11 Acute Disseminated Encephalomyelitis

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Introduction

Acute disseminated encephalomyelitis (ADEM), also called postinfectious encephalitis/encephalomyelitis, is an immune-mediated inflammatory and demyelinating syndrome of the central nervous system (CNS). It is typically multifocal but monophasic [1]. In most subjects ADEM follows within a few days to weeks of a triggering event, typically infection or more rarely vaccination (Table 11.1). The vaccine relationship has been questioned, and some studies report no association [2, 3]. A minority of patients have no identifiable prior event. A critical concept is that ADEM does not represent an ongoing CNS infection.

ADEM is predominantly a pediatric disorder. The average age at onset is 5–8 years [4–6]. ADEM is much less common in adults, where it can occur at any age but particularly affects young adults. It is rare in the very young (ages 2–3 years) and in the elderly. The incidence in children is reported to range from 0.1 to 0.64 cases per 100,000 population per year [4, 7–10]. Most series show a slight male predominance. ADEM is said to account for at least 8%, and perhaps as high as 20%, of acute encephalitis cases [11].

Table 11.1 Triggering events for postinfectious encephalitis/encephalomyelitis

Exanthematous viral infections (more historical)
Measles (0.1%), varicella zoster virus, rubella, smallpox
Other viruses (HIV, HTLV-1, hepatitis, other herpes viruses, dengue, chikungunya, Zika, mumps, parechovirus)
Viral respiratory tract infection
Viral gastroenteritis
Nonspecific febrile illness
Bacterial infection
Group A beta hemolytic streptococci
Borrelia burgdorferi
Campylobacter, leptospira, chlamydia, legionella
Mycoplasma pneumonia
Protozoal infection
Malaria [109]
Rickettsial infection
Rickettsia rickettsii
Aseptic meningitis
Vaccination (≤1–5 cases per million)
Rabies, pertussis, diphtheria
Tetanus-polio, measles-mumps-rubella, influenza, smallpox, hepatitis B, Japanese B encephalitis, hog vaccine, yellow fever, papilloma virus, meningococcus
Animal/insect bites
Viper bite with antivenom therapy
Neoplastic process
Leukemia, non-Hodgkin's lymphoma
Organ transplant

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Pathology

The pathologic hallmark of ADEM is widespread white and gray matter perivenous inflammation with demyelination [12]. The inflammatory infiltrate is made up of predominantly lymphocytes and monocytes/macrophages. Inflammation results in subsequent "sleeve-like" demyelination, with axons relatively spared [13]. In a recent pathology study, perivenous demyelination was associated with a distinct pattern of cortical microglial activation without myelin loss [12]. Perivenous lesions can coalesce to form larger demyelinated lesions. This neuropathology is quite distinct from multiple sclerosis (MS) or acute viral encephalitis. MS involves confluent demyelination [12]. Gross pathology can involve brain congestion and swelling, with engorged blood vessels within the white matter. Microscopically this is associated with hyperemia, endothelial swelling, vessel wall infiltration by inflammatory cells, and perivascular edema [14].

Acute hemorrhagic leukoencephalitis (AHLE), a hyperacute variant of ADEM discussed below, shows a somewhat different pathology, with prominent neutrophil infiltration, punctate petechial and ringlike hemorrhages, necrotizing vasculitis, and early perivascular astrocyte damage [4, 15].

Clinical Features

At least 70% of patients report an antecedent prodromal event, with neurologic symptoms beginning 2–30 days later [11]. Most often this is infection, with less than 5% following vaccination [16]. Rabies vaccine, when it contained neural tissue components, was a clear risk [4]. Viral infection is the commonest trigger, but nonviral pathogens and rare noninfectious exposures are also reported [17, 18]. Classically exanthematous infections such as measles (0.1%) were a particular risk. The prototypic clinical picture of ADEM involves multifocal neurologic deficits superimposed on a diffuse encephalopathy (Table 11.2) [19]. There may be seizures. Altered consciousness is a key feature. Drowsiness, lethargy, stupor, or coma is much more suggestive for ADEM than is simple irritability or mood disturbance. Cognitive deficits are seen [20], and multifocal deficits can involve motor, sensory, visual, coordination, and gait disturbances. Ataxia and language disturbance may be more common in children than adults [19, 21]. Lower urinary tract dysfunction can be seen in 33% and may persist [22]. It is also common to have neurologic abnormalities outside the brain itself. The spinal cord is involved in up to 67% of cases, particularly in adults [11, 13]. Peripheral nervous system (PNS) involvement (polyradiculoneuropathy) occurs in 5–44% [11, 23], perhaps reflecting that ADEM is part of a much broader immune-mediated neurologic spectrum that includes Guillain-Barre syndrome. The clinical course is rapid, with maximal deficits within 2–5 days [4]. Unusual clinical manifestations include acute psychosis, cerebellar mutism, various movement disorders, and Klüver-Bucy syndrome [24–28]. ADEM can certainly present with a picture that suggests mass lesion with increased intracranial pressure. It has also developed following aseptic meningitis [29]. Sustained high fever and hyponatremia were noted in these meningitis patients.

Based on the most current diagnostic criteria (see below), clinical features may fluctuate. New features may appear over a 3-month period and

Table 11.2 Clinical features of postinfectious encephalitis/encephalomyelitis

Encephalopathy (drowsiness/lethargy, stupor/coma)
Fever
Headache
Motor deficits
Ataxia
Sensory abnormalities
Seizures (focal or generalized)
Optic neuritis (unilateral or bilateral)
Bilateral may need to rule out neuromyelitis optica-Devic spectrum disorder
Transverse myelitis
Bladder, bowel disturbances
Language abnormalities
Cranial neuropathy/brainstem deficits
Visual field defects
Radicular, neuropathic features
Meningismus

are still considered one episode. A small minority of ADEM patients (2–4%) will have a second attack [30]. In 80%, this second attack occurs within 2 years [30]. An early follow-up brain MRI (within 6 months), if it has new or persistent lesions, predicts multiphasic ADEM [31]. Brain MRI follow-up up to 2 years did not find silent MRI lesions in the monophasic group. Some pediatric ADEM patients will go on to develop MS, neuromyelitis optica spectrum disorder (NMOSD), or ADEM followed by optic neuritis (ADEM-ON) [4].

