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Topical Review

Acute Disseminated Encephalomyelitis in Children: An Updated Review Based on Current Diagnostic Criteria

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ABSTRACT

Acute disseminated encephalomyelitis is an inflammatory disorder of the central nervous system. Uniform diagnostic criteria for acute disseminated encephalomyelitis did not exist until publication of expert-defined consensus definitions by the International Pediatric Multiple Sclerosis Society Group in 2007, with updates in 2013. In the expanding field of pediatric neuroimmunology, consistent diagnostic criteria are essential to correctly categorize patients as increasing information regarding prognosis and management becomes available. Scientific literature is relatively lacking in review articles on International Pediatric Multiple Sclerosis Society Group-defined acute disseminated encephalomyelitis. This review focuses primarily on references applying the International Pediatric Multiple Sclerosis Society Group criteria for acute disseminated encephalomyelitis presenting specific, up-to-date, and translatable information regarding the epidemiology, pathophysiology, clinical features, diagnosis, management, and prognosis of acute disseminated encephalomyelitis in the pediatric population.

Introduction

Acute disseminated encephalomyelitis (ADEM) is a well-known but historically inconsistently defined demyelinating disorder of the central nervous system (CNS) with a high incidence in the pediatric population. In 2007, the International Pediatric Multiple Sclerosis Society Group (IPMSSG) published consensus definitions for demyelinating disorders of childhood, including ADEM,[1] last updated in 2013[2] (Fig 1).

Much of the literature on pediatric ADEM did not specifically use the IPMSSG diagnostic criteria and therefore includes a wide range of cases, many of which, by strict definition, would not be categorized as ADEM, but rather as clinically isolated syndrome (CIS), multiple sclerosis (MS), or neuromyelitis optica spectrum disorder (NMO-SD). The aim of this review is to focus primarily on references applying the IPMSSG criteria to present specific, up-to-date, and translatable information regarding the epidemiology, pathophysiology, clinical features, diagnosis, management, and prognosis of pediatric ADEM.

Epidemiology

Incidence and demographic features

The estimated annual incidence of pediatric ADEM is 0.23 to 0.4 of 100,000 children.[3-6] There tends to be a slight male predominance, with most male to female ratios falling between 1.2:1 and 2.6:1,[4,7-17] although one single-center series in Taiwan reported a ratio of 4.6:1,[18] and several other series (US, Dutch, Canadian, and South Indian series) showed no difference between the sexes.[3,19-22] The average age of onset of pediatric ADEM is 3.6 to seven years.[4,7-11,14,17-23] One study assessing the geographical distribution of ADEM cases found the pattern similar to that seen in MS, with increasing disease prevalence of ADEM as distance from the equator increased.[24]

Association with preceding infection or vaccination

A majority, between 55% and 86%, of pediatric ADEM cases are reported to be preceded by symptoms of systemic viral illness.[3,4,8,9,14,16,18,22,25] Vaccination has also been reported to precede ADEM, although at much lower rates (4% to 18% of

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1. A first polyfocal, clinical, CNS event with presumed inflammatory demyelinating cause
2. Encephalopathy NOT explained by fever, systemic illness, or postictal symptoms
3. Brain MRI is abnormal during the acute (3 month) phase
4. No NEW clinical or MRI findings emerge 3 months or more after onset
5. Brain MRI is abnormal during acute (3 month) phase with diffuse, poorly demarcated, large (>1-2cm) lesions involving predominantly cerebral WM. T1 hypointense lesions in WM are rare. Deep GM lesions in thalamus or basal ganglia can be present.

FIGURE 1. IPMSSG Diagnostic Criteria for ADEM, 2013,[2] ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; GM, gray matter; IPMSSG, International Pediatric Multiple Sclerosis Society Group; MRI, magnetic resonance imaging; WM, white matter.

cases[3,4,8,9,14,18,22,25]). Whether or not there is a causal association between vaccination and childhood ADEM remains unknown. Current literature is limited to case reports and case-control studies. A large US case-control study found no statistically significant increased risk of ADEM after any vaccine except possibly Tdap, a finding that the authors concluded may be attributable to chance, but at most could account for 1.16 cases of ADEM per one million doses of the vaccine.[26] A case-control study in China found increased risk of childhood ADEM in the 31- to 60-day period post-vaccination, but concluded that this was likely coincidental as it was not confirmed by self-control analyses.[27] The investigators did not find increased risk in either the zero- to 30- or 61- to 180-day periods, and there was no association between any one vaccine type (including hepatitis B, influenza, polio, diphtheria, pertussis, tetanus, measles, mumps, rubella, Japanese encephalitis, hepatitis A, varicella, and rabies) and ADEM.[27] Case-control studies looking at broader but related populations, such as children or adults with any form of CNS inflammatory demyelination, also generally do not support a causal association with vaccines.[28-33]

