Acute Disseminated Encephalomyelitis

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Acute disseminated encephalomyelitis (ADEM) is a demyelinating syndrome of the central nervous system. It is considered to be an autoimmune response to an antecedent antigenic stimulus, most frequently a prior infectious illness (postinfectious encephalitis) or immunization (postvaccination encephalitis) occurring in the days or weeks before neurologic illness. Clinically, ADEM is characterized by encephalopathy, or focal/multifocal neurologic signs; brain MRI is characterized by diffuse multifocal or patchy areas of demyelination. The differentiation between ADEM and a first episode of multiple sclerosis, a chronic central nervous system demyelinating disease, may be difficult but has important prognostic and treatment implications. Although no clinical trials have assessed the efficacy of treatment modalities in patients with ADEM, immunomodulators, including corticosteroids and intravenous immunoglobulin, are frequently used empirically. ADEM outcome is generally favorable, with resolution over weeks to months.

Introduction

Acute disseminated encephalomyelitis (ADEM) is classically described as a monophasic syndrome of brain inflammation and demyelination, occurring in temporal association with an antecedent immunologic challenge, usually an immunization or vaccination (postvaccination encephalomyelitis) or infection (postinfectious encephalomyelitis) [1••,2]. It is thought to be an immune-mediated inflammatory process involving primarily the white matter of the brain. ADEM is probably best conceptualized as a syndrome, rather than a distinct entity, and lies within the continuum of primary inflammatory demyelinating disorders of the central nervous system (CNS), which include multiple sclerosis (MS), acute transverse myelitis, neuromyelitis optica, and other variants. ADEM can be distinguished from these other inflammatory CNS disorders by the (generally) monophasic nature of the illness, relatively rapid onset and progression of illness and similarly rapid remission, and the characteristic pattern and distribution of brain lesions on MRI [3]. However, none of these features is pathognomic of ADEM, and the absence of a definitive biologic marker for the disease further complicates the clinical-diagnostic picture; thus, ADEM in large part remains a clinical diagnosis. In general, ADEM may be distinguished from acute infectious encephalitis by a predominance of demyelinating rather than cytotoxic injury and by the relative absence of other hallmark features of acute infection, such as fever, peripheral leukocytosis, and rash [4–7].

ADEM may also be conceptualized in terms of its derivative nosology. The terms "postinfectious" and "postimmunization encephalitis" are often used when an antecedent triggering stimulus is considered. "Acute perivenous encephalitis" and "disseminated vasculomyelinopathy" have been used when the underlying histopathology is described. "Acute disseminated encephalomyelitis," "postencephalitic demyelination," and "perivenous encephalitis" have been used in describing the possible immunopathologic basis for the syndrome [1••]. In this review, the term "ADEM" is used to encompass all these various entities, but focuses primarily on postinfectious and postimmunization encephalomyelitis, recognizing the fact that some experts would favor the latter terms if an antigenic stimulus such as infection or immunization is considered and ADEM when they are not.

A variant of ADEM, characterized by a more fulminant course and hemorrhagic manifestations in addition to acute demyelination, has also been described, variously referred to as acute hemorrhagic leukoencephalitis (AHLE), acute hemorrhagic encephalomyelitis, or acute necrotizing encephalomyelitis. Some debate exists as to whether this manifestation represents a distinct syndrome, or should be considered to be a hyperacute form of ADEM, with a more rapidly progressive, fulminant course and often a less favorable outcome, thus representing an extreme in the spectrum of severity of ADEM [8–10]. Pathologically, acute demyelination is accompanied by diffuse cerebral edema and hemorrhagic areas within demyelinating lesions [11]. Hemorrhagic forms are estimated to account for 2% of ADEM cases [12].

Epidemiology

The epidemiology of ADEM is incompletely understood. Few population-based assessments have been conducted, and existing assessments have used differing diagnostic criteria and case-finding methodologies. In general, ADEM may occur in any age group, but is thought to be more common in the pediatric population [13,14••,15]; whether this is somehow linked to more frequent infections and immunizations in children has not been substantiated. Overall, it is unclear whether there is a gender predominance in ADEM [3,16]; several pediatric cohort studies have suggested a slight male predominance [12,15], but it is unclear whether this is true in adults. A seasonal distribution of illness, predominating in winter and spring, has been established in several studies, again suggesting the potential role of antecedent infectious illnesses as triggers [15,17].

