Case Report

Transient Myelin Oligodendrocyte Glycoprotein Antibody-positive Acute Disseminated Encephalomyelitis Following Influenza A Infection: A Rare Case

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Abstract

Acute disseminated encephalomyelitis (ADEM) is an uncommon disease generally with a preceding history of infectious illness. Here, we report a rare case of ADEM following influenza A infection with transient detection of anti-myelin oligodendrocyte glycoprotein (MOG) antibody in a young male patient who presented with extensive demyelination of brain and spinal cord, likely the result of dysregulated immune response from previous influenza A infection. The patient presented to the emergency with urinary retention and progressive ascending weakness of lower limbs. Magnetic resonance imaging (MRI) of the brain and spinal cord showed multiple ill-defined hyperintensities, suggestive of demyelination. The clinical presentation, MRI findings, cerebrospinal fluid examination, negative anti-aquaporin-4 antibody and metabolic and other viral infectious screening supported the diagnosis of ADEM. The patient had transiently positive anti-MOG antibodies (for 3 months) and was treated with intravenous immunoglobulin followed by oral prednisolone for 3 months. There was a significant recovery in the upper limb weakness and brainstem function. This case highlights the association of anti-MOG antibody with ADEM following viral infections and the need for prolonged follow-up to differentiate between transient antibodies from relapsing MOG antibody disease.

Keywords: Acute disseminated encephalomyelitis, glycoprotein, influenza, MOG antibody, myelin oligodendrocyte, viral infection

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INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is an uncommon disease with acute-onset multifocal white matter inflammation of the brain and spinal cord and a preceding history of infectious illness or, in rare cases, vaccination.[1] The disease is uncommon in adults with no specific biomarkers and set diagnostic criteria.[1] The diagnosis of ADEM is based on acute multifocal neurological presentation, magnetic resonance imaging (MRI) findings and exclusion of other demyelinating, infectious and metabolic disorders. ADEM has been reported in postinfectious illness of cytomegalovirus, Epstein–Barr virus, influenza, hepatitis A, human immunodeficiency virus, mycoplasma pneumonia or rarely, after immunizations.[2] About 50-75% of the ADEM cases have a preceding

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infection or vaccination; however, the causative pathogen is not always identified.[3]

The course is acute, usually monophasic, rapidly progressive with multifocal neurological symptoms requiring hospitalization.[1] The involvement of the peripheral nervous system is uncommon and associated with a worse prognosis.[1] The presence of anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in adult patients with ADEM is very rare.[4] Anti-MOG antibody-associated inflammatory demyelination has been reported after viral infections such as herpes simplex virus, Borrelia and Epstein–Barr virus infection.[5] The persistent presence of anti-MOG antibodies increases the risk of relapse and poor recovery, as compared to monophasic illness with transient antibodies.[4] The detection of anti-MOG antibodies thus needs periodical follow-up for 6 months to 1 year for a relapsing illness.[4] Here, we report the first case of ADEM in a patient with extensive demyelination of both brain and spinal cord along with transiently positive anti-MOG antibodies after influenza A infection.

CASE REPORT

A 38-year-old male presented to our emergency room with fever (39°C–40°C), retention of urine from 10 h, cough 6 days ago and no previous significant medical history. Urinary catheterization was done; bedside ultrasound showed no stone, and the urine sample was sent for microscopy and culture. The patient was advised for a routine visit to a urologist. However, the next day, the patient returned to the emergency room in a wheelchair because of weakness in the lower limbs. He was conscious and had neck stiffness and positive Kernig sign. His lower limbs were flaccid with areflexia (power grade 0/5 in the lower limbs and 5/5 in the upper limbs) and abdominal and bulbar reflexes were absent. No visual field defect was found, and fundoscopy was normal. The chest X-ray revealed no significant abnormality on admission. The patient was admitted in the high dependency unit for further assessment, where, in the subsequent 24 h, he became drowsy, and the peripheral oxygen saturation (SpO_2) dropped to 88% on room air [Figure 1a]. The repeat assessment showed the patient was dull, upper limbs were spastic and hyper-reflexic (power: Distal 4/5, proximal 5/5), lower limbs were flaccid (power: 0/5) and the gag reflex was poor.

