Acute disseminated encephalomyelitis: Treatment guidelines

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Introduction

Acute disseminated encephalomyelitis (ADEM) is a monophasic, postinfectious or postvaccineal acute inflammatory demyelinating disorder of central nervous system (CNS).[1,2] The pathophysiology involves transient autoimmune response directed at myelin or other self-antigens, possibly by molecular mimicry or by nonspecific activation of autoreactive T-cell clones.[3] Histologically, ADEM is characterized by perivenous demyelination and infiltration of vessel wall and perivascular spaces by lymphocytes, plasma cells, and monocytes.[4]

The annual incidence of ADEM is reported to be 0.4–0.8 per 100,000 and the disease more commonly affects children and young adults, probably related to the high frequency of exanthematous and other infections and vaccination in this age group.[5-9] There seems to be no gender predominance.[10]

Clinical Features

In ADEM, neurologic deficits develop 3–6 weeks following an antecedent event. The onset can be abrupt or may evolve over a period of several days. Prodromal illness may precede the neurologic symptoms.[10] ADEM can affect any part of the neuraxis and thus the clinical presentation is variable and usually polysymptomatic [Box 1]: altered mental status, pyramidal dysfunction, cerebellar ataxia, brainstem syndromes, optic neuritis, myelitis, and rarely myeloradiculopathy and extrapyramidal syndromes.[11,12] Seizures are not uncommon, can be focal or generalized. Encephalitic illness is more common in children younger than 3 years. [Box 2][12] Rarely ADEM may present with features of intracranial space occupying lesion, with tumefactive demyelinating lesions.[13-17]

Certain clinical presentations may be specific with certain infections: cerebellar ataxia for varicella infection, myelitis for mumps, myeloradiculopathy for Semple antirabies vaccination, and explosive onset with seizures and mild pyramidal dysfunction for rubella.[18,19] Acute hemorrhagic leukoencephalitis and acute necrotizing hemorrhagic leukoencephalitis of Weston Hurst represent the hyperacute, fulminant form of postinfectious demyelination.[20]

Diagnosis

Cerebrospinal fluid (CSF) is abnormal in about two-thirds of patients and shows a moderate pleocytosis with raised proteins.[21] Oligoclonal band in CSF is usually absent in ADEM

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Box 1: Acute disseminated encephalomyelitis: Clinical syndromes

- Most common–polysymptomatic presentation
- Site restricted syndromes
- Acute cerebellar ataxia
- Transverse myelitis
- Brainstem syndromes
- Optic neuritis (bilateral)
- Myeloradiculitis

Box 2: Common clinical and laboratory features of ADEM

- Clinical
  - Mostly monophasic
  - Antecedent infection/vaccination
  - Abrupt onset with prodromal symptoms
  - More common in children and no gender preference
  - Polysymptomatic
  - Encephalopathy features are more common
- Laboratory
  - Mild to moderate lymphocytic pleocytosis
  - Oligoclonal band usually uncommon or transient

whereas it is a common finding in the CSF in patients with multiple sclerosis (MS).[22]

Magnetic resonance imaging (MRI) is the imaging modality of choice to demonstrate white matter lesion in ADEM and MS. A recent study in children suggested the presence of any 2 of the MRI features: (1) absence of bilateral diffuse pattern; (2) presence of black holes; and (3) presence of 2 or more periventricular lesions help to differentiate MS from ADEM. The sensitivity and specificity of these criteria was 81% and 95%. respectively. In this study the total number of lesions did not differentiate ADEM from MS but periventricular lesions were more frequent in MS.[23] A study done to compare the MRI pattern of lesions, which could help to differentiate ADEM from MS found the following characteristics: solitary lesion, unilateral large lesion, cortical lesions, and subcortical grey matter (basal ganglia and thalamus) involvement.[24] Other studies suggested that bilateral thalamic lesion may be diagnostic of ADEM.[15,16,25-28]

Differential Diagnosis

Monophasic ADEM has to be differentiated from the first attack of MS. In the absence of a biological marker, the distinction between ADEM and MS cannot be made with certainty at the time of first presentation.[15] However, certain clinical features are more indicative of ADEM [Box 1 and Table 1].[15,16] In addition, MRI features may be diagnostic of MS or ADEM. Differentiating ADEM from the first attack of MS is of therapeutic importance as early institution of disease modifying drugs will modify the course of MS.

