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Acute disseminated encephalomyelitis

Silvia Tenembaum, MD; Tanuja Chitnis, MD; Jayne Ness, MD, PhD; and Jin S. Hahn, MD; for the International Pediatric MS Study Group*

Abstract—Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory disorder of the CNS characterized by a widespread demyelination that predominantly involves the white matter of the brain and spinal cord. The condition is usually precipitated by a viral infection or vaccination. The presenting features include an acute encephalopathy with multifocal neurologic signs and deficits. Children are preferentially affected. In the absence of specific biologic markers, the diagnosis of ADEM is still based on the clinical and radiologic features. Although ADEM usually has a monophasic course, recurrent or multiphasic forms have been reported, raising diagnostic difficulties in distinguishing these cases from multiple sclerosis (MS). The International Pediatric MS Study Group proposes uniform definitions for ADEM and its variants. We discuss some of the difficulties in the interpretation of available literature due to the different terms and definitions used. In addition, this review summarizes current knowledge of the main aspects of ADEM, including its clinical and radiologic diagnostic features, epidemiology, pathogenesis, and outcome. An overview of ADEM treatment in children is provided. Finally, the controversies surrounding pediatric MS and ADEM are addressed.

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Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory disorder of the CNS, which is commonly preceded by an infection, and predominantly affects the white matter of the brain and spinal cord.1-4 Several terms can be found in the literature to describe patients with ADEM, reflecting the more prominent aspects of the disease:

"Postinfectious or postvaccinial encephalomyelitis, postinfectious multifocal encephalitis," when the triggering events were considered.

"Acute perivascular myelinoclasia, perivenous encephalitis, disseminated vasculomyelopathy," when emphasizing the histopathologic features and distribution of lesions.

"Acute demyelinating encephalomyelitis, hyperergic encephalomyelitis, postvaccinal perivenous encephalitis, postencephalitis demyelination," relating to the probable immunopathogenetic mechanism.5-16

Based on our current clinicopathologic understanding of the disease, ADEM is probably the most appropriate nosologic designation, as the precipitating event may be absent and the pathogenesis of the disease is unclear.

In the absence of specific biologic markers, the diagnosis of ADEM is based on the clinical and radiologic features. Although ADEM usually has a monophasic course, recurrent or multiphasic forms have been reported, raising diagnostic difficulties in distinguishing these cases from multiple sclerosis (MS). This article reviews what we currently know about ADEM, including diagnostic features, pathogenesis, treatment, and outcomes, and includes a proposed definition of this disorder.

Epidemiology. ADEM can occur at any age, but it is more common in pediatric patients than in adults. Rare cases in older adults have been reported,17 although careful exclusion of other diseases should be applied in these cases. The diagnosis is often made in the setting of a defined viral illness or vaccination. Although there appears to be no gender predominance in ADEM,18,19 a male predominance has been described in two pediatric cohorts, with reported female:male ratios of 0.620 and 0.821 as opposed to a 2:1 female preponderance frequently described for MS. The mean age at presentation in children ranges from 5 to 8 years.21-23

A seasonal distribution in the winter and spring months has been found in studies conducted in the United States.19,20 A recent study conducted in San Diego County, CA, estimated the mean incidence of ADEM as 0.4/100,000/year among persons less than 20 years of age living in that region.19 Five percent of these patients had received a vaccination within 1 month prior to the ADEM event, and 93% reported signs of infection in the preceding 21 days. There are no clear studies of worldwide distributions of ADEM. Some regional cases are linked to specific vaccines, as in the case of the Semple rabies vaccine, smallpox vaccine, and older forms of the measles vaccine.

Clinical presentation. ADEM is classically described as a monophasic disorder which typically be-
gins within 2 days to 4 weeks after an antigenic challenge. Approximately 70 to 77% of patients report a clinically evident antecedent infection or vaccination during the prior few weeks.21,22,24 The typical symptoms and signs of ADEM include a rapid onset encephalopathy associated with a combination of multifocal neurologic deficits. A prodromal phase with fever, malaise, headache, nausea, and vomiting may be observed shortly before the development of meningeal signs and drowsiness. The clinical course is rapidly progressive and usually develops over hours to maximum deficits within days (mean, 4.5 days).21

The initial neurologic features are determined by the location of the lesions within the CNS. Table 1 summarizes the demographic distribution and presenting features in recently published case studies of patients with ADEM. Frequent neurologic symptoms and signs described in various combinations include unilateral or bilateral pyramidal signs (60 to 95%), acute hemiplegia (76%), ataxia (18 to 65%), cranial nerve palsies (22 to 45%), visual loss due to optic neuritis (7 to 23%), seizures (13 to 35%), spinal cord involvement (24%), impairment of speech (slow, slurred, or aphasia) (5 to 21%), and hemiparesis (2 to 3%), with invariable involvement of mental status, ranging from lethargy to coma.18-23 Although certain signs and symptoms may be observed in both pediatric and adult cases, such as changes in mental status, ataxia, motor deficits, and brainstem involvement, other features appear to be age related.25 Long-lasting fever and headaches19,21-23,26 occur more frequently in children with ADEM, while sensory deficits predominate in adult patients.17 Seizures are rarely observed in adult patients with ADEM,17 and are mainly seen in children younger than 5 years. One study has documented prolonged focal motor seizures in 70% of the younger patients, with 82% of these patients going on to status epilepticus.21

Peripheral nervous system (PNS) syndromes such as acute polyradiculoneuropathy24,27,28 may occur in ADEM but are considered rare in childhood ADEM cases. The combination of PNS and CNS features may be more common in adults and was noted in 43.6% of one cohort of adult patients.29 There is a wide variation in the severity of the illness. Occasionally, ADEM can present as a subtle disease, with nonspecific irritability, headache, and somnolence, or may show a rapid progression of symptoms and signs to coma and decerebrate rigidity.30 Respiratory failure secondary to brainstem involvement or severely impaired consciousness occurs in 11% to 16% of cases.21,30

