Case Report

# Hyper Acute Demyelinating Encephalomyelitis of Childhood: A Rare Entity

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## Abstract

A young child with catastrophic neurological illness diagnosed as a rare variant of acute demyelinating encephalomyelitis (ADEM). She succumbed to her illness despite of aggressive and appropriate management. Malignant demyelinating encephalomyelitis should be considered in children who are refractory to the treatment of ADEM.

**Keywords:** Acute demyelinating encephalomyelitis, malignant, refractory, treatment

## Introduction

Acute disseminated encephalomyelitis (ADEM) is an acute widespread demyelinating condition usually affecting young adults and children. It usually follows an infection or vaccination causing demyelination in brain and spinal cord. Failure to identify a viral agent suggests that the inciting agents are unusual or cannot be recovered by standard laboratory test. Possibly, a complex interplay among cytokines, chemokines, and adhesion molecules is responsible for the cellular events of inflammatory encephalomyelitis. Management consist of immunomodulation targeted to suppress a presumed aberrant immune response to an infectious agent or a vaccination. Malignant variants of ADEM, represent 2% of cases with catastrophic rapid symptom progression, malignant brain edema, non-responsiveness to treatment and high mortality rates.

## Case Report

A 15-year-old female presented with short history of acute onset bilateral vision loss and left-sided hemiparesis of 7 days' duration. These symptoms were preceded by a febrile illness 8–10 days back. The symptoms were sudden in onset and progressive in nature. There was no prior history of significant medical illness, drug or toxin exposure, and seizure or loss of consciousness. Personal and family history was noncontributory.

On admission, the initial evaluation, she was afebrile and her vitals were stable. The Glasgow coma scale was 15 with no signs of meningism. She had visual acuity limited to the perception of lights in both eyes. Fundoscopic examination and pupils were normal. Other cranial nerve examination was normal. Motor system examination showed 4/5 power in the left upper and lower limb with 5/5 on the right side. Deep tendon reflexes were exaggerated in all 4 limbs and planters equivocal on the right and extensor on the left. Routine hematological and biochemical investigations were normal. Cerebrospinal fluid (CSF) study revealed acellular aspirate with raised protein (53 mg/dl) and normal sugar levels. Magnetic resonance imaging (MRI) brain with contrast showed ill-defined T2 and fluid-attenuated inversion recovery (FLAIR) hyper intensity predominantly involving the subcortical white matter at the gray-white matter junction in the right frontal, bilateral parietal lobes with patchy restricted diffusion in these areas [Figure 1]. There was no blooming or parenchymal enhancement associated with these lesions. A diagnosis of postinfectious acute demyelinating encephalomyelitis (ADEM) was kept based on clinical history, evaluation and neuroimaging findings. The patient was started on 500 mg intravenous (IV) methylprednisolone pulse therapy followed by 40 mg of oral steroids.

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On further investigations, to rule out the cause of etiology for ADEM, screening for possible organism, i.e., herpes simplex (HSV), *Enterovirus*, tuberculosis, leptospira, chlamydia, *Legionella,* and dengue infection were done and found to be negative. Immunoglobulin M (IgM) for varicella zoster was mildly positive. HSV polymerase chain reaction was negative. ELISA for human immune deficiency virus (HIV) was nonreactive. Visual evoked potential was normal bilaterally. Electroencephalogram showed slow background without any spike and wave discharges. Routine chest X-ray and ultrasound abdomen were normal. Blood and urine cultures were negative, Malarial Parasite ELISA and IgM - Typhidot was negative. Her vasculitis profile was negative. CSF and serum were negative for antimeasles antibody.

On 3rd day, the patient had started deteriorating clinically despite steroid pulse therapy. She became confused and agitated. The clinical examination revealed bradycardia and increase blood pressure with decreasing level of consciousness has raised the suspicion of raised intracranial pressure (ICP). Injection mannitol 100 ml thrice daily added as a decompressive therapy. A serial MRI brain showed increase in lesional size and extent with widespread edema, increase in hyperintensities on T2 and FLAIR in the right frontal, left temporoparietal, and bilateral occipital lobes, distal body, and selenium of the corpus callosum. Effacement of the regional sulci was seen. There were patchy restricted diffusion and patchy contrast enhancement seen in involved regions of bilateral cerebral hemispheres [Figure 2]. Repeated screen for sepsis and other organ dysfunction were noncontributory. On day 7, patient's conscious level further declined, and she was electively ventilated. A study of aquaporin antibodies and oligoclonal bands was negative. The patient became comatose and started having intermittent decerebrate posturing with horizontal roving eye movements suggestive of widespread cerebral dysfunction. She was started on IVIgs (0.4 g/kg/day for 5 days). She did not improve, and meanwhile, a trephine biopsy of the brain was done from her lesion in the left parietal area on day 7.

