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CHAPTER 18

Acute Disseminated Encephalomyelitis

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INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is an acute immune-mediated inflammatory demyelinating condition involving the brain and spinal cord, which presents clinically with new-onset polyfocal neurologic features, which by definition include encephalopathy.[1] The MRI shows characteristic multifocal demyelinating abnormalities. There is often a history of infection or immunization, and ADEM is considered a postinfectious/parainfectious condition. This condition is a common cause of encephalitis in children and must be considered in the differential diagnosis of a child presenting with acute febrile encephalopathy and altered sensorium with or without fever. Children with ADEM respond well to immunosuppressive treatment (steroids) with the majority having a single event, i.e., a monophasic course. A small proportion of children with ADEM may have relapses, and in this subset, multiple sclerosis (MS) is a diagnostic consideration. In this chapter we discuss the epidemiology, pathophysiology, clinical features, investigations, treatment, and outcome of ADEM in children.

DEFINITIONS

ADEM is a clinicoradiological diagnosis because there are currently no diagnostic blood or CSF abnormalities or biomarkers (apart from anti–myelin oligodendrocyte protein [anti-MOG] antibodies, discussed later). Therefore in earlier studies there was a marked heterogeneity regarding the criteria for diagnosis. In 2007, the International Pediatric Multiple Sclerosis Study Group (IPMSSG) proposed consensus definitions for pediatric acquired demyelinating disorders of the central nervous system (CNS) to improve consistency in terminology.[2] These criteria were revised in 2013.[3]

For the diagnosis of ADEM, all of the following criteria are required[3]:

1. A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause.
2. Encephalopathy that cannot be explained by fever. Encephalopathy refers to an alteration in consciousness (e.g., stupor, lethargy) or behavioral change unexplained by fever, systemic illness, or postictal symptoms.
3. No new clinical and MRI findings emerge 3 months or more after the onset. This implies that the confirmation of the monophasic course requires follow-up and can only be done retrospectively.
4. Brain MRI is abnormal during the acute (3 months) phase.
5. Typically on brain MRI, there are diffuse poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter. T1 hypointense lesions in the white matter are rare. Deep gray matter lesions (e.g., thalamus or basal ganglia lesions) can be present.

If a child has a first monofocal or polyfocal clinical CNS event with presumed inflammatory demyelinating cause in the *absence* of encephalopathy and the MRI criteria for MS are not met, this is known as clinically isolated syndrome (CIS).[3] Examples of CIS include optic neuritis, transverse myelitis, hemiparesis, monoparesis, and brainstem syndromes. CIS has a higher likelihood of progression to MS as compared with ADEM.[4]

The clinical symptoms and radiologic findings of ADEM can fluctuate in severity and evolve in the first 3 months after onset. Accordingly, a second event is defined as the development of new symptoms more than 3 months after the start of the incident illness. There is no strong biological rationale of the use of 3 months as a cutoff, although it is hypothesized that monophasic immune dysregulation is usually resolved within a 3-month period.

A small proportion of children with ADEM (10%) will have a relapse of an inflammatory demyelinating event with encephalopathy.[2] In the 2007 criteria, two terms were used for relapses of ADEM: recurrent and multiphasic ADEM. Recurrent ADEM was defined as

a new event of ADEM with a recurrence of the same symptoms and signs, 3 or more months after the first ADEM event.[2] Multiphasic ADEM was defined as a new event of ADEM involving new anatomic areas of the CNS and occurring at least 3 months after the onset of the initial ADEM event and at least 1 month after completing steroid therapy. In the 2013 revision, the term recurrent ADEM has been dropped.[3] Multiphasic ADEM now encompasses both new as well as reemergence of previous clinical and MRI findings. Also, the timing criterion in relation to steroids for recurrent/multiphasic ADEM has been removed.