**MRI features.** Neuroimaging is extremely important in establishing the diagnosis of ADEM. MRI

### Table 1 Demographic characteristics, presenting features, and outcome findings from published ADEM series between 2000 and 2004

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age, y (range)</th>
<th>Male, %</th>
<th>Mean follow-up, y (range)</th>
<th>Preceding illness, %</th>
<th>Altered mental status, %</th>
<th>Ataxia/cerebellar, %</th>
<th>CN deficits (includes vision), %</th>
<th>Seizures, %</th>
<th>Full recovery, %</th>
<th>Residual focal neurologic deficits, %</th>
<th>Behavior or cognitive problems, %</th>
<th>Recurrent or multiphasic course, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murthy et al.,20</td>
<td>7.5 (2.5–22)</td>
<td>61</td>
<td>1.8 (0.2–5)</td>
<td>72</td>
<td>45</td>
<td>NR</td>
<td>23</td>
<td>17</td>
<td>72</td>
<td>16</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Dale et al.,18</td>
<td>7.4 (2–16)</td>
<td>54</td>
<td>5.8±0.8 (1–15)</td>
<td>74</td>
<td>69</td>
<td>51</td>
<td>45</td>
<td>17</td>
<td>72</td>
<td>29</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>Hynson et al.,22</td>
<td>6.7 (0.7–16)</td>
<td>42</td>
<td>3.8±0.8 (1–15)</td>
<td>74</td>
<td>72</td>
<td>50</td>
<td>44</td>
<td>17</td>
<td>64</td>
<td>29</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hung et al.,21</td>
<td>5.3±3.9 (0.4–16)</td>
<td>56</td>
<td>6.6 (1–19)</td>
<td>74</td>
<td>72</td>
<td>55</td>
<td>50</td>
<td>17</td>
<td>61</td>
<td>45</td>
<td>11</td>
<td>10</td>
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<tr>
<td>Tenembaum et al.,21</td>
<td>5.8±1.2 (2.5–16)</td>
<td>64</td>
<td>5.2±24 (0.5–14.9)</td>
<td>74</td>
<td>72</td>
<td>51</td>
<td>44</td>
<td>17</td>
<td>61</td>
<td>45</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Gupte et al.,26</td>
<td>5.3±4.3± (0.7–16)</td>
<td>56</td>
<td>5.2±4 (0.7–16)</td>
<td>74</td>
<td>72</td>
<td>51</td>
<td>44</td>
<td>17</td>
<td>61</td>
<td>45</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Mikaeloff et al.,29</td>
<td>5.9±3.9 (0.7–16)</td>
<td>56</td>
<td>5.2±4 (0.7–16)</td>
<td>74</td>
<td>72</td>
<td>51</td>
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<td>Idrissova et al.,107</td>
<td>5.8±1.2 (2–16)</td>
<td>54</td>
<td>5.2±4 (0.7–16)</td>
<td>74</td>
<td>72</td>
<td>51</td>
<td>44</td>
<td>17</td>
<td>61</td>
<td>45</td>
<td>11</td>
<td>10</td>
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<tr>
<td>Leake et al.,19</td>
<td>5.9±3.9 (0.7–16)</td>
<td>57</td>
<td>5.2±4 (0.7–16)</td>
<td>74</td>
<td>72</td>
<td>51</td>
<td>44</td>
<td>17</td>
<td>61</td>
<td>45</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Anlar et al.,23</td>
<td>6.5 (0.8–18)</td>
<td>63</td>
<td>5.2±4 (0.7–16)</td>
<td>74</td>
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<td>51</td>
<td>44</td>
<td>17</td>
<td>61</td>
<td>45</td>
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</table>

*Hung et al. (2001) separated postinfectious encephalomyelitis (n = 38) from ADEM (n = 13) based on the number of MRI lesions, at least three for ADEM. No difference in mental status, though 70% in both groups.
†Mikaeloff et al. (2004) initially gave the diagnosis of ADEM to 119 patients (out of 296 with demyelinating event) but reclassified all of them as MS if any recurrence. As some patients may be considered multiphasic ADEM, we kept the original 119 in analysis. However, in table 1, “¶” provides data from only the 85 monophasic cases.
‡In the series of Idrissova et al., MRI was only performed in the 14 children with more severe clinical course. They reported full recovery only if no fatigue was present. However, neurologic disability was identified by telephone contact.
§Leake et al. (2004) reclassified as MS 7% of the relapsing forms of ADEM.

ADEM = acute disseminated encephalomyelitis; NR = not reported; MS = multiple sclerosis.
abnormalities are most frequently identified on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences as patchy, poorly marginated areas of increased signal intensity. Lesions in ADEM are typically large, multiple, and asymmetric. They typically involve the subcortical and central white matter and cortical gray-white junction of both cerebral hemispheres, cerebellum, brainstem, and spinal cord. The gray matter of the thalami and basal ganglia are frequently involved, typically in a symmetric pattern. The periventricular white matter is also frequently involved, being described in 30 to 60% of cases. Lesions confined to the corpus callosum are less common. However, large demyelinating lesions of the adjacent white matter may extend into the corpus callosum and cross into the contralateral hemisphere.