The biopsy showed extensive demyelinating changes confirming our diagnosis of demyelination possibly postinfectious [Figure 3]. As she was not recovering, cyclophosphamide IV (60–120 mg/m²/day) (1–2.5 mg/kg/day) was given to her. Despite optimal available medical treatment, the patient did not recover and became vegetative and finally succumb to her illness after 20 days of admission.

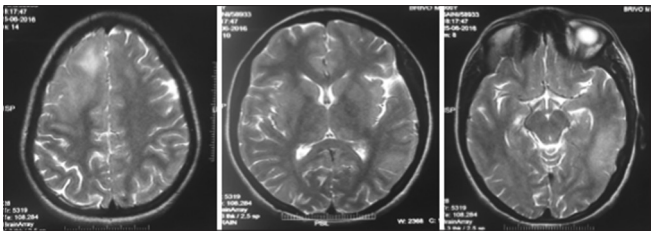

**Figure 1:** Magnetic resonance imaging brain showing – T2-weighted images showing bilateral white matter hyperintensity in parietal, temporal lobes

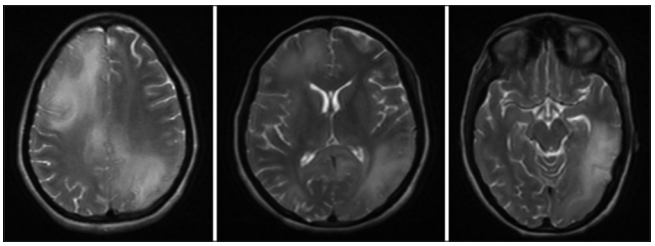

**Figure 2:** Magnetic resonance imaging brain T2 showing increase in lesion size and extent with widespread edema, increase in hyperintensities in the right frontal, left temporoparietal, and bilateral occipital lobes, distal body and selenium of the corpus callosum as compare to Figure 1

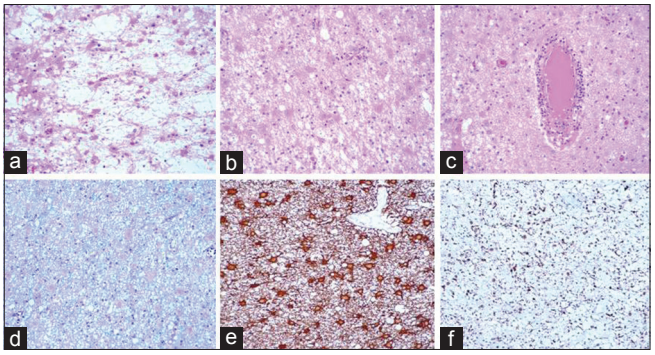


**Figure 3:** (a) Histopathology showing hypocellular loose areas (H and E, ×200). (b) Prominent large astrocytes (H and E, ×200). (c) Perivascular lymphocytic collection (H and E, ×200). (d) Widespread myelin loss (Luxol Fast Blue, ×200), (e) Glial fibrillary acidic protein-positive astrocytes (×200). (f) Decrease in preserved axons (NeuroFilament Protein, ×200)

## Discussion

ADEM is an immune-mediated inflammatory disorder that predominantly involves the white matter of the brain and spinal cord. It preferentially affects children and young adults with an estimated prevalence of 0.8 per 100,000.[1,2]

