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Acute Disseminated Encephalomyelitis: Clinical and Pathogenesis Features

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Acute disseminated encephalomyelitis (ADEM) is an immune-mediated disorder of the central nervous system (CNS). Disease typically starts with an abrupt onset of neurologic symptoms and signs within days to weeks after a viral infection or immunization. ADEM is also known as ''postinfectious,'' ''parainfectious,'' ''postexanthematous,'' or ''postvaccinal'' encephalomyelitis [1]. Although many viral agents associated with ADEM also cause acute viral encephalitis, ADEM usually occurs much later after the onset of infection and differs clinically by virtue of greater white matter involvement with respective neurologic symptoms [2]. Contrary to acute viral encephalitis, attempts to isolate the virus from postmortem ADEM brains have often failed, implying mechanisms other than direct invasion of CNS by the infectious agent. Neuropathologic examination of ADEM consistently discloses widespread perivenular inflammation and myelin disruption, giving rise to the pathologically derived terms ''perivascular myelinoclasis,'' ''perivenous encephalitis,'' and ''acute demyelinating encephalomyelitis'' [3].

The first clues to the possible pathogenic mechanisms underlying ADEM came from studies on demyelinating encephalomyelitis cases that occasionally complicated smallpox vaccination [4]. Rivers and Schwentker [5]

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reported histologic similarities between postvaccinal encephalomyelitis brains and fatal neuroparalytic accidents following rabies vaccination. Perivenular inflammation and demyelination were obvious in both cases. To examine the contribution of brain-derived proteins present in rabies vaccine to the induction of lesions, Rivers and Schwentker [5] repeatedly injected homogenates of normal rabbit brains into monkeys. Several monkeys receiving the virus-free brain homogenates developed an inflammatory, demyelinating brain disease, closely resembling clinical and pathologic features of postvaccinal encephalomyelitis [6]. Indeed, this was the first example of "experimental autoimmune encephalomyelitis" (EAE), which came to be studied extensively in the ensuing decades as a prototype autoimmune disease model, particularly multiple sclerosis (MS) [7–9].

EAE was later shown to be inducible by single injections of homologous brain tissue (ie, brain tissue removed from the same animal) when it was emulsified in complete Freund's adjuvant. The myelin protein antigens able to induce disease were subsequently identified and shown to have common sequences across species. Interestingly, disease was later shown to be passively transferable to healthy animals by injecting $CD4^+$ T lymphocytes from immunized animals [10]. EAE signs vary depending on species; strain (genetic background); age; gender; and the immunization protocol. Disease typically starts with weakness and paralysis, 7 to 21 days after inoculation of brain homogenate or myelin components. On neuropathologic analysis, mononuclear cell infiltrates consisting of lymphocytes and monocytoid cells are seen in meninges and in perivenular areas in the white matter. These findings are accompanied by activation of resident microglia and are followed by demyelination and axonal injury. Although mainly considered a disease of the CNS, inflammatory demyelinating lesions have also been described in the peripheral nervous system (ie, dorsal root ganglia in rabbits induced with EAE) [11,12]. Repair of demyelinated foci with recurrent inflammation and demyelination gives rise to a relapsing-remitting disease course in some species. A pathogenically similar but clinically distinct disease termed "experimental autoimmune neuritis" can be induced in the peripheral nervous system. Reported by Waksman and Adams [13] in 1955, rabbits receiving peripheral nerve emulsions in adjuvant develop an acute demyelinating neuropathy after a period of about 2 weeks. Similar to EAE, experimental autoimmune neuritis is characterized by mononuclear cells infiltrating out of endoneural venules followed by demyelination.

The presence of brain-derived components in rabies vaccines at the time, the striking histologic similarities between vaccine-induced encephalomyelitis and EAE, and similar latency times and clinical disease course after immunizations led to the belief that postvaccinal encephalomyelitis was a disease of an autoimmune nature. This assumption was reinforced by the observation that lymphocytes from post–rabies vaccine encephalomyelitis patients could be stimulated in vitro with myelin antigens, a feature similar to the lymphocytes isolated from EAE animals. Indeed, the incidence of

postvaccinal encephalomyelitis dramatically decreased with the introduction of rabies vaccines devoid of myelin components (ie, virus grown in embryonated eggs or cell cultures, rather than infected rabbit or sheep brain) [14]. Growing rabies virus in newborn mice brains, however, which are largely unmyelinated, failed completely to eliminate neurologic complications of vaccine [15]. Nevertheless, many of the patients receiving these vaccines developed polyradicular neuropathies with cranial nerve involvement, which have been attributed to the presence of peripheral nerve myelin components in the cranial nerves isolated with newborn mice brains [15].

