACT

Background: Antibodies to the myelin oligodendrocyte glycoprotein (MOG) have been identified in about 40% of children with acute disseminated encephalomyelitis (ADEM). The objective of this report is to describe three individuals with fulminant ADEM complicated by increased intracranial pressure associated with the presence of the anti-MOG antibodies.
Methods: This is a retrospective case series. Informed consent was obtained from the concerned patients or caregivers.
Results: High intracranial pressure associated with ADEM in the presence of MOG antibodies can result in cerebral edema, herniation, prolonged hospital stay (average intensive care unit stay: 22 days, average hospital stay: 50.6 days), and long-term disability.
Conclusion: Increased intracranial pressure complicating MOG antibody—related ADEM is a unique finding in our cases. This can complicate the clinical picture of ADEM and confers high morbidity. Long-term immunosuppression is warranted in selected cases with persistent seropositivity.

Introduction

Fulminant forms of acute disseminated encephalomyelitis (ADEM) are characterized by rapid progression of disability within several days to weeks often requiring aggressive therapy and admission to the intensive care unit.[1] ADEM requiring intensive care unit admission carries a high mortality (up to 25%) and morbidity (up to 35%) with long-lasting functional sequelae.[2] Children with myelin oligodendrocyte glycoprotein antibodies in the setting of ADEM tend to have a distinct clinical course, magnetic resonance imaging pattern, and long-term prognosis.[3,4] In this case series, we highlight issues relating to cerebral edema, elevated intracranial pressure, other systemic complications, and prognostic implications as a result of fulminant demyelination in the presence of anti—myelin oligodendrocyte glycoprotein antibodies.

Methods

We describe three patients with fulminant ADEM complicated by increased intracranial pressure associated with the presence of the anti—myelin oligodendrocyte glycoprotein antibodies. This is a retrospective case series based on a chart review. Informed consent was obtained from the patients or caregivers.

Results

Patient 1

This six-year-old Caucasian boy presented with a two-day history of influenza-like symptoms and depressed sensorium following recurrent episodes of streptococcal throat infection. On initial examination, he was somnolent, was unable to follow commands, was unable to track objects, was withdrawing all extremities to noxious stimuli, and was diffusely hyper-reflexic, but had intact brainstem reflexes. Magnetic resonance imaging (MRI) brain with and without contrast revealed multiple scattered areas of non-enhancing T2 signal abnormalities involving the gray and white matter structures (Fig). Spinal cord MRI was unremarkable. Cerebrospinal fluid studies revealed a neutrophilic pleocytosis. Infection-related studies were negative.

He was treated with high-dose corticosteroids (30 mg/kg of methylprednisolone) daily for five days and concurrent plasmapheresis (five treatments). On day four of admission, while receiving corticosteroids (three doses) and plasmapheresis (two cycles),

Conflicts of interest: None.