Four patterns of cerebral involvement have been proposed to describe the MRI findings in ADEM: 1) ADEM with small lesions (less than 5 mm; figure 1); 2) ADEM with large, confluent, or tumefactive lesions, with frequent extensive perilesional edema and mass effect (figure 2); 3) ADEM with additional symmetric bithalamic involvement (figure 3); and 4) acute hemorrhagic encephalomyelitis (AHEM), when some evidence of hemorrhage can be identified in the large demyelinating lesions (figure 4). The MRI pattern does not appear to correlate with any particular outcome or disability, as observed in a large pediatric cohort, since most lesions tend to resolve on follow-up imaging studies. However, this classification may be useful when considering the differential diagnosis of ADEM and may potentially help to identify those children for whom the initial ADEM-phenotype is really the first manifestation of MS.

The incidence of gadolinium enhancing lesions on T1-weighted sequences is quite variable in ADEM and may depend on the stage of inflammation. Gadolinium enhancing lesions have been described in 30 to 100% of patients. The pattern of enhancement is variable; complete or incomplete ring-shaped (figure 5), nodular, gyral, or spotty patterns have been described. Meningeal enhancement of the brain or spinal cord is unusual.

Spinal cord involvement in ADEM has been described in 11 to 28%. The typical spinal cord lesion is large and swollen, showing variable enhancement, and predominantly affects the thoracic region.

Sequential MRI scanning during the follow-up period plays an important role in establishing the diagnosis of ADEM. Monophasic ADEM is not associated with the development of new lesions. Complete resolution of MRI abnormalities after treatment has been described in 37 to 75% of patients with ADEM, and partial resolution in 25 to 53% of
patients. Resolution of MRI abnormalities within 6 months has been positively associated with a final diagnosis of ADEM in one study. There are no clear criteria documenting how long to continue to image patients with one ADEM event. However, the authors suggest reassessing the patient with at least two additional MRI studies after the first normal MRI, over a period of 5 years from the initial episode, as the appropriate way to confirm the absence of ongoing accrual of lesions.

Advanced neuroimaging techniques. Low levels of N-acetylaspartate (NAA) and elevated lactate levels within regions of prolonged T2-MRI signal, without increase in choline, have been observed with quantitative proton MR spectroscopy during the acute stages of ADEM. These abnormal signals resolved after normalization of clinical and MRI findings. Diffusion and perfusion weighted MRI show a diffusion pattern with reduced, normal, or increased diffusion coefficients, or reduced or normal perfusion within ADEM lesions. A global and bilateral decreased cerebral metabolism has been demonstrated by PET scanning in a case where CT scan had only showed a focal demyelinating lesion.

SPECT using 99m Tc-HMPAO has consistently shown areas of hypoperfusion that are more extensive than the MRI lesions. The time course of SPECT abnormalities also reflects the clinical course more accurately than MRI. In spite of the resolution of MRI lesions, SPECT with acetazolamide detects persistent cerebral circulatory impairment that may contribute to the neurocognitive and language deficits observed in some patients with ADEM.

Monophasic and multiphasic ADEM. Although ADEM is classically described as a monophasic disorder, several studies have described ADEM relapses, occurring at the following rates: 1/18 (5.5%), 1/14 (7%), 8/84 (10%), 4/31 (13%), 7/46 (15%), 7/35 (20%), and 9/42 (21%). It should be noted that different diagnostic criteria for relapses were used in these different studies, which may in part account for the variability. In addition, the mean length of follow-up reported in some of these ADEM series varied considerably: 18 months, 22 months, 5.3 years, 6.6 years, and again may contribute to the interstudy variability.

The final outcome of multiphasic ADEM has been described in detail in two pediatric series with long-term follow-up. In one study, no long-term impairment was observed in 86% of multiphasic ADEM patients. Similarly, eight children with multiphasic ADEM, who remained relapse-free after a follow-up of 3 to 16 years (mean 8.2 years), had a median EDSS score of 1 (range 0 to 2.5). Serial brain-spinal MRI performed in these patients revealed complete or almost complete resolution of demyelinating lesions without evidence of new active lesions.

Acute hemorrhagic leukoencephalitis. Acute hemorrhagic leukoencephalitis (AHL), AHEM, and acute necrotizing hemorrhagic leukoencephalitis (ANHLE) of Weston Hurst are variants of an acute, rapidly progressive, and frequently fulminant inflammatory hemorrhagic demyelination of CNS white matter. It is usually triggered by upper respiratory tract infections. Death from brain edema is common within 1 week of onset of the encephalopathy, but increasing evidence of favorable neurologic outcomes has been published with early and aggressive treatment using various combinations of corticosteroids, immunoglobulin, cyclophosphamide, and plasma exchange.

AHL, AHEM, and ANHLE are considered hyperacute subforms of ADEM and were observed in 2% of children in a large cohort. Lesions on MRI tend to be large, with perilesional edema and mass effect. Diffusion-weighted imaging disclosing areas of restricted diffusion in the affected areas of the brain has been recently published, and this finding might be due to acute vasculitis with subsequent vessel occlusion in AHL.

Controversies in diagnosis based on published studies: Rationale for proposed definitions. ADEM should be adequately defined and distinguished from other diseases affecting the white matter. In particular, a diagnostic challenge lies in distinguishing multiphasic forms of ADEM from MS. This is especially important, not only for prognostic
purposes, but for therapeutic purposes, since a diagnosis of MS, at least in adult patients, carries the recommendation for early treatment with immunomodulators.

Historically, different definitions of ADEM have been used in published cases of pediatric and adult patients.17-23,26,29,31 The lack of a uniform definition and clear clinical and neuroimaging diagnostic criteria has led to the classification of other neurologic conditions as ADEM. Due to this lack of uniformity, it is difficult to compare neuroimaging aspects or outcomes, establish prognostic factors, or compare percentages of patients with ADEM that evolve into MS. For example, the proportion of patients initially diagnosed with ADEM who go on to be diagnosed with MS ranges from 9.5% to 27%.18 However, two children from a cohort of seven diagnosed with “multifaceted ADEM” had monosymptomatic relapses—optic neuritis in one, and a brainstem syndrome in the other—suggestive of MS.18 Conversely, a recently published study applied the concept that “any second

Figure 4. Acute hemorrhagic encephalomyelitis. (A) Axial T2-weighted MRI with prominent bilateral hyperintense lesions, with areas of very low signal, corresponding to breakdown products of hemoglobin, in a 5-month-old boy, 2 weeks after pertussis vaccination. (B) Axial T1-weighted MRI of the same case, showing spontaneous hyperintense signal inside the large hypointense lesions.