ADEM may account for 10% to 15% of cases of acute encephalitis in the United States [5]. An assessment of overall incidence of ADEM in the pediatric population conducted in San Diego County, CA, involving a retrospective/prospective analysis of all persons younger than 20 years old presenting to the three principal pediatric hospitals in San Diego County, provides perhaps the best incidence data for pediatric ADEM [17]. This assessment identified 42 children and adolescents diagnosed with ADEM between 1991 and 2000, resulting in an overall incidence of 0.4 per 100,000 per year, with a slightly higher incidence for younger age strata. The overall incidence of ADEM in the adult population is essentially unknown, outside of those situations associated with specific infections or immunizations.

Pathogenesis

ADEM is believed to represent an inflammatory autoimmune response with resultant CNS inflammation and demyelination. However, the exact pathophysiologic underpinnings of this response are unclear. One basis for the current concepts of the pathogenesis of ADEM and other autoimmune CNS inflammatory disorders stems from findings in experimental autoimmune (or allergic) encephalomyelitis in animal models. Work conducted in the 1930s demonstrated that the demyelinating encephalomyelitis occasionally observed following the smallpox vaccine used at the time, and the perivenular demyelination sometimes seen following Semple rabies vaccine, could be replicated by repeat injection of normal rabbit brain homogenate into monkeys [18]. It also showed that a similar effect could be achieved with a single injection of brain tissue emulsified with Freund's complete adjuvant or autologous brain tissue from the same animal. These studies served as the basis of current concepts of autoimmune demyelinating disease, and it is widely thought that the basis of ADEM (and several other inflammatory CNS and peripheral nervous system processes) involves factors that stimulate the immune system to produce antigen-specific humoral and/or cellular immunity [5].

Immune stimulation induced by an infection or vaccination theoretically could result in ADEM through a variety of possible mechanisms. "Molecular mimicry" involves a situation in which epitopes of a virus, vaccine, or other antigenic stimulus could initiate the development of immune antibodies and/or T cells that could cross-react with epitopes on myelin or axonal glycoproteins of nerves [19,20]. By this paradigm, activated macrophages are targeted to antigens on the myelin sheath and subsequently invade the basement membrane and cause vesicular disintegration and stripping of myelin by macrophage cytoplasmic projections [5]. Alternatively, the initial event could be the binding of cross-reactive antibodies, with subsequent complement fixation and damage to oligodendrocytes [21,22]. Perturbation of immunoregulatory mechanisms, interfering with host myelin protein self-tolerance, could lead to immune-mediated damage. Presumably, myelin cell membrane destruction could be mediated directly through virus- or vaccine-associated products, direct infection, or damage of surrounding supporting cells, or could lead to insertion of virus-specific polypeptides into host cell membranes, resulting in humoral or cell-mediated autoimmune responses to the cell [21]. Finally, myelin cells could be damaged by the introduction of sequestered myelin antigens into the circulation, inciting autoimmunity.

It is also possible that host factors and genetic polymorphisms may result in a predisposition to ADEM in some individuals. Several studies have suggested that various polymorphisms, including specific HLA-DR linkages, may be more prominent in children developing ADEM [23,24]. Other host factors could predispose to illness in persons exposed to certain antigenic stimuli.

Histopathologically, ADEM is characterized by perivenular infiltrates of T cells and macrophages, which are associated with resultant perivenular demyelination. Other histopathologic features that have been described in ADEM include varying degrees of cerebral edema, perivascular lymphocytic infiltrates with fibrin deposition, and perivascular hemorrhagic necrosis [25,26]. The cytotoxic necrosis and gliosis often seen with acute infectious encephalitis is generally absent. Although typically considered a demyelinating syndrome with axonal preservation, axonal damage has been described in some patients, and lesions on MRI—although predominantly involving the white matter—may also involve cortex and gray matter. Although antecedent infection or immunization is frequently described in the setting of subsequent ADEM, definitive presence of signs of neurotropic infection (eg, viral inclusions, infectious agent antigens, or pathogen-specific nucleic acid) are generally not evident, although intrathecal antibodies to various pathogens have been described in some cases [27]. AHLE shares many of the histopathologic features of ADEM but is more frequently associated with acute destruction of small

venules with the resultant hemorrhagic manifestations, more widespread demyelination, and a more substantial neutrophilic infiltrate [26,28].

