

Acute Disseminated Encephalomyelitis

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Introduction

Background

Acute disseminated encephalomyelitis (ADEM) is a nonvasculitic inflammatory demyelinating condition that bears a striking clinical and pathological resemblance to multiple sclerosis (MS). However, in most instances, ADEM and MS cases occurring in children are readily distinguishable on the basis of clinical features and findings on laboratory investigations. MS is typically a chronic relapsing and remitting disease of young adults, while ADEM is typically a monophasic disease of prepubertal children. Abnormalities of findings on cerebrospinal fluid (CSF) immunoglobulin studies are likely in MS but are much less common in ADEM. The onset of ADEM usually occurs in the wake of a clearly identifiable febrile prodromal illness or immunization and in association with prominent constitutional signs and encephalopathy of varied degree, features that are uncommon in MS.

However, the division between these processes is indistinct, which is suggestive of a clinical continuum. Moreover, other conditions along the suggested continuum include optic neuritis, transverse myelitis, and Devic syndrome, clinical entities that may occur as manifestations of either MS or ADEM. Other boundaries of ADEM merge indistinctly with a wide variety of inflammatory encephalitic and vasculitic illnesses as well as monosymptomatic postinfectious illnesses that should remain distinct from ADEM, such as acute cerebellar ataxia (ACA). A further indistinct boundary is shared by ADEM and Guillain-Barré syndrome and is manifested in cases of Miller-Fisher syndrome and encephalomyeloradiculoneuropathy (EMRN).

Susceptibility to either condition is likely the product of multiple factors, including a complex interrelationship of genetics and exposure to infectious agents and possibly other environmental factors. Of particular interest are the indications that susceptibility to either condition is in part age related. Most cases of either MS or of ADEM possibly occur as the result of an inflammatory response provoked by prepubertal infection with a virus, viral vaccine, or other infectious agent. Typically, the manifestations of ADEM occur quickly after this prepubertal febrile systemic illness and are monophasic. In a minority of cases, patients with ADEM experience 1 or 2 prepubertal recurrences followed by remission.

MS, on the other hand, typically manifests as a relapsing-remitting illness in ensuing adolescence or young adulthood, a significant and unexplained latency of effect with apparent permanency of immunodysregulation. Bouts of MS occur without febrile prodrome. Uncommonly, MS develops in prepubertal individuals and ADEM develops in postpubertal individuals, and some cases of adolescent-onset MS may go into remission. In very rare instances, individuals manifest prepubertal ADEM and, after long latency, MS in adolescence.

Pathophysiology

Multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM) bear a close pathological resemblance, each resembling the pathology of experimental allergic encephalomyelitis (EAE). The prominence of perivenular round cell inflammation in either illness is a feature that is shared with many forms of encephalitis, but patchy demyelination with preservation of axon cylinders and the prominence of microglial cells in the inflammatory exudate are not.

The pathology of various developmental stages of the MS plaque is more fully characterized than the pathology of the lesions of ADEM. This is because most patients with ADEM recover completely and without apparent pathological residua. Few biopsies have been obtained or submitted to postmortem analysis. MS plaques are known to exhibit organization features, especially in the margins of active plaques, that are not found in cases of ADEM. On the other hand, the general pathological similarities suggest but do not confirm the possibility that ADEM is a forme fruste of MS that is somehow effectively and permanently controlled after one, or possibly a few, demyelinating bouts.

Patients with large tumorlike demyelinating lesions may exhibit a combination of pathological features consistent with both MS and ADEM. The possible relationship between these illnesses is further supported by the similarity of clinical manifestations in either illness and the development of MS during adolescence in a small minority of patients who have had typical ADEM bouts in the first decade of life.

The pathophysiological similarities of these illnesses suggest that the immunologic constitution of susceptible individuals is in some fashion permissive of ADEM, MS, or both and that the degree of susceptibility may describe a gradient with regard to severity and risk for recurrence. The threshold for an initial bout of demyelinating illness may be determined by the combination of this immunologic constitution and the nature of a given antigenic stimulus; the likelihood of recurrence may be determined by the fertility of that constitution for persistence of immuno-dysregulation. Immuno-dysregulation in MS or ADEM may consist of responses that are inadequate, too exuberant, or the combination of both.

If a pathophysiological continuum between MS and ADEM exists, achieving better understanding of the manner in which susceptible individuals with ADEM are able to bring a monophasic or temporarily recurrent immuno-dysregulative response under permanent control is of obvious importance. Cases with characteristics that fall in the indeterminate area of this continuum, such as those that might be labeled recurrent ADEM, represent an important challenge for accurate classification. In some of these cases, appropriately crediting the immune system with tardy but permanent compensation may be important, thus avoiding inappropriate diagnosis of MS, fraught as that is with psychosocial consequences.

The mechanisms of these demyelinating illnesses remain incompletely understood despite the extraordinary richness and complexity of immunologic abnormalities that have been identified after more than a century of clinical, pathological, and laboratory studies. Experimental observations have depended greatly on EAE, a research model that may be more pertinent to ADEM than MS.

However, the possibility of provoking spontaneously recurrent demyelination with this model further supports the concept that ADEM and MS represent a continuum. Basic studies have shown that, in the earliest stages of inflammation, both MS and ADEM are likely to be mediated by stimulated clones of T-helper cells sensitized to autoantigens such as myelin proteins. The

complex ensuing inflammatory cascade entails the local action of cytokines and chemokines as well as lymphokine-induced chemotaxis of other cellular mediators of inflammation (eg, other T cell lines, B cells, microglia, phagocytes).

Pathogenic differences of MS and ADEM are likely to arise in part because of differences in details concerning proinflammatory and anti-inflammatory cytokines and chemokines. Interleukin (IL)–1beta, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, interferon (IFN)–gamma, tumor necrosis factor-alpha, and macrophage inflammatory protein-1beta are significantly elevated in CSF compared with the CSF of controls. Granulocyte colony-stimulating factor shows a particularly striking elevation at as much as 38-fold greater concentration than is found in the CSF from control subjects. Elevations of IFN-gamma, IL-6, and IL-8 have been significantly correlated with CSF cell counts and protein concentration in individuals with ADEM. The pattern of cytokine elevation suggests that ADEM involves activation of macrophages, microglial cells, and various Th (T helper)–1 and Th2 cells.^[1]

Additionally, in 2006, Franciotta et al demonstrated that adults with ADEM have higher CSF concentrations of chemokines that recruit or activate neutrophils (CXL1 and CXL7), monocytes (CCL3 and CCL5), Th1 cells (CXCL10), and Th2 cells (CCL1, CCL17, and CCL22) than healthy normal controls.^[2] Moreover, ADEM-associated concentrations of certain of these neutrophils (CXL7 neutrophil activator and the CCL1, CCL17, and CCL22 Th2 activators) are higher in the CSF from individuals with ADEM than those with MS. On the other hand, CSF concentrations of the chemokine CCL11 is lower in adults with MS than in the CSF from adults with ADEM or in normal controls.