A third ADEM-like event is not consistent with a diagnosis of multiphasic ADEM but indicates a chronic relapsing demyelinating disorder, such as relapsing optic neuritis, neuromyelitis optica spectrum disorder associated with antiaquaporin-4 antibodies, relapsing anti-MOG antibody–associated demyelination, or MS depending the clinical phenotype, biomarker, and neuroimaging findings.[1]

EPIDEMIOLOGY

Population-based studies have shown varying incidence rates of ADEM: 0.07 per 100,000 children per year (Germany),[5] 0.3 per 100,000 children per year (China),[6] 0.4 per 100,000 children per year (San Diego),[7] and 0.64 per 100,000 person years (Japan).[8] The varying incidence may be influenced by factors such as genetic predisposition, latitude, environmental and socioeconomic factors, and study methodology.[9,10] The median age at presentation of ADEM is 5–8 years, with male predominance.[1] A recent study from a single center showed that ADEM was the most common cause of encephalitis (21% of all encephalitis).[11]

ADEM is preceded by infection or vaccination in 50%–85% of cases.[9] Common antecedent infections include flu-like illnesses (56%–61%), followed by nonspecific upper respiratory tract infections (12%–17%) and gastroenteritis (7%).[9,12,13] In children, exanthematous diseases are also reported as an infectious antecedent. ADEM has been reported more commonly in winter and spring. This seasonal distribution is likely due to seasonal viral illnesses and epidemics. Viruses (coronavirus, Coxsackie B, dengue, hepatitis A virus, hepatitis C virus, herpes simplex virus, varicella zoster virus, Epstein-Barr virus, human herpesvirus-6, human immunodeficiency virus, measles, mumps, rubella, and parainfluenza) are the infectious agents most frequently associated with ADEM.[9] Bacteria (*Streptococcus*, *Mycoplasma*, *Legionella*, *Chlamydia*, *Borrelia*, *Rickettsia*, *Campylobacter*) and parasites (*Plasmodium vivax*, *Toxoplasma gondii*) may be rarely involved.[14] The mean latency between the infectious prodrome and the onset of neurologic symptoms varies, often being between 4 and 12 days (range: 1–42 days).[9]

Postimmunization ADEM accounts for only 5% of cases of ADEM.[14] Postvaccination ADEM has been associated with several vaccines such as rabies, diphtheria-tetanus-polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza, hepatitis B vaccine, and human papillomavirus vaccine. In a recent retrospective review of Vaccine Adverse Event Reporting System (VAERS) database and the EudraVigilance Postauthorisation Module (EVPM) from 2005 to 2012, a total of 404 cases of postvaccination ADEM were reported,[15] and half of the patients were less than 18 years of age and with a slight male predominance. The time interval from vaccination to ADEM onset was 2–30 days in 61% of the cases. Vaccine against seasonal flu and human papillomavirus vaccine were those most frequently associated with ADEM, accounting for almost 30% of the total cases.

The risk of developing ADEM following vaccination is relatively low, compared with the risk of ADEM following infections against which the vaccines are aimed to protect.[1] The benefits of vaccinations are considered to far surpass the potential risk of postvaccine ADEM.

PATHOPHYSIOLOGY

The exact pathogenesis of ADEM is unclear. Postinfectious immune-mediated mechanisms are implicated. Molecular mimicry with T cell–mediated cross-activation and response against myelin proteins, such as myelin basic protein, proteolipid protein, and MOG plus B cell activation and autoantibody production, may play a role.[14] This hypothesis is supported by studies showing the presence of anti-MOG antibodies in the serum and cerebrospinal fluid (CSF) during the acute phase and their progressive decline along with disease resolution.[16] In a single study comparing the profile of myelin peptide autoantibodies in children with ADEM versus MS, ADEM was characterized by IgG autoantibodies targeting epitopes derived from myelin basic protein, proteolipid protein, myelin-associated oligodendrocyte basic glycoprotein, and α-B-crystallin.[17] In contrast, MS was characterized by IgM autoantibodies targeting myelin basic protein, proteolipid protein,

myelin-associated oligodendrocyte basic glycoprotein, and oligodendrocyte specific protein.

