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Review

# A spectrum of inflammation and demyelination in acute disseminated encephalomyelitis (ADEM) of children

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ABSTRACT

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central nervous system that involves multifocal areas of the white matter, rarely the gray matter and spinal cord, mainly affecting children and mostly occurring 1–2 weeks after infections or more rarely after vaccinations. Though a specific etiologic agent is not constantly identified, to evaluate carefully patient's clinical history and obtain adequate samples for the search of a potential ADEM causal agent is crucial. In the case of a prompt diagnosis and adequate treatment, most children with ADEM have a favorable outcome with full recovery, but in the case of diagnostic delays or inappropriate treatment some patients might display neurological sequelae and persistent deficits or even show an evolution to multiple sclerosis. The suspicion of ADEM rises on a clinical basis and derives from systemic and neurologic signs combined with magnetic resonance imaging of the central nervous system. Other advanced imaging techniques may help an appropriate differential diagnosis and definition of exact disease extension. Although there is no standardized protocol or management for ADEM, corticosteroids, intravenous immunoglobulin, and plasmapheresis have been successfully used. There is no marker that permits to identify the subset of children with worse prognosis and future studies should try to detect any biological clue for prevision of neurologic damage as well as should optimize treatment strategies using an approach based on the effective risk of negative evolution.



**Contents**



## 1. Introduction

Acute disseminated encephalomyelitis (ADEM), also named post-infectious encephalomyelitis and immune-mediated encephalomyelitis, is a multifocal and monophasic inflammatory demyelinating disease of the central nervous system (CNS) that involves multiple areas of the white matter, rarely the gray matter and spinal cord, mainly affecting children and mostly occurring after recent (1–2 weeks prior) viral or bacterial infections or more rarely after vaccinations, though a specific etiologic agent is not always identified [1–3]. Its first expression is characterized by acute onset of different neurological signs and symptoms, accompanied by encephalopathy with a monophasic course, often resolving after treatment within three months since its onset, though relapses might occur in 20–30% of cases [4]. In the case of a prompt diagnosis and adequate therapeutic support, most children

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with ADEM have a favorable outcome with full recovery, but in the case of diagnostic delays or in the case of inappropriate treatment some children might develop neurological sequelae or persistent deficits and even show a dramatic evolution to multiple sclerosis (MS) [5–7]. However, due to the absence of pertinent biological markers, diagnosis of ADEM could be unfocused and, because of uncertainties on etiopathogenesis, an appropriate therapy might be established with delay. This review summarizes the main evidences on etiology, pathogenesis, and clinical features of ADEM in children and suggests an algorithm for both diagnosis and treatment.

## 2. A complex bind of infection-triggered autoimmune phenomena and inflammation

ADEM mainly affects children under 10 years, is more common in males [1,8–10], and mostly arises 2 to 40 days after an infection or more rarely after vaccines [1,10,11]. In most cases ADEM follows a trivial infection, usually localized in the upper respiratory tract, whereas only less than 5% of cases can be classified as post-vaccine forms [12,13]. History of a precipitating event can be reported in 70–80% of children who are diagnosed with ADEM [2,10], but in almost 25% of patients no possible etiology can be identified [1,13,14].

A seasonal variation of ADEM frequency (with peaks in winter and spring) supports its infectious etiology [10,15]. The most frequent infections involved are viral and related to the upper respiratory tract, such as measles [14,16], mumps [2,17–19], rubella [2], varicella [2,14], influenza [5,20], and infectious mononucleosis [21,22]. Also enterovirus [23], coronavirus [24], human immunodeficiency virus [2], herpes simplex virus [25], cytomegalovirus [22], and hepatitis A virus [26,27] have been associated with ADEM. Other pathogens anecdotally involved in ADEM have been *Toxoplasma gondii* [3], *Plasmodium falciparum* [28], *Cryptococcus neoformans* [29], *Haemophilus influenzae* type b [30], *Leptospira* sp. [31], *Streptococcus pyogenes* [32], *Borrelia burgdorferi* [33], atypical bacteria (i.e., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*) [13], *Rickettsia* sp. [13], and *Campylobacter jejuni* [13]. However, a microbiologic diagnosis is rarely reached despite the majority of patients has a positive history of recent previous infections.

Post-vaccination ADEM has been associated with many vaccines, such as those against smallpox, measles, mumps, rubella, diphtheria–tetanus–polio, pertussis, hepatitis B, influenza, human papillomavirus, rabies, and Japanese B encephalitis [13,34–43]. In almost all the available manuscripts we find only case reports and no definitive conclusions can be drawn about the association between a specific vaccine and the real risk of ADEM.