Table 1: Differential diagnosis: Acute disseminated encephalomyelitis vs multiple sclerosis

Features	Acute disseminated encephalomyelitis	Multiple sclerosis
Antecedent events	Infections or vaccination	No recognizable infection or vaccination
Clinical characteristics	Meningism, stupor focal signs	Focal signs
Course	Nonprogressive, monophasic	Relapsing and Remitting and/or progressive
MRI features	Diffuse, bilateral symmetrical lesions	Periventricular black holes
Prognosis	Recovery is rapid and often complete	Recovery variable

Site restricted syndromes of ADEM may have to be differentiated from Clinical Isolated Syndrome (CIS) [Table 2]. CIS is characterized by the occurrence of a single, clinical (monofocal presentation), demyelinating event with no clinical evidence of MS lesion in space and time. The most common presentation includes optic neuritis, partial myelitis, brainstem syndromes, or multifocal abnormalities.[29]

The patient with a CIS would have sustained a first ever clinical demyelinating event, and has 2 clinically silent lesions on T2-weighted brain MRI, with a size of at least 3 mm, at least one of which is ovoid or periventricular or infratentorial in the first imaging. The revised MS diagnostic criteria are of great value as it enables one to make an earlier diagnosis of MS, based on the development of new lesions on MRI brain, despite the absence of a new clinical event. The MRI brain can predict the conversion to clinical definite MS (CDMS) one cohort study had shown that 88% of patients with an abnormal scan experienced a second event, whereas only 19% of patients with a normal initial scan converted to MS.[30] Most patients with CIS develop either CDMS or new brain MRI-confirmed lesions within a very short period of 18 months, and the presence of gadolinium-enhancing lesions or meeting MS MRI diagnostic criteria further increases this likelihood.[31] The diagnostic criteria of CIS are heavily weighted on imaging features.

In the Optic Neuritis Treatment Trial, the risk of conversion to MS at 10 years is 22% in patients who have a normal imaging of the brain, and 56% in patients with an abnormal brain imaging. O' Riordan *et al* found that in patients presenting with optic neuritis, transverse myelitis, and brain stem syndromes, along with an abnormal MRI of brain, had a risk of 83% going on to develop MS at 10 years, while those with a normal brain MR had only a 11% risk.[32]

CSF oligoclonal bands (OCBs) in CIS showed a sensitivity of 91.4% and specificity of 94.1%.[33] Masjuan *et al* found that 32/33 patients with OCBs went on to develop MS in 6 years, whereas only 3/19 patients without OCBs went on to develop MS.[31]

Table 2: Site restricted syndromes of acute disseminated encephalomyelitis and clinically isolated syndrome

Acute disseminated encephalomyelitis	Clinically isolated syndrome
Postinfectious/vaccineal	No antecedent events
Polysymptomatic	Mostly monosymptomatic
Restricted forms can occur	Restricted form
Bilateral optic nerve involvement	Unilateral optic nerve
PNS involvement	No PNS involvement
Long segment of spinal cord involvement	Restricted partial cord
CSF: lymphocytic pleocytosis with raised Protein	Not often
Usually monophasic	Risk for subsequent MS is high
Could have relapse/recurrence (multiphasic ADEM)	Risk for MS

PNS, Peripheral nervous system; ADEM, Acute disseminated encephalomyelitis; Bilateral, CSF, Cerebrospinal fluid.

Treatment

Spontaneous improvement has been documented in patients with ADEM.[34] However, the recovery is incomplete in patients with ADEM not receiving any form of immune modulation treatment. No therapy has been established by controlled trials in ADEM. Use of high-dose steroids, plasma exchange, and intravenous immunoglobulin are based on the analogy of pathogenesis of ADEM with that of MS.[35,36]

Treatment of ADEM includes: (1) supportive, and (2) specific—high-dose intravenous methyl prednisolone, intravenous immunoglobulin (IVIg), and plasma paresis, and (3) physical and rehabilitation therapy [Figure 1].

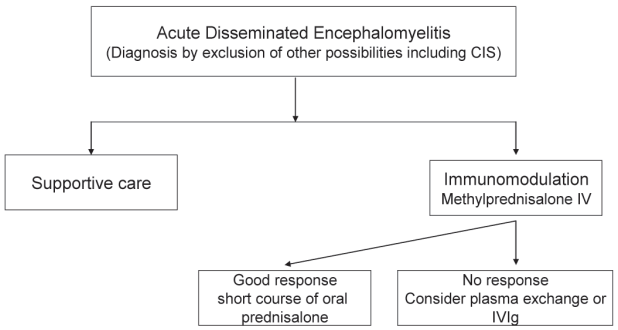

Figure 1: Treatment algorithm—acute disseminated encephalomyelitis

Supportive Care

Supportive care includes airway protection in patients with altered mental status and mechanical ventilation if required. Patients with cervical myelitis may require mechanical ventilation. Other supportive includes: antiseizure medication in patients with seizures, correction of fluid and electrolyte disturbances, and prophylactic anticoagulation for prevention of deep vein thrombosis in patients with high risk.