There may also be a nonspecific self-sensitization of reactive T cells (bystander activation) against myelin proteins secondary to infections.[18] In a recent study comparing the CSF cytokine profiles in children with ADEM, enterovirus encephalitis, and anti-NMDA receptor encephalitis, patients with ADEM showed predominant elevation of Th1 (IFN-γ, TNF-α, CXCL9, CXCL10), Th2 (IL-4, eotaxin, CCL17, IL-13), Th17 (IL-23, G-CSF, IL-6, IL-8, and IL-17A), B cell (CXCL13, BAFF, CCL19), and other cytokine (CXCL1, IFN-α 2, IL-1ra) molecules, which supports the hypothesis that both cell-mediated and humoral effector mechanisms may play a role.[19]

In a recent study comparing the cytokine profile of anti-MOG positive versus anti-MOG negative demyelinating disorders it was found that the CSF in anti-MOG antibody positive patients showed predominant elevation of B cell–related cytokines/chemokines (CXCL13, APRIL, BAFF, and CCL19) as well as some of Th17-related cytokines (IL-6 AND G-CSF) compared with anti-MOG antibody seronegative patients.[20] These findings suggest that patients with anti-MOG antibodies have a more pronounced CNS inflammatory response with elevation of predominant humoral-associated cytokines/chemokines, as well as some Th 17- and neutrophil-related cytokines/chemokines, suggesting a differential inflammatory pathogenesis associated with MOG antibody seropositivity.[20] These findings also suggest that there is a considerable pathophysiologic heterogeneity in patients with ADEM, suggesting a spectrum of inflammatory demyelination rather than a single disease entity.

Histopathologically, the hallmarks of ADEM include perivenular sleeves of demyelination, perivenous inflammation with infiltrates of myelin-laden macrophages, T and B lymphocytes, plasma cells and granulocytes, axonal injury, and edema.[1,14] The axonal damage is demonstrated by the increased level of a phosphorylated microtubule-associated protein, primarily located in neuronal axons, known as Tau protein, in the CSF, indicative of the clinical severity of ADEM.[21] Moreover, the CSF tau protein concentration in patients with partial lesion resolution in follow-up brain MRI has been shown to be significantly higher than in patients with complete lesion resolution.[21] In addition, there are diffuse cortical microglial alterations (multifocal microglial aggregates), which may be partly responsible for the encephalopathy seen in children with ADEM.[22]

CLINICAL FEATURES

ADEM clinically presents as an acute onset encephalopathy along with polyfocal neurologic deficits. The neurologic symptoms are preceded by prodromal symptoms such a fever, malaise, irritability, somnolence, headache, nausea, and vomiting.[1] Encephalopathy presents as a change in behavior and/or consciousness, varying in severity from lethargy to coma. Commonly headache/vomiting (58%–32%), seizures (13%–47%), and meningismus (5%–43%) may be associated.[9] The patient may also have focal or multifocal neurologic deficits such as hemiparesis, ataxia, aphasia, diplopia, and rarely dystonia and choreiform movements.[14] Multiple cranial nerve involvement may occur. Spinal cord involvement may be present in up to 24% of cases, with clinical features of flaccid paralysis, constipation, or urinary retention.[23,24] Myelitis is significantly more common in anti-MOG antibody–associated ADEM and is associated with longitudinally extensive lesions on the MRI.[25]

The clinical course of ADEM is rapidly progressive, with the development of maximal deficits within 2–5 days.[23] Rarely, respiratory failure occurs because of brainstem involvement. Fever and seizures are described more frequently in ADEM compared with other acute demyelinating syndromes.[1] Combined central and peripheral demyelination has been reported but is very rare in children. Clinical manifestations of peripheral neuropathy may occur simultaneously along with the CNS manifestations or after them.[9]