He was intubated and started on invasive mechanical ventilation for airway protection and hypoxia. The chest X-ray on the second day revealed right upper lobe collapse/consolidation, likely due to aspiration because of the poor gag reflex. The patient was given postural drainage and chest physiotherapy, and a repeat chest X-ray was performed after 4 h that revealed re-expansion of the collapsed lung [Figure 1b and c]. T2 and fluid-attenuated inversion recovery imaging of the brain with contrast showed noncontrast-enhancing multiple ill-defined hyperintensities in multiple areas of the subcortical white matter of the brain and spinal cord [Figures 2a and 3a]. Cerebrospinal fluid (CSF) examination showed significant pleocytosis (810 cells/ml) with lymphocytic predominance, low glucose (49 mg/dl) and increased proteins (173 mg/dl) [Table 1]. A differential diagnosis of infective meningoencephalitis with transverse myelitis versus ADEM was considered. The tracheal secretions were positive for influenza A on polymerase chain reaction (PCR); aerobic and anaerobic cultures did not show any growth.

The patient was started on intravenous (IV) antibiotics (ceftriaxone 2 g once daily for 7 days and clindamycin 600 mg 8 hourly for 5 days), acyclovir and oral oseltamivir (for 5 days). Acyclovir was stopped once CSF-PCR for herpes simplex virus I and II were negative. IV immunoglobulin (IVIG) at 0.4 mg/kg/day was started for 5 days for a provisional diagnosis of ADEM. The motor weakness of both the upper and lower limbs improved by day 3 of IVIG and the patient was extubated on day 4. He was able to swallow and had a good gag reflex. Cell-based

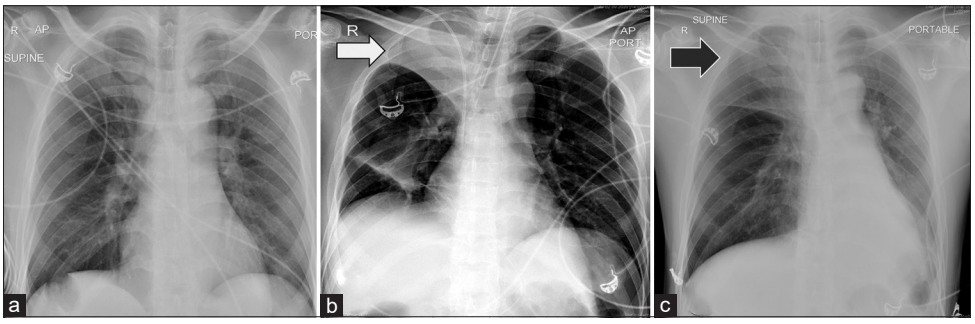

Figure 1: Chest X-ray after admission with no significant abnormality on day 1 (a) and day 2 with right upper lobe lung collapse (arrow) likely due to aspiration (b), which re-expanded (black arrow) with postural drainage and chest physiotherapy (c)

Table 1: Cerebrospinal fluid and significant laboratory investigations

	Day 1	Day 4	Day 14
Appearance	Slightly turbid	Slightly turbid	Clear
Total cells (0-5) (cells/mm^3)	810	140	20
DLC (%) lymphocytes, neutrophils	95, 5	94, 06	96, 04
Total protein (15-45) (mg/dl)	173.37	53.7	36.69
Glucose (50-80) (mg/dl)	49	77	69
Albumin (11-48) (mg/dl)	96		
IgG (0-8.6) (mg/dl)	17.8		
Index (IgG/albumin)	0.19		
Oligoclonal bands	Negative		
PCR for Enterovirus, HSV I and II and EBV	Negative		
Tuberculosis PCR	Negative		
Hemoglobin (g %)	15.1		
Total leucocyte count (×10^9/L) (neutrophil %)	13.06 (83)		
Platelets (×10^9/L)	334		
CRP (mg/L)/procalcitonin (ng/L)	47/0.02		
Anti-NMO antibody IgG	Negative		
Anti EBV (nucleocapsid, nuclear antigen) IgG and IgM antibodies	Negative		
Blood urea (mg/dl)/serum creatinine (mg/dl)	30/0.9		
Anti-HIV I and II antibodies	Negative		