Clinical presentation

The incidence of ADEM from different causes has been reported to be between 0.4 and 0.8 per 100,000 of population [16,17] with a median age of onset of 4.5 to 7.5 in pediatric studies [18,19] and 33.5 in a study of adult patients [20]. Disease has a seasonal peak in winter and spring, consistent with its putative infectious etiologies. ADEM typically appears with the abrupt onset of neurologic symptoms 2 to 30 days after the occurrence of a preceding infection or vaccination [19]. A clear preceding infection or vaccination is not found, however, in around one third of children and half of adults presenting with disease [16,19,21]. The contribution of different infections or vaccination to disease varies based on regional immunization programs, with the natural infections still reported to constitute most cases (93%) in countries with widespread immunization against childhood viral infections [16,22]. Systemic symptoms including fever (43%–52%), headache (45%–58%), malaise, and myalgias may occur shortly before the appearance of neurologic signs and symptoms [22,23]. ADEM usually presents as a monophasic demyelinating disease, and neurologic manifestations depend on which region of the CNS is affected, with the most common signs including obtundation and depressed consciousness; unilateral or bilateral long tract signs (85%); acute hemiparesis (76%); and ataxia (59%) [19]. Depressed mental status exists in cases of ADEM. Meningismus (26%–31%), caused by inflammation in subarachnoid space, can also be found on neurologic examination [22,23]. Although motor deficits occur in both adult and pediatric cases, sensory deficits are more frequent in adults but seizures predominate in pediatric cases; one study has reported prolonged focal motors seizures in 70% of children with a high tendency to develop status epilepticus. Involvement of peripheral nervous system is rare in childhood ADEM but more common in adult patients, usually in the form of acute polyradiculoneuropathy [19,20]. Although ADEM displays a monophasic disease course, rare cases of disease relapse have been described in some studies. Long-term clinical and imaging follow-up has shown the resolution of lesions with no long-lasting neurologic impairments in most of these multiphasic cases [22].

Acute hemorrhagic leukoencephalitis (AHLE) is considered a hyperacute form of ADEM and has been reported to occur in 2% of pediatric cases.

Rare adult cases have also been reported [24]. Prodromal symptoms including fever, malaise, and myalgia are more common than conventional ADEM and are followed by rapidly progressive hemorrhagic demyelination of white matter. Although there are case reports of recovery after high-dose steroid therapy or neurosurgical interventions [25–28], most patients die with brain edema within the first week after the onset of neurologic symptoms [19,28].

Acute transverse myelitis (ATM) is a common clinical presentation of postinfectious or postvaccinal ADEM that is characterized by focal inflammation of the spinal cord with subsequent neural injury [29,30] leading to sensory, motor, and autonomic dysfunction. About one third of patients have pain in the distribution of the involved segments of the spinal cord, before the development of sensory-motor or autonomic symptoms. At the peak of the disease about 50% of patients with ATM are paraplegic; 80% to 94% have been reported to have paresthesia, dysesthesia, or numbness; with almost all the patients suffering from bladder dysfunction [31–34]. Although ATM can occur in the context of multifocal CNS disease or as a part of multisystemic autoimmune disorders (eg, systemic lupus erythematosus or sarcoidosis) [35,36], it can also present as an isolated idiopathic entity [29]. The initial events leading to detrimental autoimmune responses targeting spinal cord are still a matter of debate, but disease has been pathogenically linked to postinfectious demyelinating disorders [29,37]. Indeed, in 30% to 60% of idiopathic cases there is a preceding respiratory, gastrointestinal, or systemic illness [31,32,38]. Like cerebral ADEM, ATM has also been reported following measles, rubella, influenza, and hepatitis B vaccinations (see below) [39–42]. In about 5% of cases, transverse myelitis represents the first attack of MS. Unlike ATM, however, sensory-motor impairments following myelopathic MS are usually asymmetric, making the two entities distinguishable [43]. Moreover, monosegmental involvement of the spinal cord is more commonly seen in myelopathic MS, compared with other ATM etiologies [44]. Cerebrospinal fluid (CSF) pleocytosis and abnormal IgG index can be observed in both MS and ATM. Initial severity of weakness and evidence of denervation on electromyography has been considered poor prognostic indicators for ATM [45]. Approximately one third of patients with ATM recover completely, one third show partial recovery with moderate disabilities, and the rest of the cases lead to permanent severe disabilities [46].

Pathology

ADEM usually affects white matter; however, lesions in cortical gray matter and basal ganglia have also been reported [23,47]. Pathologic features of ADEM in CNS white matter closely resemble that of EAE, with infiltration of monocytoid cells and perivenous areas of demyelination. Axons in the areas of demyelination are relatively preserved and neuronal soma are less affected. Hyperemia and periventricular edema followed by fibrosis in

the later stages of disease are also seen [48]. AHLE is characterized by petechial hemorrhages around blood vessels with infiltrates containing high numbers of polymorphonuclear cells, perivascular demyelination, and fibrosis [49]. AHLE is believed to be the outcome of the same pathogenic process as ADEM but with a more severe clinical course and poorer prognosis [50].