NEUROIMAGING

The diagnosis of ADEM is clinicoradiological. The characteristic MRI lesions are T2-weighted and fluid-attenuated inversion recovery hyperintense multifocal, irregular, poorly marginated areas with diameters between 5 mm and 5 cm.[14] ADEM lesions typically involve the subcortical and central white matter and cortical gray-white matter junction, thalami, basal ganglia, cerebellum, and brainstem (Figs. 18.1–18.4).[1] The reported frequency of gadolinium-enhancing lesions is highly variable between studies (10%–95%), perhaps depending on the timing of obtaining MRI in the course of the illness.[9] Spinal cord involvement is seen in 10%–28% of patients.[9]

Five radiologic patterns have been described in ADEM[26]: (1) ADEM with small lesions (<5 mm), (2) ADEM with large confluent white matter asymmetric lesions, (3) ADEM with symmetric bithalamic involvement, (4) ADEM with a leukodystrophic pattern with diffuse bilateral and usually nonenhanced white

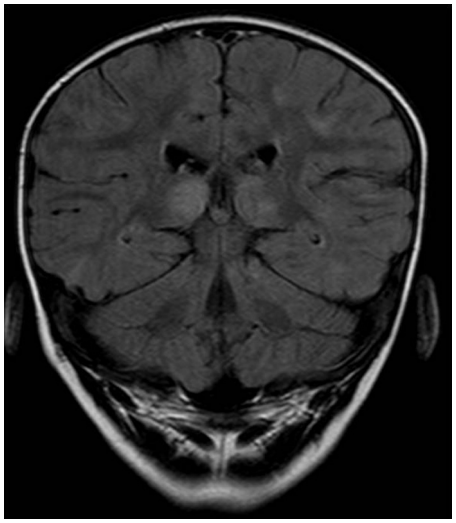

FIG. 18.1 T2 FLAIR Coronal image showing hyperintense signal abnormalities in bilateral subcortical white matter and bilateral thalami in a patient with acute disseminated encephalomyelitis.

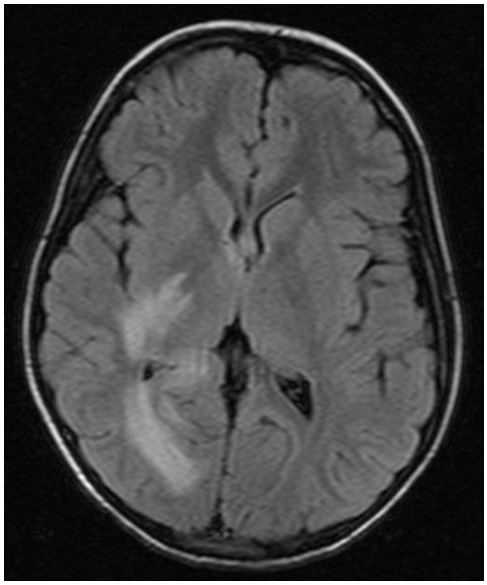

FIG. 18.2 T2 FLAIR Axial image showing large fluffy hyperintense signal abnormalities in right-sided parietooccipital white matter in a patient with acute disseminated encephalomyelitis. Abnormalities also noted in the internal and external capsule on the right side.

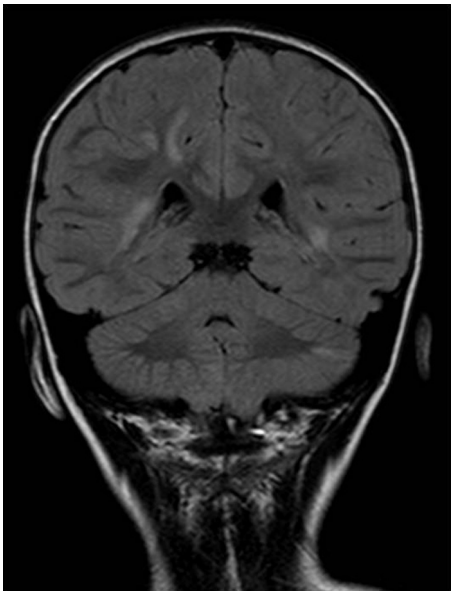

FIG. 18.3 T2 FLAIR Coronal image showing subcortical white matter, and cerebellar white matter abnormalities in a patient with acute disseminated encephalomyelitis.

