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Fulminant Acute Disseminated Encephalomyelitis in An Adult: A Case Report and Review of Literature

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Abstract

Acute disseminated encephalomyelitis (ADEM) is an acquired autoimmune disease that results in demyelination of the central nervous system. The condition is predominantly a childhood illness precipitated by vaccines or infections. However, it can occur in adults and is associated with worse prognosis. Here, we describe an adult patient who was initially diagnosed with a psychiatric illness, but had rapidly progressive neurological deterioration, which led to investigation of other causes. MRI brain was also progressively worsening and showed extensive tumefactive process. The atypical onset of age, fulminant progression (clinically and radiologically) and absence of typical preceding inciting event posed uncertainty in diagnosis. Nevertheless, ruling out most causes and considering autoimmune inflammation as likely pathophysiology, all tiers of immunomodulatory therapy were tried. Treatment failed to hasten recovery, but ultimately there was some improvement with residual neurological deficits. Alternatively, a diagnosis of Marburg disease, a fulminant type of multiple sclerosis (MS) was also considered. Only time will tell whether the process is monophasic (ADEM) or will there be relapses and recurrences (MS) to clearly distinguish between these two.

Keywords: Acute Disseminated Encephalomyelitis; ADEM; Autoimmune Encephalitis; Acquired Demyelinating Disease; Case Report; Marburg Disease; Anti-MOG Antibody

Abbreviations: ADEM: Acute Disseminated Encephalomyelitis; CIS: Clinically Isolated Syndrome; CNS: Central Nervous System; GCS: Glasgow Coma Scale; IVIg: Intravenous Immunoglobulin; MRI: Magnetic Resonance Imaging; MOG: Myelin Oligodendrocyte Glycoprotein; MS: Multiple Sclerosis; NMO-SD: Neuromyelitis Optica- Spectrum Disorder; ON: Optic Neuritis

Introduction

Acute disseminated encephalomyelitis (ADEM) is a rare neurological disorder characterized by an autoimmune insult in response to infection or immunization, resulting in demyelination of the neurons in the central nervous system. The condition predominantly occurs in paediatric population. In adults, it is not a common occurrence and is associated with less favourable outcome. Here, we describe a 26 years lady who presented with rapidly progressive neurological deterioration with MRI brain showing extensive demyelination suggesting a rare fulminant variant of ADEM and posed several challenges in diagnosis, management as well as prognostication.

Case report

A 26 years old lady presented with 2 days history of speech difficulty, confusion and bilateral lower limb weakness. Her past medical history was only significant for recent diagnosis of anxiety and depression, for which she was on fluoxetine. She had no history of drug or alcohol abuse and her menstrual cycles were normal. A diagnosis of panic disorder was made and she was discharged on promethazine. However, her symptoms worsened within 24 hours. She became increasingly drowsy, confused, and had multiple episodes of tonic-clonic seizures, so she was readmitted.

An initial suspicion of serotonin syndrome was made due to a possible interaction between fluoxetine and promethazine, and thus treatment started with cyproheptadine. Blood reports showed high inflammatory markers (white cell count of 14.2 and C-reactive protein of 196). Further studies were also done to investigate for other causes. CT head with venogram was normal. Cerebrospinal fluid (CSF) analysis showed a white cell count of only 3/mm3 with a slightly raised protein of 67mg/dL on a background of hemorrhagic tap (red blood cell 4500/mm3).

She was intubated for persistently low GCS and to facilitate an MRI. The MRI showed diffuse symmetrical T2/FLAIR hyperintensities involving deep and subcortical white matter, internal capsule, pons, cerebellum with diffusion restriction

and enhancement, which was suggestive of acute disseminated encephalomyelitis (Figure 2). She was then started on pulse methylprednisolone. However, after 3 doses, she showed no signs of clinical improvement. Treatment was escalated to a 5-day course of intravenous immunoglobulin (IVIg). As she remained unresponsive, a tracheostomy was performed and transferred to our hospital for the possibility of plasma exchange.