ATM pathology can vary based on underlying etiology and precise pathogenic process. When occurring as part of a systemic autoimmune disorder, specific pathologic findings (eg, vasculitis in systemic lupus erythematosus or granulomatosis in sarcoidosis) can be found within the spinal cord [51,52]. In idiopathic cases, which are presumably more closely related to ADEM, perivascular and intraparenchymal inflammatory infiltrates followed by demyelination and neuronal injury have been described [29].

Etiology

Viral etiologies

ADEM is more commonly preceded by a viral infection, with measles, varicella, rubella, mumps, and influenza being the more frequently reported infections (Box 1). Despite the availability of vaccines in many countries, measles virus still remains one of the most common global infectious causes of childhood mortality and neurologic morbidity. Measles infection can cause a transient but severe suppression of cell-mediated immunity, which is the chief reason for postmeasles fatal complications, including disseminated pneumonitis and bacterial infections [53]. Paradoxically, measles infection can also lead to ADEM, an autoimmune phenomenon. The incidence of ADEM is 1 to 2 per 1000 measles infections, being more common in children above 5 years of age [54]. Postmeasles ADEM varies in its time of onset, with most cases developing when the fever and rash from the primary infection are diminishing. Return of the fever together with headache and signs of meningeal irritation herald the start of inflammation in the brain. Focal or generalized convulsions that can be followed by coma have been reported in about half of the patients. Gradual or abrupt depression of consciousness may occur. Focal neurologic deficits indicative of the involvement of cerebral hemispheres, cerebellum, or spinal cord may develop. CSF shows a mild mononuclear pleocytosis with elevated protein content in most patients [55]. Mortality rate is high, reported to be between 10% and 40% in different studies, with a substantial number of survivors suffering permanent neurologic sequelae. The length of stupor or coma has been generally considered a poor prognostic factor [54,56]. On pathologic examination of postmortem brains, perivenular infiltration of mononuclear cells together with demyelination is observed, features that are reminiscent of EAE neuropathology. ADEM comprises about 95% of postmeasles neurologic complications with the rest being myelitis, polyneuritis, and toxic encephalopathy.

Box 1. Causes of postinfectious and postvaccinal encephalomyelitis

Viral infections
- Measles
- Varicella-zoster
- Rubella
- Mumps
- Influenza A and B
- Hepatitis A
- Hepatitis C
- Epstein-Barr virus
- HIV
- Nonspecific upper respiratory tract infection
- Human herpsevirus-6[a]
- Herpes simplex virus[a]
- Dengue virus[a]
- Coxsackie B[a]
- Coronavirus[a]

Nonviral infections
- Group A β-hemolytic streptococci
- *Legionella pneumophila*
- *Salmonella typhi*
- Leptospirosis
- *Plasmodium falciparum*
- *Mycoplasma pneumoniae*
- *Rickettsia rickettsii*
- *Borrelia burgdorferi*

Postvaccinal ADEM
- Rabies vaccine made in brain or spinal cord preparations
- Measles
- Japanese encephalitis virus
- Oral polivirus
- Tetanus toxoid
- Influenza
- Hepatitis B recombinant vaccine
- Tick-borne encephalitis[a]

[a] Denotes single case-reports.

Compared with measles, neurologic complications of acute varicella-zoster virus infection are much less common (1:10,000 of infections), with acute cerebellar ataxia and acute toxic encephalopathy being the most common forms. The former has a very good prognosis [57], whereas the latter, also known as ''Reye's syndrome'' can be fatal. Postvaricella encephalomyelitis is rare, and it typically starts 1 to 2 weeks after the onset of rash. Clinical manifestations are similar to measles ADEM, and include the return of fever with headache, meningismus, convulsions, and depression of consciousness [58,59]. CSF exhibits mild lymphocytic pleocytosis and elevated protein content. On pathologic examination perivenular demyelination has been reported, with cells from patients with neurologic complications showing proliferative response to myelin antigens. These indicate a pathophysiologic process similar to postmeasles ADEM and EAE [58,59].

Neurologic complications of rubella are even less common that varicella, with an incidence of around 1:20,000 infections, but with a high mortality rate of approximately 20% [6]. Occurrence of fever with headache, convulsions, and decreased consciousness occur 1 week after the appearance of rash. Unlike measles, focal neurologic signs are not common and those who recover from disease are largely free of long-lasting neurologic sequelae. On pathologic analysis of postmortem brains, perivenular demyelination is rare, more likely caused by short period of disease rather than an alternative pathogenic process. Congestion and multiple petechial hemorrhages are the principal pathologic findings [60,61].