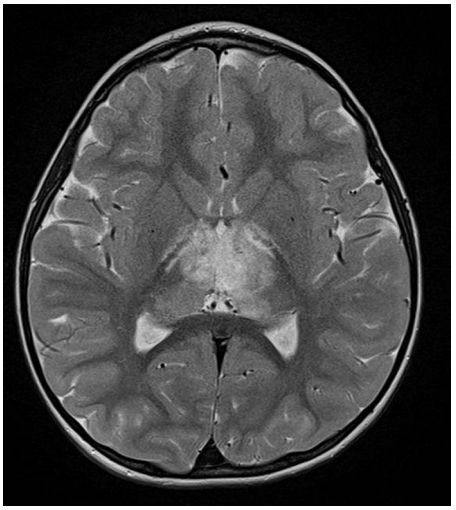

FIG. 18.4 T2 Axial image in a patient with relapsing anti-MOG seropositive patient showing bilateral symmetric thalamic hyperintensities.

matter–sited lesions, and (5) ADEM with acute hemorrhagic encephalomyelitis. The latter two phenotypes are uncommon.

MRI abnormalities may appear later than the clinical symptoms, and progression of MRI lesions has been reported during the course of illness despite clinical improvement.[9] MRI at presentation can even be normal,[27] and delays of between 5 days and 8 weeks between symptom onset and the appearance of MRI alterations have been reported.[28] In a recent

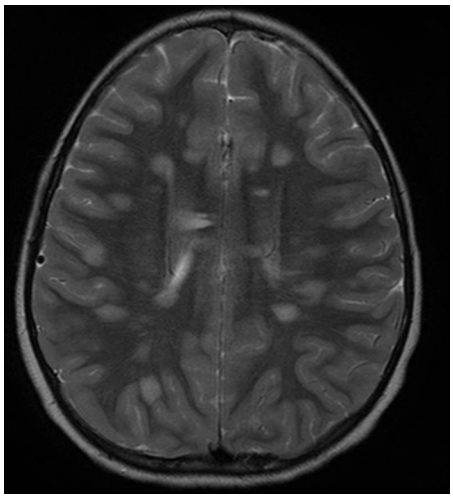

FIG. 18.5 T2 Axial image in a patient with multiple sclerosis showing multiple discrete ovoid hyperintensities involving both the subcortical and periventricular white matter. Note the periventricular Dawson fingers.

study on the evolution of MRI during ADEM episodes, it was noted that new lesions and enlargement of existing MRI lesions occurred in the first 3 months in about 50% of the performed MRIs, despite clinical recovery.[29] However, this was not noted 3 months after first onset of ADEM. Therefore it should be recommended that convalescent MRI scans performed during the first 3 months after ADEM that show new lesions should not necessarily infer the patient has MS.

To differentiate from MS, lesions of MS tend be smaller, discrete and ovoid, and periventricular, especially perpendicular to corpus callosum (Dawson fingers), in contrast to the fluffy poorly marginated subcortical lesions in ADEM.[1] The main differentiating features of ADEM compared with MS are periventricular sparing and the absence of periventricular Dawson finger lesions and black holes on T1 sequences, which are typical of MS (Fig. 18.5).

Follow-up imaging is important to demonstrate resolution of lesions and confirming that no new lesions have developed. In asymptomatic children, repeat imaging is recommended 9–12 months after the episode of ADEM.[1] An earlier repeat imaging at 3 months would be optimal.[1] In children with new symptoms, imaging should be considered earlier.