CSF Th1/Th2 cytokine concentrations were not significantly different in adults with MS, those with ADEM, or in normal healthy controls. No significant differences in serum concentrations of cytokines or chemokines were noted in the 3 adult groups. These findings raise the possibility that elevated chemokine concentrations might serve as biomarkers for ADEM and that they may provide keys to understanding of the nature of and differences in the pathogenesis of ADEM and MS.

Disturbance of the blood-brain barrier is likely to be an important event. The elaboration of antibodies occurs but remains of uncertain significance. Recent evidence in studies of the brains of individuals with MS suggest that gray matter degeneration, especially of descending subcortical fibers, may participate in the progression of MS. Gray matter involvement also occurs in ADEM. Discerning how these inflammatory changes differ in MS or ADEM and how the reactions in either illness are distinguishable from those in other inflammatory and infectious illnesses are among the important subjects of current research.

Frequency

United States

In the authors' personal series of more than 150 cases grouped under the general heading acute disseminated encephalomyelitis (ADEM), the ratio of ADEM cases in the first decade of life to adolescent multiple sclerosis (MS) cases is approximately 3:1. If the incidence of MS in the second decade of life in the United States is presumed to be approximately 1 case per 100,000, the incidence of first-decade ADEM may be approximately 3 cases per 100,000. Incidence of second-decade ADEM could be estimated, by similarly imprecise methods, at 1.5 cases per 100,000.

Whether the increasing incidence of MS at increasing distance from the equator is also true of ADEM is unknown. Occurrences of both ADEM and MS bouts describe sine wave plots of seasonal incidence in North America, with peak incidence in February to March in North America and lowest incidence in July to August. Some severe forms of ADEM, such as those that occur in the

wake of measles and the severe hemorrhagic variant called acute hemorrhagic leukoencephalopathy (AHLE) are probably less commonly encountered than they were prior to widespread immunization against measles and other formerly common and potentially serious illnesses that may serve as triggers for ADEM/AHLE.

On the other hand, the prevalence of some forms of ADEM is possibly increasing in developed nations, rather than merely being diagnosed more frequently because of the increased use of MRI. No direct evidence supports increased prevalence, but concern is raised by evidence that MS prevalence has increased in the women of such nations during the past 4 decades and that the prevalence of childhood or adolescent autoimmune diseases such as juvenile rheumatoid arthritis, systemic lupus erythematosus, and juvenile-onset diabetes mellitus is also increasing.

International

Little is known about occurrence throughout the world, except that cases are likely to occur in all regions of the world. Genetic factors, prevalence of infectious pathogens, immunization status, degree of skin pigmentation, diet, and other factors may influence risk. Of particular importance is immunization because immunization to pathogens known to provoke ADEM has reduced the incidence of severe forms of ADEM such as those that may follow cases of measles and other viral illnesses. On the other hand, early forms of the Pasteur rabies vaccine may also provoke severe ADEM, a problem that has been resolved by improvement of rabies vaccines. The role of other vaccines in ADEM remains controversial. Areas of the world where malaria is prevalent produce cases of cerebral malaria, likely to be an ADEM variant.

Mortality/Morbidity

Although older studies suggest a 10% mortality rate, the data upon which such estimates were based were obtained in epochs during which measles was prevalent, techniques for intensive care were comparatively primitive, and anti-inflammatory therapies were inadequate. Formerly, deaths occurred in patients with AHLE, a severe ADEM variant, which has become less common since children have received immunization to many common childhood illnesses.

Current acute mortality rates are probably less than 2%, involving cases with fulminant cervical transverse myelitis or brain swelling. Children younger than 2 years are particularly subject to such severe presentations.

Morbidity chiefly includes visual, motor, autonomic, and intellectual deficits and epilepsy. Overall, these problems persist after the first few weeks of illness in only about 35% of cases, and in most of these patients, the deficits resolve within 1 year of onset. Intellectual deficits (varying from attention problems to mental retardation) and epilepsy arise most often in children whose bout of ADEM occurs before the second birthday. Visual and motor deficits and problems with bowel or bladder function may persist for varying periods of time (months to permanently) in some cases, particularly in those with transverse myelitis, optic neuritis, and the combination Devic syndrome.

At particular risk for long-term consequences are patients whose ADEM becomes steroid dependent and frequently recurrent with onset before age 6 years, a condition the authors have termed steroid-dependent encephalomyelitis. Another group at significant risk are those whose much less frequent recurrences are diagnosed as MS (usually when the patient is >10 y).

Race

The scientifically imprecise concept of race does not lend itself readily to discussions of ADEM. In the authors' series of more than 150 cases, the ratio of light-skinned to dark-skinned individuals who have some contribution of genetic material from individuals who have left Africa in the past 5 centuries is approximately 6:1. In the former group, the element of African heritage from the past 5 centuries is presumed small but is in fact unknown. ADEM is found in all ethnic groups and races; referral bias complicates any assessment of relative prevalence.

Degree of skin pigmentation (irrespective of racial background) may influence risk for ADEM, as it may for MS, if recent theories concerning vitamin D metabolism and autoimmune diseases advanced by Hector DeLuca and others prove valid.

Sex

In the authors' series of more than 150 cases, the ratio of boys to girls is 1.3:1. No other substantial data are available.

Age

More than 80% of childhood cases occur in patients younger than 10 years; somewhat less than 20% of cases occur in the second decade of life. Incidence in adulthood is unclear, accounting for less than 3% of the reported cases. However, diagnostic overlap with MS may lead to underestimation of the prevalence in adults.

