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ACUTE DISSEMINATED ENCEPHALOMYELITIS: CLINICAL PRESENTATION, DIAGNOSTICS, TREATMENT, OUTCOME AND DISTINGUISHNESS FROM MULTIPLE SCLEROSIS

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Abstract: Acute disseminated encephalomyelitis (ADEM) is an immune - mediated, monophasic and multifocal demyelinating condition of the central nervous system (CNS) principally affecting the white matter of the brain and spinal cord. ADEM clinically and pathologically resembles to Multiple sclerosis (MS). Signs and symptoms of ADEM include alteration in personality, abnormal consciousness, cranial nerve palsies, hallucinations, headache, language disturbances, positive meningeal signs, nystagmus, psychiatric abnormalities, optic neuritis, ophthalmoparesis, seizures, sensory loss, visual field deficits, vomiting. Diagnosis is provided by clinical features, laboratory and imaging studied. Magnetic resonance imaging (MRI) with T2-weighted and fluid attenuated inversion recovery (FLAIR), proton-density, or echo-planar trace diffusion shows characteristic high-signal lesions in all cases of ADEM. These lesions are characterized as widespread, multiple, bilateral and asymmetric lesions of the CNS including deep cortical gray and subcortical white matter. Additional lesions may be found whereas periventricular lesions and lesions in corpus callosum are uncommon in ADEM in comparison to MS. The EEG may exhibit a disturbance of normal sleep rhythms as well as focal or generalized slowing. The absence of these abnormalities during the first acute disseminated demyelinating illness in a child may increase the suspicion for MS. The lumbar puncture is helpful in distinguishing ADEM from meningoencephalitis, whereas the immune profile is helpful in distinguishing ADEM from MS. Treatment of ADEM is implemented with high-dose intravenous corticosteroids, to which it is responsive. The most common protocol is 20-30 mg/kg/d of methylprednisolone for 3-5 days with an improvement observed within hours to several days. An alternative therapy is intravenous immune globulin (IVIG) administered as 2 g/kg intravenously as a single dose or during 3-5 days. Outpatient care includes physical, occupational, or speech therapy, especially indicated in patients with paresis, ataxia, low vision, and other focal neurologic deficits. Follow-ups require those who continue receiving doses of oral corticosteroids to ascertain the level of improvement. The most common inpatient complications include abnormalities of vision, motor function, or bladder or bowel function. Recurrence is a rare outpatient complication. Recovery is generally excellent but is poorest in children younger than 2 years, patients with myelitis, and those who have brain or spinal cord edema. The risk of patients with ADEM for development of MS in long-term follow-up is 25%, and it is highest in children whose ADEM onset was (1) afebrile, (2) without mental status change, (3) without prodromal viral illness or immunization, (4) without generalized EEG slowing, or (5) associated with an abnormal cerebrospinal fluid (CSF) immune profile. ADEM is distinguished from MS according to the clinical presentation and findings on neuroimaging and laboratory studies. Clinically, ADEM is distinguishable from MS by the presence of history of preceding infectious illness or immunization, association with fever, mental status changes and seizures, age younger than 11-12 years in ADEM and age older than 11-12 years in MS. MRI of brain in MS can be distinguished from ADEM with any 2 of the following criteria: 1.Absence of a diffuse bilateral lesion, 2. Presence of black holes and 3. Presence of two or more periventricular lesions.
Keywords: acute disseminated encephalomyelitis, multiple sclerosis, white matter, magnetic resonance, imaging studies

1. INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is a rare immune - mediated, monophasic and multifocal demyelinating condition of the central nervous system. It principally affects the white matter of the brain and spinal cord characterized by multifocal white matter lesions on neuroimaging and is self-limiting. Usually, it affects children, manifesting as an acute encephalopathy associated with neurologic deficits, generally following an acute infection (mostly viral infections with Epstein-Barr virus, cytomegalovirus, herpes simplex virus (HSV), influenza virus, enterovirus, mumps, rubella, varicella zoster virus, coxsackievirus and bacterial infections usually with mycoplasma pneumoniae, Borrelia burgdorferi, Leptospira, beta-hemolytic Streptococci) or vaccination. Various

vaccines have been suggested as the exogenous provocation of ADEM. The only vaccine proven related to ADEM is the rabies vaccine, but also have been implicated and hepatitis B, pertussis, diphtheria, measles, mumps, rubella, pneumococcus, varicella, influenza, Japanese encephalitis, and polio vaccines. ADEM is common during the cold months of the year, when the prevalence for these viral diseases is high. No identified gender predominance is known but a slight male predominance has been reported. The ratio of boys to girls is 1.3:1. More than 80% cases of ADEM occur in children younger than 10 years, with a mean age range of 5 to 8 years. A child must have all of the following criteria to be classified as ADEM: A first polyfocal clinical CNS event with inflammatory demyelinating cause, encephalopathy that cannot be explained by fever, no new clinical and MRI findings more than 3 months after the onset, abnormal brain MRI during the acute phase, typical findings on brain MRI that include diffuse, large lesions involving the cerebral white matter present in T2 weighted images as hyperintense lesions; T1 hypointense lesions of the white matter that are rare; whereas deep gray matter lesions may be present.