Pathophysiology

The precise etiology of ADEM is unknown. Evidence of the inflammatory nature of ADEM has been demonstrated by the presence of elevated cerebrospinal fluid (CSF) cytokines and chemokines (involved in helper T cells, regulatory T cells, and B cell pathways) in patients with ADEM.[15] It is theorized that molecular mimicry is involved in triggering this inflammatory cascade. Self-antigens thought to be targets of molecular mimicry due to similarities with viral sequences include myelin basic protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG).[34]

Whether B cell pathways or T cell pathways first initiate the autoreactivity to self-antigens in humans with ADEM has not been fully elucidated, but there are some mouse model data suggesting that CNS demyelination is primarily T cell driven.[35-37] T cells reactive to MBP have been identified in the CSF of patients with ADEM,[38] and immunoglobulin G antibodies to MBP, PLP, and MOG have been identified in the serum of patients with ADEM.[39] Anti-MOG antibodies (MOG-Abs), which are identified in 33% to 66% of pediatric patients with ADEM,[3,15,17,20,37,40-42] have been shown to activate complement[43] and initiate natural killer cell-mediated death[44] *in vitro*, suggesting that the antibodies themselves may contribute to pathogenesis. However, development of demyelination in the setting of MOG-Ab was found to depend on the presence of proinflammatory cytokines in one rat study,[45] suggesting that MOG-Abs alone are not sufficient to induce disease.

Clinical features

Initial presentation with ADEM is highly variable. The latent period between an inciting viral infection and onset of symptoms is typically about 12 days.[22,46] Initial symptoms most often include a nonspecific prodrome of fever, headache, and nausea.[3,4,9,13,19,22,46] The prodrome lasts an average of three to four days before onset of neurological symptoms.[22,46] Duration of hospitalization may be as short as a few days to as long as several months; on average it is between 13 and 27 days.[22,46] Pediatric intensive care unit (PICU) admission is required for up to 25% of children with ADEM, due to severe encephalopathy, seizures, or paralysis affecting the diaphragm.[47] About 75% of those admitted to the pediatric intensive care unit for ADEM required mechanical ventilation.[47] The time course to optimal recovery is discussed further in the Prognosis section.

See Table 1 for a list of symptoms and their prevalence in children with ADEM. The incidence of specific neurological findings varies significantly between studies, but the most common are encephalopathy, pyramidal signs, cerebellar signs, and cranial nerve deficits. Rare case reports have identified incidences of comorbid peripheral and central demyelination, although the prevalence of this entity among patients with ADEM is not known and it may represent a unique disorder.[48-50] Children with ADEM and MOG-Ab are more likely to have transverse myelitis compared with those who are negative for MOG-Ab.[17] The titer of MOG-Ab at disease onset has not been shown to correlate with disease severity.[20]

All children must have some component of encephalopathy during their acute illness to meet the IPMSSG criteria for ADEM.[2] Data regarding the spectrum of encephalopathy in patients with ADEM are limited, but a retrospective series from one institution

TABLE 1.
Clinical Features in Pediatric ADEM

Symptoms and Signs During Acute Illness	% Prevalence
Encephalopathy	100% by definition
Fever	12%-68%[4,7,8,14,16,18,21,22]
Headache	6%-64%[8-10,14,16,18,21,22]
Seizures	12%-50%[4,7-10,13,14,16-18,21,22,26]
Cranial nerve deficits	18%-39%[9,14,17,18]
Speech disturbance	7%-44%[9,18]
Pyramidal signs	18%-60%[9,10,13,14,17]
Sensory deficits	0%-9%[9,10,17,18]
Cerebellar signs/ataxia	36%-47%[7,13,14,17,18,22]
Optic neuritis	1%-15%[10,13,17,18,22]
Urinary disturbance	6%-25%[4,9,18,22]

Abbreviation:
ADEM = Acute disseminated encephalomyelitis

found that encephalopathy had been characterized by irritability in 36%, sleepiness in 50%, confusion in 8%, obtundation in 20%, and coma in 16% of pediatric patients ultimately diagnosed with monophasic ADEM.[21] A separate study that defined coma as a Glasgow Coma Score of ≤10 reported coma in 23% of patients.[22] Longer duration of altered sensorium has been associated with higher disability scores at hospital discharge.[22]

