

NEUROLOGY

ACUTE DISSEMINATED ENCEPHALOMYELITIS IN CHILDREN

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Abstract: *Acute disseminated encephalomyelitis is a demyelinating inflammatory disorder characterized clinically by acute-onset polyfocal neurologic deficits and encephalopathy and fluffy white matter lesions radiologically. Antecedent factors include infections, vaccinations and others. Usually, a monophasic illness, recurrences should raise a suspicion of a relapsing disorder such as myelin oligodendrocyte glycoprotein associated demyelination or multiple sclerosis. Investigations are warranted to rule out other causes of encephalopathy. Management includes immunomodulation with high dose pulse methylprednisolone, intravenous immunoglobulin and/or plasmapheresis. Prognosis depends on the recovery after the acute stage and the risk of recurrent demyelination.*

Keywords: *Demyelination, Acute disseminated encephalomyelitis, Myelin oligodendrocyte glycoprotein associated demyelination, Neuroinflammation.*

Acute disseminated encephalomyelitis (ADEM) is a demyelinating disorder of the central nervous system (CNS). It is common in children and is usually regarded as a monophasic illness often heralded by infection. It is characterized by acute onset polyfocal neurologic deficits and encephalopathy clinically. Radiologically, fluffy demyelinating lesions in the white-matter of the brain and or spinal cord with or without involvement of deep gray matter are seen. The widely followed diagnostic criteria for ADEM were initially delineated by the International

Box 1. Diagnostic criteria for ADEM

- A first polyfocal clinical CNS event with presumed inflammatory demyelinating cause
- Encephalopathy (unexplained by fever, systemic illness or post ictal symptoms)
- Brain MRI consistent with demyelination during the acute (less than 3 months) phase
- No new clinical or MRI findings 3 months or more after the clinical onset

Pediatric Multiple Sclerosis Society Group in 2007 and revised in 2013 (Box 1).^{1,2}

ADEM is one of the childhood acquired demyelinating syndromes (ADS) which comprise a group of immune-mediated disorders of CNS. These include characteristic clinico-radiologic-pathological syndromes with neurological deficit and encephalopathy, features of CNS demyelination on neuroimaging and pathology.¹ ADS may be monophasic or recurrent. Monophasic ADS include ADEM (may be recurrent), optic neuritis (ON), transverse myelitis (TM) and clinically isolated syndromes (CIS). The recurrent ADS classically include myelin-oligodendrocyte-glycoprotein (MOG) associated demyelination, neuromyelitis optica spectrum disorder (NMOSD) and multiple sclerosis (MS).

Epidemiology

The incidence of ADEM varies from 0.3 to 0.6 per 100,000 children per year with a seasonal predilection for winter and spring.^{3,4} The mean age at presentation is 3.6 - 7 years, with slight male predominance.³⁻⁵ A viral infection usually precedes ADEM by two days to four weeks.^{3,6} Other antecedent factors include vaccination such as influenza, polio, hepatitis B, rabies, measles, mumps, rubella, diphtheria, tetanus, pertussis, etc. It is important to note that besides ADEM, vaccination has also been associated with other demyelination syndromes such as Gullain Barre syndrome, optic neuritis and myelitis.⁷ However, the causality of these associations is debatable and the association of an antecedent infection is much more common than a preceding vaccination.³

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Pathophysiology

The exact etiopathogenesis of ADEM is unclear. The proposed hypothesis includes specific antibodies elicited after molecular mimicry such as anti-MOG antibody stimulating inflammatory cascade leading to demyelination. Additionally, B cell pathways, regulatory T cells and helper T cells have also been implicated.^{3,8}