Diagnosis

Diagnosis of ADEM depends on a consistent clinical and laboratory picture, with other possibilities ruled out. It is a diagnosis of exclusion [4]. Core laboratory tests involve blood work, neuroimaging, and cerebrospinal fluid (CSF) evaluation. The International Pediatric MS Study Group revised their formal consensus definition criteria for pediatric ADEM in 2012 (Table 11.3). They recognize the monophasic and multiphasic (second attack) variants. More than two attacks are now felt to reflect a chronic relapsing disorder, such as MS or NMOSD [30]. The revised diagnostic criteria propose that after pediatric ADEM, MS criteria would be met if a second clinical event occurred ≥3 months later, was non-encephalopathic, and was associated with new MRI lesions meeting dissemination in space criteria. The ADEM diagnostic criteria require polysymptomatic onset with encephalopathy. Many earlier studies did not use formal diagnostic standards, and entered patients with CNS inflammatory syndromes of unknown etiology, with or without encephalopathy. In such series up to 58% of what was considered ADEM did not have encephalopathy [32].

Table 11.3 Revised pediatric postinfectious encephalitis/encephalomyelitis ADEM diagnostic criteria [30]

Monophasic ADEM
A first polyfocal clinical CNS event with presumed inflammatory cause
Encephalopathy that cannot be explained by fever
MRI typically shows diffuse, poorly demarcated, large, >1–2 cm lesions involving predominantly cerebral WM; T1-hypointense WM lesions are rare; deep GM lesions (e.g., thalamus or basal ganglia) can be present
No new symptoms, signs, or MRI findings after 3 months of the incident ADEM
Multiphasic ADEM
New event of ADEM 3 months or more after the initial event that can be associated with new or re-emergent prior clinical and MRI findings. Timing in relation to steroids is not pertinent

WM white matter, *GM* gray matter

The diagnosis in adults is more problematic, since it is fairly easy to include multifocal clinically isolated syndrome (CIS) (representing the first attack of relapsing MS) in ADEM series, unless encephalopathy is required. Encephalopathy is virtually never seen in MS relapses. In one series of 60 patients over age 15, who presented with an acute demyelinating syndrome, ADEM was differentiated from MS by meeting at least two of three critical criteria: atypical clinical symptoms for MS, absent CSF oligoclonal bands, or gray matter involvement [33]. In another study of 40 adult ADEM cases, 35% were said to have developed MS [34]. However, encephalopathy was not required for the original ADEM diagnosis. A recent series reported on five elderly subjects (ages 57–85 years) with pathologically confirmed ADEM [35]. Their initial differential diagnosis was broad.

ADEM should be considered in anyone who presents with a suggestive neurologic syndrome. Recent illness or vaccination increases likelihood of this diagnosis, but is not required. The rare postvaccinal cases typically follow a primary rather than revaccination [13].

Neuroimaging is central for the diagnosis of ADEM. Although brain CT may show patchy areas of low attenuation in white matter, with focal or diffuse cortical enhancement, it is normal in about 70% of patients and is much less sensitive than magnetic resonance imaging (MRI) [36]. Brain MRI with and without contrast should be carried out in all patients, unless contraindicated. Normal brain MRI probably excludes a diagnosis of classic ADEM, although imaged lesions may be delayed for several weeks [37]. MRI typically shows multiple T2/

FLAIR hyperintense lesions involving white matter but also gray matter. ADEM lesions may (but do not have to) lack sharp borders. The classical imaging features for ADEM are symmetric bilateral lesions, relative periventricular sparing, and deep gray matter involvement. Deep gray matter (basal ganglia, thalamus) involvement is reported in 15–60% of adult cases [38]. Bilateral thalamic involvement is reported in 12% of pediatric cases [39]. In a recent study, MRI criteria were evaluated to differentiate ADEM from MS; the so-called Callen MS-ADEM criteria had the best sensitivity (75%) and specificity (91%) [40]. They involved meeting at least two of the following three criteria: absence of a diffuse bilateral lesion pattern, presence of black holes, and two or more periventricular lesions. Lesions affect subcortical white matter predominantly, although middle cerebellar peduncle and periventricular involvement can be seen [41]. Diffuse extensive supratentorial white matter involvement has also been seen [38]. Sometimes there can be a single tumefactive lesion, which can even be confined to the brainstem [10].

Contrast enhancement is not that helpful. Although very suggestive when it involves all lesions, there may be enhancement of only a subset of lesions, or none may enhance. There can be rare presentations with multiple ring enhancing lesions [42]. In pediatric ADEM, contrast enhancement of one or more lesions is noted in 14–30% [30].

Follow-up brain MRI 6 months after presentation should show partial or complete resolution of lesions, with no new lesions [13]. Spinal cord MRI may be abnormal as well. Cord lesions in ADEM are more likely to involve the thoracic region and may be diffuse and longitudinally extensive [43, 44].

There are limited reports using nonconventional MRI techniques. It would be helpful if a unique diagnostic imaging signature could be developed. Using diffusion MRI, apparent diffusion coefficient (ADC) was reported as decreased in early ADEM lesions and increased in later stages [41]. In another small series, diffusion tensor imaging signal was reported as abnormal in ADEM vs. MS basal ganglia [45]. A recent series showed ADC values increased in 70% of 17 pediatric ADEM cases, consistent with vasogenic edema [46]. Using MR spectroscopy, acute and chronic phases of ADEM showed distinct patterns. Reduced *N*-acetylaspartate to creatine ratios were noted in supratentorial normal-appearing white matter, while choline to creatine ratios were increased acutely, but decreased back toward normal later. Myoinositol to creatine ratios were decreased acutely, but increased in the chronic phase, consistent with gliosis. Elevated lipids and lactate were noted in the acute phase for all subjects, but later normalized [47]. Elevated glutamine/glutamate was present in 67% acutely and then dropped. The authors suggested that the decrease in myoinositol during the acute phase might distinguish ADEM from MS [47]. Unlike MS, normal-appearing brain tissue did not show abnormal magnetization transfer imaging or diffusion tensor imaging values [48].