Differential diagnosis

The differential diagnosis for a child with encephalopathy, multifocal neurological symptoms, and T2 hyperintensities on brain magnetic resonance imaging (MRI) is very broad and includes such entities as ADEM, MS, NMO-SD, MOG-Ab-associated disorder, infectious meningoencephalitis, leukodystrophy, CNS vasculitis, CNS malignancy, and CNS-isolated hemophagocytic lymphohistiocytosis. Basic CSF studies, oligoclonal bands, serum autoantibodies, and characteristics of MRI lesions are the primary results used for narrowing the diagnosis. See the next section for a description of the typical findings of these studies in ADEM. Ultimately, atypical findings on initial evaluation, combined with clinical features of the illness, such as time course, relapses, and response to immunomodulatory therapy, will dictate whether additional testing, such as CSF cytology or flow cytometry, hemophagocytic lymphohistiocytosis screening, genetic testing, or even brain biopsy are warranted for diagnostic support. No consensus recommendations currently exist regarding the timing or order of additional testing.

Diagnosis

The diagnosis of ADEM is made using the IPMSSG criteria presented in Fig 1. Findings typical of ADEM are presented below by test category.

Cerebrospinal fluid laboratory testing

There are no CSF studies specific for ADEM. Cell counts, cultures, and viral polymerase chain reaction primarily assist with ruling out infectious processes.[51] Pleocytosis (with definitions varying from >5 to >20 cells/μL) is seen in 29% to 85% of ADEM cases.[4,9,13-16,18,21,22,25] Values typically do not exceed 100 cells/μL,[3,15,18,52] but values as high as 400 to 600 cells/μL have been reported in some cases.[15,18,21] The predominant cell type is lymphocytes.[13,14,18] Cutoffs for significant protein elevation have not been consistent across case reports, but levels are considered elevated in 17% to 48% of cases.[9,14,16,21,25] Intrathecal oligoclonal bands are only present in 0% to 20% of cases.[4,7,9,13-18,25,36,52]

Serum antibody testing

Serum MOG-Ab and anti-aquaporin 4 antibody (AQP4-Ab) are useful in the setting of acute demyelinating syndromes to assist with diagnosis of MOG-Ab-associated disorder[53] and NMO-SD,[54] respectively. Based on recently proposed diagnostic criteria, all patients with ADEM who are positive for MOG-Ab would meet criteria for MOG-Ab-associated disorder.[53] MOG-Abs are positive in 33% to 66% of all pediatric ADEM cases[3,15,17,20,40,55,41,42] and are associated with development of a non-MS relapsing demyelinating disease course.[40] MOG-Abs are positive in 96% of pediatric ADEM cases that develop non-MS recurrent demyelination.[40] The prognostic value of MOG-Ab is discussed further in the Prognosis section. AQP4-Abs are 99% specific for NMO-SD.[42] Patients presenting with ADEM-like illness who have optic neuritis or transverse myelitis should be screened for AQP4-Ab; if positive, they meet diagnostic criteria for NMO-SD.[54] This is relatively uncommon, as almost all patients with ADEM are negative for AQP4-Ab[3,13,17,40,42,52] and less than 10% of AQP4-Ab-positive NMO-SD cases present with ADEM.[56,57] The incidence of AQP4-Ab-negative NMO after ADEM appears to be slightly more common, reported between 2% and 8%, with all affected patients positive for MOG-Ab.[40,42]

Neuroimaging: MRI

The IPMSSG criteria include the presence of MRI characteristics typical of ADEM: diffuse, poorly demarcated, large lesions involving mostly cerebral white matter (WM), with or without deep gray matter lesions, rarely with T1 hypointense lesions.[2] A detailed look at the initial MRI findings in IPMSSG-defined ADEM cases in the literature is presented in Table 2. Studies that reported resolution of MRI lesions over time found that 25% to 100%[9,10,12,14,16-18,25,52] of patients had complete resolution, 0% to 62%[9,10,12,14,16,17,25,52] had partial resolution, and 0% to 36%[9,10,12,14,16,17,25,52] had no resolution on follow-up scans. The amount of time between MRIs was not reported in all studies; when reported the range was one to 28 months after the acute event. One study examined age-expected WM and cortical gray matter growth in patients with monophasic ADEM over an average of 3.3 years of follow-up and found that both were reduced.[11] This finding has not been replicated.