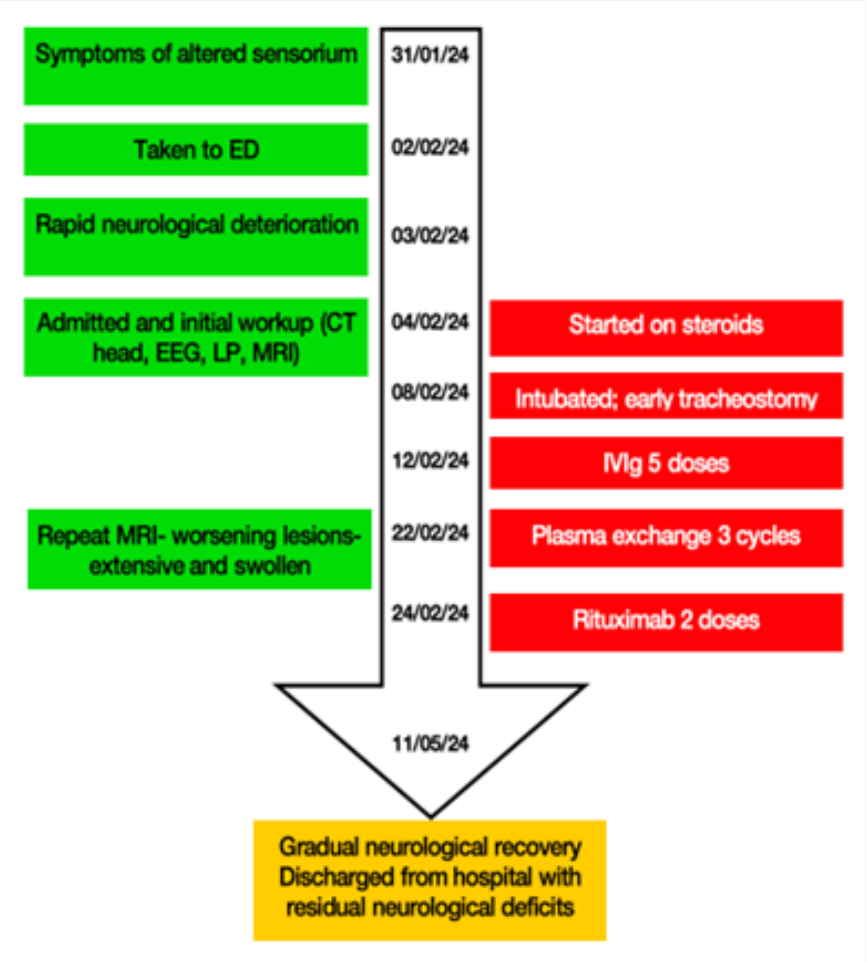

Figure 1: Clinical course of the patient.

On arrival to our hospital, her GCS was E3M2VT. She had decerebrate posturing, roving eye movements, massively dilated (7mm) but equal pupils, and bilateral blurred fundal discs. Her muscle tone was increased, and her deep tendon reflexes were greatly exaggerated (grade 4). She showed extensor plantar response and a sustained ankle clonus. She had no mucosal ulcers, suggestive of Behcet's disease.

A repeat MRI showed extensive areas of signal abnormality, which appeared swollen and extended from the subcortical white matter along the corona radiata into the posterior limb of internal capsule, cerebral peduncles, cerebellar white matter, cerebellar peduncle and central medulla (Figure 3). A conclusion of aggressive inflammatory or demyelinating or tumefactive process was made with differentials of ADEM, post viral, acute necrotising encephalopathy.

To determine the cause, a whole panel of investigations were sent that included tumor markers, autoimmune panels, paraneoplastic screen, specific antibody screen as well as an extended viral panel and a porphyria screen (Table 1), but all were negative. EEG showed non-specific encephalopathic changes without evidence of seizure activity. Meanwhile, she was started on plasma exchange. No improvement was observed even after 3 cycles. A neuroinflammatory multidisciplinary team meeting concluded that there was clinical and radiological deterioration despite steroids, IVIg and plasma exchange; and a trial of rituximab was warranted. Despite receiving 2 doses of rituximab, her progress was very slow. After around 3 months of total hospital stay, she was discharged on long term steroid and antiepileptic therapy. She still has significant disability and continues to require assistance for activities of daily living (Figure 1).

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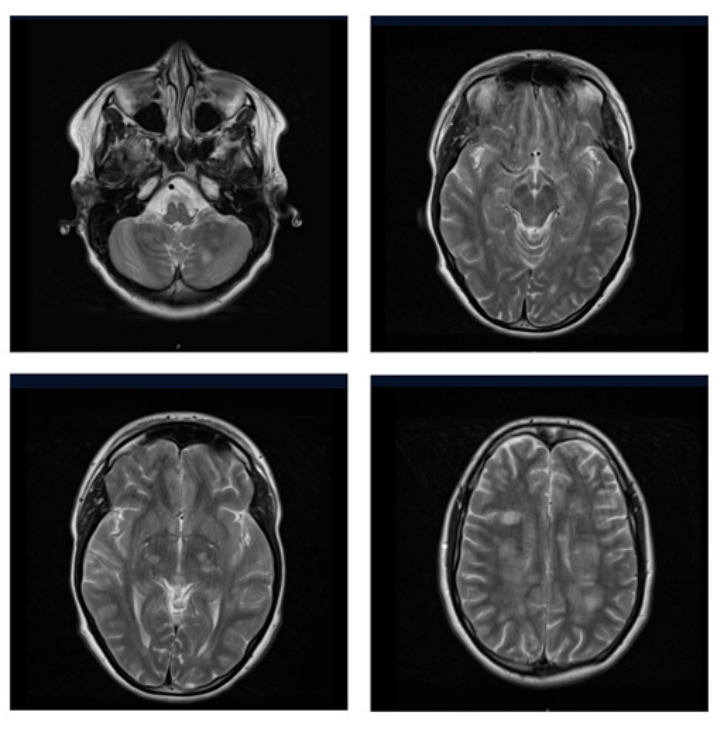

Figure 2: Initial MRI showing hyperintense lesions in cerebellum, brainstem, basal ganglia and subcortical white matter.