Clinical

History

- Clinically, acute disseminated encephalomyelitis (ADEM) is usually readily distinguishable from multiple sclerosis (MS) by the presence of certain clinical features, including the following:
 - History of preceding infectious illness or immunization
 - Association with constitutional symptoms and signs such as fever
 - Prominence of cortical signs such as 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 as many as 65-85% of cases occurring between October and March. The mean age at presentation is about 7 years, with a range that extends from the first year of life to adulthood. Typical cases of ADEM arise 1-20 days after a childhood infectious illness, which is febrile in more than 94% of cases.
 - There is usually a clearly defined phase of afebrile improvement lasting 1-20 days or more before onset of neurologic findings.
 - Generally, patients have shown partial or complete recovery from the prodromal illness at the time of onset of ADEM.
 - Whether latencies of longer than 20 days implicate a particular febrile illness as the prodrome of ADEM is unclear. Clinical experience suggests that this is possible.
 - Most of the large envelope-bearing viruses that figured prominently in older series of ADEM, of which measles was a particularly virulent example, no longer figure importantly in the etiology of ADEM because these diseases are prevented by vaccination.

- Most cases encountered now occur in the wake of respiratory or gastrointestinal illness presumed to be of viral etiology, although a specific virus is seldom identified.
- Documentation of at least 1 fever-free day is especially suggestive of ADEM, although such a hiatus is also found in postinfectious vasculitides.
- A hiatus of at least a few hours is found even in cases where the ADEM prodrome consists of weeks of fever of unknown origin.
- Occasionally, ADEM may occur in the wake of several weeks of fever of unknown origin.
- Some patients have premonitory pain in the back prior to the development of ADEM-related inflammatory myelitis.
- Various vaccines have been suggested as the exogenous provocation of cases of ADEM and may account for 3-6% of ADEM cases.
 - This remains a controversial subject, although clear evidence exists for the role of the Pasteur rabies vaccine and compelling, although somewhat less conclusive, evidence exists for the role of other vaccines.
 - The overall effect of the introduction of vaccinations for measles and other encephalomyelitogenic viruses has been a marked reduction in the number of severe or fatal cases of ADEM.
 - Measles was associated with ADEM in about 1 out of 800 cases, and in many of these cases, ADEM that was often particularly severe. Measles-associated ADEM had a high rate of both morbidity and mortality.
- A cause-and-effect relationship between a possible prodrome and ADEM is more difficult to establish in cases where longer or very short intervals exist between a possible exogenous stimulus and inflammatory result.
 - Latencies longer than 50 days have been suggested for infections or vaccines but are difficult to prove.^[3]
 - Relationships are also difficult to determine when a febrile systemic process is rapidly followed by neurologic deterioration because such cases may represent meningoencephalitis.
- A minority of cases (7-15% in several series employing various case definitions) lack a clearly defined prodrome.
 - Some of these cases are possible examples of longer than 20 days of latency from prodrome to ADEM, especially in prepubertal children, with imaging changes suggesting ADEM, with negative CSF immune profile, and with rapid and complete recovery.
 - Some members of this group, with low risk for recurrence, are prepubertal children who manifest seizure, encephalopathy, and long tract signs.
 - Another subgroup with poorly defined prodrome but low risk for recurrence are children or adolescents manifesting subacute-onset syndromes that combine neuropsychiatric abnormalities and movement disorders and imaging changes suggestive of ADEM. The course in these cases, which could be termed Johnson syndrome, is often prolonged or even progressive, improving with high-dose intravenous corticosteroids.
 - The lack of prodrome is found in more than 30% of adolescent cases of acute CNS demyelination and approximately 45% of similar adult cases.

- MRI abnormalities in these adolescent and adult cases usually more closely resemble those characteristic of MS than those characteristic of ADEM, and CSF immune profile test results are more likely to be abnormal. These patients are likely to satisfy the criteria for diagnosis of MS within months to years. This is especially true with posterior column signs and few if any cortical signs.
- The first signs of ADEM usually include abrupt onset of irritability and lethargy (>94% of cases).
 - The onset of neurologic abnormalities is abrupt in more than 95% of ADEM cases.
 - Occasionally, the development of diffuse marked neurologic abnormalities requires only a few hours. In most cases, signs and symptoms develop over several days, and a minority of cases show continued deterioration of function for periods as long as 4 weeks.
 - Changes in mental status (88% of cases) are commonly observed in ADEM.
 - Convulsive seizures occur around the onset of ADEM in as many as 25% of cases.
 - Meningismus may be present but is uncommon except in very young children with severe disease.
 - Although almost any portion of the CNS may be clinically involved, certain systems appear to be particularly prone to dysfunction; thus, the descending white matter motor tracts, optic nerves, and spinal cord are particularly commonly involved.
 - ADEM-associated optic neuritis is usually bilateral, although the onset in a second eye may follow onset in the first by days to months. Bilaterality may provide a degree of reassurance with regard to MS risk because optic neuritis in MS is frequently unilateral. Visual evoked responses may discern abnormalities in a second eye before clinical deterioration in vision is discernible.
 - A wide variety of cranial nerve abnormalities may occur in addition to optic nerve disease.
 - Long tract signs (eg, clonus, increased muscle stretch reflexes, upgoing toes) are present early in as many as 80% of cases.
 - In some instances, reflexes may be lost at the onset. When this is caused by transverse myelitis, the evolution of disease after spinal shock replaces absent reflexes with increased muscle stretch reflexes within a few days or more. A small number of cases manifest loss of reflexes as a sign of associated peripheral nerve disease with ADEM, a condition termed EMRN. Some of these EMRN cases are associated with evidence for acute infection with Epstein-Barr virus.
 - Weakness may be hemiparetic, double hemiparetic, diparetic, or generalized and symmetric. Fairly symmetric leg weakness is seen in many cases of ADEM-related transverse myelitis with associated abnormalities of bowel and bladder function. Transverse myelitis may be associated with optic neuritis. This combination (Devic syndrome) is also seen in MS, but in ADEM, it is more likely to have bilateral optic neuritis.
 - Most ADEM presentations may be summarized into 7 clinical syndromes as follows:
 - Mild encephalopathy, sometimes associated with long tract signs
 - Severe encephalopathy with bilateral paresis, often associated with brainstem signs, particularly the lower cranial nerves
 - Predominantly brainstem presentation with features suggesting Fisher syndrome in some cases or Bickerstaff brainstem encephalitis in other cases
 - Hemiparesis, ipsilateral long tract signs, with or without seizure