2. CLINICAL PRESENTATION

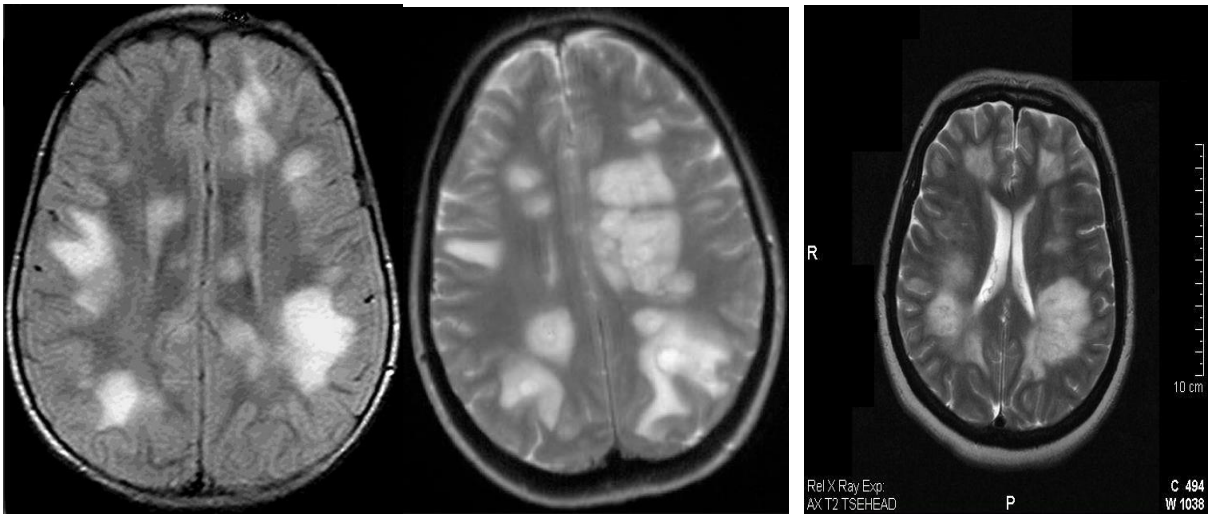
ADEM is a polysymptomatic disease. Initial symptoms of ADEM occur quickly and intensely as a single, short-lived attack, even though some children experience recurrent episodes after a couple of months. Initial symptoms usually are mild but they worsen rapidly over hours to days, reaching maximum severity in about 4-5 days. Many of the signs and symptoms of ADEM include fatigue, fever, headache, nausea, vomiting, abnormal consciousness, behavioral changes such as irritability, difficulty in coordinating muscle movements, vision impairment, weakness of limbs or one side of the body, cranial nerve palsies, hallucinations, language disturbances, positive meningeal signs, nystagmus, psychiatric abnormalities, optic neuritis, ophthalmoparesis, seizures (focal or generalized), sensory loss. Fever and headache may be present in up to 50% of cases whereas meningismus is detected in approximately 30% of cases. Multifocal neurologic deficit is reported to develop 4-7 days after the onset of symptoms. Most common neurologic abnormalities are long tract signs (clonus, increased muscle stretch reflexes, upgoing toes, present in up to 85% of cases), acute hemiparesis, cranial nerve abnormalities (including visual loss) found in 23-89% of cases, ataxia, and mental status abnormalities which include lethargy, fatigue, confusion, irritability, obtundation, and coma. Irritability and lethargy are the first common signs of ADEM. Focal or generalized seizures can occur in a minority of cases as an early sign of ADEM. Convulsive seizures may occur in 35% of cases. Ataxia is found in 28-65% of ADEM cases, whereas extrapyramidal disorders such as choreoathetosis or dystonia are also observed sometimes. Any portion of the CNS may be clinically involved but certain systems are particularly affected such as the descending white matter motor tracts, optic nerves, and spinal cord. Due to optic nerve affection, cranial nerve abnormalities may occur. Reflexes may be lost at the onset of minority of cases as a sign of associated peripheral nerve disease with ADEM, some of which are associated with acute infection with Epstein-Barr virus. Weakness may be hemiparetic, double hemiparetic, diparetic, or generalized and symmetric. Symmetric leg weakness is seen in many cases of ADEM-related transverse myelitis with associated abnormalities of bowel and bladder function. Sometimes, many cases of ADEM have a fulminant presentation. Fulminant ADEM mostly occurs in children younger than 3 years, with a rapid evolution and exhibition of severe edema on neuroimaging studies. These cases have decreased in number with the use of vaccination. High risk for morbidity in these fulminant cases of ADEM is the acute administration of very high-dose intravenous corticosteroids, which may close the blood-brain barrier and subsequently support the development of edema.

