#27

Fulminant Acute Disseminated Encephalomyelitis Associated with Increased Intracranial Pressure and anti-MOG antibodies: Presentation of Four Cases

Cynthia Wang MD[1,2] , Ram Narayan MD[3], Darryl Miles MD[2], Benjamin Greenberg, MD MHS[1,2]

[1]Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX
[2]Children's Medical Center Dallas, Dallas, TX
[3]Barrow Neurological Institute, Phoenix, AZ

UT Southwestern
O'Donnell Brain Institute

Background / Objectives

Acute disseminated encephalomyelitis (ADEM) is an acquired inflammatory demyelinating disorder that is commonly a monophasic illness with a favorable prognosis. However, fulminant forms of the disease can lead to widespread demyelination, cerebral edema, and increased intracranial pressure (ICP), resulting in high morbidity and mortality.

Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies have been reported in association with acute demyelinating syndromes such as ADEM, optic neuritis, and transverse myelitis. There has been increasing focus on the relapsing nature of the disease but few reports emphasize the morbidity associated with individual relapses.

We present a case series highlighting our institutions' experience with severe cases of anti-MOG antibody associated ADEM requiring aggressive management of increased ICP. Salient features of the patients' demographics, clinical presentations, antecedent symptoms/signs associated with increased ICP, treatment course, and outcomes are discussed.

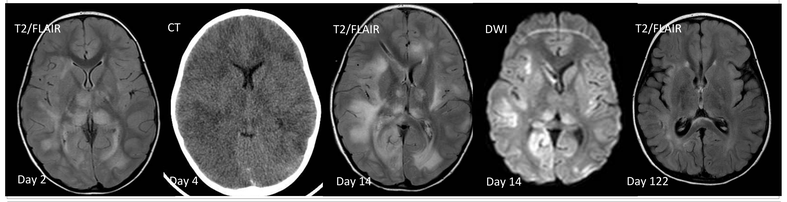
Methods

We identified children who were hospitalized at Children's Health Medical Center Dallas who were diagnosed with ADEM and had radiographic and clinical signs of increased ICP requiring urgent medical and/or surgical management. All subjects tested positive for anti-MOG antibodies, either concurrently or following ADEM. Chart review and data extraction were completed under protocols approved by the UT Southwestern institutional Review Board (STU-022011-211, STU-112016-017).

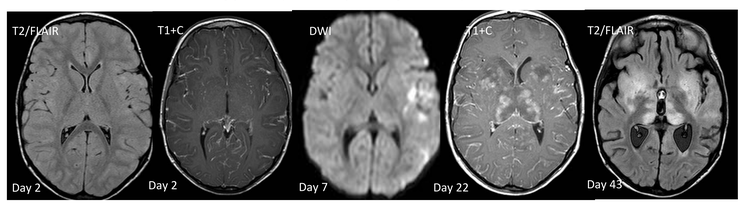
Results

- Four children were identified who presented from 2010-2018 with ADEM complicated by increased ICP and were anti-MOG antibody positive.
- Their age of presentation ranged from 3-6 years and 2 of the 4 children were female.
- Common presenting symptoms included altered mental status, headache, and vomiting.
- Abnormalities on neurological exam included hypertonia, hyperreflexia, ataxia, somnolence, and agitation.
- Clinical or radiographic signs of increased ICP became evident by day 3-6 of hospitalization.
- Intravenous methylprednisolone (IV MP), therapeutic plasma exchange (PLEX), and/or intravenous immunoglobulin (IVIg) were commonly utilized acute immunotherapies.
- Other frequently used medical treatments included hyperosmolar therapy, barbiturate coma, and hypothermia for management of increased ICP.
- 3 of the 4 patients underwent surgical management for increased ICP with external ventricular drain or lumbar drain placement.
- Pupillary abnormalities and/or decorticate posturing were associated with increasing ICP and/or brain herniation.
- Neuroimaging from all four children demonstrated restricted diffusion on MRI indicating cytotoxic edema.
- Length of hospitalization was significant, ranging from 28 days to 72 days, with the majority of the time spent in intensive care.
- Duration of follow-up ranged from 34 days to 8 years.
- Patients had varying degrees of clinical improvement, but none returned to their cognitive baseline.
- These patients tested positive for MOG antibodies, with a titer of 1:100 in the two patients tested following the initial ADEM event and 1:1000-1:10,000 in the two patients tested during the acute period.
- 2 of 4 MOG patients have had recurrent demyelinating events, while one child is only 7 months past his initial illness and one child remains hospitalized for ADEM.