- Predominantly ataxic, differing from the predominantly axial/gait ACA in that ADEM-associated ataxia is often associated with nystagmus, extremity ataxia, and long tract signs
 - EMRN (mixed upper and lower motor neuron signs)
- Some ADEM presentations are fulminant
 - Fulminant ADEM is more likely to manifest in children younger than 3 years, with rapid evolution of a low state of function and demonstration on scans of severe edema. Such cases have become uncommon with widespread vaccination against childhood illnesses.
 - Transverse myelitis may begin rapidly and be associated with severe edema, usually in the cervical region.
 - Acute administration of very high-dose intravenous corticosteroids may possibly close the blood-brain barrier and subtend the development of edema, which may, in these fulminant cases, account for the high risk for permanent morbidity.
- There are unusual presentations for possible ADEM that have uncertain classification. Some are labeled acute MS or diffuse sclerosis, and some are labeled encephalitis or necrotizing encephalitis, rather than ADEM.
 - Some cases are labeled as acute MS with prepubertal onset of acute encephalopathy, with mental status changes ranging from confusion to coma, seizures, and prominent pyramidal tract abnormalities.
 - Young children may manifest a rapidly progressive demyelinating illness that may be fatal within days to weeks and is almost universally associated with profound permanent psychomotor deficits in those who survive. Brain images differ from those typical of juvenile MS and may demonstrate confluent symmetric areas (butterfly pattern) of bright signal abnormality on T2-weighted sequences.
 - Fulminant presentation with lesions showing significant degrees of ring enhancement after contrast administration may also be found.
 - Malignant brain edema may be present, manifested by sulcal and ventricular effacement, similar to the fulminant ADEM in children younger than 3 years noted above.
 - Some patients with the large tumorlike lesions, acute MS, or Schilder disease presentations during childhood or adolescence do remarkably well as compared to adults with similar presentations.
 - The classification of these rare severe infantile cases, exhibiting features suggesting either severe acute MS or hyperacute ADEM, remains in doubt.
 - Nonetheless, pathological confirmation that some of these cases are MS has been published (Shaw, 1987), and hyperacute adult cases with similar clinical and radiographic manifestations have been reported (Vliegthart, 1985).
 - Some of these cases display more generalized T2-weighted abnormalities on MRI and may represent cases of what has been referred to as acute toxic encephalopathy.
 - Emphasizing that scan results do not reliably distinguish every case of MS from ADEM is important, but in most cases, reliable inferences may be drawn. Confusion is especially likely to arise in patients with large areas of bright signal within white matter on spin-echo sequences. Extensive white matter involvement may be found in young infants that some would label as MS (Maeda, 1989) while others would label it hyperacute ADEM.
 - Rarely, childhood, adolescent, or adult MS manifests as large unilateral or multiple tumorlike mass lesions that may appear cystic and may impart mass effects (albeit atypically and, if present, unexpectedly mildly). The

lesions are steroid responsive and may recur in other locations, such as the contralateral paraventricular white matter.

- These lesions may represent an intermediate entity between MS and ADEM. Other differential considerations are neoplasm, systemic lupus erythematosus (SLE) and other vasculitic illnesses, progressive multifocal leukoencephalomyelitis, and Schilder myelinoclastic diffuse sclerosis.
 - Schilder disease (diffuse sclerosis) is sometimes considered an MS variant, and the uncertain diagnostic status is beyond the scope of this review. Detailed discussion of that entity is available in the Neurology section of the eMedicine journal.
- Recurrent ADEM is as follows:
 - Individuals who have experienced typical ADEM are at risk for recurrence. If these are second bouts, they may satisfy the diagnostic criteria for MS, although this liability may require closer scrutiny in prepubertal children than in older individuals.
 - Recurrence may occur during the taper of corticosteroid therapy initiated for ADEM. This phenomenon is not thought to represent a second or independent bout of illness; it usually responds to increasing the corticosteroid dosage and prolonging the ensuing taper.
 - The appearance of small new lesions on MRI within a month of presentation must also be interpreted with caution, and this may be seen in ADEM.
 - Although long tapers are sometimes required and more than one taper-related worsening occurs in a small number of patients, recovery is achieved within 2-12 months without further recurrence.
 - A rare subgroup of patients exists who cannot be weaned entirely from anti-inflammatory therapy. Most of the 8 examples the authors have encountered were in boys, and the onset of illness usually occurred at age 2-6 years.
 - Mental status changes, visual disturbance, and pyramidal weakness are typical findings; seizures occur in most cases.
 - Imaging changes resemble those found in cases of typical ADEM (ie, multiple plaques at the grey-white junction and in deep white matter), a feature that distinguishes these cases from chronic cases considered a manifestation of Schilder disease.
 - The CSF immune profile remains normal despite recurrences, although myelin basic protein may be elevated.
 - The neurologic abnormalities in this group improve significantly with intravenous methylprednisolone treatment (20 mg/kg/d for 3 successive doses) followed by oral methylprednisolone (2 mg/kg/d) with slow taper to achieve alternate-day dosing.
 - Trouble is encountered during the taper, each patient having a particular threshold for recurrence. In most of the authors' cases, this threshold is encountered when the daily methylprednisolone dose is lowered to approximately 12-14 mg every other day.
 - The neurologic worsening responds to higher corticosteroid doses, but this threshold effect cannot be overcome, and steroid therapy has been continued in these patients for periods as long as 8 years.
 - Although prolonged daily steroid therapy is generally well tolerated, osteopenia may develop, and one of the authors' patients developed vertebral compression fractures.

Physical

Irritability and lethargy are common first signs of acute disseminated encephalomyelitis (ADEM). Fever returns in nearly half of cases, headache is reported in 45-65%, and meningism is detected in 20-30% of cases. Over the course of minutes to 6 weeks or more, neurologic abnormalities develop. The long interval of possible worsening is much longer than the 0-14 days over which manifestations of an early bout of multiple sclerosis (MS) or cases labeled as adult ADEM may worsen. Among the most common abnormalities are visual disturbances and language, mental status, and psychiatric abnormalities. Mental status disturbances include lethargy, fatigue, confusion, irritability, obtundation, and coma and are found in 65-85% of children with ADEM. Psychiatric changes include irritability, depression, personality change, and psychosis. Focal or generalized seizures occur as an early sign in 10-25% of cases.

Weakness (50-75% of cases) is more commonly discerned than sensory defects (15-20%). The combinations of these signs may suggest cortical, subcortical, brainstem, cranial nerve, or spinal cord localization. Long tract signs develop in about half of all cases. Cranial nerve palsies are found in 35-50% of cases of childhood ADEM. Mental or psychiatric disturbances, seizures, and cranial nerve palsies are significantly less common in adolescents or adults with a first or second bout of MS and in many adults with an illness labeled ADEM. Sensory changes may be underappreciated in young children. However, posterior column deficits and hemisensory changes are possibly much less common than in adult cases of ADEM or in early bouts of adolescent or adult MS, where sensory changes (particularly posterior column signs) are found in two thirds of cases. Band or girdle dysesthesia or Lhermitte sign are seldom if ever found in cases of childhood ADEM.