Advanced neuroimaging techniques such as diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy appear useful to exclude other diseases, such as strokes and neoplasms, to discriminate between acute and chronic lesions, and to add information about the extent of the affected areas.[14] In a recent study of DWI in 16 children with ADEM, vasogenic edema was demonstrated on DWI and corresponding apparent diffusion coefficient (ADC) maps in 12 of 16 patients; cytotoxic edema was identified in 2 patients while the other 2 patients displayed no changes on DWI/ADC.[30]

CEREBROSPINAL FLUID ABNORMALITIES

Because the presentation of ADEM frequently mimics acute encephalitis, CSF studies are often done, and although they may confirm an inflammatory process, they are nondiagnostic in ADEM. CSF examination is, however, important, especially to exclude an infectious pathology, which is a common differential diagnosis. CSF examination in ADEM reveals inflammatory findings in most patients, consisting of elevated protein levels, up to 1.1 g/L (seen in 15%–60% of patients) and lymphocytic pleocytosis, which is typically mild (seen in 25%–65% of patients).[1,9] The CSF may be normal in 25%–33% of patients.[9,13,31] Intrathecal oligoclonal bands are rare, and if present should raise consideration of MS.[1] In three recent series, of 53 patients, oligoclonal bands were reported in only 1 patient (1.9%).[32–34]

ANTI–MYELIN OLIGODENDROCYTE PROTEIN ANTIBODIES

Recently, it has been shown that serum IgG antibodies to MOG are present in up to 40% of children with ADEM. High-titer anti-MOG antibodies have also been found in children with bilateral often relapsing optic neuritis and aquaporin-4 seronegative neuromyelitis optica.[35] Although some relapsing patients with positive anti-MOG antibodies can fulfill 2013 consensus criteria for MS, anti-MOG antibodies generally do not associate with MS and, instead, suggest anti-MOG–associated autoimmune demyelination.[36,37] These antibodies are seen almost exclusively in demyelinating illnesses and may help to differentiate from viral encephalitis.[38]

In patients with ADEM, the majority of children with anti-MOG antibodies have a monophasic course with a rapid decline of anti-MOG antibodies.[16] The presence of anti-MOG antibodies is likely to be a negative predictor for a future diagnosis of MS.[36] In a study comparing children with ADEM with and without positivity for anti-MOG antibodies, children with ADEM who were seropositive for anti-MOG antibodies had MRI characterized by large, bilateral, and widespread lesions with an increased frequency of

longitudinal extensive transverse myelitis and a favorable clinical outcome in contrast to children lacking MOG antibodies.[25] Corpus callosal lesions have been found to be uncommon in children with anti-MOG antibodies.[39] CSF pleocytosis is more common in children with anti-MOG antibodies, suggesting more inflammatory burden in the acute phase as compared with seronegative patients. Some children with ADEM and seropositivity for anti-MOG antibodies may have a relapsing course with future development of optic neuritis or myelitis,[40] or multiphasic ADEM,[41] but development of MS is rare.[42]

DIFFERENTIAL DIAGNOSIS

The diagnosis of ADEM is based on the clinical features and suggestive MRI findings. The clinical picture mimics acute meningoencephalitis, and excluding infectious causes is the first priority. This is done by CSF examination for Gram stain, bacterial culture, and viral studies. Peripheral smear should be obtained for malarial parasites in endemic areas. The MRI obtained should be a gadolinium-enhanced image to look for any leptomeningeal enhancement or any other feature of infection (e.g., basal exudates, brain abscess).

In a child with unexplained altered sensorium and neurologic deficits, other possibilities include autoimmune encephalitis (especially anti-NMDA receptor encephalitis), viral-associated encephalopathies such as acute necrotizing encephalopathy, Hashimoto encephalopathy, CNS vasculitis, primary and secondary (systemic lupus erythematosus, anti-phospholipid antibody syndrome), metabolic (both inherited and acquired) disorders, and rarely toxins and nutritional deficiencies. Anti-NMDA receptor encephalitis must be suspected if the patient has behavior problems, psychosis, sleep disturbances, and movement disorders (especially orofacial dyskinesias) along with encephalopathy.