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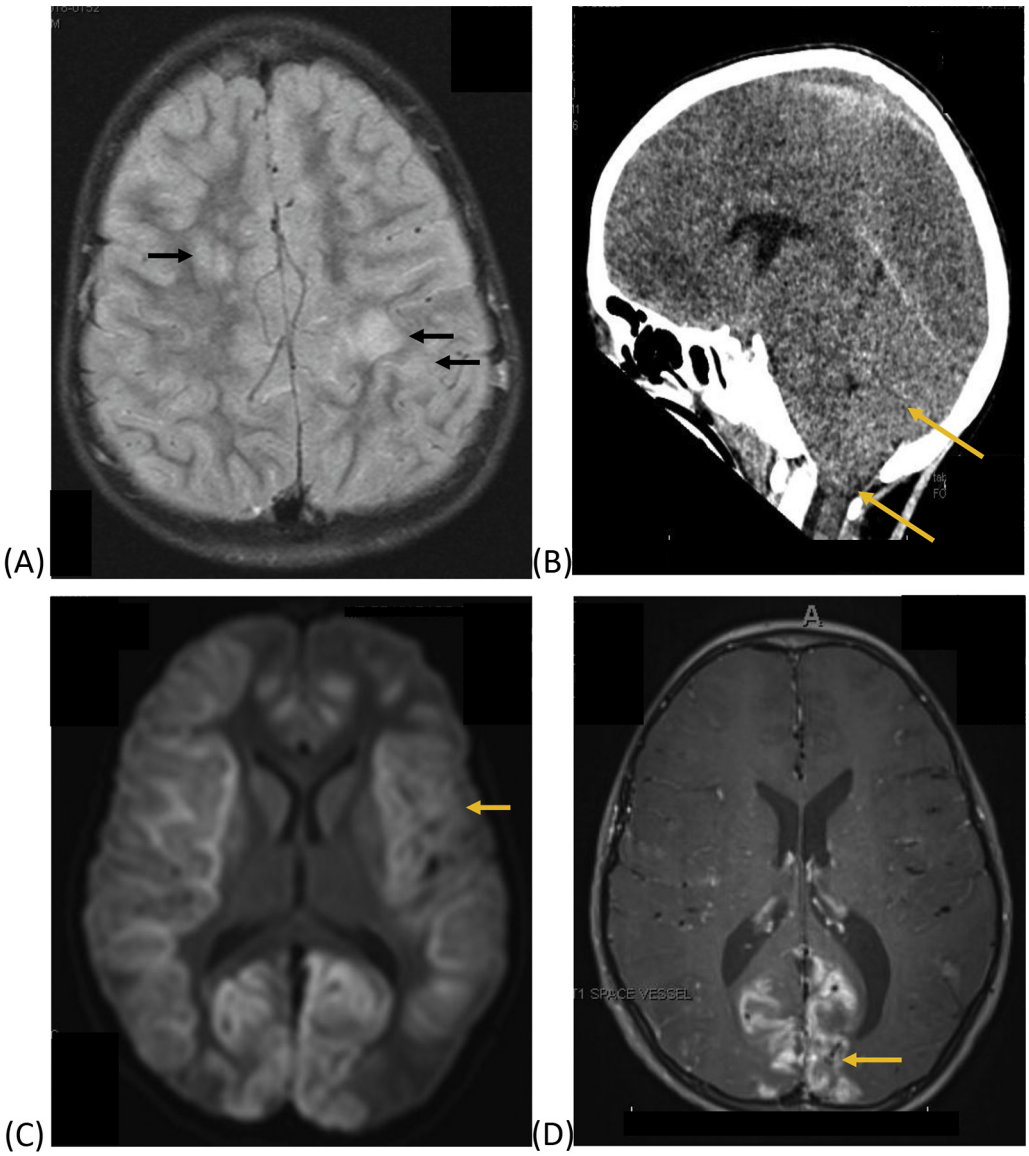

FIGURE. (A) Day 1, T2 fluid-attenuated inversion recovery axial image showing multiple fluffy lesions in the deep white matter. (B) Day four, computed tomographic sagittal image showing diffuse cerebral edema, loss of gray-white matter junction, effacement of cisterns, and downward herniation. (C) Day eight, diffusion-weighted imaging sequence showing diffuse restriction of diffusion along the cortical and subcortical areas (indicated by arrows). (D) Day 10, T1 axial image with gadolinium enhancement along the medial parietal-occipital lobes bilaterally (indicated by arrows). The color version of this figure is available in the online edition.

his neurological condition acutely deteriorated, with fixed, dilated, and anisocoric pupils. Computed tomography (CT) revealed diffuse cerebral edema and signs of elevated intracranial pressure (ICP) and herniation. Antiedema measures were instituted. Repeat MRI one week after admission (after corticosteroids, plasmapheresis, and antiedema measures) showed improved cerebral edema but diffuse diffusion restriction along the gray-white interface consistent with hypoxic-ischemic injury.

His clinical course was complicated by stress cardiomyopathy (Takotsubo cardiomyopathy), subclinical seizures, and deep venous thrombosis of the lower extremities. During week three of admission, his anti–myelin oligodendrocyte glycoprotein (MOG) antibodies (abs) returned positive at 1:10,000 titer. He was subsequently treated with high-dose cyclophosphamide (750 mg/m^2), and a month later with rituximab (375 mg/m^2). He continued to be minimally responsive requiring prolonged intubation and parenteral feeds. At the end of three weeks, he exhibited minimal improvement. He was extubated after four weeks and was discharged to inpatient rehabilitation. At four months after symptom onset, he was able to blink to answer questions, was unable to track objects, had facial dystonic movements and diffuse spasticity, and was nonambulatory.

Patient 2

This three-year-old Caucasian girl presented with a three-day history of progressive mental status changes following an upper respiratory tract infection. At presentation, she was noted to have episodes of agitation, bruxism, and lower-extremity hypertonia and hyper-reflexia with extensor plantar response bilaterally. CT of the head was unremarkable. MRI of the brain with and without contrast demonstrated extensive gray and white matter T2 hyperintense signal abnormalities and an area of contrast enhancement in the right parieto-occipital subcortical white matter. Cerebrospinal fluid analysis revealed a neutrophil- and monocyte-predominant pleocytosis. She

TABLE.
Summary of the Thee Patients With ADEM Who Tested Positive for Anti-MOG Antibodies