Figure 5. Sagittal T1-weighted imaging demonstrating two lesions with open-ring enhancement in an 8-year-old girl, 1 week after an upper respiratory viral infection.
attack after an initial diagnosis of ADEM had to be reclassified as MS, and reported a frequency of second attacks as high as 29%. Thus, the use of a uniform definition may help to distinguish ADEM from other lifelong demyelinating conditions and provide a foundation for consistent prospective outcome studies. Nevertheless, the long-term outcome and evidence of multiple recurrent demyelinating events are required conditions to clearly delineate MS from ADEM.

Unusual cases of ADEM have been described in patients with demyelinating lesions confined to the brainstem, when the presentation was more indicative of a clinical isolated syndrome (CIS) with brainstem involvement or brainstem encephalitis. A case of atypical acute disseminated encephalomyelitis is described in a 3-year-old girl, with a longitudinal lesion restricted to the spinal cord in the absence of brain lesions, consistent with longitudinal myelitis. Unfortunately, the report does not provide imaging of the brainstem to better explain the child’s alteration of consciousness. A neurodegenerative picture with progressive decline in mental and motor skills was reported in an 11-month-old baby following a meningoencephalitis. This infant was misdiagnosed as having ADEM because the MRI showed subtle areas of hyperintense signal in the frontal and parieto-occipital white matter that seemed to be transitional areas of myelination or delayed myelination. A recent report describes a patient with recurrent simple and complex partial seizures, who then progressed to intractable epilepsy partialis continua and cognitive decline. Although this case represented a classic picture of chronic Rasmussen’s encephalitis, because the patient started symptoms after a viral illness and the initial MRI disclosed hyperintense lesions (although predominantly involving cortical and subcortical structures), a diagnosis of ADEM was suspected. Furthermore, when the seizures recurred after 3 months from onset, the patient was misdiagnosed with multiphasic ADEM.

A variety of terms and definitions have been used to describe patients with ADEM who relapse. Recurrent, relapsing, pseudorelapsing, bi- or multiphasic ADEM have all been applied using different criteria: time from the first event varies from less than 4 to more than 8 weeks; neurologic deficits are defined as same or different; individuals are either monosymptomatic or polysymptomatic; and finally MRI lesions are described as either in the same or different areas.

ADEM definitions. To avoid misdiagnosis and develop a uniform classification, the International Pediatric MS Study Group (Study Group) proposes that the following three terms be applied to variations of ADEM (see Krupp et al., in this conference report):

ADEM: A first clinical event with a polycystic encephalopathy, with acute or subacute onset, showing focal or multifocal hyperintense lesions predominantly affecting the CNS white matter; no evidence of previous destructive white matter changes should be present; and no history of a previous clinical episode with features of a demyelinating event. If a relapse takes place within 4 weeks of tapering steroid treatment or within the first 3 months from the initial event, this early relapse is considered temporally related to the same acute monophasic condition and would replace the terms “steroid dependent ADEM” or “pseudorelapsing ADEM.”

Recurrent ADEM: New demyelinating event fulfilling diagnostic criteria for ADEM, occurring at least 3 months after the initial ADEM event and at least 4 weeks after completing steroid therapy, showing the same clinical presentation and affecting the same areas on MRI as the initial ADEM episode.

Multiphasic ADEM: Refers to one or more ADEM relapses, including encephalopathy and multifocal deficits, but involving new areas of the CNS on MRI and neurologic examination. Relapses take place at least 3 months after initial ADEM attack and at least 4 weeks after completing steroid therapy.

Differential diagnosis. Acute encephalopathy and disseminated demyelination of the CNS in children represent a diagnostic challenge for pediatric clinicians and neurologists. Many inflammatory and noninflammatory disorders may have a similar clinical and radiologic presentation and should be considered in the diagnostic evaluation.

If an acute encephalopathy is suspected based on history and physical examination, the first priority should be to rule out an acute bacterial or viral infection of CNS, and to start empiric antibacterial and antiviral treatment. A gadolinium-enhanced MRI of the brain and spinal cord (to better define the disease burden) and a lumbar puncture should be performed as soon as possible. Evidence of an inflammatory process (CSF pleocytosis, elevated CSF proteins and immunoglobulin index, gadolinium enhancement on MRI) should be determined in addition to screening for viral, bacterial, or fungal infectious agents (See “Differential diagnosis and evaluation of pediatric MS” in this conference report for complete outline of the workup for infectious causes of acute encephalopathy). In the absence of clear evidence of an infectious cause, the neuroimaging findings should define the regional distribution of the demyelinating-inflammatory process.

Neuroimaging at the time of the initial event may be useful in the diagnosis. When the MRI shows large focal tumor-like lesions, one should consider brain tumors, Shilder disease, Marburg variant of MS, and brain abscesses. An MRI pattern with symmetric bithalamic involvement may be seen in children with acute necrotizing encephalopathy, deep cerebral venous thrombosis, hypernatremia, and extrapontine myelinolysis, as well as in children with ADEM after Japanese B encephalitis vaccination. Basal ganglia involvement may be consistent with organic aciduria, poststreptococcal ADEM, or infantile bilateral striatal necrosis.
The presence of complete ring-enhanced lesions in the cerebral white matter is unusual in ADEM, and brain abscess, tuberculomas, neurocysticercosis, toxoplasmosis, and histoplasmosis should be excluded.36

The diagnosis of MS should be considered in cases of recurrent or multiphasic demyelination, and is discussed in detail later in this review.

