Acute Disseminated Encephalomyelitis

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Acute disseminated encephalomyelitis (ADEM) is a monophasic inflammatory disorder of the central nervous system (CNS). Unlike viral encephalitis, microorganisms do not invade the CNS. Instead, ADEM is a postinfectious disease mediated by autoreactive cells or molecules. Clinical characteristics of ADEM are consistent with disseminated involvement of the CNS, including encephalopathy and pyramidal, cerebellar, and brainstem signs. Bilateral optic neuritis and transverse myelitis are particularly suggestive of demyelinating diseases such as ADEM. Unlike viral encephalitis, seizures rarely are a prominent symptom. The most useful diagnostic investigation is magnetic resonance neuroimaging that commonly shows multifocal lesions throughout the brain and spinal cord. As ADEM is an immune-mediated disorder, treatment includes immunomodulatory therapies (particularly steroids), although no clinical trials have been performed to define the most efficacious agent. In view of the treatment differences between ADEM and viral encephalitis, being familiar with ADEM is essential for pediatricians managing acute neurological disorders.

Acute disseminated encephalomyelitis (ADEM) is a monophasic inflammatory disorder of the central nervous system (CNS). Unlike viral encephalitis, no evidence of microorganisms or viral particles should be found in the CNS.[1,2] ADEM, also termed postinfectious encephalomyelitis, usually occurs after minor infectious illnesses. Occasionally, ADEM may occur after vaccination. The proposed pathogenesis is an immune-mediated inflammatory disease with perivenous lymphocytic infiltration and demyelination.[2]

Worldwide, the most common precipitants of ADEM remain the childhood exanthems such as measles, mumps, rubella, and chickenpox (after 1:1000 to 1:20,000 infections).[3] In developed countries where successful vaccination programs have reduced the prevalence of these exanthemata, ADEM more commonly is precipitated by a variety of upper respiratory tract infections. The exact prevalence of ADEM in pediatric populations is difficult to determine, but ADEM is estimated to represent approximately 30 percent of all encephalitides.[4]

This review addresses the clinical and investigation features of ADEM and the potential differential diagnoses. Making a diagnosis of ADEM has important management implications, as the treatment and outcome are different from those of the invasive encephalitides.

Clinical Characteristics of ADEM

Until recently, the literature on ADEM was confined to case reports and small case series. In the last 3 years, 4 large case series of ADEM have been conducted (Table 1).[5-8] All series have similar inclusion and exclusion criteria.

No clear sex predominance was found for ADEM; the disease usually affects prepubescent children but rarely children younger than 3 years of age.[5-8] Most cases of ADEM occur as a postinfectious phenomenon. Indeed, all 4 studies described a preceding infectious illness in more than 70 percent of cases.[5-8] Apparently, a wide variety of infections can precipitate ADEM. To mention all of the reported precipitating infections would be unnecessarily exhaustive. Historically, measles, mumps, rubella, and chickenpox are the most common precipitants of ADEM. Other notable precipitating infections include group A *Streptococcus*, *Mycoplasma pneumoniae*, and influenza.[9,10] However, most precipitating infections are nonspecific upper respiratory tract infections for which the exact causative microorganism is not defined. Compatible with an infection-mediated process, the incidence of ADEM is increased significantly in the colder winter months.[5,7] Vaccinations

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Table 1. Clinical Characteristic in ADEM[5-8]

Study Design	*Retro.*[5]	*Retro.*[6]	*Retro.*[7]	*Prosp.*[8]
Number of patients	35	31	18	84
Antecedent illness	74%	71%	72%	74%
Encephalopathy	69%	68%	45%	69%
Pyramidal	71%	23%	77%	85%
Cerebellar	49%	65%	n.s.	50%
Cranial neuropathy	51%	45%	23%	44%
Optic neuritis	23%	13%	n.s.	23%
Transverse myelitis	23%	n.s.	22%	24%
Extrapyramidal	6%	0%	0%	12%
Sensory disturbance	17%	3%	28%	2%
Seizures	17%	13%	17%	35%
Meningism	31%	26%	6%	43%
Headache	58%	45%	23%	32%
Fever	43%	52%	39%	n.s.
Relapse (MDEM)	20%	13%	0%	10%

n.s. = not stated; retro = Retrospective; Prosp = prospective.