CSF is routinely examined as part of the diagnostic workup. It helps to exclude direct infection. CSF can be normal in up to 33% of cases [11]. Most often there is a low-grade mononuclear pleocytosis, with mildly elevated protein and normal glucose. Rarely neutrophils may predominate. All cultures and stains, and any PCR or antigen tests, should be negative. CSF pressure may be elevated. Positive oligoclonal bands or elevated intrathecal IgG production is reported in a minority of cases. ADEM can be associated with oligoclonal bands in both CSF and serum [11]. If positive, they are transient and not persistently abnormal. Myelin basic protein (MBP) is often elevated in CSF, as a nonspecific acute injury marker.

With regard to other laboratory testing, about 50% of patients show peripheral leukocytosis or elevated acute-phase reactants [21]. Myelin oligodendrocyte glycoprotein (MOG) IgG antibody should be obtained if possible (see below). Electroencephalogram (EEG) generally shows diffuse background slowing [19]. Brain biopsy is rarely necessary but may be indicated in confusing cases (particularly with continued deterioration).

Table 11.4 Differential diagnosis of postinfectious encephalitis/encephalomyelitis

Acute infectious encephalitis/encephalomyelitis
Viruses (herpes viruses, West Nile virus)
Bacteria (legionnaires, listeria, tuberculosis)
Parasites (amebae)
Brain abscess
Systemic disorders
Autoimmune connective tissue disease
Hemophagocytic (cytokine storm) syndrome
Neurosarcoidosis
Vasculitis
Neoplastic and paraneoplastic disorders
Lymphoma, angioendotheliomatosis, gliomatosis cerebri
Multiple sclerosis
Tumefactive
Marburg variant
Toxic leukoencephalopathy
Inhaled heroin ("chasing the dragon")
Carbon monoxide
Mitochondrial disorders
Metabolic disorders
Central and extrapontine myelinolysis
Marchiafava-Bignami disease
Wernicke-Korsakoff encephalopathy
Posterior reversible encephalopathy syndrome
X-linked Charcot-Marie-Tooth disease

Differential Diagnosis

The differential diagnosis of ADEM involves principally other causes of encephalitis or encephalomyelitis, stupor, or brain MRI white matter lesions (Table 11.4) [1, 49–54]. The differential is influenced somewhat by age, since conditions such as mitochondrial disorders are more likely in the young, while toxic abuse is more likely in adults.

Management

Symptomatic management involves general supportive measures, such as assuring airway and venous access, controlling fever, and treating electrolyte imbalance. Seriously ill patients or those who decompensate should be managed in an intensive care unit (ICU) setting, since increased intracranial pressure is a major concern in severe cases. Appropriate measures are taken to prevent venous thrombosis, and any seizures are treated.

There are no randomized controlled trials for treatment of ADEM. Corticosteroids are standard therapy based on class III evidence [55]. The most typical dose is 1 g intravenous (IV) methylprednisolone for 3–7 days. Occasionally higher doses (up to 2 g) are used. Plasma exchange (typically seven exchanges) can be considered in steroid-unresponsive patients. The expected response rate is at least 44% [56]. Males, those with preserved reflexes, and those who receive early (within 21 days) plasma exchange appear to do better. In one study early treatment, and improvement at discharge, predicted good response 6 months post exchange [57]. Treatment with intravenous immune globulin (IVIG) can also be considered in steroid-resistant patients, typically 1–2 g/kg over 2–5 days [36, 58]. IVIG is preferred to plasma exchange for postvaccinal ADEM [13, 59]. PNS involvement, milder onset disability, and lower CSF albumin have predicted IVIG treatment response [11]. IV cyclophosphamide has also been used for patients who continue to deteriorate. Rarely aggressive surgical decompression or hypothermia may be needed to control brain swelling [60–62].

Prognosis

With the exception of the AHLE hyperacute variant, ADEM overall has a good prognosis. Mortality rate is less than 5% in pediatric series, but has been reported as high as 8–25% in adults requiring ICU admission [38, 63]. Most patients make a good recovery from ADEM, though there may be permanent deficits in 10–30% including cognitive and psychosocial deficits [27, 28, 32, 34, 64]. In a pediatric series, initially severe course was associated with cognitive and visual spatial deficits years later [65]. In recent studies pediatric ADEM patients showed significantly reduced age-expected brain volume growth, and white matter development, compared to controls [66, 67]. Adults are reported to have a worse disease course and outcome than children [21].

In one small series of eight patients, brainstem involvement was associated with poorer outcome [68]. Peripheral nervous system involvement may also be associated with poorer recovery and higher risk of relapse [69]. Seizures and coma are also suggested to indicate worse prognosis [19, 27]. Other features associated with poorer outcome were older age onset, female gender, increased CSF protein, and spinal cord involvement [23]. In another very small series (two patients), decreased ADC in the internal capsule, consistent with cytotoxic edema, predicted poor motor outcome [70]. Patients with a relapsing attack are reported to have a good outcome in long-term (9–13 years) follow-up [71].

ADEM Spectrum Overlap Disorders

ADEM can be considered part of a spectrum of CNS disorders (Table 11.5). As discussed previously, ADEM is typically monophasic but can involve a repeat episode in 2–4% of cases. A repeat episode must occur beyond 3 months. By convention, this is considered multiphasic ADEM.

MOG IgG antibody is reported in a subset of demyelinating CNS disorders. It is more common in pediatric cases and with optic neuritis (especially bilateral). It requires a cell-based assay for reliable detection of conformationally sensitive IgG. ELISA and immunoblot, used previously, provided unreliable results [72]. Anti-MOG IgG is rarely if ever detected in MS. However, it accounts for about 10% of seronegative NMOSD (negative for aquaporin 4 IgG antibodies). It is reported in subjects with optic neuritis, encephalitis with brain demyelinating lesions, and myelitis. Some have suggested the eponym MOG-IgG-associated optic neuritis, encephalitis, and myelitis (MONEM) for this cohort [73]. The highest titers have been reported in ADEM but are generally transient and clear with recovery [72]. However persistent antibodies are also found in an unusual subset of ADEM that is followed by one or more attacks of optic neuritis (ADEM-ON).