Clinical presentation, course and classification

ADEM has varied clinical presentations. The clinical course consists of a non-specific prodrome (fever, headache, etc., lasting for 3-4 days) followed by neurological symptoms.³ The site of lesions determines the clinical features. Encephalopathy remains mandatory for the diagnosis of ADEM (Box 1). Other features may include fever, cranial nerve palsies, diminution of vision, seizures, paresis, pyramidal signs, cerebellar signs, etc. Although the maximum deficits are usually seen within 2-5 days, the clinico-radiological findings may evolve over the initial three months. The appearance of any new findings beyond three months is considered a second event. ADEM, though classically considered as a monophasic illness, maybe consequently diagnosed as an initial presentation of recurrent ADS such as MS, NMOSSD, or MOG associated demyelination.⁹⁻¹¹

MOG is a small component of the myelin exclusively expressed in CNS. Anti-MOG antibodies are a common association in pediatric ADEM. MOG associated demyelination frequently affects the spinal cord and optic nerve and is associated with a relapsing course.⁸ Furthermore, younger children may have more severe illness due to immaturity of myelin, leading to secondary injury and permanent axonal loss.

ADEM may be classified retrospectively based on the clinical course and relapses. The subtypes include monophasic ADEM, multiphasic ADEM, acute hemorrhagic leukoencephalitis (AHLE) and ADEM optic neuritis (ADEM-ON).²⁻⁴ Monophasic ADEM refers to a single event without any recurrence or a phenotype of AHLE. The term recurrent ADEM is not used as per recent terminology. A second event with encephalopathy, three months beyond the initial event, is referred to as multiphasic ADEM. More than two episodes suggest a different diagnosis such as MS, depending on the clinicoradiological and serological profile. ADEM-ON includes patients with monophasic or multiphasic ADEM with one or more episodes of optic neuritis and is classically associated with

anti-MOG seropositivity.⁸ Multifocal hemorrhages and necrosis, along with demyelination, characterize AHLE. This condition has a grave prognosis and is often life-threatening.^{3,12} The diagnosis of MS is established after ADEM, if it is followed by another non-ADEM event occurring after three months of the initial event with dissemination in space.

Diagnosis

ADEM is a diagnosis of exclusion. Investigations are warranted to exclude the other causes of encephalopathy. The primary differential diagnoses include infectious meningoencephalitis, intoxication, CNS vasculitis, leukodystrophy, CNS malignancy, metabolic disorders and other disorders that affect the white matter. Brain MRI, cerebrospinal fluid (CSF) studies, serum autoantibodies and oligoclonal bands may help in reaching the diagnosis.

Neuroimaging: A contrast-enhanced MRI of brain with optic nerve cuts and spinal cord is the imaging modality of choice. Several radiological patterns have been described in brain MRI for ADEM (Box 2).¹³ Multifocal, large, ill-defined, T₂ hyperintense lesions in cerebral white matter with or without deep gray matter/ brainstem involvement are characteristic neuroimaging findings in ADEM³ (Fig.1-3). T1 hypointense lesions (black holes, typical of MS) and cortical gray matter lesions are rarely seen. Contrast enhancement is common and ring-like enhancement may also be seen in tumefactive ADEM. Diffusion restriction and hemorrhagic lesions are rare. There might be concurrent optic neuritis or transverse myelitis. The image may resemble other disorders affecting the brain white matter and a careful review of history, and other findings help in the clinical distinction (Fig.4).

CSF studies: They are non-specific and help in ruling out other disorders. CSF should be sent for cell count, protein, sugar, oligoclonal bands, and workup for infective causes. In ADEM, CSF is often unremarkable, but may show lymphocytic pleocytosis (29-85%), elevated proteins (17-48%) and oligoclonal bands (up to 20% of cases).³

Box 2. ADEM - MRI patterns¹³

1. Small lesions <5mm
2. Large tumefactive lesions
3. Bithalamic involvement
4. Acute hemorrhagic leukoencephalitis (Weston Hurst Disease)
5. Pseudo leukodystrophic pattern