Clinical Features

ADEM is generally characterized as a monophasic illness involving global or, more commonly, focal neurologic deficits. Most cases are associated with some sort of antecedent antigenic challenge or stimulus; approximately 75% of persons report a clinically apparent infectious illness or immunization during the weeks before onset of neurologic illness [1••,29]. Onset generally begins between 2 days and 4 weeks following this antigenic stimulus; an onset 1 day or less after exposure would be considered to be an insufficient amount of time to allow for the immune response to be mounted and produce illness and would be more suggestive of acute infection. Alternatively, data on long-term persistence of antigenic stimuli are unavailable, and cases of ADEM developing many months or years following a suspected stimulus become more difficult to substantiate epidemiologically. Although a prodromal phase of fever, headache, or malaise may be present shortly before the onset of neurologic signs, these are more often absent and initially may be more suggestive of acute infectious encephalitis [30].

Neurologically, ADEM presents with a rapid onset of encephalopathy, with or without meningeal signs, and/or focal neurologic deficits. Initial neurologic features depend on the location of lesions within the neuraxis. Altered mental status, ranging from lethargy to severe stupor or coma, may be present, representing global cerebral dysfunction. Frequently, focal neurologic deficits are seen, including extrapyramidal or pyramidal signs (60%–90%), hemiplegia (50%–75%), cranial nerve deficits including optic neuritis (7%–45%), ataxia (18%–65%), and concomitant spinal cord involvement (25%) [1••]. Brainstem involvement has also been described, with associated bulbar features and coma. In some series, brainstem involvement was observed more frequently in adult than in pediatric ADEM patients. Seizures have been reported in 13% to 35% of patients, and they appear to be somewhat age-related (ie, more prevalent in children with ADEM) [1••,17,31]. Seizures appear to be less prevalent in ADEM than in acute infectious encephalitis. In some cases, the presentation of ADEM may be much more benign and subtle.

In general, laboratory findings in ADEM are unremarkable. Peripheral leukocytosis has been reported in approximately 40% to 60% of children [15,17], and elevated erythrocyte sedimentation rate was reported in approximately 40% of patients in one study [15]. Significant metabolic laboratory abnormalities are generally absent. Cerebrospinal fluid (CSF) is typically characterized by a mild (generally < 50 cells/mm^3) lymphocytic-predominant pleocytosis, moderate protein elevation, and normal glucose [12,15,17]. Oligoclonal bands (OCB) may be present but seem to be observed less frequently than in MS; absence of OCB may help differentiate between ADEM and MS [32•].

With the wide availability and enhanced capabilities of neuroimaging, the mainstay of diagnosis of ADEM has been brain MRI, which has changed the approach to diagnosis of ADEM and other CNS demyelinating disorders (Fig. 1). Classically, the MRI picture of ADEM is that of multifocal or diffuse subcortical demyelinating lesions with high signal on T2 and fluid-attenuated inversion recovery sequences, with varying degrees of enhancement with gadolinium administration [33]. Lesions in ADEM tend to be asymmetric, involving subcortical white matter, cortical gray-white junction, and white matter of the spinal cord. ADEM lesions tend to be of the same stage of progression and, if enhancing, do so in a uniform fashion, suggestive of similar stages of development. Also, thalami or basal ganglia involvement is observed frequently. More recently, four patterns of MRI involvement in ADEM have been described: ADEM with small (< 5 mm) lesions; ADEM with large confluent lesions with edema and mass effect; ADEM with symmetric bilateral thalamic involvement; and acute hemorrhagic encephalomyelitis with features of hemorrhage within demyelinating lesions [12]. No correlation seems to exist between MRI pattern of ADEM and clinical outcome.