Table 11.5 Postinfectious encephalitis/encephalomyelitis CNS spectrum overlap disorders

Multiphasic ADEM
ADEM followed by optic neuritis (ADEM-ON)
Acute hemorrhagic leukoencephalitis (AHLE)
Acute necrotizing encephalopathy
Bickerstaff brainstem encephalitis
Pediatric MS

In a Dutch study, this variant accounted for only 1.2% of pediatric acquired demyelinating disease [74]. Anti-MOG antibodies are said to predict a non-MS disease course [75]. ADEM-ON is typically anti-MOG IgG positive in blood. In an analysis of 17 pediatric patients, relapses involved a unilateral or bilateral optic neuritis (94.4%) or ADEM (5.6%) [76]. During a median follow-up of 5.3 years, half of relapses occurred at the time corticosteroids were being tapered (to <10 mg) or within 4 weeks of discontinuation. Residual deficits were found in 71%. Interattack intervals could exceed 5 years. There is a case report of good response to rituximab [77]; others report corticosteroid responsiveness [76]. The acute attack in MOG-related syndromes is treated with corticosteroids, plasma exchange, IVIG, or cyclophosphamide [73]. The optimal long-term therapeutic approach to MOG-related syndromes is unclear, but currently includes prolonged corticosteroids over months, pulse IVIG, anti-CD20 monoclonal antibody, or immunosuppression [73]. It is important to follow titers, since loss of antibodies may allow withdrawal of therapy.

AHLE (Hurst syndrome) is a very rare disorder. It is the hyperacute and most severe form of ADEM [78, 79]. AHLE typically follows nonspecific respiratory tract infection. Clinical onset involves fever, confusion proceeding to stupor and coma, seizures, and focal neurologic deficits that mimic a rapidly expanding mass lesion within the brain. Mortality approaches 70% and occurs within days, with severe morbidity in survivors. MRI shows large hemispheric white matter lesions, with relative sparing of gray matter (although basal ganglia and thalamus may be involved, as can brainstem/cerebellum and spinal cord) [15]. There may be limited MRI enhancement despite

Table 11.6 Management of acute hemorrhagic leukoencephalitis

Admit to ICU
Ensure airway, breathing, oxygenation, IV access
Control fever, seizures
Monitor and control intracranial pressure (intracranial transducers, sedation, hypothermia, other measures)
Glucocorticoids; consider concomitant plasma exchange or IVIG
Surgical decompression to control swelling
Consider IV cyclophosphamide for ongoing process

ICU intensive care unit, *IV* intravenous, *IVIG* intravenous immune globulin

evidence of edema and hemorrhage. On diffusion MRI, both acute and subacute lesions showed increased ADC values [15]. CSF shows pleocytosis with RBCs. Neuropathology involves polymorphonuclear cell infiltration with fibrinoid necrosis of small blood vessels, perivascular exudates, microhemorrhages, and cerebral edema. Myelin loss occurs in the setting of relative preservation of axons. There are no formal guidelines on treatment, but one can formulate a reasonable approach based on small case series (Table 11.6). Therapy requires aggressive treatment of increased intracranial pressure and other complications [36]. Corticosteroids with plasma exchange, IVIG, and/or immunosuppressants (cyclophosphamide) may be tried, and surgical intervention and hypothermia may be needed for severe cases [60–62, 80–82]. Clinical improvement has been noted within 2 days of starting plasma exchange.

Acute necrotizing encephalopathy, formally characterized in 1995, is a rare disease which follows influenza, parainfluenza, human herpesvirus-6, measles, or mycoplasma infections [83, 84]. Young children under the age of 5 years, particularly from an Asian background (Japan and Taiwan), seem to be preferentially vulnerable [85]. The clinical syndrome is fulminant, with fever and altered mental status within 1–4 days of the viral febrile illness, progressing to coma within 24–72 h. Seizures (often refractory to treatment) are common, and mortality is 30–70%, typically due to cardiorespiratory issues [86]. Brain MRI shows multiple symmetric lesions involving the thalami, brainstem tegmentum, cerebellum, periventricular white matter, and putamen [85]. The differential diagnosis includes Reye syndrome, Leigh's disease (subacute necrotizing encephalomyelopathy), Wernicke encephalopathy, Sandhoff disease, cerebrovascular event, or tumor [87]. CSF shows increased protein without pleocytosis and has been PCR positive for virus in only a minority of cases. Serum aminotransferases but not blood ammonia may be elevated. Postmortem studies show tissue necrosis, vascular changes with petechial hemorrhages, local vessel congestion, microthrombi, and vasogenic edema [86]. Some patients show high circulating levels of interleukin-6 and tumor necrosis factor [83]. Corticosteroids administered within 24 h of onset may be associated with better outcome, at least when brainstem is not involved [87]. An autosomal dominant disorder, involving recurrent bouts of acute necrotizing encephalopathy, has been associated with missense mutations in the Ran-binding protein 2 (RANBP2) gene on chromosome 2. This gene codes for a nuclear pore component [85, 88]. Acute necrotizing encephalopathy shows many similarities to AHLE. A recent case of AHLE in a 6-year-old girl with sickle cell disease was associated with a novel RANBP2 variant [89]. It is interesting to speculate whether acute necrotizing encephalopathy is an expression of AHLE in the very young.

Bickerstaff brainstem encephalitis is characterized by ophthalmoparesis, ataxia, and other CNS features including impaired consciousness. It appears to be part of a very broad neuroimmune spectrum which includes Guillain-Barré syndrome, especially the Miller Fisher variant [90, 91]. Reflexes in these brainstem encephalitis patients may be increased, normal, or even absent. Patients can show central motor and sensory abnormalities, and up to 66% have anti-GQ1b antibodies [92]. CSF shows cytoalbuminologic dissociation most often, but 32% do have a pleocytosis. Brain MRI is abnormal in up to 30%, with T2-hyperintense lesions most often within the brainstem [93]. Bickerstaff brainstem encephalitis is treated with either

IVIG or plasma exchange [94]. Outcome is generally good with spontaneous recovery, but several deaths have occurred [95].