Before the availability of vaccines, mumps was the most common nonexanthematous disease followed by neurologic complications. Mumps frequently causes acute viral meningitis and mild encephalitis, both with generally good prognoses. In rare fatal cases of mumps encephalitis, perivenular demyelination has been reported in half of the brains. Whether this merely reflects severe inflammation, or is caused by an autoimmune process and hence representing true ADEM is not clearly known. Unlike postmeasles, varicella, and rubella ADEMs, postmumps encephalomyelitis is not readily distinguishable from more common acute viral encephalitis [62,63].

In the postvaccine era, nonspecific flulike upper respiratory tract infections have been more frequently linked etiologically to ADEMs. Benign postinfectious encephalitides have been reported in influenza virus A and B epidemics, but reports linking influenza infections to inflammatory perivenular demyelination are rare [64,65]. Other neurologic complications, however, including toxic encephalopathies, myelitis, and polyradiculoneuropathies have been more reliably associated with influenza infections [66]. Acute necrotizing encephalopathy is another neurologic complication of influenza A virus infection, which is frequently reported from East Asia but is rare in western countries [67]. Nonspecific upper respiratory tract infections have been associated more commonly with the most severe form of disease (AHLE). Interestingly, this association has existed even before the advent of vaccines for measles, varicella, and rubella, indicating the participation

of a different group of viruses in AHLE induction, as compared with classical ADEM [28,50]. ADEM has also been reported in association with hepatitis A [68–70], hepatitis C [71], and Epstein-Barr virus infections [72]. There are few, but pathogenically interesting, reports of ADEM as a manifestation of primary HIV infection [73,74].

Bacterial etiologies

Streptococcal infections of childhood are more likely to cause neurologic complications including Sydenham's chorea and autoimmune neuropsychiatric symptoms; however, ADEM has also been reported after infection with group A β-hemolytic streptococci [75]. The disease phenotype in reported cases was shown to be a novel extrapyramidal movement disorder and other ADEM clinical features [75].

ADEM has also been reported after *Legionella pneumophila* infections [76], typhoid fever, and leptospirosis [77]. ADEM has been reported as a neurologic syndrome after malaria infection, and distinguishable from cerebral malaria. The latter syndrome occurs during parasitemia, whereas a negative blood smear together with convulsions, confusion, tremor, and ataxia suggests ADEM [78].

Nonmicrobial etiologies

Encephalomyelitis following noninfectious events, including autologous stem cell transplantation [79], autoimmune hemolytic anemia [80], and systemic lupus erythematosus [81], has also been described. Although the inherent immune alterations in any of these disease processes, perhaps in the presence of subclinical infections, might set the stage for development of an autoimmune demyelinating response, clear pathologic association with autoimmune brain disease has not been shown for any of these entities.

Encephalomyelitis following antiviral therapies

Postvaccinal acute disseminated encephalomyelitis

Vaccines produced in CNS tissue pose a higher risk of postvaccinal encephalomyelitis. With the introduction of nonneural human diploid cell vaccines for rabies, ADEM induced by rabies neural vaccine (Semple form) is now only of historical interest [82–84]. Vaccines to Japanese encephalitis virus prepared from mouse brain–derived virus, however, is still the principal form of vaccine used for this mosquito-borne encephalitis that occurs throughout East Asia and Australia. Neurologic disorders, sometimes with clear-cut diagnosis of encephalomyelitis, have been described after Japanese encephalitis virus vaccinations [85].

The occurrence of postvaccinal encephalomyelitis following vaccination with live attenuated measles vaccine is not well documented. Some children

develop fever, rash, and conjunctivitis in the second week after immunization. This is rarely followed by neurologic manifestations of encephalomyelitis. Indeed, the reported incidence is one to two per million doses, which is not above the background incidence. Nevertheless, there is a much higher incidence of encephalomyelitis following measles infection (20–30 per million infections), which can be prevented by vaccination [86]. Live attenuated varicella vaccine might cause a mild case of chickenpox, which can be followed by cerebellar ataxia. This resolves completely, however, as is the case for natural varicella infection [86]. Rubella vaccine has not been implicated in encephalomyelitis, although transient paresthesias and mild signs of neuropathy have been reported 1 to 3 weeks after vaccination. Encephalomyelitis associated with tetanus toxoid [87], oral polio [88], influenza [42,89], and hepatitis B recombinant vaccines [90] have also been described [86] (see also [91] for adverse events associated with childhood vaccines). The pathogenic process leading to development of postvaccinal encephalomyelitis is generally believed to be the same as the virus-associated ADEM (ie, molecular mimicry or altered immunoregulation). In the case of oral polio–associated paralytic events, however, it might be simply recapitulating poliomyelitis disease course (see Box 1).