3. DIAGNOSTICS

Diagnosis is provided by laboratory studied and imaging studied such as brain computerized tomography (CT) scan and MRI as well as additional studies such as electroencephalography (EEG), visual evoked potential (VEP) and lumbar puncture, which are used for differential diagnosis. In laboratory studies platelet counts may be elevated as well as sedimentation rates. In more than 50% of cases low-density abnormalities are found in CT scan of the brain, but it is less sensitive than magnetic resonance imaging (MRI). MRI techniques with T2-weighted and fluid attenuated inversion recovery (FLAIR), proton-density, or echo-planar trace diffusion show characteristic high-signal lesions in all cases of ADEM. These lesions are characterized as widespread, multiple, bilateral and asymmetric lesions of the CNS including deep cortical gray and subcortical white matter found in more than 90% of children with ADEM. Additional lesions may be found in deeper white matter, basal ganglia (30-40%), thalamus (30-40%), brainstem (45-55%), cerebellum (30-40%), and the spinal cord whereas periventricular lesions and lesions in corpus callosum are uncommon in ADEM compared to Multiple Sclerosis. Sometimes, ADEM may be represented with normal findings on MRI but if the study is repeated several weeks later, MRI findings will be

abnormal suggestive for ADEM. This suggests that characteristic features may be missed and normal findings on a scan do not exclude the ADEM diagnosis. The EEG may exhibit focal or generalized slowing while epileptiform discharges are rarely seen in ADEM. The absence of these features during the first acute disseminated demyelinating illness in a child may increase the suspicion for MS. Visual evoked potentials (VEP) may prove helpful when optic neuritis is suspected but not apparent on clinical examination. The lumbar puncture is helpful in distinguishing ADEM from meningoencephalitis, whereas the immune profile is helpful in distinguishing ADEM from MS. The IgG index, IgG synthetic rate, or oligoclonal bands are positive in more than 60% of all first clinically diagnosed MS and in 90-98% of individuals who have experienced multiple MS bouts. These studies are less positive in ADEM.

Picture A) Picture B) Picture C)



Picture A), B) and C) presents brain MRI scan samples of patients who experienced ADEM

Picture A) T2 weighted MRI brain scan in ADEM revealing multiple asymmetrical hyperintense lesions throughout the white matter (Krupp,Banwell,Tenembaum.Neurology2007; 68(Suppl2): S7-S12)
Picture B) T2 weighted MRI brain scan in ADEM demonstrating multiple asymmetrical lesions throughout the white matter (Dale, Russell C. "Acute disseminated encephalomyelitis." *Seminars in pediatric infectious diseases* 14 2 (2003): 90-5)
Picture C) T2 weighted MRI brain scan in ADEM showing large, patchy areas of subcortical and deep white matter hyperintensity in the bilateral corona radiata. Some of these areas extend to the lateral ventricles (Dale RC, Branson JA Acute disseminated encephalomyelitis or multiple sclerosis: can the initial presentation help in establishing a correct diagnosis? *Archives of Disease in Childhood* 2005;**90:**636-639.

4. TREATMENT

Treatment of ADEM is implemented with high-dose intravenous corticosteroids, to which it appears to be responsive. The common protocol is 20-30 mg/kg/d of methylprednisolone (maximum dose of 1 g/d) for 3-5 days. The alternative therapy is intravenous immune globulin (IVIG). It is administered as 2 g/kg intravenously as a single dose or over the course of 3-5 days. IVIG may be preferable in instances where meningoencephalitis cannot be excluded based upon the hypothesis that corticosteroids might worsen the course of infection. Severe ADEM has been treated with such alternative treatment as (1) combination of intravenous corticosteroids and IVIG, (2) cyclosporine, (3) cyclophosphamide, or (4) plasma exchange/plasmapheresis. Improvement may be observed within hours to several days. Sometimes oral corticosteroids are given for 4-6 weeks or some other interval. Two studies have reported that the use of oral corticosteroids during 3 weeks or less may increase the risk for relapse in ADEM. In patients with paresis, ataxia, low vision, and other focal neurologic deficits outpatient care is indicated which includes physical, occupational, or speech therapy. Some follow-up is required for those who continue

receiving doses of oral corticosteroids to determine the level of improvement. The patients with severe neurologic disabilities are transferred to rehabilitation units. Patients who represent relapse during the use of oral corticosteroids consultation may be requested and the relapse is controlled by a higher dosage of oral corticosteroids.