MS is the major acquired CNS inflammatory demyelinating disease. It is certainly in the differential diagnosis for ADEM but can also be considered part of this immune-mediated spectrum. This is especially true for pediatric MS but also for adult-onset MS. Pediatric MS is discussed in a separate chapter. Compared to ADEM, pediatric MS is not monophasic. It has onset typically over age 10 years, shows female predominance, and has no triggering event. It is more likely to have a monosymptomatic vs. polysymptomatic onset and is much less likely to involve any encephalopathic features, bilateral optic neuritis, fever, headache, meningismus, or seizures [32, 96]. Family history of MS also favors MS over ADEM [32]. However up to 20% of pediatric MS patients experience ADEM as their initial event and then go on to clear-cut MS [97, 98]. These children tend to be under 10 years of age. Laboratory distinctions are helpful. In MS the CSF is more likely to show oligoclonal bands which persist, without increased protein or pleocytosis. Brain MRI is much more likely to show periventricular perpendicular and corpus callosum ovoid lesions with well-defined margins, without gray matter or brainstem/cerebellar macroscopic lesions [32, 96]. MS MRI lesions increase over time and do not resolve the way ADEM lesions do. MS spinal cord MRI lesions are virtually never longitudinally extensive (extending three or more vertebral segments) except in rare pediatric cases. MRI diffusion-weighted imaging shows MS vs. ADEM differences. ADC values within the corpus callosum were consistently elevated in MS compared to ADEM or neurosarcoidosis patients, consistent with nonrestricted water diffusion due to demyelination.

For adult-onset MS, multifocal CIS can be confused with ADEM, but a key feature is the lack of encephalopathy as a component of the CIS presentation.

Etiology

ADEM is considered an immune-mediated CNS syndrome. It is believed that myelin components are generally the autoimmune targets. Several hypotheses have been proposed. The first is based on molecular mimicry. In this scenario an environmental pathogen or external vaccination contains antigenic epitopes that cross-react with myelin components and results in a misdirected systemic immune attack against the CNS. This would be akin to the major animal model for MS, experimental allergic/autoimmune encephalomyelitis, because it involves a systemic immune pathogenesis. This hypothesis is partially supported by early reports that rabies vaccines developed in CNS tissues had an excessive high rate of postinfectious sequelae.

A second hypothesis involves a transient infection of the CNS that results in blood-brain barrier damage, with release of sequestered myelin antigens to the systemic immune system. This is temporally linked to a secondary organ-specific immune attack against the CNS.

A third hypothesis requires a critically timed two-hit infection, with the second infection reactivating previously primed autoreactive lymphocytes.

In a limited number of cases, there is one final interesting observation: a mutation in the SCNIA sodium channel that has been associated with postvaccination ADEM [13, 99, 100].

T cells sensitized to MBP have been reported in ADEM. In an immunologic study of ADEM, most patients showed lymphocyte proliferation to MBP [101]. Some patients show antibodies to glycolipids such as galactocerebroside, as well as myelin proteins. IgG antibodies to MOG (but not to proteolipid protein or aquaporin 4) are present in most ADEM patients but are typically transient [102]. IgM antibodies to MOG were only found in 3 of 19 ADEM cases. In another series involving 19 children with ADEM vs. 25 with CIS, 28 other neurologic disease patients, and 30 healthy controls, IgM to EBV early antigen was present in 16% of ADEM cases only. Serum IgG to EBV was no different between ADEM and controls, but titers were higher in CIS patients. High IgG

titers to native MOG were found only in the ADEM and CIS cohorts and were unrelated to the EBV antibody response [103]. There has been a particular interest in anti-MOG antibodies because they demyelinate in vitro MOG. MOG is expressed on the outer lamella of the myelin sheath. Persistent MOG antibodies in ADEM mark a group at risk for subsequent optic neuritis (ADEM-ON).

Cytokines are implicated as well [104], and lesion formation is said to involve cytokines such as interleukin-2 (IL-2), interferon-γ, and tumor necrosis factor [105]. In a study of chemokines and cytokines in ADEM, MS, and healthy control subjects, ADEM showed elevated CSF levels of chemokines involved in neutrophil and T helper 2 cell attraction [106]. There was no difference in serum cytokine/chemokine levels.

Human leukocyte antigen alleles have been studied a little bit in ADEM and in various populations have been similar (but not identical) to those associated with MS [107]. A recent child with biopsy-documented ADEM showed two heterozygous mutations of the polymerase gamma gene, consistent with mitochondrial disease [108]. The significance of this association in a single case is unclear.

Summary

ADEM is an important neuroimmune syndrome that is part of a spectrum of CNS inflammatory demyelinating diseases. It is distinct from MS and carries overall a good prognosis with the exception of the hyperacute AHLE variant. The immunopathogenesis is not well understood, which limits development of preventive strategies and definitive therapies. A recent focus on IgG to MOG is helping to define useful ADEM subsets.

Diagnostic paradigms continue to be refined. Management involves appropriate supportive care and early institution of immunomodulatory therapies such as corticosteroids, plasma exchange, and IVIG. Aggressive management is always justified to control increased intracranial pressure, since such patients can ultimately do very well once this monophasic syndrome has ended.

References

1. Young NP, Weinshenker BG, Lucchinetti CF. Acute disseminated encephalomyelitis: current understanding and controversies. Semin Neurol. 2008;28:84–94.
2. Baxter R, Lewis E, Goddard K, et al. Acute demyelinating events following vaccines: a case-centered analysis. Clin Infect Dis. 2016;63(11):1456–62.
3. Chen Y, Ma F, Xu Y, et al. Vaccines and the risk of acute disseminated encephalomyelitis. Vaccine. 2018;36(26):3733–9.
4. Pohl D, Alper G, Van Haren K, et al. Acute disseminated encephalomyelitis: updates on an inflammatory CNS syndrome. Neurology. 2016;87(9 Suppl 2):S38–45.
5. Mikaeloff Y, Suissa S, Vallee L, et al. First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. J Pediatr. 2004;144:246–52.
6. Torisu H, Kira R, Ishizaki Y, et al. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. Brain Dev. 2010;32:454–62.
7. Leake JA, Albani S, Kao AS, et al. Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. Pediatr Infect Dis J. 2004;23:756–64.
8. Pohl D, Hennemuth I, von Kries R, et al. Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey. Eur J Pediatr. 2007;166:405–12.
9. Banwell B, Kennedy J, Sadovnick D, et al. Incidence of acquired demyelination of the CNS in Canadian children. Neurology. 2009;20:232–9.
10. VanLandingham M, Hanigan W, Vedanarayanan V, et al. An uncommon illness with a rare presentation: neurosurgical management of ADEM with tumefactive demyelination in children. Childs Nerv Syst. 2010;26:655–61.
11. Sonneville R, Klein IF, Wolff M. Update on investigation and management of postinfectious encephalitis. Curr Opin Neurol. 2010;23:300–4.
12. Young NP, Weinshenker BG, Parisi JE, et al. Perivenous demyelination: association with clinically defined acute disseminated encephlomyelitis and comparison with pathologically confirmed multiple sclerosis. Brain. 2010;133:333–48.
13. Huynh W, Cordato DJ, Kehdi E, et al. Post-vaccination encephalomyelitis: literature review and illustrative case. J Clin Neurosci. 2008;15:1315–22.
14. Garg RK. Acute disseminated encephalomyelitis. Review. Postgrad Med J. 2003;79:11–7.
15. Lee HY, Chang KH, Kim JH, et al. Serial MR imaging findings of acute hemorrhagic leukoencephalitis: a case report. AJNR Am J Neuroradiol. 2005;26:1996–9.