Electroencephalogram

Routine electroencephalography (EEG) is often done in patients with ADEM because of their encephalopathy or clinical seizures. Acutely, the majority of interictal EEGs are abnormal,[14,16,18,21,25] but with nonspecific findings. Diffuse slowing is the most common finding, reported in up to 88% patients.[14,16,18,21,25] Focal spikes or focal slowing are reported in about 25% patients.[14,16,18,21,25] No significant association between EEG abnormalities and clinical or MRI features has been demonstrated, although conclusions are limited by small sample sizes.[14,16,21] Epilepsy is a relatively uncommon sequelae of ADEM, occurring in 0% to 16% of patients.[17,18,61] Children are at higher risk of post-ADEM epilepsy if they have seizures at presentation, have positive oligoclonal bands, or have relapsing episodes of demyelination.[61] Almost all children with post-ADEM epilepsy are positive for MOG-Abs.[61] No studies have assessed whether EEG findings during ADEM can predict development of epilepsy.

Histopathology

Diagnostic evaluation often ends after the above-mentioned evaluatrion, but if diagnostic uncertainty persists, a decision may be made to pursue brain biopsy; this is most typically done when CNS malignancy or primary CNS vasculitis remain diagnostic possibilities. There are no clear diagnostic criteria for ADEM by biopsy, as all findings are nonspecific. However, ADEM is pathologically characterized by the presence of perivenous demyelination in the WM,[62-64] and this is in contrast to confluent demyelination, the structural hallmark of MS.[62,65,66] Both demonstrate infiltration of macrophages and lymphocytes.[62,64,66] In ADEM, all lesions will be at a uniform stage of demyelination,[62] whereas in MS both active and inactive lesions simultaneously exist.[65] Cortical demyelinating lesions can be seen in both MS and ADEM.[62,67] Biopsy can also be useful for diagnosing acute hemorrhagic leukoencephalitis, a subtype of ADEM. The histopathology in acute hemorrhagic leukoencephalitis varies by the acuity of disease. Early on, perivascular hemorrhage, fibrinous exudates, edema, and predominantly

TABLE 2.
Characteristics of MRI Lesions in IPMSSG-Defined ADEM Cases

Lesion Description	Prevalence on Initial MRI
Bilateral involvement	89%-100%[9,17,58]
Supratentorial *and* infratentorial involvement	56%[9]
Subcortical WM lesions	47%-79%[4,16,18,25]
Large (>2 cm) lesions	80%-97%[8,17]
Periventricular WM lesions	6%-60%[4,17,18,25,59]
T1 hypointensities/black holes	3%-18%[12,17,59]
Cortical GM lesions	0%-6%,[17,18] although 46% in one study[4]
Brainstem involvement	29%-67%[4,12,16-18,25]
Cerebellar involvement	29%-52%[4,16-18]
Thalamic involvement	20%-58%[16,18,22,25]
Basal ganglia involvement	20%-54%[9,16,18,25]
Spinal cord involvement*	18%-80%[4,9,13,15-18,22,25]
LETM (≥3 segments involved)†	60%-100%[5,13,18,60]
Gadolinium enhancement‡	18%-50%[8,9,14,16,18,22,59,58]
Vasogenic edema on DWI/ADC	75%[58]
Cytotoxic edema on DWI/ADC	12.5%[58]

Abbreviations:
ADC = Apparent diffusion coefficient
ADEM = Acute disseminated encephalomyelitis
DWI = Diffusion-weighted imaging
IPMSSG = International Pediatric Multiple Sclerosis Society Group
LETM = Longitudinally extensive transverse myelitis
GM = Gray matter
MRI = Magnetic resonance imaging
WM = White matter
* Not all patients received spinal MRI. Often tested only if clinical symptoms present.
† Refers to the % of patients with abnormal spinal MRIs who met criteria for LETM.
‡ Not all patients received contrast. Percentages reflect yield among those tested.

neutrophilic inflammation are present.[68-70] Later, reactive astrocytosis and demyelination are seen.[70]

Subtypes

Categorization into ADEM subtypes is primarily done retrospectively, as distinctions between subtypes are mainly related to propensity for relapsing episodes and become more clear as long-term follow-up allows determination of clinical relapses or imaging changes. A brief summary of ADEM subtypes including monophasic ADEM, multiphasic ADEM (MDEM), ADEM-optic neuritis (ADEMON), and acute hemorrhagic leukoencephalitis is provided in Table 3. It should be noted that none of these diagnoses are definitively final; if patients subsequently go on to develop additional attacks without encephalopathy or imaging changes remote from the initial attack and therefore meet criteria for MS (see Fig 2), their previous episode(s) are considered their initial episodes of MS.[72] It is also important to recognize that the MS criteria were not developed to differentiate MS from other conditions and clinician expertise with pediatric demyelinating disorders remains fundamental in making a correct diagnosis.