Central nervous system involvement in immune reconstitution inflammatory syndrome

Paradoxical deterioration of clinical status following highly active antiretroviral therapy (HAART) in HIV-AIDS patients is an increasingly recognized clinical entity [92]. This phenomenon has been ascribed to partial restoration of immune function following HAART with ensuing infiltration of different organs by reactivated immunocompetent cells; hence the nomination ''immune reconstitution inflammatory syndrome'' (IRIS). IRIS has also been recognized in the context of other infectious diseases including tuberculosis, where commencement of therapy leads to a transient deterioration of clinical status. With the increasingly widespread availability of HAART and its impact on restitution of immune status, however, reports of HAART-associated IRIS now constitute the bulk of reported cases.

Diagnosis of HAART-induced IRIS usually relies on the occurrence of a clinical event following the initiation of therapy with concurrent improvement in host immune status, as reflected by diminished viral loads. Presence of an external pathogen against which the exuberant immune-inflammatory response is directed is usually required, although IRIS can also be directed toward innate antigens. Infection with *Mycobacterium avium* complex, *Cryptococcus neoformans*, JC virus, and cytomegalovirus are the more closely associated microbial etiologies [92–94]. Exacerbation of rheumatoid arthritis and systemic lupus erythematosus are two examples of IRIS-mediated reaction against self-antigens. As expected from the underlying immunopathogenesis, clinical IRIS might represent as an anatomically

compartmentalized phenomenon (ie, where the microbial or self-antigen is already present). Lower $CD4^+$ T cell counts and higher plasma viral load at the time of HAART initiation together with younger age at the onset of HAART have been reported as risk factors for IRIS development [95–97].

Reports of reactivated cryptococcal meningitis after the initiation of HAART were among the first examples that raised the possibility of CNS involvement in IRIS. Other opportunistic infections of CNS were later reported, however, to be more likely to put the CNS parenchyma at risk of exaggerated IRIS immune responses [98,99].

Progressive multifocal leukoencephalopathy is a demyelinating disease of the CNS, caused by the JC virus, a human polyomavirus infecting and replicating in human glial cells. Before the advent of HAART, there were no effective therapies for progressive multifocal leukoencephalopathy. Some progressive multifocal leukoencephalopathy patients' clinical status deteriorates after the start of HAART, however, a phenomenon attributed to the restoration of immune function (ie, IRIS) [94,100]. Indeed, NeuroIRIS occurs in the context of other CNS disorders associated with HIV infection including CNS tuberculosis, cryptococcal meningitis, and HIV-associated dementia. Imaging of NeuroIRIS shows contrast enhancement in all cases of clinical deterioration. Neuropathologic analyses in these cases have shown perivascular and intraparenchymal infiltration of T lymphocytes [101] and severe demyelinating lesions [98]. In fatal cases, the inflammatory infiltrates are chiefly composed of $CD8^+$ cytotoxic T lymphocytes, whereas in less severe cases $CD4^+$ cells with macrophage activation have been more evident [98]. NeuroIRIS has also been reported in conjunction with cytomegalovirus infection of brain [93]. Although chiefly described in association with opportunistic infections, few cases of NeuroIRIS have been reported as acute deterioration of HIV-associated dementia following the initiation of HAART [102,103]. Perivascular and intraparenchymal infiltration of inflammatory cells, chiefly $CD8^+$ cytotoxic T lymphocytes, have been described in neuropathologic examinations in these cases of NeuroIRIS [102,103].

Although supportive care is usually all that is needed in nonnervous system IRIS, immunomodulatory treatment including short periods of therapy with corticosteroids has been suggested to help resolve NeuroIRIS [99], which usually has a good clinical outcome unless the underlying clinical disorder (ie, progressive multifocal leukoencephalopathy) continues to progress.

Acute disseminated encephalomyelitis pathogenesis

Multiple observations have convincingly demonstrated the presence of pathogenic correlates between experimentally induced autoimmune disorders in the nervous system and post–rabies vaccine encephalomyelitis. The