5. OUTCOME

Most patients who experience ADEM may recover completely or have persistence of only mild deficits (diminished visual acuity). The most common inpatient complications include abnormalities of vision, motor function (pyramidal, extrapyramidal, cerebellar), or bladder or bowel function. Residual focal neurologic deficits remain in 4-30% of cases. Furthermore, depending on age of the child at the time of disease onset, intellectual and behavioral impairments are variable. Recurrence is an outpatient complication and it is rare. Recovery is generally excellent but is poorest in children younger than 2 years, patients with myelitis, and those who have significant edema of the brain or spinal cord. Full recovery is reported to occur in 57-92% of patients and it may be observed even in children who become blind, comatose, and quadriparetic. Current acute mortality rates are less than 2%, especially in children younger than 2 years. Only 1.5 % of reported cases have resulted in mortality due to ADEM complications even though mortality rate is suggested to be up to 10%. Other studies have reported mortalities of 0% cases of ADEM, which have been treated. The risk of patients with ADEM for development of MS in long-term (10-years) follow-up is 25%, and it is highest in children whose ADEM onset was (1) afebrile, (2) without mental status change, (3) without prodromal viral illness or immunization, (4) without generalized EEG slowing, or (5) associated with an abnormal CSF immune profile. Treatment with administration of high doses of corticosteroids may improve the outcome for these patients, but there are no data that support this hypothesis. Has been observed that the children who experience ADEM in the first decade of life may manifest MS during the second decade, after a symptom-free period of more than 10 years and the risk is less than 6%. There exists a single study regarding the prognostic factors associated with relapse of ADEM including the presence of optic neuritis, family history of CNS inflammatory demyelination, Barkhof MS criteria on MRI, and the absence of neurologic sequelae after the initial attack of ADEM. A relapse following ADEM occurring after a second encephalopathy is considered to be more suggestive for a chronic disorder, and MS needs to be taken in consideration.

6. DISTINGUISHNESS FROM MULTIPLE SCLEROSIS

ADEM bears a clinical and pathological resemblance to other acute demyelinating syndromes (ADS) of childhood, including multiple sclerosis (MS). It is distinguished from MS according to the clinical presentation and findings on neuroimaging and laboratory studies. Long-term follow-up is important, as there are instances where an initially diagnosed ADEM is replaced with MS diagnosis. ADEM is a monophasic disease of children while; MS is a chronic relapsing and remitting disease of young adults. Clinically, ADEM is usually readily distinguishable from multiple sclerosis (MS) by the presence of certain clinical features, including history of preceding infectious illness or immunization, although a clear preceding event may be absent in up to a quarter of patients, association with fever, prominence mental status changes and seizures, comparative rarity of posterior column abnormalities, which are common in MS, age younger than 11-12 years in ADEM and age older than 11-12 years in MS. ADEM is more common in the winter months, with most cases occurring between October and March. Typically ADEM appears 1-2 days to several weeks after acute infection. Usually there is an afebrile improvement lasting 2-21 days or more before the onset of neurologic findings. Abnormal findings on cerebrospinal fluid (CSF) immunoglobulin studies are less common in ADEM. Usually ADEM occurs as the result of an inflammatory response provoked by an infection with a virus, vaccine, or other infectious agent while MS occurs without a febrile prodrome. Rarely children who experience ADEM may manifest MS in adolescence. MRI of brain in MS could be distinguished from ADEM with any 2 of the following criteria (sensitivity 81%, specificity 95%): (1) absence of a diffuse bilateral lesion pattern, (2) presence of black holes, and (3) presence of 2 or more periventricular lesions. MS and ADEM resemble pathologically but they differ in the pathology of developmental stages of the MS plaque, which is more fully characterized than the pathology of the lesions of ADEM. This is the reason why most patients with ADEM recover completely and without apparent pathological residua. Serum autoantibodies to myelin proteins have been identified to help differentiate ADEM from MS. ADEM appears to be characterized by class-switched IgG autoantibodies, while MS is characterized by serum IgM autoantibodies. There has been demonstrated that the presence of serum IgG antibodies to myelin oligodendrocyte glycoprotein (MOG) is present in 40% of children with ADEM. Even though these antibodies do not appear to be specific to ADEM, their presence in ADEM may affect the nature and course of the disease. A recent study has reported that MOG-positive ADEM patients are more likely to have large,

bilateral and widespread lesions on MRI and are more likely to have a favorable clinical outcome in comparison to MOG-negative ADEM. Recurrent ADEM previously was defined as a new episode of ADEM with a recurrence of the initial symptoms and signs 3 or more months after the first ADEM. This entity now is included under the entity known as multiphasic ADEM. 10% of children with an initial diagnosis of ADEM experience another ADEM attack usually within the first 2-8 years after the initial attack. Relapse that follows a second ADEM attack now is no longer considered as multiphasic ADEM. These cases represent a chronic neuroinflammatory disorder such as MS.

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