	Case 1	Case 2	Case 3
Prior existing conditions	None	None	None
Preceding infection	Recurrent streptococcus pharyngitis (rapid strep test) and influenza (respiratory swab PCR) until the day of onset of encephalopathy	Unclear URI; weeks before initial presentation	Influenza URI; 5 days before initial presentation
Number of days of neurological symptoms before hospital presentation	3	3	9
Presenting symptoms	Headache, fever, somnolence, emesis	Somnolence, irritability, agitation, lower extremity stiffening	Seizures, confusion, combativeness
Constitutional symptoms	Present	Present	Present
Alteration in higher mental function	Present	Present	Present
Seizures	Present	Present	Present
Other deficits	None	Increased lower-extremity tone	None
Glasgow Coma Scale	10	11	3-8
Head CT	Day 1, unremarkable; day 4, severe supratentorial edema with loss of gray-white differentiation, and downward herniation; dilation of ventricles, effacement of basal cisterns	Day 1, unremarkable; day 4, extensive WM, basal ganglia, and thalamic lesions with increased cerebral edema and bilateral uncal and transtentorial herniation	Day 1, mild cerebral edema with loss of gray-white differentiation; day 4-5, low-lying tonsil; increased ventricular size, effacement of sulci, effacement of cisterns in the floor of the posterior cranial fossa
Magnetic resonance imaging on admission	Day 2, white matter changes consistent with ADEM; week 1 (after steroids and plasmapheresis), extensive cortical and subcortical diffusion restriction and associated edema	Day 2, predominant white matter involvement with some involvement of basal ganglia; week 2,interval progression of extensive T2 hyperintensity centered around supratentorial white matter. Frontal and parietal lobes at the vertex and right temporal and occipital lobes most severely affected; interval development of focal cortical enhancement	Day 2, regions of patchy cortical increased T2 with restricted diffusion and mild leptomeningeal enhancement; day 12, cortical laminar necrosis; interval development of central gray involvement; day 28, confluent basal ganglia and thalamic involvement, progressive cerebral cortical involvement, new cerebellar and brainstem involvement, effaced sulci and infratentorial subarachnoid spaces, and cerebellar tonsillar herniation
CSF findings	16 white cells, 57% PMN, 62 mg/dl glucose, 30 mg/dl protein, negative OCB IgG index 0.38 Negative N-methyl-D-aspartate (ARUP) and autoimmune encephalopathy panel (Mayo) Negative enterovirus PCR, HSV-1, 2 PCR Negative CSF culture	20 white cells, 50% monocytes, 32% PMNs, 12 red cells, 90 mg/dL glucose, 44 mg/dL protein, IgG/OCB not checked Enterovirus PCR, HSV-1, 2 PCR Negative CSF culture	56 white, 54% PMN, 48 mg/dL glucose, 23 mg/dL protein, normal indices, and negative OCB IgG 0.27 HSV-1, 2 PCR John Cunningham virus PCR
Additional infectious testing	Negative blood and urine cultures serum EBV VCA IgG, IgM, adenovirus PCR, Human herpesvirus 6 PCR, human immunodeficiency virus-1 PCR Quantiferon TB Gold	Negative blood, respiratory, and urine cultures Serum California encephalitis virus IgG, IgM; Saint Louis encephalitis virus IgG, IgM, Eastern equine encephalitis virus IgG, IgM; Western equine encephalitis virus IgG, IgM; West Nile virus IgG, IgM; EBV early and nuclear Ag Ab; EBV VCA IgG, IgM; Mycoplasma IgG, IgM; Quantiferon TB Gold	Negative Brucella IgG, IgM California encephalitis virus IgG, IgM; Eastern Eq Enceph IgG, IgM; EBV early and nuclear Ag Ab; EBV VCA IgG, IgM; *Ehrlichia chaffeensis* IgG; Haemophilus influenzae B Ab; HSV-1,2 IgG, IgM; enterovirus PCR; VZV PCR, West Nile virus PCR, human immunodeficiency virus-1 PCR; Quantiferon TB Gold
Electroencephalography on admission	General electrodecremental segments, polymorphic delta slowing	Generalized slowing, no epileptiform activity	Generalized slowing
Number of days since symptom onset to developing elevated ICP	Day 5	Within 3 days	Within 5 days of symptom onset
EVD placed	None	Day 4	Day 14
Number days requiring EVD	N/A	13	21
Herniation	Present	Present	Present
Cerebral edema	Present	Present	Present
Number of days intubated	38	16	17
ICU days	44	21	29
Tracheostomy needed?	None	None	None
Percutaneous gastrostomy	None	None	None
Total hospital stay (days)	72	27	53