missing link with regard to other virus-induced ADEMs, however, is that patients have not been inoculated with myelin components. Instead, they are usually recovering from exanthematous or nonspecific upper respiratory tract viral infections. Although immune-activation is a major contributor to the pathogenesis, initial events induced by the infectious agent might be more subtle and alternative nonimmune mechanisms are not unlikely to contribute. To investigate the chain of events leading from an infection to CNS inflammation more precisely, several animal models of acute and chronic virus-induced demyelination have been extensively studied. Among murine coronaviruses, the JHM strain of murine hepatitis virus represents an interesting example. Murine hepatitis virus induces acute inflammatory lesions in the brains and spinal cords of mice with concomitant demyelination [104]. Although direct infection and lysis of oligodendrocytes takes place in murine hepatitis virus infection, the pathogenic process seems to involve immune-mediated mechanisms. Immunodeficient SCID mice do not develop demyelination after murine hepatitis virus infection [105] and immunosuppression with irradiation also inhibits demyelination [106]. Theiler's murine encephalomyelitis virus infection in mice is another example of infection-related demyelination in rodents. Like murine hepatitis virus, direct Theiler's murine encephalomyelitis virus infection and apoptosis of oligodendrocytes have been described in the spinal cord in cases of chronic infection. Nevertheless, depletion of macrophages but not T lymphocytes diminishes demyelination [107]. Involvement of different humoral or cellular arms of the immune system and their interplay with direct viral effects on the CNS has also been shown for murine rhabdoviruses [108] and togaviruses [109] and mammalian lentiviruses [110–112].

In the face of extensive observations and the evidence derived from vaccine and animal studies, there remain substantial gaps in the understanding of the exact disease mechanisms underlying ADEM. Here are categorized mechanisms proposed for ADEM that are most relevant to human pathogens.

Nonimmune mechanisms

Most pathogens that are associated with human ADEM have not been shown to cause myelin damage by direct infection and injury of myelin-producing cells (ie, oligodendrocytes in CNS). Myelin damage by viral products has been proposed, however, for some of the viruses. An interesting example is the susceptibility of myelin basic protein to vaccinia virus core protein kinase [113]. Incorporation of viral proteins into the myelin membranes can also alter membrane biology and function.

Immune-mediated mechanisms

Molecular mimicry is one of the proposed mechanisms by which pathogens might lead to autoimmune responses. If self- and non–self-pathogen-derived antigens share the same epitopes, presentation of the epitope to

the immune system with concomitant activation of a primary innate immune-mediated inflammatory reaction might lead to activation of self-reactive lymphocytes, with subsequent infiltration of the target organ. Although subject to thymic negative selection, some self-reactive lymphocytes including lymphocytes reactive to different components of myelin still persist in adult immune system [114]. Sequence similarity searches to find common linear epitopes between different ADEM-inducing pathogens and myelin basic protein have yielded some results, including a sequence similarity between myelin basic protein and hepatitis B nonstructural polymerase [115]. Epitope sharing is more likely to be in tertiary structures of antigens, however, which necessitates three-dimensional structural homology searches using currently available software and algorithms.

Even in the absence of epitopes common with self-antigens, pathogens can cause autoimmunity by perturbing the intrinsic balance of the immune system, the so-called "immunoregulatory mechanisms." This could take place in the peripheral immune system, leading to a breakdown in the so-called "self-tolerance" to self-antigens. Interestingly, most of the viral infections associated with ADEM cause a transient period of mild to moderate immunosuppression. It remains to be elucidated whether recovery from immunosuppression caused by measles infection might lead to perturbed immunoregulation or perhaps reactivation of self-reactive lymphocytes.

Although involvement of adaptive immune system with generation or activation of self-reactive antigen-specific cells is a major aspect of autoimmune processes, the involvement of innate immune system in disease process is also pivotal to pathogenesis. Infection of cells within the nervous system (eg, monocytoid cells, astrocytes) with subsequent release of factors compromising oligodendrocyte physiology or myelin integrity has been shown for nonhuman lentiviruses and remains a less-explored possibility in the case of rare HIV-associated ADEM [112].

Differential diagnosis

Diagnosis of ADEM is based on the clinical history, neurologic and neuroimaging findings, and CSF analysis with the principal diseases to be considered in the differential diagnosis being MS and acute viral encephalitis. Although ADEM and MS share common pathophysiologic aspects, they are usually distinguishable based on clinical features and disease course. ADEM is typically a monophasic disease of children with a slight male preponderance, whereas MS is usually a chronic relapsing-remitting disease that has its first onset in young adults, with a female predilection. A history of a preceding infection followed by the return of fever, and systemic symptoms, altered level of consciousness, multifocal neurologic dysfunction, seizures, and movement disorders are cardinal features of ADEM, but as a syndrome are not seen together in MS. From a clinical viewpoint, however, ADEM can be difficult to distinguish from the first attack of MS

and a clouded sensorium is often the most prominent distinguishing feature (Table 1).

CSF immunologic analysis usually provides clues to the diagnosis. Elevated CSF/serum IgG index and the presence of oligoclonal bands in CSF, which are indicative of endogenous immunoglobulin production in CNS, are seen in MS. Transient appearance of oligoclonal bands have been rarely reported in ADEM, unlike the persistent presence of these bands in MS cases, although pleocytosis is common in both MS and ADEM, albeit greater in ADEM.