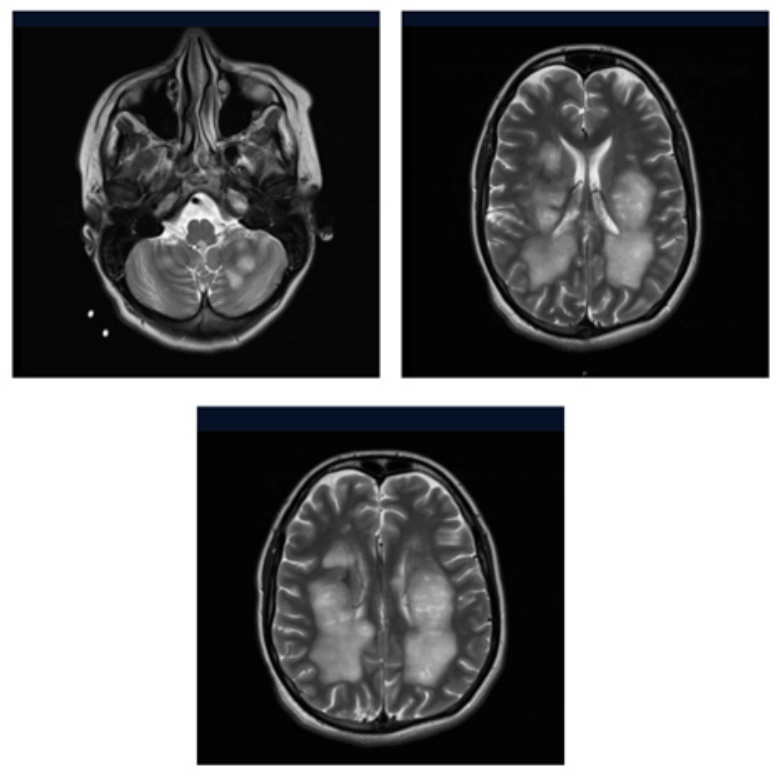

Figure 3: Repeat MRI showing worsening of lesions compared to previous.

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Table 1: Investigations done for cause of encephalitis.

Tumor markers	Autoimmune/ Connective Tissue Disease Screen	Paraneoplastic Screen	Specific Antibody Screen	Other Investigations
AFP 6 CEA 1.2 Ca19-9 21.5 Ca125 14.2 hCG < 1	ANA, RF, dsDNA LKM, SM, U1RNP, SSA (Ro), SSB (La), CENP, Scl-70, Jo-1, Fibrillarin, RNA Pol III, Rib-P, Pm-Scl, PCNA, Mi-2	NMDA Ab Voltage gated K channels MPO/PR3 Ab GAD Ab Antineuronal Ab (Yo, Hu, Ri)	Anti-MOG Ab Aquaporin 4 Ab Fixed NMDAR Ab ANTI-VGCC Caspr2 Ab Lgi1 Ab	Porphyria screen Extended viral panel Glycine Abs (PERM)

Discussion

ADEM is an acute monophasic autoimmune disorder of the central nervous system (CNS) that results in demyelination of the axons. Its temporal relation to viral infections (e.g. measles) and vaccines, were already evident since the 18th century. Improvement in health care led to a decline in the prevalence of viral infections and production of purified vaccines. As a result, ADEM is now much rarer, with a worldwide incidence of 0.2-0.5 per 100,000 [1]. As the name implies, ADEM is an acquired demyelinating disease. This group of diseases includes other conditions such as multiple sclerosis (MS), optic neuritis (ON), transverse myelitis, neuromyelitis optica- spectrum disorder (NMO-SD), clinically isolated syndrome (CIS) as well as some overlapping conditions [2]. Due its autoimmune mechanism, it is also classified under a spectrum of acquired autoimmune encephalitis, which can be grouped into different subsets based on the implicated antigen.