also can precipitate ADEM, although when compared with the number of vaccinations given, ADEM would appear to be an extremely rare complication. Indeed, vaccinations have been incriminated as the precipitant of ADEM in only 0 to 12 percent of reported ADEM series in developed countries.[5-8] ADEM used to be a common complication of rabies vaccination, but newer vaccines prepared without neural extract have reduced the prevalence of this complication significantly.[11] Typically, a latent period of 12 to 14 days transpires between the precipitating infection and neurological onset,[5,8] and frequently the precipitating infection no longer is clinically evident once neurological disease has ensued.

The clinical characteristics of the neurological syndrome are presented in Table 1. The onset often is explosive, and some children become profoundly encephalopathic within 24 hours, although an insidious presentation may occur. Isolated symptoms and signs would be atypical of ADEM. More commonly, multiple signs compatible with extensive CNS dysfunction are found.[5-8] ADEM has been referred to as an inflammatory CNS disorder involving predominantly the white matter. Although white matter disease is characteristic, involvement of gray matter (particularly deep gray) also is a common finding. As can be seen in Table 1, the most common characteristics are encephalopathy (reduced consciousness and behavioral change), pyramidal long tract signs, cerebellar signs, and cranial neuropathy. The presence of bilateral optic neuritis (presenting with blindness) and transverse myelitis (presenting with paraplegia and urinary retention) are diagnostically suggestive of inflammatory CNS disease such as ADEM. Commonly, fever, headache, and meningism are accompanying symptoms. Seizures occur in a minority of cases and rarely pose a management problem. Extrapyramidal signs (chorea and dystonia) are suggestive of involvement of the basal ganglia and occur infrequently in ADEM.[12] Of note, group A Streptococcus can induce an ADEM with predominant involvement of the basal ganglia and dystonia.[9]

Investigations

Blood and Cerebrospinal Fluid Investigation

None of the blood and CSF findings is specific to ADEM. Investigations are aimed predominantly at excluding alternative causes of acute CNS dysfunction. When the clinical and imaging features are not characteristic of ADEM, excluding invasive encephalitis and metabolic leukoencephalopathy often is important (discussed later).

Attempting to identify the precipitating microorganism has potential clinical importance because eradication may prevent recurrence and potentially speed recovery. Serology for group A Streptococcus, *Mycoplasma pneumoniae*, enterovirus, Epstein-Barr virus, and *Borrelia burgdorferi* are measured at our institution. Obviously, serological investigation should be tailored to the clinical features of the precipitating infection. White blood cell count, erythrocyte sedimentation rate, and C-reactive protein are elevated in approximately one-half of patients, although none of these markers is sensitive nor specific to ADEM.[5-8] CSF examination probably is mandatory in the setting of CNS dysfunction (when safe). Reducing the possibility of the presence of herpes simplex encephalitis with a negative herpes simplex polymerase chain reaction (PCR) is necessary before antiviral agents can be stopped. By definition, no evidence of bacteria or viral particles should be found in the CNS. Therefore, culture and viral PCR should be negative in ADEM. The CSF is abnormal (modest lymphocytosis or elevated protein) in approximately 70 percent of patients.[5-7] Intrathecal oligoclonal IgG bands rarely are present in ADEM (although a mirrored pattern of oligoclonal bands can be seen),[5,8] and oligoclonal bands are performed mainly to discriminate ADEM from multiple sclerosis (discussed later). As with the blood investigations, the CSF findings are neither sensitive nor specific to ADEM.

Electrophysiology

Electroencephalography (EEG) is a useful investigation in acute neurological disease. The EEG is abnormal almost universally in ADEM and reveals slow activity (often diffusely) compatible with an encephalopathic process.[5,6,8] Epileptic spikes are rare findings in ADEM,[8] unlike established herpes simplex encephalitis, for which epileptic activity occurs commonly. Visual-evoked potentials can be helpful when optic neuritis is suspected, and this investigation can support the presence of optic nerve demyelination.