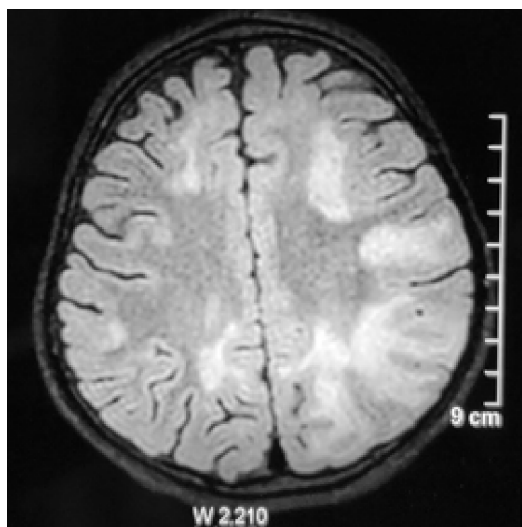


Fig. 1. ADEM - MRI brain axial FLAIR image – Well / ill-defined multifocal white matter hyperintensities

Specific serum antibody testing: Anti-MOG antibody and anti-aquaporin 4 antibody (AQP4 -Ab) testing in serum are useful for the diagnosis of MOG associated demyelination and NMO. MOG antibody is frequent in childhood ADEM and may be seen in 33- 66% cases.^{8,14} They are related to a non-MS relapsing course.¹⁴ Aquaporin-4 antibody positivity is rare in ADEM. Antinuclear antibodies may rarely be seen in childhood ADEM.

Electroencephalogram (EEG): EEG may be done as a part of the workup for encephalopathy to rule out non-convulsive status. In ADEM, it usually reveals non-specific findings such as diffuse or focal slowing and focal spikes.¹⁵

Histopathology: This may be rarely warranted in cases with diagnostic dilemmas such as those with large

tumefactive lesions. The essential purpose is to rule out CNS malignancy or CNS vasculitis in cases with diagnostic uncertainty. Pathologically, perivenous demyelination, along with the presence of inflammatory infiltrate is characteristic of ADEM.¹⁶

Treatment

The management of ADEM is based on consensus opinions and expert guidelines with evidence from case reports and case series. There are no randomized controlled trials till date to guide the management. The management of ADEM may be divided into three parts: a) supportive, b) specific immunomodulatory therapies and c) rehabilitative measures.

Supportive measures include maintenance of systemic functions (airway protection, seizure control, fluid and electrolyte balance) during the acute illness. Specific immunomodulatory therapies include steroids, immunoglobulins and plasma exchange. The most widely accepted first-line treatment is high-dose corticosteroids.^{3,4} Pulse methylprednisolone therapy at a dose of 20-30 mg/kg/day (maximum of 1000 mg/day) for 3-5 days, followed by tapering over 4-6 weeks with oral steroids, remains the treatment of choice. Complete recovery is reported in 50-80% of the cases treated with corticosteroids. If corticosteroids fail, other options include intravenous immunoglobulin (IVIG) and plasmapheresis. Plasma exchange is a well-tolerated procedure that improves outcomes in more than 70% of the patients who fail high-dose steroids.¹⁶ Evidence suggests that earlier the initiation of therapy, better the outcomes.¹⁷ IVIG has also been used for patients non-responsive to pulse steroids.¹⁸ Cyclophosphamide may also be used in fulminant ADEM if steroids, IVIG or plasmapheresis fail.¹⁹



Fig. 2. MRI brain axial T2 images - Multifocal hyperintensities in pons (A) and cerebral white matter (B,C).

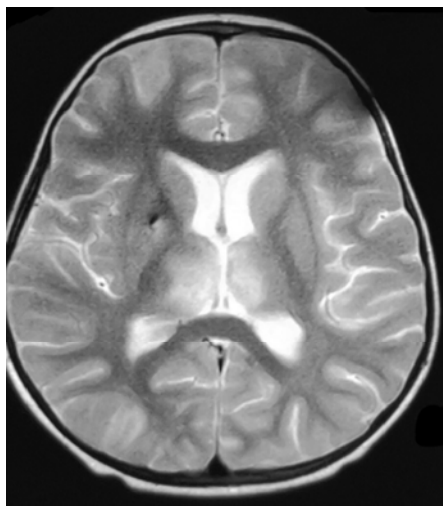


Fig.3. MRI brain axial T2 images - Typical thalamic involvement.