The clinical diagnosis of ADEM is made by the temporal relationship between the acute onset of the neurological deficit with encephalopathy following the history of febrile illness and vaccination. Only 5% of the ADEM cases are attributed to be due to immunization. The systematic symptoms begin 4–21 days after the febrile illness. The presentation of neurological deficit can be heterogeneous depending on the location of the white matter tracts involvement which can be seen on neuroimaging. Encephalopathy is characteristically found and progress rapidly with multiple neurological deficit. The severe phase of ADEM usually lasts for 2–4 weeks. Hyperacute or malignant variants of ADEM, which represent 2% of cases, are associated with rapid symptom onset and progression, malignant brain edema, and high mortality rates due to herniation of brain.[1,3] The acute onset and rapid progression of the of symptoms of our case resemble the clinical profile of hyperacute ADEM. Malignant disseminated encephalomyelitis and acute hemorrhagic leukoencephalitis (AHLE) may be a part of the spectrum of

the central nervous system (CNS) demyelinating disease, the clinical differentiation is difficult. Autoimmune process is the basic pathology is in both. AHLE is a rare and fulminant demyelinating disease considered to be the most severe form of ADEM. AHLE is diagnosed with neuroimaging and presence of hemorrhage in biopsy findings. The closest differential diagnosis of white matter involvement is multiple sclerosis is being ruled out on evaluating the clinical profile and the neuroimaging which shows the lesions are asymmetric and typically spares the periventricular area which differentiates it from multiple sclerosis. The T2-weighted and FLAIR images define the white matter involvement in ADEM. The lesions are usually bilateral and multiple in deep cortical and subcortical areas. Lesions are asymmetrical and poorly defined, thalami and basal ganglia are frequently affected. Brain stem and spinal cord involvement are commonly seen.[4,5] CSF may be normal, but frequently it shows some changes. Typical CSF changes include increased pressure, lymphocytic pleocytosis (as much as 1000/mm$^3$, sometimes polymorphonuclear leukocytosis initially), and raised protein (usually <1.0 mg/l).

The pathogenesis of ADEM is not completely understood, and it is considered to be an autoimmune response causing inflammation affecting the CNS secondary to the direct inoculation by the neurotropic pathogens. There are consistent findings of nonspecific febrile illness preceding the onset of the disease all over the world.[6] In developing countries, due to poor implementation of immunization programs and poor hygiene practices measles and other viral infections are still widely prevalent and account for frequent occurrences of postinfectious demyelinating diseases. ADEM in developing countries is much more frequent than reported. Viral infections such as measles, rubella, and mumps have been reported in the Indian studies.[7,8] Although our patient had a history of febrile illness, the screening for the common virus was negative. Numerous causative agents have been identified all over the world; some of them include *Coronavirus*, coxsackie virus, *Cytomegalovirus*, Epstein-Barr virus, HSV virus, hepatitis B virus, HIV, influenza, measles, rubella, and West Nile virus.[1] Failure to identify a viral agent suggests that the inciting agents are unusual or cannot be recovered by standard laboratory methods.[9]

Treatment usually consists of supportive therapy and steroids. Initially, IV steroids (10–30 mg/kg/day up to maximum dose of 1 g/day) in acute phase followed by oral steroids tapered over 3–6 weeks. The patients usually respond to steroid therapy within few days to weeks. In cases where corticosteroids have failed to work, use of plasmapheresis or IVIG has been shown to produce dramatic improvement.[10,11] Severe cases of ADEM require the combination of immunosuppression with cyclophosphamide and mitoxantrone.[3,12] The management of raised ICP consists of intubation and controlled ventilation, elevation of the head of the bed, administration of analgesics, sedatives, and paralytics, and IV mannitol (1 g/kg) with placement of an ICP monitor as done in our case. A group from mayo Keegan *et al*. recently reviewed 59 consecutive patients with plasma exchange for acute severe attacks of CNS demyelination at the Mayo clinic, and it was concluded that certain factors such as male sex, preserved reflexes, and early initiation of treatment were associated with improvements. Successfully treated patients improved rapidly after plasma exchange, and improvement was sustained. In some cases, cytotoxic agents have been used with success.[13] The mortality varies between 10% and 30%, with complete recovery in 50%. Poor prognosis is correlated with severity and abruptness of onset of the clinical syndrome as in our case who has fulminant course with rapid onset and progression of symptoms leading to raised intracranial tension and refractory to the standard timely treatment.

Our patient's presentation with headache, irritability, and hemiparesis that had progressed to stupor, decerebrate rigidity, coma, respiratory failure, or death due to herniation from severe intracranial hypertension along with radiological and biopsy-proven evidence and nonresponse to the optimal treatment qualifies for the malignant variant of ADEM which is rarely been described.

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### Conflicts of interest
There are no conflicts of interest.

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