Neuroimaging

Neuroaxis imaging is an essential diagnostic investigation in ADEM. Without magnetic resonance imaging (MRI) of the brain, making the diagnosis and providing subsequent management of ADEM are difficult. Computerized tomography (CT) is an inadequate investigation and is abnormal in only 11 to 78 percent of patients,[5,7,8] although obtaining CT scans is sometimes necessary to exclude an intracranial mass or hemorrhage. MRI is far more sensitive at demonstrating ADEM lesions, and most studies have used characteristic MRI features as an inclusion criteria. T2 and

Table 2. MR Lesion Localisation in ADEM[5-7]

Study (Reference)	*5*	*6*	*7*
Periventricular white matter	44%	29%	60%
Any white matter	91%	90%	93%
Cortical grey matter	12%	n.s.	80%
Brainstem	54%	42%	47%
Cerebellar white matter	31%	n.s.	13%
Thalamus	41%	32%	27%
Basal ganglia	28%	39%	20%
Spinal cord	28%	16%	n.s.

n.s. = not stated.

FLAIR sequences demonstrate lesions better than do T1 sequences.[5-8] The lesions often are multiple and disseminated asymmetrically throughout the CNS. The asymmetric distribution is an important imaging feature of ADEM, in contrast to the metabolic leukodystrophies (eg, adrenoleukodystrophy), for which the white matter lesions characteristically are symmetrical.[13] The lesions range in size from a few millimeters in diameter to confluent lesions throughout a hemisphere. Although multiple lesions typically occur, single mass-like demyelinating lesions are seen occasionally and have been mistaken for intracranial tumors.[14] Localization of lesions has been analyzed by numerous studies, and the findings are summarized in Table 2.

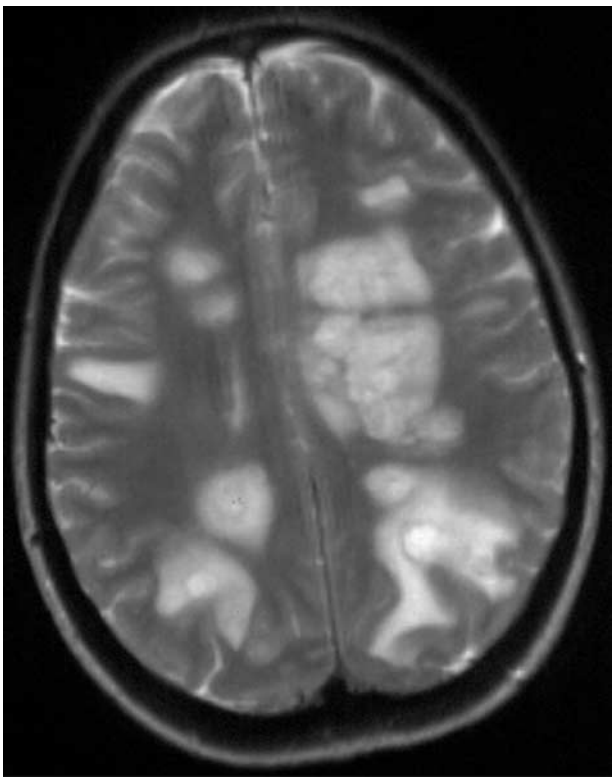

Figure 1. T2-weighted MR brain scan in ADEM demonstrating multiple asymmetrical lesions throughout the white matter.