(*continued on next page*)

TABLE. (*continued*)

	Case 1	Case 2	Case 3
Discharge examination	N/A	Awake, fixate and tracks, nonverbal with providers, asks mom for ice cream but speech not at baseline	Spontaneous eye opening, grimace and withdraw to stimuli, groans and cries. Dysconjugate gaze. Spasticity legs, brisk deep tendon reflexes, clonus bilateral ankles
Disability on follow-up	Currently within 6 years of symptom onset	Present	Present
Immunosuppressive regimen	Cyclophosphamide, day 18; rituximab, days 55 to 60	Rituximab (7 years)	Rituximab, 4 years
Brain biopsy	Not done	Not done	Yes, changes consistent with acute disseminated encephalomyelitis versus infectious process
Recurrence	N/A	Yes; 7 years with unilateral optic neuritis	4-5 years with ADEM and unilateral optic neuritis
Time taken to order the Anti-MOG antibody test since symptom onset (years)	On admission	7.5 years	5 years
MOG titer	1:10,000	1:100	1:100

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
Ag = Antigen
Ab = Antibody
CT = Computed tomography
CSF = Cerebrospinal fluid
EBV = Epstein–Barr virus
EVD = External ventricular device
HSV = Herpes simplex virus
ICU = Intensive care unit
ICP = Intracranial pressure
MOG = Myelin oligodendrocyte glycoprotein
N/A = Not applicable
OCB = Oligoclonal band
PCR = Polymerase chain reaction
PMN = Polymorphonucleocyte
URI = Upper respiratory infection
VCA = Viral capsid antigen

initially improved after being on high-dose corticosteroids for suspected ADEM.

Three days after admission, she became obtunded and was noted to have a fixed and dilated right pupil. CT of the head showed signs of cerebral edema and foramen magnum herniation. An extraventricular device (EVD) was placed, and the patient's ICP peaked at 50 cm of water requiring antiedema measures. She underwent therapeutic hypothermia, and pentobarbital induced coma. She received a course of intravenous (IV) immunoglobulin, IV methylprednisolone, and plasma exchange. ICP decreased gradually, and the EVD was weaned off after two weeks.

Over the next few weeks, she had episodes of tachycardia, hypertension, and dystonic posturing. At discharge, she had left hemiparesis and left-sided hemianopia. She was discharged on a steroid taper. At three months follow-up, the patient had markedly improved motor abilities. She could run and hop on each leg. Neuropsychological assessment revealed low average intellectual ability with relative weaknesses in processing speed and visual-motor integration with a full-scale IQ of 84. After seven years of the ADEM presentation, she developed left optic neuritis that improved promptly with high-dose steroids. Anti-MOG ab testing returned positive (1:100). She was subsequently started on rituximab for relapse prevention.

Patient 3

This four-year old Caucasian girl presented with encephalopathic symptoms and generalized tonic-clonic seizures following a week's course of bilateral otitis media and influenza illness. On examination, she was stuporous with no focal signs. Brain MRI revealed multifocal regions of cortical increased T2 signal with restricted diffusion, mild leptomeningeal enhancement, papilledema, and cerebral edema. She improved with empirical antibiotic and antiviral therapy during the first four days of admission. On day five of admission, she was noted to have fluctuations in mental state, was unable to walk, and was paretic on the left side. Repeat MRI showed worsening of the previously identified findings. Her symptoms improved over the next two weeks with no specific intervention.

On day 19 of admission, she experienced generalized tonic-clonic seizures. MRI revealed marked progression of the previous findings with increased hydrocephalus, worsening cerebral edema, and cerebellar tonsillar herniation. She was readmitted to the intensive care unit, and an EVD was placed. Brain biopsy revealed changes consistent with ADEM. She was treated with high-dose cortico steroids and plasma exchange, IV immunoglobulin, and IV cyclophosphamide. Repeat brain MRI showed resolving cerebral edema and hydrocephalus and diffuse cerebral atrophy with

complete resolution of leptomeningeal enhancement. She was discharged on a steroid taper. At the time of discharge, she was opening eyes spontaneously, grimacing to noxious stimuli, moving all limbs spontaneously, and had dysconjugate gaze, spasticity, and hyper-reflexia throughout. She continued to improve steadily after discharge, and at one-year follow-up, optical coherence tomography revealed bilateral retinal nerve fiber thinning (52 μm in the right eye and 54 μm in the left eye). After four years of initial presentation, she was found to have new enhancing lesions of the bilateral subcortical and cortical areas and right optic neuritis. She was treated with steroids and plasma exchange. She was subsequently treated with rituximab after her anti-MOG ab resulted positive (1:100). At five years after symptom onset, she was left with impaired processing speed, auditory attention, visual-motor integration, visual perception, spasticity, and gait impairment.