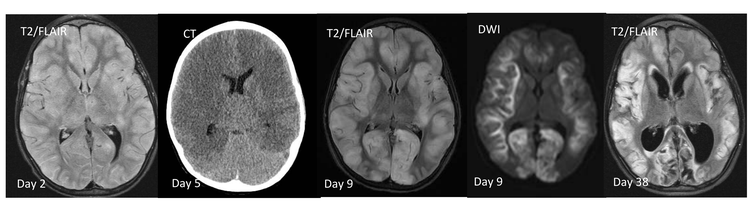
Patient 1: A 3-year-old girl presented with headache, vomiting, and lethargy following a URI. She was agitated, hypertonic, and hyperreflexic on exam. MRI brain demonstrated extensive gray and white matter T2 hyperintensities with minimal contrast enhancement and no restricted diffusion. CSF showed 20 WBCs with monocytic and neutrophilic predominance. She was initiated on IV methylprednisolone (IV MP) for presumed ADEM. On hospital day 4, she developed progressive obtundation, decorticate posturing, and a fixed, dilated right pupil. CT showed cerebral edema and foramen magnum herniation. An external ventricular drain (EVD) was placed (initial ICP 60 cm H2O) and underwent medical management of ICP including hypothermia and pentobarbital coma. She received therapeutic plasma exchange (PLEX) and intravenous immunoglobulin (IVIG) following IV MP. Subsequent MRI showed areas of restricted diffusion. ICP normalized over 2 weeks and EVD was removed. She stayed 28 days in hospital and was discharged to inpatient rehabilitation. 3 months later, she exhibited marked motor and speech improvement. Neuropsychological testing revealed full scale IQ of 83 at age 6. At age 11, she developed left optic neuritis and was found to be positive for anti-MOG antibodies (1:100, not previously assessed) and was initiated on rituximab.



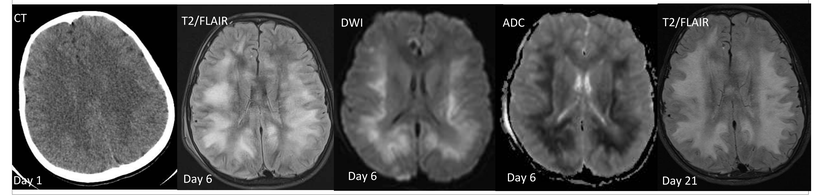
Patient 2: A 4-year-old girl with history of craniosynostosis presented with headache, vomiting, slurred speech, and seizures after being diagnosed with influenza and otitis media. She was irritable but could speak and follow commands. CT was concerning for increased ICP so LP was deferred. MRI brain showed patchy areas of cortical increased T2 signal, diffusion restriction, and leptomeningial enhancement. She was thought to have infectious meningoencephalitis and received antimicrobial and anti-seizure medications. Her mental status improved but fluctuated. On day 15, she became febrile and CSF studies were obtained, showing elevated opening pressure of 52 cm H2O, WBC 56 with neutrophilic predominance. Due to continued decline in mental status and dilated pupils, CT head was obtained on day 19, showing hydrocephalus, deep gray matter involvement, and tonsillar herniation. An EVD was subsequently placed with initial ICPs greater than 30 cm H2O. She received hypertonic saline and pentobarbital with continued ICPs in upper 20s. Brain biopsy was performed on day 22, showing inflammatory cells and demyelination consistent with ADEM. Treatment with IV MP and PLEX was initiated. The child subsequently had clinical improvement and decreased cerebral edema on imaging. She was discharged on hospital day 53 to acute rehabilitation. She improved in motor and speech but has significant learning deficits. 4 years later, she presented with new enhancing cortical and subcortical lesions and right optic neuritis. She tested anti-MOG antibody positive (1:100, not previously assessed).