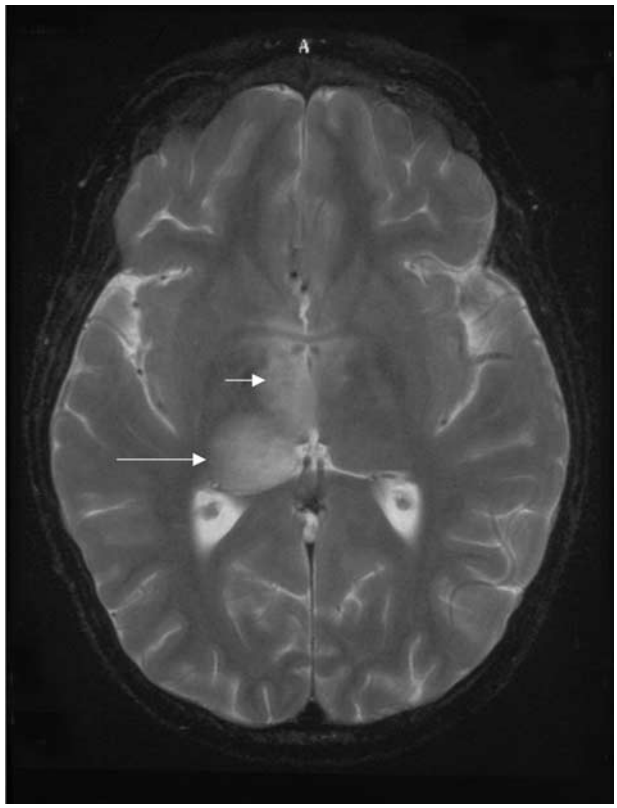

Figure 2. T2-weighted MR brain scan in ADEM demonstrating deep gray matter lesions (thalamus-long arrow: hypothalamus-short arrow).

The white matter is affected nearly universally in ADEM (Fig 1). Sometimes relative sparing of the periventricular white matter with increased lesion load in the subcortical white matter region is found. As can be seen in Table 2, the lesions otherwise are disseminated throughout the CNS, although the cortical gray matter often is relatively spared (in contrast to herpes simplex encephalitis). Notably, involvement of deep gray matter structures, including the basal ganglia and thalamus, frequently is present. Bilateral involvement of the deep gray matter is well recognized in ADEM[5,8,9,15] and re-emphasizes the fact that ADEM is not purely a disease of white matter (Fig 2). Although a large proportion of basal ganglia lesions do not cause extrapyramidal movement disorders,[8] they can be associated with dystonia in the context of poststreptococcal ADEM.[9] Spinal cord involvement often shows large confluent lesions that involve large cord areas. Spinal imaging should be performed only when clinical evidence of cord involvement is found. Gadolinium enhancement (which infers blood brain barrier damage) is present in a proportion of patients and can help identify very acute lesions. Mass effect is a recognized phenomenon, but it occurs in a minority of patients. In summary, MRI is an essential investigation in the diagnosis of ADEM. Multiple disseminated asymmetrical lesions seen on T2-weighted images are characteristic.

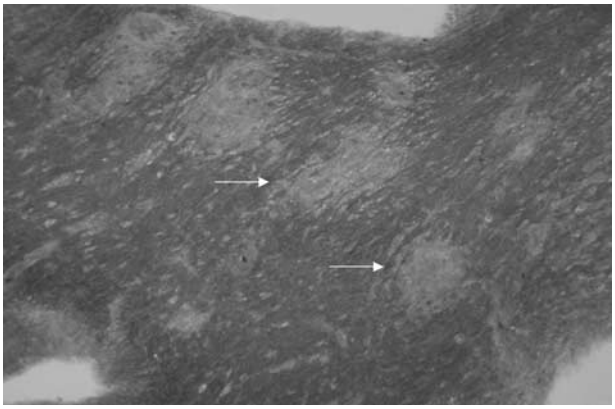

Figure 3. Histology demonstrating patchy demyelination in established ADEM (arrows).

Pathogenesis

Pathology

The pathogenesis of ADEM is understood incompletely. Unlike multiple sclerosis (MS), ADEM has not been investigated extensively. It would be wrong to assume that ADEM is a monophasic form of MS.