Ataxia is found in 35-60% of childhood ADEM cases, which tends to differ from cases of ACA because it is more commonly appendicular with nystagmus or generalized ataxia than the distinctive gait/trunk ataxia of ACA. Extrapyramidal disorders such as choreoathetosis or dystonia are sometimes observed.

Signs and symptoms found in cases of ADEM:

- Alteration in personality
- Abnormal consciousness (65-75%)
- Ataxia (appendicular more than axial or gait)
- Cranial nerve palsies (35-40%)
- Hallucinations
- Headache
- Language disturbances (10%)
- Meningeal signs
- Nystagmus
- Psychiatric abnormalities
- Optic neuritis (10-30%)
- Ophthalmoparesis
- Seizures, focal or generalized (25%)
- Sensory loss/dysesthesia
- Visual field deficits

- Vomiting

Causes

Acute disseminated encephalomyelitis (ADEM) may develop in the wake of a wide variety of infectious illnesses or immunizations, especially those associated with large envelope-bearing viruses. Among the agents most commonly identified by titer rise suggesting responsibility for the prodromal phase are Epstein-Barr virus, cytomegalovirus, herpes simplex virus (HSV), and mycoplasma. However, a particular agent is identified only in a minority of ADEM cases.

ADEM is somewhat more common in the colder months of the year, during which these various viral illnesses are more prevalent. Prior to widespread immunization programs, measles was the most common associated illness. ADEM occurred in approximately 1 out of 800 cases. Now, most cases occur in the wake of respiratory or gastrointestinal illnesses that are presumed to be of viral etiology; specific viral agents are seldom identified.

The hiatus between onset of viral symptoms and onset of ADEM may range from 2-20 days; the two phases of illness are typically separated by a phase of recovery from fever and other constitutional manifestations of the initial infectious phase of illness. ADEM may possibly arise after intervals as long as 30 or more days after an infectious prodrome. The longer the interval between presumed prodrome and ADEM, the less certain the etiologic association. A minority of cases lack a prodromal phase. Establishing the etiologic role of immunizations has proven controversial.

Clear links between the Pasteur rabies vaccine and ADEM have been established. Immunizations less frequently associated with ADEM include pertussis, measles,^[4] Japanese B virus, tetanus, and influenza.

The provocation provided by an infectious agent likely requires participation of other genetic or immuno-experiential factors of the individual in order to give rise to ADEM. These factors likely include genetically or experientially determined aspects of immunoregulation, particularly T-helper cell function.

Alves-Leon et al have found that the alleles HLA DQB1*0602, DRB1*1501, and DRB1*1503 confer genetic susceptibility to acute disseminated encephalomyelitis.^[5]

Differential Diagnoses

Acute Inflammatory Demyelinating
Polyradiculoneuropathy

Aseptic Meningitis

Bell Palsy

Brucellosis

Cardioembolic Stroke

Cauda Equina and Conus Medullaris Syndromes

Metastatic Disease to the Brain

Multiple Sclerosis

Neurological Sequelae of Infectious
Endocarditis

Neurosarcoidosis

Neurosyphilis

Pelizaeus-Merzbacher Disease

Cavernous Sinus Syndromes
Cerebral Venous Thrombosis
Churg-Strauss Disease
Diffuse Sclerosis
Dissection Syndromes
First Seizure: Pediatric Perspective
Focal Status Epilepticus
Glioblastoma Multiforme
Guillain-Barre Syndrome in Childhood
Herpes Simplex Encephalitis
HIV-1 Associated CNS Complications (Overview)
Inherited Metabolic Disorders
Lyme Disease
Medulloblastoma
Metabolic Disease & Stroke: MELAS

Polyarteritis Nodosa
Posterior Cerebral Artery Stroke
Primary CNS Lymphoma
Primary Lateral Sclerosis
Sarcoidosis and Neuropathy
Spinal Cord Infarction
Spinal Epidural Abscess
Systemic Lupus Erythematosus
Viral Encephalitis
Viral Meningitis
Wegener Granulomatosis
Whipple Disease

Other Problems to Be Considered

Abducens (VI) nerve palsy
Adrenoleukodystrophy
Adrenomyeloneuropathy
Non-Downs atlanto-occipital instability
Chiari malformation
Behçet disease
CNS vasculitis
Echinococcosis
Hypersensitivity vasculitides
Moyamoya disease
Neuroaxonal dystrophy
Subacute sclerosing panencephalitis
Toluene encephalopathy
Toxic subacute myelopticoneuropathy

Workup

Laboratory Studies

- Platelet counts are elevated in a substantial number of children with ADEM. Sedimentation rates are occasionally mildly elevated; greater elevation suggests the possibility of vasculitis or infection.

- Modest-to-moderate elevation of CSF white and red blood cell counts may be found in childhood ADEM. Red blood cells may be due to modest degrees of AHLE. Elevated CSF HSV or Lyme titers do not exclude the possibility of associated ADEM. Results of CSF immune profile testing (eg, CSF:serum immunoglobulin G [IgG] index, CNS IgG synthetic rate, oligoclonality) employing age-appropriate normative data are positive in fewer than 10% of prepubertal children with ADEM (Rust, 1989; Rust, 1988). CSF myelin basic protein concentration, reflecting demyelination, is frequently elevated.