Neuroimaging plays a key role in the diagnosis of ADEM from other similar entities. Both CT scanning and MRI have been used to diagnose ADEM; however, MRI is much more informative. CT scan of brain can be normal at the onset and start to reveal abnormalities as late as 5 to 14 days after the start of the disease, showing multifocal subcortical lesions in the white matter [116]. Hemorrhage and edema can be detected in CT scans of AHLE cases [116]. MRI changes occur much earlier, usually

Table 1
Differential clinical and diagnostic features of acute disseminated encephalomyelitis and multiple sclerosis

	Acute disseminated encephalomyelitis	Multiple sclerosis
Predominant age of onset	Childhood (5–8 y)	Young adults
Prodromal febrile illness or vaccination	50%–75% cases	Rare
F:M ratio	Slight male preponderance (F:M 0.8)	Strong female preponderance (F:M 2:1)
Clinical manifestations	Fever, headache, malaise, altered mental status, meningismus Multifocal neurologic dysfunction	Monosymptomatic presentation, sensory symptoms, unilateral optic neuritis, pyramidal signs, ataxia, chronic fatigue
Cerebrospinal fluid analysis	Lymphocytic pleocytosis Elevated protein levels transient if any oligoclonal bands	Intrathecal Ig synthesis (persistent oligoclonal bands, increased cerebrospinal fluid/serum IgG index)
Neuroimaging	Multiple ill-defined lesions on MRI, lacking any orientation Basal ganglia gray matter involvement Less variability in contrast enhancement Rare appearance of new lesions	Single or few sharply demarcated lesions Long axis perpendicular to lesions Different levels of enhancement between lesions Common appearance of new lesions
Recurrence	Chiefly monophasic, recovery over 1–6 months, self-limiting disease even in the absence of therapy	Recurrent, relapsing-remitting disease course

when the neurologic signs and symptoms appear. MRI abnormalities are more likely to be seen on T2-weighted and fluid-attenuated inversion recovery images. ADEM MRI typically shows multiple, large lesions in subcortical and central white matter in cerebral hemispheres, cerebellum, brainstem, and spinal cord [23]. Lesions might involve gray matter of basal ganglia and the junction of gray-white matter in cerebral hemispheres [19,117]. The margins of ADEM lesions are usually blurry, unlike the well-defined sharply demarcated lesions of MS. ADEM lesions are more amorphous than MS plaques and they lack the vertical orientation to the midline axis of brain, which is frequently seen in MS plaques. Gadolinium enhancement in T1-weighted images has been reported in 30% to 100% of patients in different studies, likely reflecting the stage and severity of inflammation. Unlike MS, different lesions in ADEM appear at the same time, hence less variability in contrast enhancement between lesions [118]. Complete resolution of lesions after treatment has been reported in 37% to 75% of patients and partial resolution in 25% to 53% of cases [23,119]. More advanced imaging techniques have also been used in cases with the suspicion of ADEM. Positive emission tomography scanning in one study has shown decreased global and bilateral cerebral metabolism and reduced cerebral blood flow [120]. Reduced blood flow and metabolism has been linked to ADEM severity and clinical course in this study [120].Tc-99m single photon emission CT shows areas of hypoperfusion, whereas MRI has been showing more limited lesions in the same cases [121]. SPECT with acetazolamide has shown longer-lasting lesions compared with MRI [122]. It is likely that longer-lasting cerebral circulatory impairment evident in SPECT might underlie the neurocognitive deficits observed after the resolution of neurologic abnormalities and MRI lesions [122].

Specific neurologic syndromes including optic neuritis, demyelinative transverse myelitis, and Devic disease may occur as manifestations of either MS or ADEM; hence, both disorders should be considered and assessed for as the underlying disease entity.

ADEM should be distinguished from acute viral encephalitis, acute noninfectious encephalitis, and toxic encephalopathies [123]. Acute viral encephalitis occurs as a result of direct infection of brain parenchyma by an infectious agent and can occur at any age. It generally happens as part of a systemic infectious disease and signs and symptoms of other organs' involvement might be present. The clinical profile is variable, depending on the infectious agent. A common clinical feature of viral encephalitis is of an abrupt onset of a febrile disease, accompanied by headache, altered consciousness, and cognitive and behavioral disturbances [123]. Herpes simplex virus is the commonest agent for acute sporadic viral encephalitis. Other common viral agents are varicella-zoster virus, measles, mumps, and enteroviruses, hence the same causative agents as ADEM [123,124]. Having common clinical features and etiologic agents with ADEM, the diagnosis is not always straightforward. Younger age of onset, history of prodromal infection or vaccination, focal neurologic signs including visual loss, spinal