Brain biopsies rarely are required in the management of ADEM and should be considered only when the course is atypical. ADEM pathology is characterized by a perivenous inflammatory myelinopathy. On gross appearances, the brain is slightly swollen. Microscopically, perivenous infiltrates by mononuclear cells, particularly lymphocytes, are seen. Secondary demyelination occurs around small veins (Fig 3). By contrast, axons are relatively spared.[2,5,8] Occasionally, a more severe form of ADEM can occur with secondary punctate hemorrhages, fibrinoid necrosis, and neutrophil infiltration of the vessels. This severe form is called acute hemorrhagic leukoencephalitis (AHLE).[16]

Immunology

ADEM is a clinical and radiological phenotype. ADEM probably is heterogeneous, with numerous different immune processes resulting in the ADEM phenotype. The absence of viral or bacterial antigens within the CNS is nearly universal in ADEM.[1,2] Therefore, researchers have proposed that the disease is secondary to autoreactive lymphocytes or molecules. The induction of ADEM after administration of inactivated vaccines supports this immune "allergic" hypothesis. T cells are suspected widely to be the primary mediators of disease in ADEM, and the neural targets are myelin proteins such as myelin basic protein (MBP), proteolipid protein, and myelin-oligodendrocyte glycoprotein. Indeed, MBP-reactive lymphocytes are present in patients with ADEM, although they also are found in other neurological disorders.[1,17-19] Furthermore, these lymphocytes have not been demonstrated to be pathogenic. Proposed pathogenic mechanisms include 'molecular mimicry.' This hypothesis states that epitopes on precipitating microorganisms induce T-lymphocytes or antibodies that cross-react with neural epitopes and expand clonally within the CNS. Other hypotheses state that exact mimicry is not required, but activated T-lymphocytes migrate into the CNS and cause disease if they recognize neural epitopes.[2] Alternatively, other immune molecules such as cytokines may play an important role in ADEM evolution. Tumor necrosis factor-beta is a pro-inflammatory cytokine and was elevated in one ADEM study.[20] Interleukin-6 (IL-6) also was elevated in this study: IL-6 can induce T and B lymphocytes, but also has direct effects on neurons (a neurotropic cytokine).[21] To complicate matters, humoral immunity also may have a role in ADEM pathogenesis. We have demonstrated autoantibodies reactive against basal ganglia epitopes in poststreptococcal ADEM with associated dystonia and basal ganglia lesions.[9]

In summary, the pathogenesis of ADEM is understood incompletely. ADEM possibly is heterogeneous with cell-mediated, humoral, and even innate immunity playing important roles in disease evolution and recovery. The immune abnormalities may depend partly on the precipitating infection. Multicenter studies are required to further define the pathogenesis.

Differential Diagnoses

The differential diagnoses of ADEM should include metabolic leukoencephalopathy, viral encephalitis, and multiple sclerosis. The clinical and investigation features of these differentials are considered now, with comparison to the features of ADEM.

Metabolic Leukoencephalopathy

Metabolic disease often is on the pediatric neurology differential diagnosis list. Leukodystrophies can present in a stepwise fashion with postinfectious exacerbations (eg, adrenoleukodystrophy, metachromatic leukodystrophy, and mitochondrial cytopathy).[13] As previously mentioned, the white matter MRI abnormalities in metabolic disorders are characteristically symmetrical, although MELAS (Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) presents a particular diagnostic difficulty. Investigations to exclude these syndromes may be necessary in some cases of ADEM.

Invasive Viral Encephalitis

Commonly, a child presenting with ADEM is treated with antibiotics and antiviral agents until the MRI has provided the correct diagnosis. However, some clinical and investigation features help differentiate ADEM from herpes simplex encephalitis (HSE). HSE commonly presents with encephalopathy and partial or secondary generalized seizures that are difficult to treat,[22] whereas seizures rarely are a central feature in ADEM. EEG and MRI also can help differentiate HSE from ADEM (as previously mentioned). Regardless of these potential differentiating features, continuing acyclovir until herpes simplex PCR is negative would be recommended.