Imaging Studies

- The CT scan low-density abnormalities are found in more than half of childhood or adolescent ADEM cases, but this technique is far less sensitive than MRI for the disclosure of extent and number of lesions.
- T2-weighted, proton-density, or echo-planar trace diffusion MRI techniques disclose high-signal lesions in more than 80-90% of cases of ADEM. Apparent diffusion coefficient maps show high-signal changes consistent with vasogenic edema.^[6] ADEM lesions are characteristically centrifugal at the junction of the deep cortical gray and subcortical white matter. Such lesions are found in more than 90% of children with ADEM. They are found in less than 40% of adults initially diagnosed as having ADEM, many of whom are later diagnosed as having MS.
 - Many of the diseases that constitute the differential diagnosis of ADEM produce MRI abnormalities that emulate various ADEM-associated lesions. Some cases of encephalitis result in the development of multiple tiny or small patches of bright signal on T2-weighted images that have been mislabeled as ADEM, but response to corticosteroid therapy is poor and follow-up scans may show severe encephaloclasia. HSV2 encephalitis or Lyme disease may be difficult to distinguish from ADEM and may involve ADEM mechanisms in pathogenesis. Pial enhancement does not occur in ADEM and suggests meningoencephalitis. Metazoal parasitic diseases of the brain (eg, cysticercosis), neoplasia, and ADEM are occasionally mistaken for one another.
 - Additional lesions may be found in deeper white matter, optic nerves, basal ganglia (30-40%), the thalamus (30-40%), the brainstem (45-55%), the cerebellum (30-40%), and the spinal cord. Periventricular lesions (30-45%) and corpus callosum lesions (20-25%) are uncommon in childhood ADEM compared with MS.^[7]
 - The indistinct margins of childhood ADEM lesions tend to suggest a "smudged" edge rather than the crisp margin typical of the classic ellipsoid plaques of MS.
- ADEM lesions may contain areas of hemorrhage suggestive of HSV2 encephalitis, changes never found in MS plaques. The distribution of ADEM lesions ranges from fairly symmetrical to very asymmetrical, and few if any are aligned in the Dawson finger orientation. As many as 90% of childhood ADEM lesions enhance with gadolinium. The degree of contrast enhancement of ADEM lesions is typically uniform and usually not very dense. In contrast, MS plaques tend to vary in degree of contrast enhancement and may at times enhance quite densely.^[8,9,10]
- MRI abnormalities may be highly suggestive of ADEM and may help greatly in distinguishing ADEM from MS or other alternative diagnoses. ADEM gives rise to a much wider variety of appearances than MS. ADEM may produce large unilateral T2 bright lesions, some of which appear to have striking central cavitation, although encephaloclasia may not be found on follow-up scanning after recovery. These lesions may suggest neoplasm, stroke, parasitism, abscess, or MS. Ring enhancement or mass effect sometimes found in ADEM may suggest abscess or tumor.^[11] In rare cases,

symmetrical, linear, posteriorly emphasized white matter changes on T2 weighting suggest leukodystrophy. Recognize that no changes on MRI are pathognomonic of ADEM or for that matter of demyelination.

- Some patients with ADEM have normal findings on MRI on initial presentation that become abnormal and characteristic of ADEM if the study is repeated several weeks later, even though patients are then showing clinical improvement.^[12] This suggests that characteristic features may be missed because of sampling error, that normal findings on a scan do not exclude the ADEM diagnosis, and that the appearance of new lesions during recuperation from ADEM may not represent recrudescence of disease.^[10]
 - Magnetization transfer MRI, single photon emission CT scanning, or nuclear magnetic resonance (NMR) spectroscopy may possibly prove helpful in distinguishing ADEM from alternative diagnoses, although the development of a pathognomonic imaging result is unlikely.
 - For these reasons, diagnosing ADEM on the basis of findings on scanning alone is dangerous. Diagnosis of ADEM should always rest on clinical grounds in children as in adults.
 - Radiographic studies and other laboratory tests are especially valuable in ruling in or out alternative diagnoses.
- From a retrospective analysis, Callen et al propose diagnostic criteria for MRI to distinguish a first MS attack in children from those with acute disseminated encephalomyelitis. Any 2 of the following criteria could distinguish MS from acute disseminated encephalomyelitis (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.^[7]

Other Tests

- The EEG often exhibits disturbance of normal sleep rhythms. Focal or generalized slowing, sharp waves, rhythmic delta, or spikes may be found in the waking state during the early stages of ADEM, features that distinguish ADEM from MS. The absence of such abnormalities during the first bout of acute disseminated demyelinating illness in a child significantly increases the risk for ultimate MS diagnosis. Similar EEG abnormalities are found in adult ADEM.

Procedures

- The lumbar puncture is an essential aspect of acute disseminated encephalomyelitis (ADEM) workup.^[13] It assists in distinguishing ADEM from various forms of meningoencephalitis, especially upon the basis of titers for the various bacteria, viruses, or other agents that may produce a directly infectious form of meningoencephalitis.
 - The immune profile is also helpful in distinguishing ADEM from MS. The IgG index, IgG synthetic rate, or oligoclonal bands are positive in more than two thirds of all first clinically recognized MS bouts and in 90-98% of individuals who have experienced multiple MS bouts. One or more of these studies is positive in no more than 10% of ADEM cases.
 - Note that the findings on immune profile studies may be positive in various infectious conditions such as neurosyphilis, subacute sclerosing panencephalitis (SSPE), Lyme disease, stroke, and various forms of acute or chronic bacterial or viral meningoencephalitis. The CSF:serum IgG index or synthetic rate formulations may show positive results in neurosyphilis, Lyme disease, Guillain-Barré syndrome, some brain tumors, sarcoid, and a wide variety of bacterial or viral meningoencephalitides or other forms of CNS inflammation.

- Occasionally, brain biopsy is necessary to distinguish ADEM from other diagnostic possibilities. The diagnosis of ADEM is confirmed when typical perivenular demyelinative changes with axonal sparing are observed.

Treatment

Medical Care

Acute disseminated encephalomyelitis (ADEM) is often treated with high-dose intravenous corticosteroids, to which it appears to be responsive. One common protocol is 20 mg/kg/d of methylprednisolone (maximum dose of 1 g/d) for 3-5 days. Improvement may be observed within hours but usually requires several days. An oral taper for 3 weeks or some other interval is sometimes appended. The chief alternative therapy is intravenous immune globulin (IVIG).^[14] It is administered as 2 g/kg intravenously for 2-3 days. IVIG may be preferable in instances where meningo-encephalitis cannot be excluded based upon the hypothesis that corticosteroids might worsen the course of infection.^[14]

Available published information concerning efficacy is inadequate to accurately assess much concerning the impact of either form of therapy, although it appears likely that both forms of therapy increase the pace of initial recovery. Whether these forms of therapy influence times to final outcome or extent of final recovery is not known.

Theoretically, very high-dose corticosteroids (30-50 mg/kg) administered intravenously at presentation to patients with transverse myelitis may be advantageous from the vantage point of its capacity to close the blood-brain barrier and limit swelling. Marked cord swelling may account for poor outcome in some cases of transverse myelitis because of circulatory impairment and cord infarction. The same argument may hold true for severe cerebral ADEM such as tends to arise in some young children (

There is as yet no convincing evidence that treatment with the combination of intravenous corticosteroids and IVIG confers any advantage in such cases, although this approach is employed by some clinicians.