DLC – Differential cell count; IgG – Immunoglobulin G; EBV – Epstein bar virus; HIV – Human immunodeficiency virus; NMO – Neuromyelitis optica; CRP – C-reactive protein; PCR – Polymerase chain reaction; HSV – Herpes simplex virus

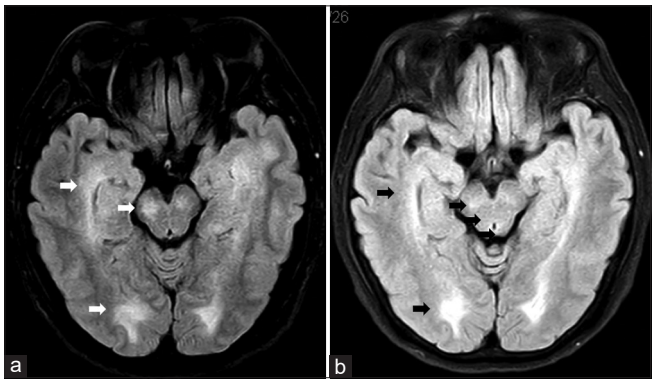

Figure 2: Fluid-attenuated inversion recovery brain imaging showing multiple ill-defined hyperintensities (arrows) at midbrain level. (a) Pretreatment, (b) Posttreatment (after 2 weeks)

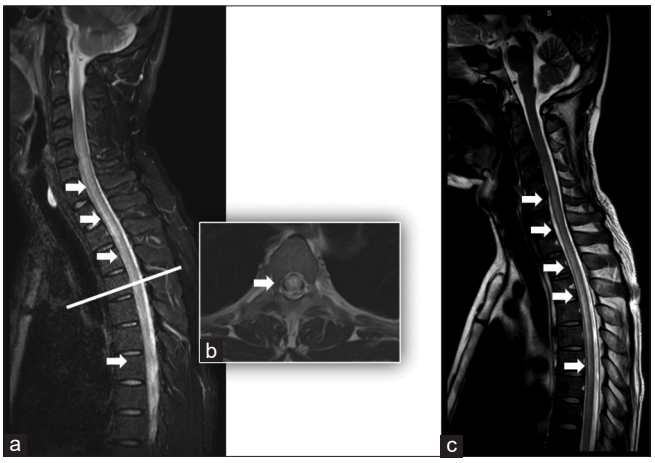

Figure 3: T2-magnetic resonance imaging spine showing long ill-defined hyperintensity of cord (arrows) from C3 to T8 vertebrae. (a) Pretreatment axial view, (b) Posttreatment (after 2 weeks) sagittal view at T4 and (c) axial view

assay showed a significantly high titer of anti-MOG antibodies (6289 U/mL). Oral prednisolone 40 mg once daily was started, and progressively tapered over 30 days to 20 mg/day. The follow-up MRI of the brain and spinal cord (2 weeks from admission) showed improvement in lesions [Figures 2b, 3b and c].

The patient was discharged on day 18 of admission with advice for monitoring blood sugar and any new symptoms such as fever, cough, and worsening of weakness. Oral prednisolone was continued for 3 months in tapering doses along with outpatient physiotherapy and rehabilitation. The anti-MOG antibodies became negative after 3 months. At 8 months, the patient had a residual neurological deficit of paraparesis (power: 2/5 of lower limbs) with sensory level up to D5, and areflexic bladder (on urinary catheter), while the anti-MOG antibodies were negative. The patient was advised continuous physiotherapy, rehabilitation and regular follow-up for anti-MOG antibodies titer for up to 3 years, with consideration of immunomodulators in the case of anti-MOG antibodies reappearance.

DISCUSSION

To the best of the authors' knowledge, this is the first case where extensive demyelination was detected simultaneously in the brain and spinal cord following influenza A infection, with transient anti-MOG antibodies.