cord symptoms, and involvement of peripheral nerves point to ADEM. If not accompanied by meningitis, signs of meningeal irritation are less common in acute viral encephalitis. CSF analysis of ADEM usually shows features similar to that of acute viral encephalitis (ie, lymphocytic pleocytosis, elevated protein levels, normal glucose, with negative cultures). Unlike viral encephalitis, however, virus culture or PCR detection of pathogens shows negative results. Red blood cells appear in CSF most commonly in the cases of AHLE and herpes encephalitis [123–125]. MRI in acute viral encephalitis can identify characteristic changes caused by specific pathogens in brain (eg, frontotemporal changes in herpes simplex encephalitis or striatal-thalamic lesions in Japanese or West Nile encephalitis). T2-weighted images of acute viral encephalitis usually show one or more diffuse areas of increased intensity affecting the cortical gray matter and subjacent white matter [123], although the gray matter of basal ganglia or brainstem might be involved but to a lesser extent [123].

Treatment

Vaccination against viral etiologies has significantly decreased the incidence of viral cases of ADEM, and the risk imposed by vaccines themselves is significantly less than natural infections. There is a lack of placebo-controlled double-blind studies to evaluate different treatment options for ADEM. Nevertheless, high-dose glucocorticoid therapy has been the most widely used treatment for ADEM. Adrenocorticotropic hormone and prednisone have been successfully used in the past [126,127]. Currently, intravenous methylprednisolone (10–30 mg/kg/d) or dexamethasone (1 mg/kg) for 3 to 5 days are the most commonly used steroids in pediatric cases [18,23]. Intravenous glucocorticoid therapy needs to be tapered with administration of oral steroids for 4 to 6 weeks, following intravenous therapy. Shorter tapering might increase the risk of relapses [128]. In the first few days of disease, intravenous methylprednisolone might be combined with intravenous acyclovir if there is still a suspicion of acute viral encephalitis. Intravenous immunoglobulin has been used alone or in combination with glucocorticoids with a dose of 1 to 2 g/kg single-dose or divided over 3 to 5 days [129,130]. Although reports of success exist for intravenous immunoglobulin treatment of autoimmune disorders, intravenous immunoglobulin therapy for ADEM remains at the level of case-reports. One study recommends high-dose intravenous immunoglobulin, given separately or in combination with high-dose methylprednisolone, in cases of severe debilitating pediatric-onset acute encephalomyelitis [131]. The mechanism of intravenous immunoglobulin action is not well-known; it might have immunomodulatory effects through binding to pathogenic antibodies or myelin basic protein–mimicking antigens, thereby inhibiting the generation or activation of myelin-reactive T cells.

Plasma exchange has been reported to improve the clinical status in some patients who fail to respond to high-dose intravenous glucocorticoids. This

is perhaps through removal of antibodies that contribute to demyelination or by partly modifying the cytokine milieu in peripheral immune system, where self-reactive lymphocytes are being generated or reactivated. Plasmapheresis is usually regarded as a last resort, however, and there are no studies assessing its efficacy if used early in the course of disease [132].

Prognosis

The long-term prognosis of ADEM varies with etiology, with postmeasles cases having a high mortality rate and a high rate of neurologic sequelae in survivors. The prognosis of nonmeasles cases is generally favorable. Many studies have reported a full recovery in 50% to 75% of patients, in a period of 1 to 6 months after the appearance of symptoms and signs [22,23]. The most common neurologic sequelae following ADEM are focal motor deficits. This could range from mild ataxia to hemiparesis. It is generally believed that duration and severity of inflammation in brain with the extent of neuronal and axonal damage are determinants of clinical outcome. Sudden onset, severe neurologic symptoms, and unresponsiveness to glucocorticoids have been considered poor prognostic factors.

Gradual recovery from ADEM over a period of a few weeks has been reported with 50% to 70% of patients completely recovering without neurologic sequelae. Some studies have described a correlation between untreated ADEM outcome and the type of precedent infection. Cases diagnosed with postvaricella and postrubella ADEM showed 54% and 43% full recovery, respectively, whereas approximately 70% of ADEM cases following nonspecific infections fully recovered. Muliphasic ADEM has been generally associated with longer recovery periods [119].

Although resolution of neurologic symptoms and signs together with normal imaging profile have been considered indicative of full recovery, minor neuropsychologic abnormalities have been reported in pediatric cases years after the disease. One study evaluated intellectual, educational, and social functioning of children who had recovered from ADEM. Impairments in cognitive and social domains with a higher incidence of severe behavioral and emotional problems were found in children who had experienced ADEM below 5 years of age [133]. Of interest, younger age of onset in pediatric cases of MS has also been closely associated with subsequent neurocognitive deficits. This evidence underscores the sensitivity of the developing brain to transient inflammatory demyelinating events.

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