Severe ADEM has also been treated, apparently successfully, with such alternative approaches as (1) combination of intravenous corticosteroids and IVIG, (2) cyclosporin, (3) cyclophosphamide, or (4) plasma exchange/plasmapheresis^[15,16]. Greater understanding of trimolecular complex regulation, adhesion molecules, and inflammatory cytokines may permit development of more specific and effective ADEM therapies. The polymorphism of the human major histocompatibility complex and apparent heterogeneity of T cell response to autoantigens render this a daunting project, although anticytokines represent an intriguing avenue of therapeutic research.^[17]

Taper-related recurrence occurs in as many as 3-5% of cases and usually responds to prolongation of taper. Similar phenomena occur in other postinfectious diseases, such as Guillain-Barré syndrome or opsoclonus-myoclonus. A subset of patients manifest repeated recurrences that prevent discontinuation of corticosteroids or necessitate changing to various steroid-sparing treatments such as cyclophosphamide or beta-interferons. This rare and interesting subgroup tends to have onset of disease before 6 years of age, and despite recurrence, these children do not manifest evidence for CSF immune profile (ie, IgG index, IgG synthetic rate, oligoclonal bands) abnormality. The relationship of this group to patients with ADEM or MS or some other form of inflammatory CNS illness remains unclear.

Non-taper-related recurrences occur in as many as 5% of children with ADEM. In such instances most children have just a single recurrence, although some prepubertal children manifest 2 or even 3 recurrences within a year or two of the initial bout but then manifest no further recurrences for follow-up intervals as long as 18 years. Although it has been suggested that IVIG administered in treatment of a single recurrence may prevent further recurrence, the evidence for this remains inconclusive because most children with a single recurrence of ADEM that are treated with corticosteroids also have no further recurrences.

Surgical Care

Surgical treatment for severely elevated intracranial pressure has been undertaken for cases of AHLE, hemorrhagic brain purpura, and non-Reye syndrome, examples of what have been termed obscure encephalopathies of infancy. Some of these cases were likely examples of hyperacute ADEM. Surgical interventions have ranged from placement of pressure bolts to decompression of the intracranial fossae by unroofing of the cranium. Outcome of such interventions was mixed.

Although such severe cases were regularly noted in the medical literature from the 1920s until the mid 1970s, few examples have been noted since that time. Prevalence clearly has dramatically decreased. Because these severe cases often followed measles, mumps, and other diseases for which effective vaccines have been developed and because the disappearance of such cases has followed the availability and use of such vaccines (earlier disappearance in the United States and Western Europe, subsequent disappearance in Asia and the Middle East), this change in prevalence likely reflects the removal of pathogens that are provocative of such severe forms of ADEM.

Consultations

Consultations with infectious disease specialists are occasionally warranted to consider alternative diagnoses. Pediatric intensivists generally become involved in severe cases for management of airway, breathing, and circulation.

Activity

No clear restrictions on activity exist except as indicated by the severity of disease. The possible exceptions are ADEM-related postinfectious demyelinating syndromes, sometimes in association with the development of brain edema, that arise in the wake of illnesses such as brucellosis or malaria. In the case of acute brucellosis, recovery is clearly more rapid and relapse is less likely if patients are treated with enforced bedrest. This rule may also be true of the relapsing neurobrucellose illnesses, including the types that closely resemble or are examples of ADEM. Although somewhat less clear in the case of cerebral malaria, little doubt exists that enforced bedrest with appropriate positioning (because of elevation of intracranial pressure) is of importance. In the case of cerebral malaria and in cases of the more severe varieties of neurobrucellosis, bedrest is often necessary because of the low mental status and weakness of such individuals.

Medication

The goals of pharmacotherapy are to reduce morbidity and prevent complications.

Anti-inflammatory Agents

These agents have anti-inflammatory properties and cause profound and varied metabolic effects. Both corticosteroids and intravenous IVIG modify the body's immune response to diverse stimuli.

Methylprednisolone (Adlone, Medrol, Solu-Medrol, Depo-Medrol)

Considerable experience has accumulated in the use of various corticosteroids in the treatment of ADEM. No conclusive evidence exists that this form of therapy is effective. The weight of evidence at present supports the view that corticosteroids may shorten the time to onset of improvement. Whether this form of therapy shortens time to maximal recovery is unclear, and whether deleterious effects, such as enhancement of tendency to recurrence, exist is unknown. Generally, however, this form of therapy appears, within the considerable limits of present knowledge, to be safe. The usual approach is administration of methylprednisolone for 3-5 d IV (or the equivalent dose of some other anti-inflammatory corticosteroid). The initial dose should be administered under close supervision because rare instances of anaphylaxis after initial dose have been reported.

Dosing

Adult

1 g IV qam for 3-5 d; this may be followed, where deemed appropriate, by 2 mg/kg PO (maximal dose 80 mg/d), followed with taper over 3-5 wk

Pediatric

20 mg/kg IV for 3-5 d initially; this may be followed, where deemed appropriate, by 2 mg/kg/d PO (maximum 80 mg/d), followed with taper over 3-5 wk

Interactions

Coadministration with digoxin may increase digitalis toxicity secondary to hypokalemia; estrogens may increase levels of methylprednisolone; phenobarbital, phenytoin, and rifampin may decrease levels of methylprednisolone (adjust dose); monitor patients for hypokalemia when taking medication concurrently with diuretics

Contraindications

Documented hypersensitivity; systemic fungal infection; use in some patients receiving amphotericin B; concomitant cerebral malaria; latent or active amoebiasis; active chickenpox or measles; active tuberculosis; recent myocardial infarction; ulcerative colitis; active or latent peptic ulcer disease; impending gastrointestinal perforation; enteric abscess

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Hyperglycemia, edema, osteonecrosis, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, growth suppression, myopathy, and infections are possible complications of glucocorticoid use

Human immune globulin (Gammagard, Gamimune, Sandoglobulin, IVIg)

Believed to treat conditions associated with inflammation and immune dysregulation by neutralizing circulating myelin antibodies through anti-idiotypic antibodies. May down-regulate proinflammatory cytokines, including IFN-gamma. Blocks Fc receptors on macrophages, suppresses inducer T and B cells, and augments suppressor T cells; blocks complement cascade. May promote remyelination. May increase CSF IgG modestly.