Patient 3: A 6-year-old boy with recent pharyngitis presented with a 2 day history of somnolence. Initial exam demonstrated withdrawal to noxious stimuli and diffuse hyperreflexia. MRI brain revealed multiple areas of non-enhancing T2/FLAIR signal abnormality involving cortical and deep gray matter structures and periventricular and subcortical white matter. CSF showed 16 WBC with neutrophilic pleocytosis. ADEM was suspected and he was initiated on IV MP and PLEX on hospital day 1. On day 4 of admission (s/p 3 days steroids, 2 PLEX), he developed anisocoria and then fixed, dilated pupils. CT head revealed diffuse cerebral edema, loss of gray-white differentiation, and transtentorial herniation. He became hypotensive while undergoing CT and requiring vasoactive support for likely neurogenic cardiomyopathy. Medical management of ICP was initiated including mannitol, hypertonic saline, and pentobarbital. Neurosurgical intervention was felt to be contraindicated due to coagulopathy. Repeat MRI brain showed diffuse pattern of restricted diffusion consistent with hypoxic-ischemic injury. Serum testing for anti-MOG antibodies was positive, 1:10,000. He subsequently received IV cyclophosphamide and rituximab. After 3 weeks, he began to exhibit some signs of improvement including tracking family members. He spent total of 72 days in hospital and was discharged to inpatient rehabilitation. At 6 months following ADEM event, the child remains quadraplegic and largely non-verbal.



Patient 4: A 6-year-old boy presented with altered mental status after fever, URI symptoms, and diarrhea a week earlier. He exhibited head and neck pain, inability to walk, and was increasingly lethargic. When he presented to a local ED, CT head showed no acute findings. LP demonstrated WBC 372, glucose 63, protein 136, 0 oligoclonal bands, IgG index 3.17. He was initially treated for infectious meningoencephalitis and an MRI brain was not obtained. His mental status improved temporarily but he continued to complain of headache. On hospital day 6, he became increasing somnolent and then exhibited decorticate posturing. He became hypertensive and bradycardic and was intubated for worsening neurological status. Repeat CT showed effacement of the cerebral sulci and basal cisterns. He was treated with hyperosmolar agents and neurosurgery was consulted for placement of an ICP monitor. ICPs fluctuated with spikes in the 30-50 mmHg range. MRI brain showed extensive T2 signal abnormalities and restricted diffusion in the white matter. He was placed in a pentobarbital coma and paralyzed. He received IV MP and 7 treatments of PLEX. On day 12, ICPs fluctuated uncontrollably and a lumbar drain was placed, and required opening multiple times a day for ICPs exceeding 25 mm Hg for 5 minutes. On day 18, the patient began to spontaneously open his eyes. Day 21 MRI brain showed more confluent T2 signal abnormalities with some improvement in regions including cerebellum. No contrast enhancement was present and previous areas of restricted diffusion had significantly improved. MRI spine did not show any notable abnormalities. He was positive for anti-MOG antibodies (1:1000). IVIG was started following PLEX. Lumbar drain removed on day 22 and he was extubated on day 24. The patient began following simple commands and speaking on day 25 and was discharged to inpatient rehabilitation on day 34.



Conclusions

- Increased ICP is an uncommon but life-threatening complication of aggressive acute disseminated encephalomyelitis.
- This syndrome may be initially misdiagnosed was an infectious meningoencephalitis, leading to delays in initiating immunotherapy.
- Early signs of severe disease and increasing ICP includes headache, vomiting, and lethargy.
- Pupillary asymmetry, decorticate posturing, and Cushing's triad are late findings and often associated with rapidly increasing ICP and impending herniation.
- Both medical and surgical management strategies should be considered in fulminant cases of ADEM.
- Length of hospitalization is significant and acute rehabilitation is often indicated.
- Neurological morbidity results from both the primary demyelinating syndrome as well as secondary injury from elevated ICP.
- Recurrent demyelinating events were observed 4-8 years after ADEM for the patients with longer durations of follow-up.
- MOG antibodies can be associated with ADEM with fulminant demyelination, cerebral edema, and life-threatening increased ICP.
- Future directions include devising guidelines for escalation of medical and surgical management of ADEM associated with increased ICP and determining the impact of MOG serostatus and titer on ADEM severity and recurrence of CNS demyelination.

Disclosures

Dr. Greenberg has received grant support from the NIH, PCORI, NMSS, Guthy Jackson Charitable Foundation for NMO, Genentech, Chugai, Medimmune and Medday. He has received consulting fees from Alexion and Novartis. He serves on the advisory board for the Transverse Myelitis Association.

Dr. Wang's fellowship was supported by the Transverse Myelitis Association.