The anti-MOG ab testing in all the above cases was performed using live-cell-based assays and was obtained from the Mayo Medical Laboratories, Rochester, MN, USA. Results are summarized in Table.

Discussion

We describe three patients with possible ADEM, which are thought to be rare presentations in the spectrum of MOG-ab phenotypes. Notable among these patients was the presence of significantly increased ICP complicated by cerebral edema and herniation. The average hospital stay was 50.6 days, and the average intensive care unit stay was 22.3 days.

There are several implications from these observations. First, it is important to consider early ICP monitoring and surveillance for subclinical seizures based on the poor neurological status on admission and the lesion load on MRI with early signs of cerebral edema. Of note, in two of our three patients, an EVD was placed, and whether this was associated with an improved outcome is unclear. Second, how much of the long-term outcome is determined by the primary pathology (inflammation and demyelination) versus secondary injury (from elevated ICP, subclinical seizures, cerebral edema, herniation, mechanical injury from herniation) is largely unknown at this time. There is anecdotal evidence of better outcomes with early surgical intervention (hemicraniectomy) in severe cases of encephalitis with elevated ICP.[5,6] Finally, the presence of leptomeningeal involvement, optic nerve or spinal cord involvement (as in case 3), and deep gray matter involvement (as in all our patients) in a patient with possible ADEM should raise the suspicion for anti-MOG antibody syndrome.[7,8] In our case series, we do acknowledge that a more sensitive assay for infectious agents like metagenomics next-generation sequencing (mNGS) has not been carried out.

Seropositivity for the MOG antibody might predict future clinical events.[9] In a study of about 210 children, 60 of whom had ADEM (34 MOG-ab positive and 26 MOG-ab negative), patients with a recurrent non–multiple sclerosis course (either recurrent ADEM, optic neuritis, neuromyelitis optica spectrum disorder phenotypes) tended to have (1) higher antibody titers (greater than 1:1280) at onset and (2) persisting antibodies at six months or beyond.[10] Several centers consider long-term immunosuppression in cases wherein the initial MOG-ab titers are high (greater than 1:1280) or if antibody titers persist at six-month follow-up or beyond.

In conclusion, fulminant forms of ADEM can occur with the presence of anti-MOG antibodies. The relationship of the condition with the antibody is unclear at this time. Early institution of aggressive monitoring and treatment measures can prevent poor outcomes. The presence of high MOG-ab titers at disease onset or at six-month follow-up could predict a recurrent course, thereby necessitating long-term immunosuppression.

References

1. Rahmlow MR, Kantarci O. Fulminant demyelinating diseases. Neurohospitalist. 2013;3:81–91.
2. Sonneville R, Demeret S, Klein I, et al. Acute disseminated encephalomyelitis in the intensive care unit:clinical features and outcome of 20 adults. Intensive Care Med. 2008;34:528–532.
3. Baumann M, Sahin K, Lechner C, et al. Clinical and neuroradiological differences of paediatric acute disseminating encephalomyelitis with and without antibodies to the myelin oligodendrocyte glycoprotein. J Neurol Neurosurg Psychiatry. 2015;86:265–272.
4. Probstel AK, Dornmair K, Bittner R, et al. Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis. Neurology. 2011;77:580–588.
5. von Stuckrad-Barre S, Klippel E, Foerch C, Lang JM, du Mesnil de Rochemont R, Sitzer M. Hemicraniectomy as a successful treatment of mass effect in acute disseminated encephalomyelitis. Neurology. 2003;61:420–421.
6. Schwab S, Jünger E, Spranger M, et al. Craniectomy: an aggressive treatment approach in severe encephalitis. Neurology. 1997;48:412–417.
7. Ramanathan S, Dale RC, Brilot F. Anti-MOG antibody: the history, clinical phenotype, and pathogenicity of a serum biomarker for demyelination. Autoimmun Rev. 2016;15:307–324.
8. Cobo-Calvo A, Ruiz A, Maillart E, et al. Clinical spectrum and prognostic value of CNS MOG autoimmunity in adults: the MOGADOR study. Neurology. 2018;90:e1858–e1869.
9. Misu T, Sato DK, Nakashima I, Fujihara K, et al. MOG-IgG serological status matters in paediatric ADEM. J Neurol Neurosurg Psychiatry. 2015;86:242.
10. Hennes EM, Baumann M, Schanda K, et al. Prognostic relevance of MOG antibodies in children with an acquired demyelinating syndrome. Neurology. 2017;89:900–908.