Although most ADEM subtypes are distinguished based on relapses and the time course of illness, acute hemorrhagic leukoencephalitis, also known as acute hemorrhagic encephalomyelitis, is an exception, as this diagnosis is suggested in the acute setting by a severe, rapidly progressive, often fatal

TABLE 3.
Categories or Subtypes of ADEM

Subtype	Description
Monophasic ADEM	A single ADEM episode with no further demyelinating events or new MRI lesions outside the acute three-month period after onset[2]
Multiphasic ADEM	Two episodes of ADEM separated by at least three months in time. The second event can involve the same or new symptoms, signs or MRI lesions compared with the first event. This diagnosis is limited to two episodes of ADEM. Three or more suggest ultimate diagnosis of MS, NMO, or other disorder[2,*]
ADEMON	Monophasic *or* multiphasic ADEM plus one or more recurrent episodes of optic neuritis. No other demyelinating attacks occur. Most often monophasic ADEM followed by recurrent ON. All described cases have been MOG+[40,55,52]
AHL/AHEM	A severe fulminant presentation of ADEM with rapid deterioration and frequent mortality; associated with multifocal hemorrhages and necrosis in addition to typical demyelinating lesions[64,71]

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
AHEM = acute hemorrhagic encephalomyelitis
ADEMON = ADEM-optic neuritis
AHL = Acute hemorrhagic leukoencephalitis
MOG = myelin oligodendrocyte glycoprotein
MRI = Magnetic resonance imaging
MS = Multiple sclerosis
NMO = Neuromyelitis optica
ON = Optic neuritis
* In the event that a patient has repetitive encephalopathic events, careful diagnostic evaluation for CNS vasculitis, CNS malignancy, or neurometabolic disorder must be undertaken. It is not yet defined exactly when or if such a patient would be diagnosed with MS.

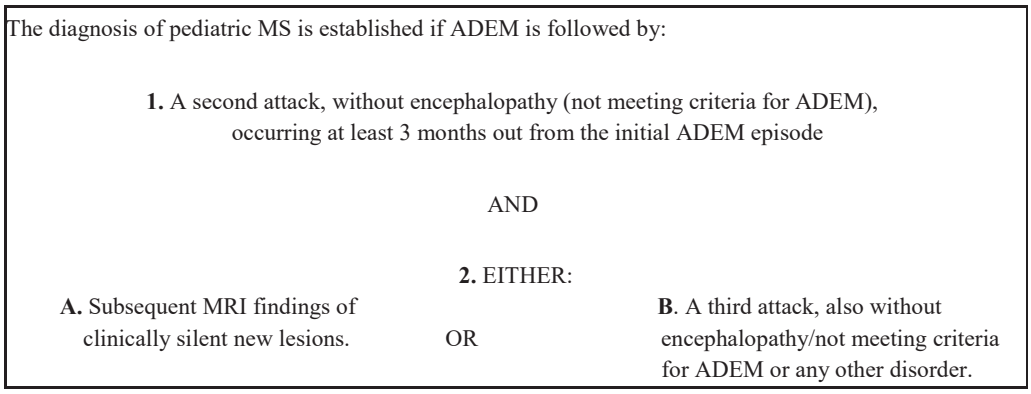

FIGURE 2. Criteria for diagnosis of MS after ADEM presentation.[2,72] ADEM, acute disseminated encephalomyelitis; MS, multiple sclerosis.

phenotype.[64,71] Death can occur in as little as 24 hours due to cerebral edema or herniation.[64] MRI typically demonstrates multifocal hemorrhages, visualized best on sensitivity-weighted imaging.[73]

Those who do not display the acute hemorrhagic leukoencephalitis phenotype are given an initial diagnosis of monophasic ADEM at the time of the first ADEM episode. ADEM is still considered to be monophasic even if additional demyelination or MRI changes occur within three months of onset.[2] If an ADEM event occurs more than three months after the initial episode, however, this is considered a second event and is diagnostic of MDEM.[2] Patients who have ADEM (whether monophasic or MDEM) who experience one or more episodes of optic neuritis fall into the subtype of ADEMON, a recurrent, although non-MS, demyelinating disorder.[52] Additional information about the risk factors for and rates of development of these subtypes is provided in the Prognosis section of this article.