Treatment and management. There is no standard therapy for ADEM. Most treatment approaches have employed some form of nonspecific immunosuppressant therapy similar to that used for MS and other autoimmune diseases, including steroids, IV immunoglobulin (IVIg), or plasmapheresis. Most of the data describing treatment for ADEM are derived from case reports and small series. To date, there have been no randomized, controlled trials for the treatment of ADEM in either children or adults.

Steroids. Steroid treatment has been the most widely reported therapy for ADEM, typically at high doses. However, there has been great variety in the specific steroid formulations employed, routes of administration, dosing, and tapering regimens. The earliest report describing steroid treatment for ADEM was published in 1953 using ACTH.87 Later reports in the pre-MRI era described successful use of prednisone, corticotropin, or dexamethasone with marked improvement of symptoms in both adult and pediatric patients with ADEM.12,88 Several patients in these reports had recurrence of their symptoms when the steroid therapy was discontinued and improved when steroids were reinstituted.

Most pediatric groups describing their high dose steroid treatment in detail have used IV methylprednisolone (10 to 30 mg/kg/day up to maximum dose of 1 g/day) or dexamethasone (1 mg/kg) for 3 to 5 days18,21,22,26,89,90 followed by oral steroid taper for 4 to 6 weeks with full recovery reported in 50 to 80% of patients.18,21,22 In the only comparison of specific corticosteroid regimens, methylprednisolone-treated patients had significantly better outcome with respect to EDSS scores compared to those treated with IV dexamethasone.21 Outcome may also be influenced by the length of steroid taper since an increased risk of relapse has been reported with steroid taper of 3 weeks or less.18,23

High-dose steroid treatment is not without risk. Gastric perforation and death due to gastrointestinal bleeding related to methylprednisolone treatment for ADEM has been reported.91 Hyperglycemia, hypokalemia, high blood pressure, facial flushing, and mood disorders have also been reported in association with high-dose corticosteroid treatment. It is advisable to provide gastric ulcer prophylaxis while patients are on high dose steroids, in addition to a careful monitoring of blood pressure, urine glucose, and serum potassium.

Immunoglobulin. IVIg has been used successfully in a variety of autoimmune diseases although its effectiveness in MS is limited. There are multiple case reports of IVIg being used successfully alone92,93 or in combination94 with corticosteroids in both pediatric and adult cases of ADEM, but there have been no studies which have directly compared IVIg with steroids, plasmapheresis, or other immunomodulatory treatments. In some cases, IVIg was administered after failed IV pulse steroid therapy94,95 in cases of recurrent demyelination.86,70 Reported dosing for IVIg has been quite consistent, using a total dose of 1 to 2 g/kg, administered either as a single dose or over 3 to 5 days. In general, IVIg is well tolerated in the pediatric population. There have been isolated case reports of repeated IVIg administration to treat recurrent episodes of demyelination,97 although it is questionable whether these cases were definitely MS.

Plasma exchange. The use of plasma exchange in ADEM has been reported in only a small number of cases, typically severe cases when steroid treatment has failed. A recent series98 examined the outcome following plasma exchange for 59 patients with a variety of CNS demyelinating conditions, including 10 cases of ADEM, and found that 40% of patients (including the ADEM group) had moderate to marked improvement following plasma exchange. In this cohort, a mean number of seven exchanges was performed (range 2 to 20) although a breakdown by demyelinating disease type was not given. In the literature, there were reports of six pediatric ADEM cases treated with plasma exchange. Four of these patients were reported as having a complete recovery,99-101 one had a residual left hemiparesis,102 and the outcome for one patient was not described.103

Plasma exchange may serve to remove the autoantibodies that are presumably triggering the demyelination in ADEM, but may also shift the dynamics of B- and T-cell interaction within the immune system. There is some evidence from case reviews that plasma exchange may be more effective when given early in the disease course.104 However, due to the need for trained personnel with specialized equipment and central venous access for multiple treatments over a period of days to weeks, plasma exchange has often been used as a last resort. Symptomatic hypotension, severe anemia, and heparin-associated thrombocytopenia have been described in association with plasma exchange.98 The role and timing of this intensive treatment for ADEM deserves further investigation; however, for the foreseeable future plasma exchange will likely continue to be used as a rescue therapy in ADEM when other modalities fail.

Other therapies. To our knowledge, there have been no published reports of interferon-β or glatiramer acetate used in the acute stage of ADEM although there are anecdotal descriptions of interferon-β use for episodes of recurrent demyelination consistent with multiphasic ADEM. Some
improvement has been reported with cyclophosphamide use in adult ADEM patients who responded poorly to methylprednisolone, but we are unaware of any published reports of cyclophosphamide, azathioprine, or other cytostatic drug use in pediatric ADEM.

Outcome and prognosis. Untreated ADEM. Limited data exist about the natural history of ADEM in the post-MRI era. In the available case studies, there is considerable diversity with respect to antecedent infections, clinical presentation, and neuroimaging findings, further complicating outcomes analysis. Classification of recurrence is a major inconsistency as there is considerable disagreement about when to classify recurrent demyelination as multiphasic ADEM vs defining all recurrent demyelination as MS. Case series from Japan, India, and Russia suggest that the natural history of ADEM in most children is one of gradual improvement over several weeks, with 50 to 70% of patients experiencing full recovery. Improvement in serial MRIs was also shown in seven Japanese patients with untreated postinfectious encephalitis, although three patients had residual lesions on MRI. Seven of 21 patients with partial recovery in the South India group had more extensive white matter lesions compared to MRIs of children with complete recovery. No other factors, including antecedent infections, correlated with outcome.