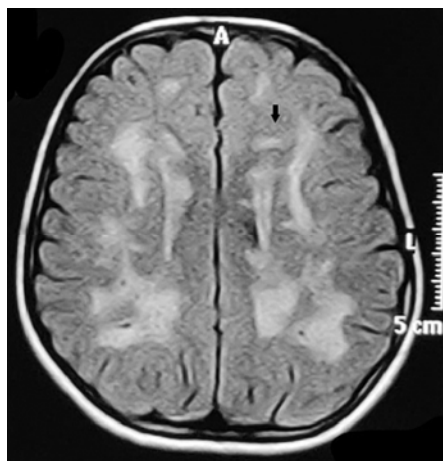


Fig.4. MRI brain axial FLAIR image - Well defined multifocal white matter hyperintensities. Note the linear pericallosal hyperintensities (Black arrow)

Treatment of MOG - associated demyelination: Although MOG-Ab-associated demyelination is usually described to be less severe and has a better outcome compared to AQP4-Ab associated disease, disability can result from incomplete recovery.^{8,14} The treatment recommendations for acute management of MOG associated demyelination is similar to that of ADEM and includes intravenous corticosteroids, IVIG and plasma exchange with steroids tapered over 4-6 weeks as the results of the antibody testing may become available by that time.²⁰ Initiation of maintenance treatment for relapse prevention depends on the likelihood and the number of relapses, the extent of recovery from each event and the severity of the acute event. Rituximab, mycophenolate mofetil, azathioprine and monthly IVIG have been reported to be associated with improvement in the annualized relapse rates

(ARR). Regular IVIG (every four weeks) with its added benefit of not inducing immunosuppression, is reported to be associated with maximum improvement in the ARR and Expanded Disability Status Scale (EDSS) scores.²⁰

Prognosis

Prognosis following the acute episode of ADEM depends on the recovery after the acute stage and the risk of recurrent demyelination episodes. Prognosis in children is considered to be better than in adults with lower chances of progression to MS. Prognosis of MOG associated demyelination is better with more resolution of clinical and radiological features; however, there is an increased risk of non-MS recurrences.³

Points to Remember

- *ADEM is an inflammatory disorder of the brain, characterized by acute-onset polyfocal neurologic deficits and encephalopathy.*
- *Fluffy white matter demyelinating lesions are the typical MRI findings.*
- *ADEM is monophasic, but it may be the first presentation of related inflammatory disorders such as MOG associated demyelination.*
- *Treatment includes immunomodulation with pulse steroids resulting in a brisk improvement in most children.*
- *IVIG is initiated if there is no clinical improvement within seven days of completing pulse steroids.*

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CLIPPINGS

The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application.

A novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in China in December 2019. Study was undertaken to evaluate the incubation period of COVID 2019 (Corona virus disease 2019). Pooled analysis of cases confirmed between between 4 January 2020 and 24 February 2020 were analysed. 181 COVID 19 confirmed patients outside Wuhan were studied.

Authors have stated the following. Median incubation period was estimated to be 5.1 days (95% CI, 4.5 to 5.8 days) and 97.5% of those who develop symptoms will do so within 11.5 days (CI, 8.2 to 15.6 days) of infection. Under conservative assumptions, 101 out of every 10 000 cases (99th percentile, 482) will develop symptoms after 14 days of active monitoring or quarantine. The authors concluded that the existing policy of quarantine for 14 days be justified.

Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann Intern Med* 2020; [Epub ahead of print 10 March 2020]. doi: <https://doi.org/10.7326/M20-0504>.