Treatment

As ADEM symptoms often mimic acute infection of the CNS, it is not unusual for children with ADEM to initially be treated with broad-spectrum antibiotics and antiviral medications. However, once the diagnosis of ADEM has been reached, treatment strategies shift to ADEM-specific treatments, detailed below. There are no large, prospective, randomized, clinical trials of experimental therapeutics in pediatric ADEM, so the definitive optimal treatments are unknown. The treatment approach presented here is based on case reports, clinical series, and expert opinions, most of which were reported before the introduction of the IPMSSG diagnostic criteria.

The most common acute treatment approach for pediatric ADEM is a three- to five-day course of high-dose intravenous glucocorticoids (either 10 to 30 mg/kg/day methylprednisolone up to maximum dose of 1000 mg daily or 1 mg/kg/day dexamethasone, no clear maximum daily dose) followed by a prolonged oral steroid taper.[74-76] Few comparative studies exist with regard to differing steroid regimens. One small study compared outcomes of patients treated with methylprednisolone (n = 21) to those treated with dexamethasone (n = 25) and found a statistically significant improvement in outcome, as measured by the median Expanded Disability Status Scale scores, among those treated with methylprednisolone.[76] Steroid tapers vary widely by study, although commonly prednisone was started at 1 mg/kg/day (up to a maximum of 60 mg/day) and then tapered over four to six weeks. There are few comparative studies of the various steroid tapers reported. One observational case series noted that patients with monophasic ADEM (n = 19) had an average steroid taper of 6.3 weeks, whereas those with relapsing or MADEM (n = 6) had an average steroid taper of 3.2 weeks.[74] Another observational case series (n = 46) reported a nonstatistically significant higher relapse rate in patients having a taper over less than three weeks when compared with those having a taper over more than three weeks.[77]

An alternative acute treatment approach is IVIG, dosed at a total dose of 1 to 2 g/kg administered either as a single dose (usually of 1 g/kg) or divided over three to five days (usually 400 mg/kg/day).[78-81] Another alternative acute treatment approach is plasma exchange. Plasma exchange is generally utilized in patients who fail to respond to steroids or IVIG.[82-85] We uncovered no prospective studies comparing IVIG or plasma exchange to glucocorticoids. We also found none comparing IVIG to plasma exchange.

Beyond treatment of the initial event, it is important to have a plan for long-term clinical and radiographic follow-up to exclude a multiphasic disorder, which would warrant further diagnostic evaluation and a different therapeutic approach. The optimal frequency for follow-up imaging remains controversial.

Among children with recurrent MOG-Ab-positive demyelinating syndromes such as MDEM or ADEM-ON, disease-modifying drugs azathioprine, mycophenolate mofetil, and rituximab have been found to decrease frequency of, but not eliminate, relapses.[86] Regular IVIG infusions have also been found to reduce relapse frequency and additionally, have been associated with clinical improvement over time.[86]

Prognosis

The prognosis of pediatric ADEM can be assessed in two major domains: (1) clinical recovery outcomes and (2) recurrent demyelination syndrome outcomes. Occurrence of death during the acute demyelinating episode fortunately appears to be rare, with most studies reporting no deaths,[3,7,8,14,16,18,25,58] and four studies with a 3% mortality rate.[13,22,40,47]

Clinical recovery outcomes

The definition of clinical recovery after ADEM has not been uniformly applied among the literature. In general, articles have tended to categorize patients into “complete” or “partial” recovery based on either the application of formal disability scores or on the reported deficits at follow-up visits. The timeline to recovery after the acute ADEM episode is not well described in most studies. Among those that achieve complete recovery, time to do so is relatively short, with one study reporting recovery at an average of 31 days after hospital discharge[18] and another an average of 26 ±

34 days from onset of symptoms.[48] However, another study suggests that optimal recovery may take much longer, reporting that patients with long follow-up (average duration of 12 years) had significantly better scores in attention domains of neuropsychological testing when compared with patients with shorter follow-up times.[10] Discrepancies in recovery outcomes are likely related to differences in outcome measures, with studies that assess for subtler, especially cognitive, deficits generally reporting longer time to and lower rates of complete recovery. For example, in the Dutch cohort, at least one cognitive domain was affected in 34% of tested children with ADEM, at a median of 15 months after onset.[3] Other subtle impairments including excessive fatigue, decreased exercise capacity, and borderline-to-low function on Motor Assessment Battery for Children, Second Edition, can be seen in about half of the patients with ADEM assessed on average 40 months after onset.[87] A summary of recovery outcomes is provided in Table 4.