In contrast, the Moscow group stratified 90 pediatric ADEM patients with respect to antecedent infections (33% rubella, 29% varicella, 22% with unknown viral antecedent) and recurrence (11% were classified as multiphasic ADEM, most with preceding upper respiratory symptoms). Diagnosis was based on clinical symptoms following a prior viral infection. MRI was routinely obtained only in the multiphasic group. Outcome varied with antecedent infections with a good outcome reported in 70% of the ADEM cases without definite infection vs 54% and 43% normal outcome reported for post-varicella and post-rubella ADEM, respectively. Specific recovery times were described as approximately 3 weeks for post-rubella ADEM and up to 12 weeks for multiphasic ADEM, with intermediate but more variable recovery time in the post-varicella and unknown ADEM groups. Taken together, these reports suggest that approximately two-thirds of patients make a complete recovery without specific treatment, but that recovery may require weeks.

Treated ADEM. Table 1 summarizes the outcome in recently published case series of 15 or more patients with ADEM. Over half the patients treated had a good recovery with minimal or no deficit. The most common problems seen following ADEM were focal motor deficits ranging from mild clumsiness and ataxia to hemiparesis or blindness. Behavioral and cognitive problems were identified in 6 to 50% of children, but are likely underreported in some series. Less frequent late effects included development of seizures following ADEM resolution.

Most patients were treated with high-dose steroids, although some patients were treated with IVIg (with or without steroids), and plasmapheresis was used in some severe steroid-resistant cases. Following initiation of treatment, rapid improvement was sometimes seen within hours although recovery typically evolved over days. More severely affected children (sometimes obtunded and mechanically ventilated) often required weeks or months to improve and were often treated with multiple immunosuppressant regimens, making it unclear whether the treatment influenced outcome or whether these patients improved on their own. Complete recovery was reported for some of these severe cases, albeit less frequently. The prognosis of ADEM in adult patients has been uniformly reported as favorable.

Neurocognitive outcome. More attention is being given to subtle neurocognitive deficits following CNS demyelination in childhood, including ADEM. Even children thought to have full recovery demonstrated subtle neurocognitive deficits in attention, executive function, and behavior when reevaluated more than 3 years after ADEM, although these deficits were not as severe as those reported for pediatric patients with MS. One study compared 19 children with ADEM to a normal age- and sex-matched control group and found that patients younger than 5 years at ADEM diagnosis had significantly lower IQ and educational achievement when evaluated at 3.9 years (mean) since illness, while the older-onset patients had slower verbal processing, having been evaluated at 2.2 years (mean) after presentation. Behavioral problems were also more prominent in the young-onset ADEM group. Additional studies are required to further characterize neurocognitive deficits following ADEM. These studies will help to guide assessments in individual patients and will facilitate appropriate educational interventions.

It appears that symptom resolution is more rapid in steroid or IVIg-treated patients. However, due to the heterogeneity of the patient populations and treatment regimens, it is difficult to draw any specific conclusions about the impact of treatment relative to long-term outcome. Multicenter prospective trials with consistent diagnostic criteria, treatment protocols, and uniform data collection are critical to improve our knowledge regarding management of children and adolescents with cognitive deficits.

ADEM and MS. MS in children can initially present with symptoms and signs that are indistinguishable from ADEM. However, subsequent neurologic events or changes on MRI typical of MS lead to the diagnosis of MS. The possibility that a child may develop MS is a concern for parents and clinicians, particularly in cases of recurrent or multiphasic ADEM. MS in children can also present
with CIS that more closely resemble typical neurologic events seen in adults with MS. CIS differs clinically from ADEM, and is defined as either a monofocal or multifocal demyelinating event in the absence of fever or encephalopathy (except in cases of brainstem syndromes).

Our current consensus definition of pediatric MS states that a first event of ADEM is not considered the first event required for a diagnosis of MS, nor can it be used to determine dissemination in time and space. In these children, a second demyelinating event not meeting criteria for recurrent or multiphasic ADEM would qualify as an initial event, after which subsequent MRI changes or new demyelinating episodes would lead to a diagnosis of MS. While studies suggest that children with an initial ADEM event are at higher risk for the eventual development of MS, the actual risk of MS following ADEM remains unclear. Identifying prognostic indicators including biomarkers are needed to further clarify the relationship between ADEM and subsequent risk of an MS diagnosis.

At present, there are no clear prognostic factors that determine if a child with a first event of either ADEM or CIS will eventually develop MS. The risk of developing MS after ADEM has been reported as 0%, 9.5%, 19 to 27%, 18 and 28% 39 by different studies. It should be noted that in these studies, varying criteria were used to define pediatric MS, and differing lengths of follow-up were used, which may contribute to the wide range in incidence. As a general trend, ADEM carries a lower risk of developing MS than CIS events. A study examining patients with a first demyelinating event, including CIS-like and ADEM events, showed that overall, 57% developed MS as defined by two demyelinating events. 39 Of patients with an initial diagnosis of ADEM, 28% developed MS. Of those with initial CIS-like events, 86% with optic neuritis and 50% with an initial brainstem syndrome developed MS. Overall, positive predictive factors for the development of MS were age at onset 10 years or older (hazard ratio [HR], 1.67; 95% CI), MS-suggestive initial MRI (HR 1.54), or optic nerve lesion (HR 2.59). A lower risk of developing MS was found in patients with myelitis (HR 0.23) or mental status change (HR 0.59) at presentation. 29 Twenty-nine percent (34 of 119) of children with a prior diagnosis of ADEM developed MS, while 75% (134 of 177) of children with a first event consistent with CIS developed MS. Although these clinical findings are helpful and serve as a guide, a definitive diagnosis of MS cannot be made based on these data. Moreover, use of standardized criteria to define MS in future studies would greatly enhance interpretation.