The clinical course of ADEM is generally quite rapid, with evolution from onset to clinical nadir occurring within days (mean, 4.5 days in one series) [12]. Resolution of deficits may be equally rapid, and spontaneous recovery over a period of weeks to months is considered the rule. However, in some cases, persistent neurologic deficits, including persistent motor deficits, cognitive impairment, and recurrent seizures, have been observed. One study suggested that adult ADEM may be associated with a generally favorable outcome [34].

ADEM and Multiple Sclerosis

The main diagnostic consideration in ADEM is distinguishing it from a *forme fruste* of MS, a chronic progressive or relapsing CNS demyelinating disorder. This differentiation has important implications in terms of prognosis and treatment. Further complicating this differentiation is the fact that in rare instances, ADEM may reoccur. Multiple-episode ADEM has been described in 5% to 21% of patients in various series, but it has been complicated because definitions of multiphasic ADEM and the length of ongoing follow-up varies considerably among these studies [1••,12,15,35]. Additionally, rapid or early cessation of therapy in ADEM may result in clinical recrudescence of a monophasic event [36••]. A recent consensus group has recommended the term "recurrent ADEM" for episodes involving the same clinical and MRI features as the initial episode and occurring at least 3 months after the initial episode and at least 4 weeks after completing steroid therapy [37••]. The term "multiphasic

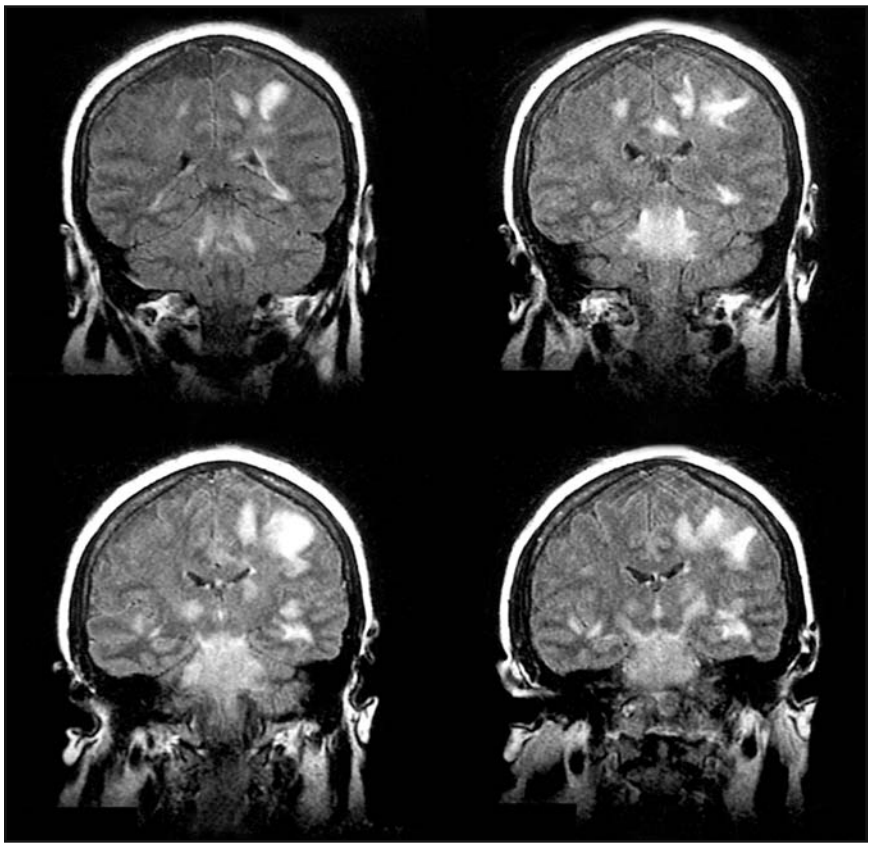

Figure 1. Coronal T2-weighted MRI of a patient with acute disseminated encephalomyelitis demonstrating areas of confluent demyelination.