Dosing

Adult

2 g/kg IV administered over 2-5 d

Pediatric

Not established, adult dosage is usually employed, administered IV

Interactions

Globulin preparation may interfere with immune response to live virus vaccine (MMR) and reduce efficacy (do not administer within 3 mo of vaccine)

Contraindications

Documented hypersensitivity; IgA deficiency

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Check serum IgA before administering IVIg (use an IgA-depleted product, eg, Gammagard S/D); may increase serum viscosity and thromboembolic events; may increase risk of migraine attacks, aseptic meningitis (10%), urticaria, pruritus, or petechiae (2-30 d postinfusion); increases risk of renal tubular necrosis in elderly patients and in patients with diabetes mellitus, volume depletion, or preexisting kidney disease; laboratory result changes associated with infusions include elevated antiviral or antibacterial antibody titers for 1 mo, 6-fold increase in ESR for 2-3 wk, and apparent hyponatremia

Follow-up

Further Inpatient Care

- After initial evaluation and initiation of therapy, further inpatient care is dictated by the evolution of disease and rate of recovery exhibited by the patient.
- Physical and occupational therapy may be indicated in patients with paresis, ataxia, low vision, and other focal neurologic abnormalities that impair function.
- Provision for feeding and for the treatment of abnormalities of bowel or bladder function may be indicated.
- When seizures occur, they usually do so transiently at the onset of disease. In rare instances, additional management issues for seizures arise during the subsequent course of treatment.

Further Outpatient Care

- Outpatient care indications depend on the course of illness and the extent of recovery at the time of discharge. It may include the involvement of physical, occupational, or speech therapists. Some patients require follow-up with urologists or gastroenterologists because of persistent bladder or bowel problems.
- Patients who are placed on tapering doses of oral corticosteroids require follow-up to ascertain the rate and extent of improvement. Urgent return or consultation may be warranted by patients who display relapse during taper of corticosteroids. In such instances, the relapse is usually controlled by restoration of a higher medication dosage with slower ensuing taper. Some difficult cases require slow tapers.

Transfer

- Some patients with more severe degrees of neurologic disability are transferred to rehabilitation facilities for some period of time before they are judged sufficiently recovered to be discharged home.

Complications

- The most common inpatient complications include abnormalities of vision, motor function (ie, pyramidal, extrapyramidal, cerebellar), or bladder or bowel function.
- Recurrence is the chief outpatient complication and is rare.

Prognosis

- The outlook for recovery is generally excellent. Although some older series suggest up to a 10% mortality rate, only 1.5% of the authors' cases have resulted in mortality due to ADEM-related complications. Degree of recovery is unrelated to severity of illness. Complete recovery may be observed even in children who become blind, comatose, and quadriparetic. Recovery is poorest in children younger than 2 years, patients with myelitis, and those who have significant edema of the brain or spinal cord. Whether ultra-high-dose corticosteroid therapy and other treatments for edema might improve the outcome for these groups is not yet known, although limited experience suggests this possibility. In other cases of ADEM, modest visual or motor deficits may persist, as may sphincter abnormalities in

patients with spinal cord disease. Disturbances of mood and personality may outlast motor deficits, but they may also wane over ensuing months.

- The long-term (10-y follow-up) risk of patients with ADEM for development of MS is 25%. Risk for MS 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 (Rust, 1989).
- Most patients who experience a bout of ADEM can look forward to complete recovery or the persistence of only mild deficits, such as modestly diminished visual acuity. This excellent outlook even applies to patients who experienced a global low state of function during the acute illness.
 - Whether any available form of treatment has a favorable effect on the time to maximal recovery or the risk for deficits is unknown. Exceptions to the excellent outlook are patients with transverse myelitis and infants younger than 2 years. Cord swelling may account for the high rate of residual paresis and the occasional death of patients with severe acute inflammatory myelitis. Prompt administration of high doses of corticosteroids can possibly improve the outlook for these patients, but no reliable data yet support this hypothesis. The risk of MS for prepubertal children who have a bout of ADEM is less than 10%.
 - The authors have observed children with a typical bout of ADEM in the first decade of life who manifest MS during the second decade, after a symptom-free hiatus of more than 10 years.
- In the authors' experience, the risk for MS for children who have had a single prepubertal bout of ADEM is less than 6%. MS is defined, for these children, as persistence of an illness satisfying clinically definite multiple sclerosis (CD-MS) criteria into adolescence.
 - The risk for MS in children who have had 1-3 prepubertal relapses of ADEM, none of which was related to steroid withdrawal, ranges from 15-33%. Risk increases in proportion to the number of relapses that occur, especially relapses that occurred without exogenous provocation (eg, febrile prodrome, vaccination).
 - Children with more than 3 prepubertal clinical relapses are at significant risk of having rare vasculitic or inflammatory processes that must be diagnosed by biopsy of brain tissue or other organs (eg, CNS vasculitis, hypersensitivity vasculitides, sarcoidosis, histiocytic lymphogranulomatosis) and in some instances are found to be harboring neoplasm (the results of their imaging studies having been misinterpreted).
- The hesitancy to apply a diagnosis of CD-MS has not prevented the authors from using immunomodulatory therapy (eg, IFN-beta1a) in the treatment of children with recurrences or persistent lesions that do not appear to respond to corticosteroid therapy or those who develop a pattern suggesting steroid dependence (steroid withdrawal–related recurrence); the sometimes gratifying response to IFN-beta1a has not been viewed as confirmation of MS.
 - These uncertainties have generated several additional worries, particularly whether too much delay is entailed in administration of immunomodulatory therapy to a prepubertal child for whom an MS diagnosis is withheld and whether at some point discontinuing immunomodulatory therapy is safe in a child who has experienced a good response to such therapy for a recurrent illness that may be MS despite the absence of characteristic changes in the CSF immune profile.
 - In this context, remember that as many as 8% of adults who are identified as having CD-MS do not have immune profile abnormalities even after the second or third clinical bout.

Patient Education

- For excellent patient education resources, see eMedicine's Brain and Nervous System Center and the article Multiple Sclerosis. All these materials may be printed free of charge.

Miscellaneous

Medicolegal Pitfalls

- Medicolegal issues that arise in association with ADEM include the following:
 - Delay in diagnosis and treatment of ADEM
 - Complications occurring in the course of ADEM either as the result of natural evolution of the disease or because of treatments
 - Allegations that immunizations are the cause of ADEM

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Keywords

ADEM, acute disseminated perivenous encephalomyelitis, acute post-vaccinial encephalitis, demyelinating encephalomyelitis, acute disseminated vasculomyelinopathy, recurrent disseminated vasculomyelinopathy, drug-induced perivenular demyelination