Immunomodulation

Intravenous methyl prednisolone is the first-line drug (10–30 mg/kg/day, up to a maximum of 1 g/day) for 3–5 days are being used (Class IV).[3,4,12,37,38] With this modality of treatment, full recovery has been reported in 50%–80% of patients. Methylprednisolone-treated patients had significantly better outcome with respect to disability status when compared with those treated with dexamethasone.[39] Oral corticosteroid treatment is continued with gradual tapering over 6 weeks to reduce the risk of relapses. However, these regimens are not based on controlled randomized trials. The role of corticosteroids in patients presenting late in the course of the disease is questionable. Any type of vaccination should be avoided during the first 6 months following recovery.

If high-dose corticosteroids fail, the next step will be plasma exchange (PE) and there is Class Ib evidence for PE.[40-42] A course of 4–6 PEs have been shown to be associated with moderate to marked and sustained improvement. One could remove a large volume of plasma per exchange if there are no problems of autonomic dysfunction. Predictors associated with improvement include male sex, preserved reflexes, and early initiation of treatment.[39,40] In centers that do not have this facility for conventional PE, one could modify and improvise to do a small volume manual plasma exchange—by doing a phlebotomy, centrifuging the blood, remove 250–300 mL of plasma and return the cells. One could do this twice a day for 7–10 days.[43]

Intravenous immunoglobulin (IVIg) (0.4 gm/kg/day for 5 days) is another option, but there is a constraint of high cost and the evidence for this modality of treatment in ADEM is Class IV.[44] The improvement is seen within 2–3 days.[45-47] In the absence of randomized controlled trials and with the available evidence, either plasma exchange or IVIg, could be the second-line treatment, when corticosteroids fail. The choice of second-line treatment should be individualized, depending on the severity of the disease, complications, and comorbidities. For example, autonomic dysfunction and hypotension would preclude the use of PE.[42] Anecdotal reports suggest that IVIg may be more effective in patients with peripheral nervous system involvement and PE in patients with tumefactive demyelination. Methyl prednisolone along with IVIg has been successfully used in patients with atypical features and could be tried for fulminant, aggressive, and atypical disease.[48]

Cyclophosphamide[10] and hypothermia[49] have been used with success in patients with fulminant ADEM. Decompressive hemi-craniectomy has been reported to be life saving in patients with massive life-threatening cerebral edema refractory to conventional medical management.[50,51]

Relapsing/Recurrence/Multiphasic Acute Disseminated Encephalomyelitis

Although ADEM is typically a monophasic illness, occasionally it can have biphasic or multiphasic course. Different terminologies have been used for an event that occurs within 4 weeks of treatment or within the first 3 months, relapsing ADEM. However, some researchers view new event temporally related to the initial disease process, and thought to be related to early steroid withdrawal and hence terminology steroid dependent or pseudo-relapsing ADEM.

If there is another event 4 weeks after steroid withdrawal or 3 months after the first episode, and if both clinically and radiologically, the same site is involved, this entity is called recurrent ADEM.[52] But there needs to be a prerequisite that this patient was in complete remission or as in a stable plateau phase of incomplete remission. If one or more ADEM relapses occur, including encephalopathy and multifocal deficits occur, involving new areas of the neuraxis on MRI and neurologic examination, this entity is multiphasic ADEM.[53] If only the imaging criteria are used these entities would fulfill the criteria for MS and hence these patients need to be referred to a tertiary center with expertise in management of these problems. The present evidence suggests that these episodes are probably related to the ongoing active disease and the autoimmune disease is probably due to persistent antigen/epitope progression and these episodes occur in relation to the initial episode.

Prognosis

Earlier studies reported a mortality rate of 20% with a high incidence of neurologic sequelae in those who survived probably it was related to high incidence of postmeasles ADEM.[8] However, recent studies suggest a favorable prognosis.[2,24,54] Prolonged altered mental state was associated with both mortality and morbidity. Multiple or single extensive lesions on MRI lesions may be associated with disability.[18]

The long-term prognosis of this entity depends on the etiology, with postmeasles patients having a higher mortality rate and significant morbidity in survivors. The prognosis of nonmeasles cases is favorable and most studies report a full recovery in 50%–75% of patients, in a period of 1–6 months after the illness.[3,4] The most common sequelae are focal motor deficits, could range from mild ataxia to hemiparesis. The principal determinants for the extent of neuronal and axonal damage are duration and severity of inflammation in brain and spinal cord. A hyperacute onset, severe neurologic deficits as a result of aggressive disease, and unresponsiveness to steroids are poor prognostic indicators.

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