ADEM" has been recommended for use in one or more ADEM relapses involving new areas of the CNS clinically and neuroradiologically, again at least 3 months after the initial episode and 4 weeks following steroid therapy. Thus, the distinction between ADEM, particularly multiphasic ADEM, and MS can be difficult. It has widely been suggested that anywhere between approximately 10% and 30% of patients initially diagnosed with ADEM will develop MS [1••,35]. However, the historical lack of a standardized case definition for ADEM makes it difficult to compare results among studies and to make a reliable estimation of the frequency of progression from true ADEM to MS. The recent development of standardized case definitions for ADEM will hopefully lead to more comparable data [36••,37••].

Differentiation between ADEM and MS carries significant prognostic and diagnostic implications, as MS is associated with more overall morbidity and in most cases involves ongoing or lifelong treatment with immunomodulatory medications. A number of features have been suggested as being helpful in the distinction between ADEM and MS (Table 1). These include presenting neurologic features, with optic neuritis or brainstem involvement at presentation being more suggestive of MS, and presentation with mental status changes or spinal cord involvement more suggestive of ADEM. Multifocal white matter lesions at the gray-white junction and involvement of basal ganglia and thalami on MRI may be more suggestive of ADEM, whereas periventricular white matter lesions, involvement of the corpus callosum, and lesions of varying stages and degrees of enhancement are thought to be more indicative of MS [38]. OCB in CSF may be found more frequently in MS than in ADEM [32]. In a series of 60 adult patients, ADEM was more likely in patients with two of the following three criteria: clinical features that would be atypical for MS (alteration of mental status, seizures, cognitive impairment, or bilateral optic neuritis); absence of OCB in the CSF; and gray matter (basal ganglia or cortical) involvement seen on MRI [32]. However, it is important to emphasize that all the features described for MS may also be present in ADEM, and to date, no reliable laboratory or radiologic features can reliably distinguish which patients with apparent ADEM will go on to develop MS. Long-term, ongoing follow-up of a patient with an initial CNS demyelinating event is important to establish an MS diagnosis.

Treatment

There is currently no standardized therapy for ADEM, nor have there been any randomized, placebo-controlled trials assessing the efficacy of ADEM treatments. The use of immunomodulating agents in ADEM is currently based on anecdotal success in case reports or small case series. Corticosteroids are generally considered first-line treatments for ADEM, and are probably the most widely used [1••]. Most treatment regimens use high-dose (20–30 mg/kg/d) intravenous methylprednisolone or dexamethasone (1 mg/kg), for 3

Table 1. Helpful features in distinguishing between acute disseminated encephalomyelitis (ADEM) and multiple sclerosis

	ADEM	Multiple sclerosis
Prodromal febrile illness	Common	Unusual
Signs and symptoms	Frequent widespread CNS disturbance; coma/drowsiness common	Frequently monosymptomatic
Temporal pattern of illness	Monophasic	Relapsing and remitting
Neuroimaging features	High lesion load	Generally lower lesion load
	Large, bilateral white matter lesions	Smaller plaques in deep white matter
	Thalamic involvement sometimes present	Thalamic or other deep gray involvement unusual
	Lesions of same age	Lesions of different ages
Cerebrospinal fluid	Oligoclonal bands frequently absent	Oligoclonal bands frequently present

to 5 days, followed by an oral taper for 3 to 6 weeks. Steroid treatment for less than 3 weeks has been associated with a higher occurrence of relapsing illness. Intravenous immunoglobulin (IVIG) has been described as having success in various case reports, either in combination with steroids or as monotherapy. Frequently, IVIG is used in the setting of failed steroid therapy or relapse. Standard dosing is 1 to 2 g/kg divided over 3 to 5 days. Use of plasma exchange has also been reported, again, sometimes used if steroid therapy has been unsuccessful. Because adverse events (eg, hypotension, thrombocytopenia, and sepsis) have occasionally been associated with plasma exchange, it is generally considered only if steroids and IVIG have failed.