Radiologic parameters provide supportive evidence for the diagnosis of MS; however, they cannot be used as predictors for the development of the disease, since many features thought to be unique to MS are also seen in cases of ADEM. 20 Lesions in the corpus callosum, periventricular white matter, and deep gray matter structures were seen more commonly in patients who developed MS. 22 However, in other series the same features have been documented in typical cases of ADEM. 18, 20

Oligoclonal IgG bands in the CSF were found to be positive in 64 to 92% of pediatric MS cases, and in 0 to 29% of ADEM cases. 18, 21, 22, 111 but this difference was not statistically significant 18 and so cannot be used as a reliable marker of MS. Thus far, immunologic testing has not yielded a reliable marker for the development of MS from initial demyelinating events in children.

To date, there are no clear clinical or radiologic parameters that predict which cases of ADEM or CIS will develop MS. 112, 113 Early treatment of MS is strongly advocated in adult patients, and has been shown to be beneficial in reducing long-term disability. 114, 115 Moreover, use of beta-interferon-1a in pediatric MS patients has recently been shown to be safe and tolerable. 116, 117 However, the risk of an inaccurate diagnosis of MS, which carries a lifetime burden and requires ongoing treatment, is generally thought to outweigh the risk of delaying diagnosis in order to be certain of the diagnosis of MS. The proposed definition of pediatric MS may eventually require modification as more information is gathered regarding the predictability of developing MS after an initial demyelinating event. Clinical prognostic indicators or a biomarker that predicts the development of MS after an initial demyelinating event in childhood is needed to facilitate an early and accurate diagnosis of pediatric MS.

Pathogenesis. ADEM is characterized histologically by perivenular infiltrates of T cells and macrophages, associated with perivenular demyelination. Although ADEM shares common pathologic features with MS, distinct pathologic criteria distinguishing the two diseases have not been defined. There are no systematic studies comparing the histopathology of ADEM and MS, although such studies would undoubtedly yield important information on the relationship between these two diseases. A variety of pathologic features have been described in biopsy and autopsy samples from ADEM and AHEM patients. An autopsy from a 5-year-old boy with fatal ADEM grossly described diffuse brain edema, uncal and tonsillar herniation. 19 Multifocal perivascular lymphocytic infiltrates associated with fibrin deposition within vascular lumens and adjacent demyelination were observed. There was diffuse anoxic-ischemic neuronal degeneration and interstitial edema. Viral inclusion bodies were not seen in H-E sections. A brain biopsy performed in a 10-year-old girl with severe AHEM demonstrated subcortical WM with perivascular hemorrhagic necrosis with subacute inflammation consisting of macrophages, neutrophils, and rare lymphocytes. No evidence of viral, bacterial, fungal, or parasitic infection was noted. Although ADEM is typically described as demyelination with relative preservation of axons, axonal damage has been identified in the brains of...
some patients. Lesions largely involve the white matter, but can also involve the cortex and deep gray matter structures. The CSF is characterized by elevated protein and white blood cells. Oligoclonal bands are an acute manifestation in up to 30% of patients with ADEM, and may be transient. Elevated CSF levels of the pro-inflammatory cytokines IL-6, IL-10, and TNFα have been described.

Acute hemorrhagic and acute necrotizing hemorrhagic leukoencephalitis (AHEM, AHL, ANHLE) of Weston Hurst shares some inflammatory histologic features with ADEM; however, demyelination is often more widespread throughout the CNS and is associated with a pronounced neutrophilic infiltrate. ANHLE is characterized by destruction of small blood vessels associated with acute hemorrhage and fibrin deposition. CSF analysis reflects the hemorrhagic nature of this disease with elevations in protein, RBC, and WBC counts.

ADEM may be classified as either postvaccinial or postinfectious; however, in many cases no clear antecedent history of either is present. Rare cases of ADEM have been described following organ transplantation. Postinfectious forms of ADEM typically begin within 2 to 21 days after an infectious event; however, longer intervals have also been described. Viral infections commonly associated with ADEM include influenza virus, enterovirus, measles, mumps, rubella, varicella zoster, Epstein Barr virus, cytomegalovirus, herpes simplex virus, hepatitis A, and coxsackievirus. Bacterial triggers include Mycoplasma pneumoniae, Borrelia burgdorferi, Leptospira, and beta-hemolytic Streptococcus. Acute hemorrhagic leukoencephalomyelitis (AHLE) typically follows influenza or upper respiratory infection. The only epidemiologically and pathologically proven association of ADEM with vaccinations is with the Semple form of the rabies vaccine. Vaccines produced in CNS tissue including the Semple form of the rabies vaccine carry a higher risk of ADEM. It is important to note that in general, vaccination forms with high rates of complications are no longer in use. Some reported incidences of encephalomyelitis associated with various forms of vaccination are listed in table 2.

The pathogenesis of ADEM is unclear; however, given its histologic features and typically monophasic course of disease, it has been likened to the animal model experimental autoimmune encephalomyelitis (EAE). EAE is an autoimmune demyelinating disease, which can be induced in a variety of animal species by immunization with myelin proteins or peptides. Moreover, the postvaccinial form of ADEM associated with the Semple rabies vaccine, which contains rabies virus–infected neural tissue, reinforces this analogy to EAE. Viral or bacterial epitopes resembling myelin antigens have the capacity to activate myelin-reactive T cell clones through molecular mimicry, and can thereby elicit a CNS-specific autoimmune response. Thus, it has been suggested that microbial infections preceding ADEM elicit a cross-reactive anti-myelin response through molecular mimicry. Alternatively, ADEM may be caused by the activation of existing myelin-reactive T cell clones through a nonspecific inflammatory process.