Other inflammatory demyelinating conditions must also be considered in the differential diagnosis. If the patient has monofocal or polyfocal symptoms in the absence of encephalopathy, then clinically isolated syndrome is diagnosed. If the predominant presentation is optic neuritis and myelitis, then neuromyelitis optica must be considered, and testing for aquaporin antibodies must be done if possible. Neuromyelitis optica with anti-aquaporin-4 antibodies is an uncommon form of CNS demyelination in children; therefore autoantibody testing for aquaporin 4 antibodies should probably be done only with optic neuritis, myelitis, and brainstem symptoms with typical AQP4 antibody–associated features.[43] The diagnosis of MS is not made during the first event but may be considered if the MRI findings are suggestive, such as the presence of old and new lesions, and fulfillment of McDonald or other criteria.[44,45]

TREATMENT

The treatment of ADEM is based on observational studies and expert guidelines, because there are no randomized controlled trials. High-dose intravenous corticosteroids are generally considered the first-line treatment. The treatment regimen consists of IV methylprednisolone at a dose of 30 mg/kg/day (maximally 1000 mg/d) for 3–5 days, sometimes followed by an oral taper over 4–6 weeks with a starting dose of prednisone of 1–2 mg/kg/day.[1] The risk of relapse is increased if the steroid tapering period is less than 3 weeks, although not all experts use tapered prednisolone.[24] The aim of steroid treatment is primarily to reduce the CNS inflammatory reaction and accelerate clinical recovery. Recovery rates with steroid treatment are generally good, with full recovery reported in 60%–85% of the patients.[23,24] A repeat pulse of intravenous steroids may be considered in the case of unsatisfactory clinical improvement or early relapse.[46]

IV immunoglobulin (IVIg) treatment has been described in case reports and small case series, mostly in combination with corticosteroids or as a second-line treatment in steroid unresponsive ADEM.[47] The usual total dose is 2 g/kg, administered over 2–5 days. Treatment with IVIg has proven effective in about 40%–50% of steroid-resistant patients.[12,48] IVIg presumably acts by binding and neutralizing autoantibodies, inhibiting cytokine release, and modulating lymphocyte activation.[14]

Plasmapheresis may be considered in therapy-refractory patients with fulminant disease, with an estimated efficacy of 40%.[49] The usual regimen is five to seven exchanges but there are not infrequent complications in the form of anemia, hypotension, hypocalcemia, thrombosis, and line infections.[14] Moreover, plasmapheresis is technically difficult to perform in young children. Rarely, patients with fulminant ADEM and cerebral edema have been treated with hypothermia in which the body temperature is reduced to 34°C and intracranial pressure and cerebral perfusion pressure levels are maintained low using mannitol and dopamine.[50,51] Decompressive craniectomy may be considered in cases of refractory intracranial hypertension.[52]

OUTCOME

In pediatric series, ADEM has a favorable prognosis, with a good functional recovery reported in 60%–85% of patients. Neurologic improvement is usually seen within days following initiation of treatment, and recovery to baseline usually occurs within weeks.[1] Mortality has been reported in 1%–3% of affected patients in recent series.[53,54] Residual severe disability is rare, reported in 7% of children in recent studies.[55]