Multiple Sclerosis

MS is a chronic relapsing or chronic progressive inflammatory disorder. When an adult presents with a first episode of acute CNS inflammation, a high possibility is that it represents a first episode of MS. In children, monophasic ADEM occurs much more commonly than does MS. When a child recovers from an acute demyelinating CNS episode, the parents often ask about the possibility of relapses. However, the presence of relapses shortly after ADEM does not necessarily mean than the child has MS. Relapses can occur shortly after ADEM as part of the same monophasic immune-mediated process and have been given the name multiphasic (MDEM), biphasic (BDEM), or relapsing (RDEM) disseminated encephalomyelitis.[5,8,23] These relapses occur in between 0 and 20 percent of patients who have ADEM and typically occur in the months after presentation of ADEM. Relapses may be precipitated by further infections or on withdrawal of steroid therapies.[5,23] Follow-up of patients with MDEM has suggested that these patients do not go on to develop MS.[5,8,23] If relapses occur many months or years after their first demyelinating episode, then a diagnosis of MDEM becomes less tenable and MS much more likely. Some clinical and investigation features of a first demyelinating episode are suggestive of MS (rather than ADEM).[5] In MS, presentation of disease often is more insidious and less fulminant. In MS, isolated focal deficits are characteristic, whereas multiple signs often are manifest in ADEM. Unilateral optic neuritis occurs more commonly in MS, whereas bilateral optic neuritis occurs more commonly in ADEM.[5,8] Comparisons of MR neuroimaging characteristics have suggested that sparing the periventricular white matter is common in ADEM, whereas periventricular white matter involvement is nearly universal in MS.[5] Possibly the best differentiating factor is the presence of intrathecal oligoclonal bands that usually are present during MS presentation but are uncommon findings in ADEM.[5-8] However, distinguishing ADEM from MS presentation definitively is impossible. Thankfully, ADEM is a far more common disease than is MS in children, particularly young children. In adolescents, this fact is less true and the prognosis needs to be more guarded. When counseling parents, one must explain that relapses may occur, although they are unlikely to do so.

Treatment

Symptomatic treatment of reduced consciousness, seizures, sphincter disturbance, and fluid imbalance should be managed in appropriate ways. Likewise, physiotherapy and occupational therapy are essential. As previously outlined, a child presenting with acute CNS dysfunction often is treated with antibacterials and antivirals until invasive encephalitis is excluded. When the diagnosis of ADEM is proposed on the basis of clinical and imaging features, the next decisions are whether and how to treat.

Unfortunately, no clinical trials exist to determine the best immunomodulatory treatments. As many children make a good recovery, some physicians propose that no treatment is necessary. However, most physicians agree that when significant encephalopathy and impairments are present, immunomodulatory treatments should be used.[5,8,24,25] It is our practice to use intravenous methylprednisolone 30 mg/kg/d for 3 days (maximum 1 g). Other physicians use oral steroids such as dexamethasone or prednisolone. After the intravenous regimen, our practice is to use oral prednisolone 2 mg/kg/d for 2 weeks followed by a 4-week weaning regimen. Retrospective analysis has shown that this weaning regimen appeared to reduce the risk of relapses occurring.[5,23] Given the proposed immune-mediated pathogenesis, alternative therapies that modulate the immune system are theoretically of use. Case reports demonstrating the benefit of intravenous immunoglobulin[26,27] and plasmapheresis[28,29] in steroid-resistant ADEM support this hypothesis. One must reiterate that little evidence exists for determining the best immune therapies in ADEM.

Outcome

Despite the dramatic presentation, the outcome often is surprisingly good. Some children respond rapidly to steroid therapies (or spontaneously), suggesting that a proportion of the pathology is reversible within hours. However, recovery may require many weeks or months. A complete recovery occurs in 57 to 81 percent of patients with ADEM, but one should note that subtle cognitive or behavioral sequelae could have been missed by the follow-up methodology in these studies.[5-7] Morbidity includes visual impairments (after optic neuritis), motor deficits, cognitive impairment, and behavioral alterations.[5,8] The worst outcome appears to occur after cord involvement (paraplegia and urinary incontinence).[5,7,30] Follow-up imaging commonly shows complete or partial resolution of the lesions.[5,8,31,32] New lesions on convalescent imaging would be atypical of ADEM and suggestive of MS.[5,8,31] Convalescent MRI should be performed approximately 6 months after presentation (unpublished observation).

Conclusion

ADEM presents acutely with a disseminated CNS disorder after infections or vaccines. MRI plays an important role in making a diagnosis. ADEM represents a significant proportion of the acute encephalitides and requires a separate treatment protocol to viral encephalitis.

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