16. Bennetto L, Scolding N. Inflammatory/post-infectious encephalomyelitis. J Neurol Neurosurg Psychiatry. 2004;75:i22–8.
17. De Lau LM, Siepman DA, Remmers MJ, et al. Acute disseminated encephalomyelitis following legionnaires disease. Arch Neurol. 2010;67:623–6.
18. Tripathy S, Routray PK, Mohapatra AK, et al. Acute demyelinating encephalomyelitis after anti-venous therapy in Russell's viper bite. J Med Toxicol. 2010;6:318–21.
19. Panicker JN, Nagaraja D, Kovoor JM, et al. Descriptive study of acute disseminated encephalomyelitis and evaluation of functional outcome predictors. J Postgrad Med. 2010;56:12–6.
20. Deery B, Anderson V, Jacobs R, et al. Childhood MS and ADEM: investigation and comparison of neurocognitive features in children. Dev Neuropsychol. 2010;35:508–21.
21. Ketelslegers IA, Visser IER, Neuteboom RF, et al. Disease course and outcome of acute disseminated encephalomyelitis is more severe in adults than in children. Mult Scler. 2011;17(4):441–8.
22. Panicker JN, Nagaraja D, Kovoor JME, et al. Lower urinary tract dysfunction in acute disseminated encephalomyelitis. Mult Scler. 2009;15:1118–22.
23. Marchioni E, Ravaglia S, Piccolo G, et al. Postinfectious inflammatory disorders: subgroups based on prospective follow-up. Neurology. 2005;65:1057–65.
24. Nasr JT, Andriola MR, Coyle PK. ADEM: literature review and case report of acute psychosis presentation. Pediatr Neurol. 2000;22:8–18.
25. Krishnakumar P, Jayakrishnan MP, Beegum MN, et al. Acute disseminated encephalomyelitis presenting as acute psychotic disorder. Indian Pediatr. 2008;45:999–1001.
26. Har-Gil M, Evrani M, Watemberg N. Torticollis as the only manifestation of acute disseminated encephalomyelitis. J Child Neurol. 2010;25:1415–8.
27. Jha S, Ansari MK. Partial Kluver-Bucy syndrome in a patient with acute disseminated encephalomyelitis. J Clin Neurosci. 2010;17:1436–8.
28. Parrish JB, Weinstock-Guttman B, Yeh EA. Cerebellar mutism in pediatric acute disseminated encephalomyelitis. Pediatr Neurol. 2010;42:259–66.
29. Fujiki F, Tsuboi Y, Hori T, et al. Aseptic meningitis as initial presentation of acute disseminated encephalomyelitis. J Neurol Sci. 2008;272:129–31.
30. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler. 2013;19(10):1261–7.
31. Koelman DLH, Benkeser DC, Klein JP, et al. Acute disseminated encephalomyelitis: prognostic value of early follow-up brain MRI. J Neurol. 2017;264(8):1754–62.
32. Alper G, Heyman R, Wang L. Multiple sclerosis and acute disseminated encephalomyelitis diagnosed in children after long-term follow up: comparison of presenting features. Dev Med Child Neurol. 2009;51:480–6.
33. De Seze J, Debouverie M, Zephir H, et al. Acute fulminant demyelinating disease. A descriptive study of 60 patients. Arch Neurol. 2007;64:1426–32.
34. Schwarz S, Mohr A, Knauth M, et al. Acute disseminated encephalomyelitis: a follow-up study of 40 adult patients. Neurology. 2001;56:1313–8.
35. Kaunzner UW, Slamon E, Pentsova E, et al. An acute disseminated encephalomyelitis-like illness in the elderly: neuroimaging and neuropathology findings. J Neuroimaging. 2017;27(3):306–11.
36. Sonneville R, Klein I, de Broucker T, et al. Post-infectious encephalitis in adults: diagnosis and management. J Infect. 2009;58:321–8.
37. Honkaniemi J, Dastidar P, Kahara U, et al. Delayed MR imaging changes in acute disseminated encephalomyelitis. AJNR Am J Neuroradiol. 2001;22:1117–24.
38. Sonneville R, Demeret S, Klein I, et al. Acute disseminated encephalomyelitis in the intensive care unit: clinical features and outcome of 20 adults. Intensive Care Med. 2008;34:528–32.
39. Dardiotis E, Kountra P, Kapsalaki E, et al. Acute disseminated encephalomyelitis with bilateral thalamic necrosis. J Child Neurol. 2009;24:1001–4.
40. Ketelslegers IA, Neuteboom RF, Boon M, et al. A comparison of MRI criteria for diagnosing pediatric ADEM and MS. Neurology. 2010;74:1412–5.
41. Balasubramanya KS, Kovoor JME, Jayakumar PN, et al. Diffusion-weighted imaging and proton MR spectroscopy in the characterization of acute disseminated encephalomyelitis. Neuroradiology. 2007;49:177–83.
42. Kamel MH, Kelleher M, O'Riordan C, et al. CT and MRI ring sign may be due to demyelination: diagnostic pitfall. Br J Neurosurg. 2007;21:309–11.
43. Farber RS, DeVilliers L, Miller A, et al. Differentiating multiple sclerosis from other causes of demyelination using diffusion weighted imaging of the corpus callosum. J Magn Reson Imaging. 2009;30:732–6.
44. Yiu EM, Komberg AJ, Ryan MM, et al. Acute transverse myelitis and acute disseminated encephalomyelitis in childhood: spectrum or separate entities. J Child Neurol. 2009;24:287–96.
45. Holtmannspotter M, Inglese M, Rovaris M, et al. A diffusion tensor MRI study of basal ganglia from patients with ADEM. J Neurol Sci. 2003;206:27–30.
46. Zuccoli G, Panigrahy A, Sreedher G, et al. Vasogenic edema characterizes pediatric acute disseminated encephalomyelitis. Neuroradiology. 2014;56(8):679–84.
47. Ben Sira L, Miller E, Artzi M, et al. H-MRS for the diagnosis of acute disseminated encephalomyelitis: insight into the acute-disease stage. Pediatr Radiol. 2010;40:106–13.