Recurrent demyelination outcomes

The majority of patients with ADEM will have monophasic disease, with no recurrent demyelination after at least two years of follow-up,[7-9,14,17,18,23,40,59,60] and up to 12 years in one study.[10] However, up to 36% will have another demyelinating event of some kind.[42] The incidence of MADEM and development of ADEMON and MS are described in Table 5. It is worth highlighting the relatively low incidence of progression from ADEM to MS at 0% to 17% in studies with follow-up periods lasting years.[3,7-10,14,15,17,18,23,25,40,42,59,60] This is in great contrast to the progression of patients with CIS reported in some of the same patient cohorts, with incidence of MS in 40% to 75%.[3,8,40,42,60] The table also includes features from the initial episode of ADEM that may be associated with, or predictive of, development of the specified recurrent syndromes, most notably, MOG-Ab positivity. Of note, although we have restricted our references primarily to articles enforcing the IPMSSG criteria for ADEM, we did not require that articles use the IPMSSG criteria for progression of ADEM to MS, as many articles did not explicitly state their criteria for this diagnosis. In a few instances, when the necessary data were available to do so, we recategorized patients based on the current IPMSSG guidelines.[2,72] Otherwise, we relied on the authors' diagnostic discretion.

The prognostic features of MOG-Ab in ADEM deserve further description. A 2014 prospective cohort study on 33 patients with pediatric ADEM compared outcomes between MOG-Ab-positive and MOG-Ab-negative patients.[17] Overall, patients with MOG-Ab positivity at initial presentation had significantly better clinical recovery and a higher percentage had complete MRI resolution.[17] The study did not directly compare outcomes based on the duration of persistently positive titers. Titers declined consistently in those with monophasic disease course, but were more likely to remain elevated in those with recurrent, although non-MS, disease course.[17] Other studies have also demonstrated an association of MOG-Ab positivity with propensity for developing recurrent non-MS disease course.[40,42]

Last, it should be noted that a significant amount of prognostic literature regarding progression to MS in children is focused on acquired demyelinating syndromes (ADS) as a whole rather than on ADEM alone. These studies show that female sex,[23] older age at onset,[23,60] positive family history of MS,[60] CIS presentation,[3,8,40,60] absence of encephalopathy,[3,7,60] presence of intrathecal oligoclonal bands,[8,23,40,60] and elevated immunoglobulin G index[60] are all associated with MS development in patients who present with ADS. Presence of both $\geq$1 periventricular lesion and $\geq$1 T1-hypointense lesion on baseline MRI was found to be strongly predictive of MS, with 84% sensitivity and 93% specificity, in a prospective study up of 183 children with ADS (25% with ADEM, 20% transverse myelitis, 25% optic neuritis, 12% other monofocal CIS, and 18% polyfocal CIS).[59] Multiple other studies have also found that periventricular MRI lesions at baseline are associated with MS.[8,40,60] Children with MOG-Ab positivity at onset of ADS are significantly less likely to develop MS than MOG-Ab-negative children.[40,55,41]

Conclusion

Childhood ADEM has an incidence of 0.4 per 100,000 patients. Predominant clinical features include encephalopathy, ataxia,

TABLE 4.
Clinical Recovery After Pediatric ADEM

Amount of Recovery	% of Patients	Definitions of Recovery Category
Complete	56%-94%	• Modified Rankin Scale[88] of 0-1[15] • EDSS of 0[14,87] • No reported deficits on standardized questionnaire at follow-up[17,84] • Normalization of neurological examination[9,10,16,18,25] • Lack of any reported deficits by telephone or in written outpatient follow-up records[9,10,16,18,25]
Mild to Moderate deficits	6%-56%	• Modified Rankin Scale[88] of 2[15] • EDSS of 1[14,87] • Persistent mild deficit or symptom[3,9,10,16-18,25,87] including: ◦ Excessive fatigue ◦ Mild gross motor symptoms or signs ◦ Urinary retention ◦ Mild visual symptoms or signs ◦ Mild cognitive problems ◦ Limited exercise capacity
Moderate to severe deficits	0%-18%	• Modified Rankin Scale[88] of 3[15] • EDSS $\geq$ 1.5[14,87] • Persistent moderate to severe deficits[9,10,16-18,25] such as: ◦ Epilepsy ◦ Learning disability ◦ Marked attention difficulties ◦ Ataxia ◦ Severe gross motor symptoms or signs