About 10%–40% of children are reported to experience residual cognitive impairment or changes in mood and behavior, and the neurocognitive burden of ADEM is probably underappreciated.[24,31,33] Few studies have analyzed the neuropsychological profile of monophasic ADEM patients. Although, overall, these patients showed a satisfactory global performance, a number of children demonstrated isolated deficits in one or more cognitive domains, most frequently the attentive and executive domains.[9] Greater vulnerability to cognitive dysfunction and behavioral problems has been noted in ADEM patients diagnosed before the age of 5 years.[56] Optic nerve involvement at presentation[23] and antecedent viral infection[24] have also been suggested as indicative of a poor outcome. In a recent study of the long-term neurocognitive outcome of children with ADEM, the most common residual symptoms were concentration difficulties (30%), behavior problems (28%), and learning difficulties (26%).[55] On the Kaufman intelligence test, a full-scale IQ of more than 85 was found in only 60% of patients, and 44% of patients fulfilled the criteria for ADHD. Male gender was a predictor for a worse neurocognitive outcome in this study.[55] The attention and behavioral impairment in ADEM may be attributed to the cerebral white matter damage that may interfere with information processing and attention skills, which are critical for emotional functioning and behavioral regulation.[56] When persisting symptoms continue after ADEM, persisting chronic immune activation should be considered, and a retrial of immune therapy can be used to determine if there is a reversible cause for ongoing symptoms.

RELAPSES

Although in most cases ADEM has a monophasic course, a variable number of patients (10%–30% in previous studies) experience relapses.[9] Because of the high interstudy variability and inconsistency of definitions in the past studies, it is difficult to have conclusive findings on relapsing patients from the current literature. Latency from first episode to relapse is variable, ranging from 2 months to 8 years,[23] and even after 33 years in one case.[41] Relapses have been reported to be more common in the first 6 months after the first episode, mostly occurring in children who underwent oral steroid tapering for 3 weeks or less.[57] Most children experience a single relapse, but as many as three relapses are reported in some studies.[23,57] An increased risk of relapse after ADEM has been associated with coexistent optic neuritis, familial history of CNS inflammatory demyelination, the presence of MS findings criteria on MRI, and the absence of sequelae after the first attack in one study.[58]

Multiphasic ADEM is uncommon. In literature, multiphasic ADEM was diagnosed in only 2 of 117 (1.7%) children in one series,[59] and in 5 of 132 (3.8%) children in another series.[58]

After the initial episode of ADEM, a subsequent diagnosis of MS is not common. A long-term follow-up study using the 2007 International Pediatrics Multiple Sclerosis Study Group criteria evaluated the parameters at initial diagnosis and eventual conversion to MS in a cohort of 123 children with a first episode of acute CNS demyelination.[4] Of the 47 patients initially diagnosed with ADEM, only 4 (8.5%) were eventually diagnosed with MS at follow-up versus 38.8% of those initially diagnosed with clinically isolated syndrome had MS. On multivariate analysis, the following predictors for developing MS were identified: female gender, clinical presentation with monofocal brainstem or hemispheric dysfunction, and fulfillment of the MRI criteria for MS. In a patient with first episode of ADEM, criteria for MS are met, if after the initial ADEM, a second clinical event (1) is non-encephalopathic, (2) occurs 3 or more months after the incident neurologic illness, and (3) is associated with new MRI findings consistent with revised radiologic criteria for dissemination in space.[3]

Patients with anti-MOG antibodies who relapse typically have further episodes of ADEM[60] or optic neuritis,[61] and typically do not have new lesions on MRI during asymptomatic periods.

CONCLUSION

ADEM is a polyfocal immune-mediated inflammatory demyelinating disease of the CNS that involves multiple areas of the white matter, which mostly affects children under 10 years of age. Common antecedents include a recent viral or bacterial infection or more rarely immunization. The diagnosis is made in the clinical setting of acute onset of encephalopathy with other neurologic deficits and MRI findings of multifocal demyelination after excluding CNS infections. Commonly, ADEM has a monophasic course in

70%–80% of cases, with most children having a good recovery with high-dose intravenous steroid pulse treatment. IVIg and plasmapheresis may be considered as second- and third-line therapies. ADEM overall has a good prognosis, but 10%–40% of children may have neurocognitive dysfunction on follow-up. Relapses may occur in 10%–30% of patients in the form of multiphasic ADEM, optic neuritis, myelitis, or MS. There is need for further evaluation of biomarkers such as anti-MOG antibodies for prediction of relapses and prognosis.

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