Therefore, the exact pathogenesis of ADEM remains still unclear. This encephalomyelitis can be considered a transient autoimmune disease, that predominantly involves children under 10 years following T cell-mediated cross-activation and response against myelin proteins, such as myelin basic protein, proteolipid protein, and myelin oligodendrocyte protein (MOG), through a mechanism of molecular mimicry [1]. Another pathogenic possibility is a non-specific self-sensitization of reactive T cells against myelin proteins secondary to infections localized in the CNS [44,45]. The autoimmune hypothesis is supported by the presence of anti-MOG antibodies in the cerebrospinal fluid (CSF) and their progressive decline along with disease resolution [46]. However, there is no clear relationship between anti-MOG antibody levels at onset and disease severity, and furthermore they are not predictive of ADEM persistence.

Together with demyelination, other hallmarks of ADEM include axonal injury, perivenous inflammation, and edema [46]. 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, reflecting the clinical severity of ADEM [47]. The detection of inflammatory cells in the CNS also suggests an alteration of blood–brain barrier permeability [45,46].

Interestingly, T cell activation and cytokine oversecretion during the different ADEM phases have been described [48]. A serum elevation of different adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and E-selectin, typically expressed on the membranes of endothelial cells and leukocytes, can be found during the hyperacute phase of ADEM [48]. An increased serum concentration of two enzymes produced by T cells, endothelial cells, and macrophages: the matrix metalloproteinase-9 (MMP-9) and the tissue inhibitor of metalloproteinases, known as tissue metallopeptidase inhibitor-1, which modulates MMP-9 activity, can also be observed in the active phase of the disease [48]. In addition, ADEM acute phase is dominated by the predominance of T helper-1 lymphocytes and their cytokines, such as tumor necrosis factor-α, interferon-γ (IFN-γ), interleukin (IL)-1, IL-6, and IL-8. The latter upregulates also ICAM-1 and E-selectin biosynthesis. Conversely, during the phase of clinical remission, there is a shift to T helper-2 cells with elevation of IL-4, IL-10, transforming growth factor-β, downregulation of ICAM and E-selectin, and enhanced expression of vascular cell adhesion molecule-1 [48]. Lastly, there is an increment of serum IL-12 levels, which stimulates IFN-γ-producing CD4+ memory T cells, still in the last phase of ADEM [48].

## 3. A clinical scenery with manifold faces

Many clinical features can herald the onset of ADEM. They can be both neurologic and systemic, with fever, headache, weakness, and vomiting, mostly related to the location of the lesions in CNS and generally appearing 4 to 13 days after the triggering infectious episode or after vaccination [8,10,49].

Among neurological signs, encephalopathy, defined as a change in behavior and/or in consciousness (from lethargy to coma), is ADEM prominent clinical feature, though its absence should not preclude a clinical diagnosis of ADEM [50]. Other signs described in various combinations could be multifocal or focal deficits, such as hemiparesis, ataxia, dystonia, choreiform movements, aphasia, diplopia, and dyslexia [51]. Multiple cranial nerve involvement has been reported, especially optic nerves associated with optic disk edema [52]. Finally, signs of spinal cord involvement might be present, such as flaccid paralysis, constipation, or urinary retention [10].

ADEM clinical course is often monophasic, but also recurrent or multiphasic forms have been reported. Monophasic ADEM, that is the most frequent form occurring in 70–80% of cases, is defined as a first demyelinating or inflammatory clinical event in a previously healthy child, with acute onset affecting multiple areas of the CNS and resolving in a 3-month period [4,13]. Recurrent ADEM describes the appearance of a new episode of ADEM occurring 3 or more months after the first ADEM event or 1 month after completing corticosteroid therapy, within 2 years after the first episode: this form is characterized by the same symptoms of the first episode and by the absence of new lesions on brain magnetic resonance imaging (MRI) [4,13]. Multiphasic ADEM refers to a new ADEM-related clinical event that involves new CNS areas, and occurs 3 months after the first event or 1 month after completing corticosteroid therapy: clinical signs and symptoms may be different from those of the first event, and lesions associated with the onset of the disease may be partially or also completely resolved [4,13].

## 4. A diagnostic algorithm for children with acute disseminated encephalomyelitis

Diagnosis of ADEM is puzzling due to the lack of specific markers of the disease. The peculiar clinical scenery combining systemic and neurologic signs may raise the suspicion of ADEM, and then a lumbar puncture is usually performed to exclude an active meningoencephalitis. CSF can be normal or show lymphocytic pleiocytosis and/or increased level of proteins [53,54]. The most important CSF finding is the absence of olygoclonal bands, which are typical of MS. Cell culture and molecular