ADEM and Antecedent Infections and Immunizations

Although ADEM has rarely been associated with organ transplantation or toxin exposure, infections and immunizations are the most consistently associated antecedent stimuli, and a number of antecedent viral infections or vaccinations have been temporally associated with subsequent development of ADEM. As many as 90% of patients report an infectious illness or immunization in the weeks before ADEM onset [5,39]. Historically, measles virus was considered the most common antecedent infection associated with postinfectious encephalomyelitis, and it was a frequent cause of acute viral encephalitis. ADEM incidence following measles infection has been estimated to be approximately 1 per 1000 infections [5]. The widespread use of measles vaccine has reduced this complication in North America and Europe, but post-measles encephalomyelitis is still observed in areas with lower immunization rates. Subsequently, several different viral infections including mumps, rubella, varicella-zoster, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, hepatitis A virus, and coxsackie virus have been associated with ADEM [5]. Influenza infection, particularly influenza B, has been associated with CNS demyelinating events, and particularly with AHLE [40]. In addition, a condition known as influenza encephalopathy, which is associated with diffuse cerebral edema but relatively little demyelination, may be seen with influenza infection, particularly in pediatrics and particularly associated with influenza B infections [41]. Additionally, many bacterial and parasitic infections have been temporally associated with subsequent ADEM—most frequently including *Mycoplasma pneumoniae*, β-hemolytic streptococcal infections, malaria, and *Borrelia burgdorferi* [39].

Various immunizations have also been temporally associated with subsequent ADEM, including vaccines for Japanese encephalitis, yellow fever, measles, influenza, smallpox, anthrax, and a host of other infectious agents [42,43]. The occasional association of ADEM with immunizations has been a particularly relevant topic. By nature, immunizations are intended to stimulate the immune system, which has implications in neuroautoimmune diseases; therefore, it is perhaps not unexpected that ADEM has infrequently been temporally associated with several vaccines. However, with very rare exceptions, these associations have been based entirely upon temporal proximity of the antecedent vaccination to subsequent ADEM, and have appeared as case reports or very small case series. Thus, a causal association of particular vaccines with ADEM has not been substantiated, and the tremendous morbidity and mortality from infectious diseases prevented by vaccines must be considered against the small, theoretic risk of postvaccination ADEM.

Of the more commonly associated vaccines, the Semple rabies vaccine and earlier strains of vaccinia (smallpox) vaccine have the strongest correlation. The only epidemiologically and pathologically proven association of an antecedent event has been with the Semple rabies vaccine. Elevated concentrations of anti-myelin basic protein (MBP) antibody titers have been observed in patients following rabies vaccination, and lymphocytic proliferation in the presence of myelin has been demonstrated in patients with neurologic complications following rabies vaccine, suggesting that MBP is the encephalitic antigen in post-rabies vaccine ADEM [44].

Table 2. Reporting rate of acute disseminated encephalomyelitis (ADEM) for selected vaccines

Vaccine	Reporting rate of ADEM*
Rabies	
Semple vaccine	1/300–1/7000
Duck embryo vaccine	1/25,000
Human diploid cell culture vaccine	< 1/75,000
Japanese encephalitis	
Mouse-brain derived (Nakayama)	0.2/100,000
Smallpox	
Austria (1948–1953; Budapest strain)	1219/1 million
England/Wales (1951–1960; Lister strain)	30/1 million
Bavaria, Germany (1945–1953; Bern strain)	121/1 million
Hamburg, Germany (1939–1958; Bern strain)	449/1 million
Netherlands (1940–1943; Copenhagen strain)	348/1 million
USA (1968; New York City Board of Health strain)	2/1 million
USA (2002–2004; New York City Board of Health strain)	3/665,000
Diphtheria/pertussis/tetanus	0.9/100,000
Yellow fever (17D)	0.4/1 million

*Unless otherwise specified, reporting rates are events per unit vaccinee. Yellow fever is event per distributed dose of vaccine.
(*Data adapted from* Tenembaum et al. [1••], McMahon et al. [50], and Henderson et al. [51].)