48. Inglese M, Salvi F, Iannucci G, et al. Magnetization transfer and diffusion tensor MR imaging of acute disseminated encephalomyelitis. AJNR Am J Neuroradiol. 2002;23(2):267–72.
49. Borhani Haghighi A, Ashjazadeh N. Acute disseminated encephalomyelitis-like manifestations in a patient with neuro-Behcet disease. Neurologist. 2009;15:282–4.
50. Centers for Disease Control and Prevention. Balamuthia mandrillaris transmitted through organ transplantation. MMWR Morb Mortal Wkly Rep. 2010;59:1165–70.
51. Goraya J, Marks H, Khurana D, et al. Subacute sclerosing panencephalitis (SSPE) presenting as acute disseminated encephalomyelitis in a child. J Child Neurol. 2009;24:899–903.
52. Richard HT, Harrison JF, Abel TW, et al. Pediatric gliomatosis cerebri mimicking acute disseminated encephalomyelitis. Pediatrics. 2010;126:79–82.
53. Summerfield R, Al-Saleh A, Robbins SE. Small cell lung carcinoma presenting with acute disseminated encephalomyelitis. Br J Radiol. 2010;83:e54–7.
54. Zadro I, Brinar VV, Barun B, et al. Primary diffuse meningeal melanomatosis. Neurologist. 2010;16:117–9.
55. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008;47:303–27.
56. Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol. 1999;46:878–86.
57. Llufriu S, Castillo J, Blanco Y, et al. Plasma exchange for acute attacks of CNS demyelination: predictor of improvement at 6 months. Neurology. 2009;73:949–53.
58. Ravaglia S, Piccolo G, Ceroni M, et al. Severe steroid-resistant post-infectious encephalomyelitis general features and effects of IVIG. J Neurol. 2007;254:1518–23.
59. Van Dam CN, Syed S, Eron JJ, et al. Severe post-vaccinia encephalitis with acute disseminated encephalomyelitis: recovery with early intravenous immunoglobulin, high-dose steroids, and vaccinia immunoglobulin. Clin Infect Dis. 2009;48:47–9.
60. Takata T, Hirakawa M, Sakurai M, et al. Fulminant forms of acute disseminated encephalomyelitis: successful treatment with hypothermia. J Neurol Sci. 1999;165:94–7.
61. Payne ET, Rutka JT, Ho TK, et al. Treatment leading to dramatic recovery in acute hemorrhagic leukoencephalitis. J Child Neurol. 2007;22:109–13.
62. Ahmed AI, Eynon CA, Kinton L, et al. Decompressive craniectomy for acute disseminated encephalomyelitis. Neurocrit Care. 2010;13:393–5.
63. Absoud M, Parslow RC, Wassmer E, et al. Severe acute disseminated encephalomyelitis: a pediatric intensive care population-based study. Mult Scler. 2011;17(10):1258–61.
64. Beatty C, Bowler RA, Farooq O, et al. Long-term neurocognitive, psychosocial, and magnetic resonance imaging outcomes in pediatric-onset acute disseminated encephalomyelitis. Pediatr Neurol. 2016;57:64–73.
65. Rostasy K, Nagl A, Lutjen S, et al. Clinical outcome of children presenting with a severe manifestation of acute disseminated encephalomyelitis. Neuropediatrics. 2009;40:211–7.
66. Aubert-Broche B, Weier K, Longoni G, et al. Monophasic demyelination reduces brain growth in children. Neurology. 2017;88(18):1744–50.
67. Longoni G, Brown RA, MomayyezSiahkal P, et al. White matter changes in paediatric multiple sclerosis and monophasic demyelinating disorders. Brain. 2017;140:1300–15.
68. Donmez FY, Asian H, Coskun M. Evaluation of possible prognostic factors of fulminant acute disseminated encephalomyelitis (ADEM) on magnetic resonance imaging with fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging. Acta Radiol. 2009;50:334–9.
69. Marchioni E, Tavazzi E, Minoli L, et al. Acute disseminated encephalomyelitis. Curr Infect Dis Rep. 2008;10:307–14.
70. Kawashima S, Matsukawa N, Ueki Y, et al. Predicting the motor outcome of acute disseminated encephalomyelitis by apparent diffusion coefficient imaging: two case reports. J Neurol Sci. 2009;280:123–6.
71. Mar S, Lenox J, Benzinger T, et al. Long-term prognosis of pediatric patients with relapsing acute disseminated encephalomyelitis. J Child Neurol. 2010;25:681–8.
72. Weber MS, Derfuss T, Metz I, et al. Defining distinct features of anti-MOG antibody associated central nervous system demyelination. Ther Adv Neurol Disord. 2018;11:1–15.
73. dos Passos GR, Oliveira LM, da Costa BK, et al. MOG-IgG-associated optic neuritis, encephalitis, and myelitis: lessons learned from neuromyelitis optica spectrum disorder. Front Neurol. 2018;9:217.
74. Ketelslegers IA, Catsman-Berrevoets CE, Neuteboom RF, et al. Incidence of acquired demyelinating syndromes of the CNS in Dutch children: a nationwide study. J Neurol. 2012;259(9):1929–35. https://doi.org/10.1007/s00415-012-6441-6.
75. Di Pauli F, Reindl M, Berger T. New clinical implications of anti-myelin oligodendrocyte glycoprotein antibodies in children with CNS demyelinating diseases. Mult Scler Relat Disord. 2018;22:35–7.
76. Wong YYM, Hacohen Y, Armangue T, et al. Paediatric acute disseminated encephalomyelitis followed by optic neuritis: disease course, treatment response and outcome. Eur J Neurol. 2018;25(5):782–6.
77. Nagashima M, Osaka H, Ikeda T, et al. Rituximab was effective for acute disseminated encephalomyelitis followed by recurrent optic neuritis with anti-myelin oligodendrocyte glycoprotein antibodies. Brain Dev. 2018;40(7):607–11.