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
EDSS = Expanded Disability Status Scale
Definitions of recovery categories are described in further detail in the articles referenced in this table.[89]

TABLE 5.
Development of Recurrent Demyelination After ADEM

Type of Demyelinating Syndrome	Incidence after ADEM	Time to Diagnosis	Associated Features from Initial ADEM Episode	Outcome
MDEM*	0%-23%[3,4,7-10,12,14,17,25,40,42,60]	The second ADEM event almost always occurred within 12 months of the first event. The longest reported time to first relapse is 28 months[6,15,17,18,25,40,86]	MOG-Ab+[42]	Over several years' follow-up, the median total number of relapses is 2.5, with a range of 1-5 relapses. The median EDSS score at follow-up is 1.5. Up to 50% of patients report cognitive problems[86]
ADEMON†	0%-9%[3,7-10,12,14,17,18,25,40,42,52,60]	Time between ADEM and the first episode of ON was between 3 weeks to 28 months, with an average of 10 months[52,86]	• MOG-Ab+[42]	A slight majority of patients will have residual visual symptoms.[52,86] Over several years' follow-up, the median total number of relapses is 2, with a range of 1-9.[52,86] About 30% will have cognitive problems long term.[86] Some also experience recurrent episodes of ADEM[52]
MS	0%-17%[3,7-10,14,15,17,18,23,25,40,42,59,60]	Time to diagnosis was between 6 months and 8 years after initial ADEM episode	• + OCB[23] • MOG-Ab negativity[17] • AQP4-Ab negativity[56,90] • MRI with any two: (1) ≥2 periventricular WM lesions, (2) presence of black holes, (3) non-diffuse or bilateral lesion distribution[12]	Analysis of outcomes in this specific group of pediatric patients with MS compared with other patients with MS has not been done

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
ADEMON = ADEM-optic neuritis
AQP4-Ab = Anti-aquaporin 4 antibody
EDSS = Expanded Disability Status Scale
MDEM = Multiphasic ADEM
MOG-Ab = Anti-myelin oligodendrocyte glycoprotein antibody
MRI = Magnetic resonance imaging
ON = Optic neuritis
OCB = Oligoclonal bands
WM = White matter

* Included here are some patients previously classified as "recurrent ADEM," a category no longer recognized by the IPMSSG.[2]

† Of note, some of these patients also had multiple ADEM episodes, but we have chosen to include them here rather than in MDEM as this appears to be a separate entity. Also, the incidence reported here should be interpreted with the acknowledgment that many articles do not explicitly state the absence of progression to ADEMON, but rather allow this inference to be made based on their reported incidence of monophasic or multiphasic ADEM and progression to MS.

pyramidal signs, and headache. Diagnosis is made through exclusion of other etiologies and fulfillment of the IPMSSG-defined criteria for ADEM. MRI most often demonstrates bilateral, diffuse, large WM lesions, with brainstem or cerebellar involvement in about half of the patients, and with deep the gray matter (thalamic/basal ganglionic) involvement in about half of patients. These MRI lesions typically demonstrate at least partial, often complete, resolution over time. ADEM is most often treated with a three- to five-day course of intravenous glucocorticoids, although IVIG and plasma exchange have also been described.

ADEM subtypes include monophasic ADEM, MDEM, ADEMON, and acute hemorrhagic leukoencephalitis. The majority of patients belong to the monophasic group. However, as many as one in three patients will have a recurrent demyelinating episode of some kind. Diagnosis of MS after ADEM occurs in 0% to 17% of cases, which is significantly less common than after CIS. Factors that increase the risk of MS after ADEM include positive oligoclonal bands, MOG-Ab negativity, and atypical MRI findings. Of those who have non-MS relapses, the vast majority will be MOG-Ab positive. The majority of patients with ADEM appear to have a full clinical recovery, although studies assessing more subtle cognitive deficits have shown that up to half may have mild difficulties, and moderate to severe deficits can be seen in up to 18% patients. Future directions of research could include direct comparison of patients with monophasic ADEM with patients with ADEM who develop MS, studies on treatment regimens in IPMSSG-defined ADEM specifically, further evaluation of brain development post-ADEM, and further assessment of subtle cognitive and motor recovery after ADEM.

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