Theiler murine encephalomyelitis virus–induced demyelinating disease (TMEV-IDD) model is induced by direct CNS infection of the neurotropic TMEV picornavirus, initially resulting in an immune-mediated reaction primarily involving TMEV-specific CD4 and CD8 T cells. However, during the chronic stages of disease, T cell reactivity to host myelin peptides has been observed, indicating

Table 2 Incidence of vaccination-associated ADEM

<table>
<thead>
<tr>
<th>Vaccination forms</th>
<th>Reported incidences of ADEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>1–2/million (compared to 20–30/million incidence of measles virus–induced encephalitis)</td>
</tr>
<tr>
<td>Rabies</td>
<td>1/300–1/7,000</td>
</tr>
<tr>
<td></td>
<td>1/25,000</td>
</tr>
<tr>
<td></td>
<td>&lt;1/75,000</td>
</tr>
<tr>
<td></td>
<td>0.2/100,000 (Japan)</td>
</tr>
<tr>
<td></td>
<td>0/813,000 (USA)</td>
</tr>
<tr>
<td>Smallpox</td>
<td>3/665,000 (reporting encephalitis or myelitis)</td>
</tr>
<tr>
<td></td>
<td>0.9/100,000</td>
</tr>
<tr>
<td>Diphtheria/pertussis/tetanus</td>
<td>Eight cases of CNS inflammation within 10 weeks</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Four cases of partial myelitis within 3 months</td>
</tr>
</tbody>
</table>

ADEM = acute disseminated encephalomyelitis.
epitope spreading has occurred secondary to T cell responses to myelin breakdown products, resulting in an autoimmune response. Both microglia and dendritic cells from the CNS of TMEV-infected mice are able to present myelin peptides to naïve T cells, thereby facilitating epitope spreading to nonviral, host myelin antigens. The TMEV model highlights the phenomenon of epitope spreading secondary to a destructive CNS viral infection resulting in a secondary autoimmune response and chronic inflammation. Although this model superficially bears some resemblance to ADEM, it is important to note that overwhelming evidence has shown that ADEM is not due to direct viral infection of the CNS, but is a secondary immune-mediated phenomenon. Epitope spreading is likely to be an important phenomenon in chronic inflammatory diseases such as MS, but involvement in ADEM is unknown.

Sequences in myelin basic protein have been shown to resemble several viral sequences, and in some cases, cross-reactive T cell responses have been demonstrated. Examples of cross-reactive T cells with MBP antigens include HHV-6, coronavirus, influenza virus hemagglutinin, and EBV. Proteolipid protein (PLP) shares common sequences with Haemophilus influenzae. Semliki forest virus (SFV) peptides mimic myelin oligodendrocyte glycoprotein (MOG). Enhanced myelin basic protein (MBP)-reactive T cell responses have been demonstrated in patients with postinfectious forms of ADEM. Elevated titers of anti-myelin antibodies in sera from patients with ADEM have recently been demonstrated as compared to patients with MS or viral encephalitis. Previous studies have demonstrated enhanced anti-MBP antibody titers in patients with postvaccinal ADEM following vaccination with the Semple rabies vaccine. One of these studies demonstrated elevated anti-MBP antibody titers in ADEM samples compared with MS samples. Although there is controversy surrounding the characterization of anti-myelin antibody responses in MS, studies in ADEM have consistently shown detectable levels, suggesting differences in pathogenesis. Collectively, these studies suggest that enhanced T and B cell myelin responses play a role in the pathogenesis of both postinfectious and postvaccinal ADEM; however, further studies are required to determine causal relationship.

ADEM was associated with the class II alleles HLA-DRB1*01 and HLA-DRB*03 in a Russian study. A similar study from Korea showed an association of ADEM with HLA-DRB1*1501, as well as HLA-DRB5*0101. The same Korean study showed an association of HLA-DRB3*0202 and HLA-DQB1*0502 with acute necrotizing forms of encephalopathy. The gene most frequently linked with MS is HLA DRB1, with DR2 being the most frequently involved allele. Similar associations have been found in the pediatric MS population. Thus, class II alleles may play a role in MS as well as ADEM; however, the disparity between the alleles associated with the two diseases suggests differences in pathogenesis.

**Research/future directions.** ADEM often poses both a diagnostic and prognostic dilemma for clinicians. In the acute stage, there should be a low suspicion of infection before initiation of corticosteroid or immunosuppressive therapy. Diagnostic tests that increase the rapidity of an accurate diagnosis are recommended. Over the long term, one of the most pressing questions of a child presenting with ADEM, particularly recurrent or multiphasic forms of ADEM, is the potential risk for conversion to MS. Although ADEM and MS share many similar pathologic features, prognosis is drastically different. Therefore, identification of a biomarker that can predict the development of MS after an ADEM event is critical.

Additional studies are required to understand the worldwide epidemiology and distribution of ADEM. These studies may give insight into the pathogenesis of the disease and potential preventative measures. Early identification of triggers for ADEM, such as specific batches of vaccines, is facilitated by stringent monitoring mechanisms.

Current treatments for ADEM generally lead to acceptable outcomes; however, further studies are required to investigate the use of additional agents, particularly for refractory or multiphasic cases. There is a paucity of literature on the use of chemotherapeutic agents for ADEM, although anecdotal use is prevalent. In addition, use of β-interferons for multiphasic forms of ADEM requires further investigation.

The use of standardized definitions for ADEM and MS in children and adolescents will help to facilitate future studies, regarding the prognosis, pathogenesis, and treatment of these two diseases.

**Appendix**

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**References**


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