These include intracellular proteins (Hu, Ma2, GAD), synaptic receptors (NMDA, AMPA, GABA, dopamine 2) and cell- surface proteins including ion channels (GQ1B, LGI1) [3]. One cell surface protein that has been implicated in the causation of ADEM is the myelin oligodendrocyte glycoprotein (MOG).3 Although there are a proportion of ADEM cases where anti MOG antibody may be absent, the presence of anti MOG antibody may have some prognostic significance. ADEM is more common in children and young adults. A multicenter population based prospective study that investigated causes and clinical presentations of encephalitis in England, reported around half of ADEM cases to have occurred in the age group 1-4 years and almost 80% occurring in those below 19 years [4].

Diagnosis of ADEM is challenging. Over 80% of the time, it is misdiagnosed on the first visit [5]. Clinical features are non-specific. Common symptoms include fever, headache and vomiting, as in all meningoencephalitis syndromes. Patients usually present after they develop altered mental status. They may be misdiagnosed initially as other conditions and may take over a week after the initiation of symptoms until ADEM is suspected. [5] A diagnostic criteria has been developed by The International Pediatric Multiple Sclerosis Study Group in 2013 to help standardize the definition, and include 1) a polyfocal CNS event with presumed demyelinating cause, 2) encephalopathy not explained by fever, 3) No new clinical/ MRI findings ≥ 3 months after the onset, and 4) abnormal MRI findings in the acute phase [6]. There are no separate criteria for adults, and the same criteria have been adopted.

Table 2: Key differences between ADEM and MS.

ADEM	MS
Widespread CNS involvement with encephalopathy	Partial CNS affection
Bilateral optic neuritis	Unilateral optic neuritis
Monophasic	Recurring
Prior history of infection/ vaccination- 60% (35% have serological evidence, mainly Mycoplasma)	Prior history of infection/vaccination absent
CSF oligoclonal bands - absent/ transient	CSF oligoclonal bands- Positive/permanent
Perivenular inflammation	Located around large cerebral veins

The most common differential diagnosis is multiple sclerosis, which is also an acquired demyelinating disease. However, there are several clinical, radiological and pathological differences, which may help differentiate MS from ADEM (Table 2). Although anti MOG antibodies are implicated in the causation of ADEM, its inclusion has not been yet considered in the diagnosis due to several reasons. Firstly, antibodies can be present in demyelinating disorders with encephalopathy, but without MRI features of ADEM. Secondly, antibodies can be present in patients with demyelinating disorders even without encephalopathy. Lastly, antibody testing remains unavailable at many centers [7].

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Treatment of ADEM includes supportive care of a patient with disordered consciousness, such as airway protection and mechanical ventilation and control of symptoms such as seizures and dysautonomia. The definitive treatment, however, is immunomodulatory therapy, of which pulse methylprednisolone for 3 to 5 days remains the first line of choice. If the disease does not respond to steroids, then either intravenous immunoglobulin or plasma exchange can be tried as a second line therapy. For that refractory to even second line therapy, immunosuppressants such as rituximab or cyclophosphamide can be used [8].

Recovery is generally good. Even spontaneous improvement without any therapy is possible, though, the likelihood of recovery in such cases can be incomplete. In adults, however, the prognosis is less favorable compared to children. Studies show that adults with ADEM have longer hospital stays, a higher likelihood of requiring ICU admission, a greater chance of incomplete recovery as well as worse survival chances. The mortality rate has been reported to be approximate 12% in adults in contrast to only 1% in children. The probability of death or disability has been estimated to be around 30% in adults [9-11]. There are case reports similar to this, where the patients did not respond to any treatment modality [10,12]. Apart from age, other risk factors associated with a poor outcome include a low GCS and seizures at presentation [11].

Although, ADEM is typically considered to be a monophasic process, and it is this characteristic that helps distinguish it among other conditions, there have been cases of relapses and recurrences, which makes the diagnosis even more challenging. These may occur in multiphasic ADEM, or when there is an overlap with other conditions such as optic neuritis (ADEM-ON), MS (ADEM-MS), or NMSOD (ADEM-NMSOD). Marburg disease, a rare type of MS has a rapidly progressive course and sometimes is considered a variant of ADEM when monophasic. If antiMOG antibodies are positive, then monitoring their levels can help predict recurrences [13].

Conclusion

To summarize, this was a rare case of ADEM in an adult with a fulminant course refractory to all modalities of immunotherapy. A proper diagnosis can be difficult to make because of non-specific clinical and radiological findings and presence of overlapping conditions. Absence of any preceding implicating event such as infection or immunization, and absence of anti-MOG antibody, in our patient made the diagnosis even more challenging. It still remains to see whether the patient will have further recurrences and relapses, which could alter the diagnosis. A diagnosis of Marburg disease has also been considered, of which only 349 cases have been reported [14]. Overall, evidence is scarce with lack of high-quality studies and much understanding has been based on case reports and series. Research related to biomarkers, such as MOG antibodies, could be beneficial in providing better insights to the pathophysiology, diagnosis, management and prognosis of ADEM and related diseases.

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