ADEM in adults is a diagnosis of exclusion, always necessitating exclusion of metabolic, demyelinating and infectious disorders.[1] The ADEM diagnostic criteria[1] require presence of all of the following: 1. polyfocal

clinical neurological event explained by inflammatory demyelination, 2. presence of encephalopathy, 3. brain MRI abnormalities consistent with demyelination and 4. monophasic illness (with no new clinical or MRI findings after ≥3 months from the onset of clinical symptoms). The CSF analysis can show lymphocytic-dominant pleocytosis (white cell counts usually <100 cells/ml) with a mild increase in CSF protein (<70 mg/dl).[1] ADEM is reported postvaccination or after viral infection including influenza A infection and likely is a result of viral antigen-induced autoimmune priming due to molecular mimicry.[1,2]

MOG antibody disease (MOG-AD) is a recently coined term characterized by inflammatory demyelination of the central nervous system, with a median incidence in the fourth decade of life.[6] The different phenotypes reported in MOG-AD are optic neuritis (most common form with incidence 54%–61%), transverse myelitis, ADEM or an ADEM-like presentation (e.g., brainstem attack).[6] The involvement of both CNS and peripheral nervous systems is uncommon (2.5%) and reported with a worse prognosis.[7] ADEM presentation of MOG-AD is uncommon in adults and associated with relapsing course and poor outcomes.[6,7] Preceding viral infections such as herpes simplex virus, Borrelia and Epstein–Barr virus infections or, in few cases, vaccination are known to trigger transient anti-MOG antibodies.[6,8-11]

ADEM without anti-MOG antibodies is conventionally a monophasic disease, while the presence of MOG-antibodies increases the risk of relapse.[1,6] Relapses are frequently observed either during the weaning or within 2 months of withdrawal of corticosteroids.[4] The factors that increase the risk of relapse include treatment with corticosteroids for <3 months, persistent seropositivity (anti-MOG antibodies), high initial antibody titers and adult patients. The residual disability in patients with anti-MOG antibodies is also common (reported in up to 47% of the patients).[7] The presence of transverse myelitis is an important predictor of residual neurological deficit.[6]

The diagnosis of ADEM along with detection of anti-MOG antibodies thus requires follow-up for 6 months to 3 years to differentiate transient antibodies from multiphasic MOG-AD.[6]

As there are no clinical studies available in patients with MOG-AD or ADEM along with anti-MOG antibodies, treatment protocol follows that of the anti-aquaporin-4 neuromyelitis optica (AQP4−NMO) disorder.[4] The principle of treatment includes acute management and disease-modifying treatment. For acute treatment, IV methylprednisolone is the initial drug of choice and if high-dose corticosteroids fail or are contraindicated, plasma exchange or IVIG can be initiated.[1,4] In terms of disease-modifying treatment, long-term treatment with low-dose steroids (prednisolone dose of >10 mg/day for adults >40 kg), IVIG (monthly dose of 1 gm/kg infusion) or immunomodulators (such as mycophenolate mofetil, azathioprine or rituximab) have been used to reduce risk of relapse.[12]

In our case, the acute clinical presentation (fever, neck stiffness and multifocal neurological deficit), history of preceding respiratory infection with influenza A, MRI findings, absence of CSF oligoclonal bands and negative AQP4-NMO antibody supported the diagnosis of ADEM. Our patient had significant CSF cellularity (810 cells/ml) and protein (173 mg/dl) [Table 1]. The right upper lobe collapse, in this case, was likely due to aspiration of mucus plug with poor gag reflex, which relieved with postural drainage. The diagnostic work for other infectious etiology was negative and CSF analysis after IVIG showed progressive resolution [Table 1]. The CSF hypercellularity was likely the result of extensive encephalomyelitis. The patient was given IVIG over IV methylprednisolone because of the rapid deterioration and initial possibility of an infective pathology (high cellularity in CSF). The single event with transient anti-MOG antibodies was likely a dysregulated immune response following the influenza A infection. However, the patient had residual disability even after 8 months and this could be related to the protracted course observed with anti-MOG antibodies.

CONCLUSION

The association of anti-MOG antibody with ADEM is uncommon after a viral infection such as influenza A and needs a prolonged follow-up to differentiate between transient antibodies triggering from MOG-AD.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given consent for his images and other clinical information to be reported in the Journal. The patient understands that his names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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