78. Hurst EW. Acute hemorrhagic leukoencephalitis: a previously undefined entity. Med J Aust. 1941;2:1–6.
79. Lann MA, Lovell MA, Kleinschmidt-DeMasters BK. Acute hemorrhagic leukoencephalitis: a critical entity for forensic pathologists to recognize. Am J Forensic Med Pathol. 2010;31:7–11.
80. Leake JA, Billman GF, Nespeca MP, et al. Pediatric acute hemorrhagic leukoencephalitis: report of a surviving patient and review. Clin Infect Dis. 2002;34:699–703.
81. Jasowiak JM. Treatment of hemorrhagic acute disseminated encephalomyelitis with cyclophosphamide. Am J Health Syst Pharm. 2016;73(4):202–5.
82. Ryan LJ, Bowman R, Zantek ND, et al. Use of therapeutic plasma exchange in the management of acute hemorrhagic leukoencephalitis: a case report and review of the literature. Transfusion. 2007;47:981–6.
83. Martin A, Reade EP. Acute necrotizing encephalopathy progressing to brain death in a pediatric patient with novel influenza A (H1N1) infection. CID. 2010;50:e50–2.
84. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza virus infection. Curr Opin Neurol. 2010;23:305–11.
85. Gika AD, Rich P, Gupta S, et al. Recurrent acute necrotizing encephalopathy following influenza A in a genetically predisposed family. Dev Med Child Neurol. 2010;52:99–102.
86. Manara R, Franzoi M, Cogo P, et al. Acute necrotizing encephalopathy: combined therapy and favorable outcome in a new case. Childs Nerv Syst. 2006;22:1231–6.
87. Yadav S, Das CJ, Kumar V, et al. Acute necrotizing encephalopathy. Indian J Pediatr. 2010;77:307–9.
88. Neilson DE, Adams MD, Orr CMD, et al. Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, RANBP2. Am J Hum Genet. 2009;84:44–51.
89. Alawadhi A, Saint-Martin C, Bhanji F, et al. Acute hemorrhagic encephalitis responding to combined decompressive craniectomy, intravenous immunoglobulin, and corticosteroid therapies: association with novel RANBP2 variant. Front Neurol. 2018;9:130.
90. Kimoto K, Koga M, Odaka M, et al. Relationship of bacterial strains to clinical syndromes of campylobacter-associated neuropathies. Neurology. 2006;28:1837–43.
91. Roos RP, Soliven B, Goldenberg F, et al. An elderly patient with Bickerstaff brainstem encephalitis and transient episodes of brainstem dysfunction. Arch Neurol. 2008;65:821–4.
92. Steer AC, Starr M, Kornberg AJ. Bickerstaff brainstem encephalitis associated with mycoplasma pneumoniae infection. J Child Neurol. 2006;21:533–4.
93. Odaka M, Yuki N, Yamada M, et al. Bickerstaff's brainstem encephalitis: clinical features of 62 cases and a subgroup associated with Guillain-Barre syndrome. Brain. 2003;126:2279–90.
94. Mori M, Kuwabara S. Fisher syndrome. Curr Treat Options Neurol. 2011;13:71–8.
95. Yuki N. Fisher syndrome and Bickerstaff brainstem encephalitis (Fisher-Bickerstaff syndrome). J Neuroimmunol. 2009;21:1–9.
96. Atzori M, Battistella PA, Perini P, et al. Clinical and diagnostic aspects of multiple sclerosis and acute monophasic encephalomyelitis in pediatric patients: a single centre prospective study. Mult Scler. 2009;15:363–70.
97. Banwell B, Krupp L, Kennedy L, et al. Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study. Lancet Neurol. 2007;6:773–81.
98. Visudtibhan A, Tuntiyathorn L, Vaewpanich J, et al. Acute disseminated encephalomyelitis: a 10-year cohort study in Thai children. Eur J Pediatr Neurol. 2010;14:513–8.
99. Berkovic SF, Harkin L, McMahon JM, et al. De-novo mutations of the sodium channel gene SCN1a an alleged vaccine encephalopathy retrospective study. Lancet Neurol. 2006;5:488–92.
100. Sell E, Minassian BA. Demystifying vaccination-associated encephalopathy. Lancet Neurol. 2006;5:465–6.
101. Johnson RT, Griffin DE, Hirsch RL, et al. Measles encephalomyelitis – clinical and immunologic studies. N Engl J Med. 1984;310:137–41.
102. Brilot F, Dale RC, Selter RC, et al. Antibodies to native myelin oligodendrocyte glycoprotein in children with inflammatory demyelinating central nervous system disease. Ann Neurol. 2009;66:833–42.
103. Selter RC, Brilot F, Grummel V, et al. Antibody responses to EBV and native MOG in pediatric inflammatory demyelinating CNS diseases. Neurology. 2010;74:1711–5.
104. Kadhim H, De Prez C, Gazagnes MD, et al. In situ cytokine immune responses in acute disseminated encephalomyelitis: insights into pathophysiologic mechanisms. Hum Pathol. 2003;3:293–7.
105. Sabayan B, Zolghadrasli A. Vasculitis and rheumatologic diseases may play a role in the pathogenesis of acute disseminated encephalomyelitis (ADEM). Med Hypotheses. 2007;69:322–4.
106. Franciotta D, Zardini E, Ravaglia S, et al. Cytokines and chemokines in cerebrospinal fluid and serum of adult patients with acute disseminated encephalomyelitis. J Neurol Sci. 2006;247:202–7.
107. Alves-Leon SV, Veluttini-Pimentel ML, Gouveia ME, et al. Acute disseminated encephalomyelitis. Arq Neuropsiquiatr. 2009;67:643–51.
108. Harris MO, Walsh LE, Hattab EM, et al. Is it ADEM, POLG, or both? Arch Neurol. 2010;67:493–6.
109. Carreira J, Casella MI, Ascenção BB, et al. Acute disseminated encephalomyelitis, a rare post-malaria neurological complication: case report and review of the literature. Travel Med Infect Dis. 2019;28:81–5. https://doi.org/10.1016/j.tmaid.2018.03.005.