The reporting rates of ADEM following Semple rabies vaccine have been estimated to be between 1 per 300 to 1 per 7000 doses [5]. It is presumed that this was based on the use of the neurally-derived vaccine, made from inoculation of rabies virus into sheep or goat brain and inactivated with phenol. Embryo-based and cell-culture–based formulations of rabies vaccine have been associated with far fewer cases of ADEM.

The most widely used and available vaccine for Japanese encephalitis virus (JEV) is also from neural tissue, derived from suckling murine brain. Reporting rates of ADEM following JEV vaccine have been estimated to be 0.2 per 100,000 [45]; new, cell-culture–based formulations of JEV vaccine are expected to be widely available in the near future.

Historically, strains of vaccinia virus, used as the vaccine against variola (smallpox), have been associated with a condition referred to as post-vaccinial encephalopathy and a particular pathologic subtype, termed "microglial encephalomyelitis" [46], which clinically and pathologically appears consistent with ADEM. Reporting rates of postvaccinial microglial encephalitis ranged anywhere between 2 per 1 million vaccinees in an assessment in the United States in 1968 to 1.2 per 100,000 vaccinees during an assessment in Austria from 1948 to 1953 [47,48] (Table 2). The various strains of vaccinia virus used are thought to have had differing antigenic properties, with some more likely to lead to neurologic illness. More recently, an assessment of neurologic events following vaccination with the New York City Board of Health strain during the reinstatement of smallpox vaccination in the United States estimated a reporting rate of "encephalitis or myelitis" at 3 per 665,000 vaccinees, and an additional case of ADEM [48].

It is difficult to demonstrate a true causal association of any particular vaccine or antecedent infectious illness with subsequent development of ADEM. In general, such association of a prior infection or vaccination with the development of ADEM is based on a close temporal relationship and additional supportive epidemiologic data. However, the difference between association and causality is particularly complicated in the setting of post-vaccination encephalomyelitis, where multiple vaccinations are often given simultaneously. In this setting, it is likely impossible to identify the single vaccine that may have served as the antigenic trigger; alternatively, it may be impossible to say that the combination of vaccines was not involved. Further, in many cases it cannot be certain that an antigenic challenge unrelated to immunization (eg, prior mild upper respiratory illness or other exposure) served as the instigating challenge. With respect to infectious pathogens, serologic evidence for a previous infectious agent is frequently absent in cases of ADEM; virus or viral nucleic acid is seldom isolated from CNS; and demonstration of intrathecal synthesis of pathogen-specific antibodies is generally not present. In some cases, however, structural protein sequences in viral capsid or bacterial cell wall epitopes have been found to have similar homology to protein sequences in human myelin epitopes, suggesting the possibility of molecular mimicry in the case of some specific pathogens. In particular, T cells generated in the setting of Epstein-

Barr virus and human herpesvirus 6 have been found to cross-react with MBP antigens, and epitopes on the cell wall of *Haemophilus influenzae* are structurally similar to sequences in human proteolipid protein [49]. Thus, there is biologic plausibility to the concept that cross-reactive B and T cells generated against viral, bacterial, or vaccine epitopes are involved in the pathogenesis of ADEM. However, with rare exceptions, causal association with most of these agents awaits definitive substantiation.

Conclusions

ADEM represents an intriguing aspect of immunologic response to infectious agents and immunizations. Although causality remains to be established with respect to most of the infectious agents and vaccines that have been temporally associated with ADEM, there is growing evidence that various viral, bacterial, and vaccine epitopes may serve as antigenic stimuli for subsequent autoimmune-mediated CNS demyelination and nervous system disease. Blinded, controlled trials directly assessing the efficacy of various immunomodulating treatments for ADEM are needed, and in some cases persistent severe neurologic sequelae may occur; however, the syndrome has a favorable outcome with or without treatment, and recovery is generally the rule. The most important diagnostic consideration with respect to ADEM is its differentiation from MS, as the latter carries with it a poorer prognosis and the frequent necessity for lifelong immunotherapy. A better understanding of the underlying pathogenic mechanisms involved with ADEM has important implications for understanding the role of infectious pathogens in nervous system disease and for further understanding adverse events associated with vaccines.

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Disclosure

The author has reported no potential conflicts of interest relevant to this article.

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