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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

biology techniques for bacteria and viruses in CSF are commonly used, but their diagnostic value is uncertain because they are often negative and not contributive to the diagnosis [55,56].

MRI is the most useful technique to ascertain diagnosis of ADEM: lesions are more often identified in T2-weighted and fluid-attenuated inversion recovery images as multifocal, irregular, poorly marginated areas with diameters between 5 mm and 5 cm [8,10]. They usually involve the subcortical and central white matter of the entire CNS, particularly frontal and temporal lobes, including also spinal cord and brainstem. Even gray matter of thalamus and basal ganglia can be involved, but lesions are mainly in the cortical gray–white junction [8,10].

Five patterns have been proposed to describe CNS lesions: ADEM with small lesions (<5 mm), ADEM with large confluent white matter asymmetric lesions, ADEM with symmetric bithalamic involvement, ADEM with a leukodystrophic pattern with diffuse bilateral and usually non-enhanced white matter-sited lesions, and ADEM with acute hemorrhagic encephalomyelitis [55]. However, these patterns seem unrelated to the overall clinical course [55].

Acute lesions can be enhanced after administration of gadolinium, and this could be helpful to identify regional distribution of CNS involvement [54]. Other advanced neuroimaging techniques such as diffusion-weighted imaging and magnetic resonance spectroscopy appear useful to exclude other diseases, like strokes and neoplasms, to discriminate between acute and chronic lesions, and to add information about extension of the affected areas [56].

Many different immune-mediated encephalitides, basically characterized by inflammation of brain parenchyma, have been described and should be differentiated from ADEM [57–86]. Table 1 summarizes the main epidemiologic and clinical features, diagnostic findings and response to treatment of the most relevant types among immune-mediated encephalitides of childhood, different from ADEM, as Hashimoto encephalitis (with high serum levels of anti-thyroid peroxidase antibodies), anti-NMDA receptor encephalitis (with antibodies directed against the NR1 subunit of the N-methyl-D-aspartate receptor), limbic encephalitis (exceptionally rare in pediatrics), and Rasmussen encephalitis (with cortical, subcortical, and caudate head atrophy). Other primary neurologic disorders defined by epilepsy or movement disorders are rare and have an uncertain autoimmunity-based pathogenesis. Since encephalitides are considered a neurologic emergency, because of substantially high rates of morbidity and mortality, a correct diagnosis and a well-timed treatment are essential conditions to reverse CNS clinical signs and reduce the risk of long-term sequelae.

5. Treatment strategies: controversies and ascertained truths

There is no standardized therapy for ADEM [1]. Currently, the most widely used treatment is immunosuppression because of the presumed autoimmune etiopathogenesis of this encephalomyelitis. Pohl & Tenembaum have suggested the administration of intravenous high-dose methylprednisolone (20–30 mg/kg/day, maximally 1 g) for 3–5 days, followed by prednisolone (1–2 mg/kg/day given orally for 1–2 weeks), tapering off within 2–6 weeks as the optimal treatment [6]. However, the second line therapy is a total dose of 2 g/kg of intravenous immunoglobulin G (IVIG) given over 2–5 days in corticosteroid-resistant or refractory patients, with the aim of binding ADEM autoantibodies, neutralizing them, and finally inhibiting cytokine release [6,87]. In patients with failure of treatment after corticosteroids and/or IVIG or in children with a severe fulminant disease another working option is plasmapheresis, a procedure that separates patient's plasma from other components, such as antibodies and cytokines, in order to remove autoantibodies and downregulate the immune system activation: the standard procedure suggests 5–7 exchanges, but complications as anemia, hypotension, and hypocalcemia are rather frequent [6].

Cases of fulminant ADEM, such as acute hemorrhagic leukoencephalitis or forms complicated by severe brain edema, could be treated with mild hypothermia therapy, in which body's temperature is reduced to 34 °C and intracranial pressure and cerebral perfusion pressure levels maintained low using mannitol and dopamine [24,28]. In selected cases with persistently high intracranial pressure a decompressive craniectomy could be performed [88].

6. Conclusive remarks

There is new considerable interest in autoimmune forms of encephalitides, which are variably associated with specific antibodies directed against different neuronal antigens [57–86]. A T cell-driven pathophysiology has been reported in all these cases, and clinical presentation of these encephalitides are remarkably similar in childhood, usually consisting of a combination of neuropsychological impairment and seizures. Different observations have also led to a shift from a merely clinic approach to an antibody-focused viewpoint for ADEM, suggesting a more rational choice in the immunomodulatory treatment of these disorders [57–86].

ADEM usually occurs after recent infections or rarely after vaccinations [1–3]. Also for systemic lupus erythematosus, the prototype of autoimmune disorders, the underlying trigger has remained elusive, and multiple interacting environmental and genetic factors probably contribute to the onset and perpetuation of the disease: among environmental influences, infectious agents have been suggested to play a pivotal role in driving an autoimmune pathogenesis via structural or functional molecular mimicry, the expression of proteins that induce cross-reactive responses against self-antigens, and the aberrant activation or apoptosis of different immune system cells in the context of a peculiar genetic background [89]. Moreover, the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (also known as PANDAS), basically characterized by obsessive–compulsive symptoms and tics triggered by group-A beta-hemolytic *Streptococcus* infections, are another proof of the potential relationship existing between complex neurologic phenotypes and infections [90].

Though a specific etiologic agent is not constantly recognized in children with ADEM, it is of paramount importance to evaluate carefully patient's clinical history and to obtain adequate samples for the search of a potential etiology. ADEM suspicion is clinical on the basis of systemic and neurologic signs, while MRI represents the main investigation tool for diagnosis confirmation [8,10,55]. Other advanced imaging techniques may be helpful for differential diagnosis and for the exact evaluation of disease extension [54,56]. Although there is no standardized treatment approved for ADEM, actual therapeutic strategies include immunomodulatory therapies (particularly corticosteroids and IVIG), although no clinical trials have been performed to define the most efficacious agent; also plasmapheresis has been successfully used [1,6,87]. Although the majority of children with ADEM show a favorable outcome, some might develop neurological sequelae or persistent deficits, while others might show relapses and some a dramatic evolution to MS. There is no marker that permits to identify children with a negative outcome and in view of the treatment differences between ADEM and viral encephalitides, being familiar with ADEM is essential for pediatricians managing acute neurological disorders. Future studies are needed to define patients' characteristics or biohumoral parameters that permit to identify the subset of patients with a worse prognosis.

Take-home messages

- ADEM is a multifocal inflammatory demyelinating disease of the central nervous system that involves multiple areas of the white matter, which mostly affects children under 10 years after recent viral or bacterial infections or more rarely after vaccinations.
- T cell-mediated cross-activation and response against myelin proteins, such as myelin basic protein, proteolipid protein, and myelin oligodendrocyte protein, are considered the predominating

Table 1
Main characteristics of immune-mediated encephalitides that should be differentiated from acute disseminated encephalomyelitis (ADEM) in the pediatric age.

Disease	Epidemiology	Clinical features	Antigen or antibody detected	Brain MRI and EEG abnormalities	Response to treatment and long-term outcome	Associations
Hashimoto's encephalopathy	Prevalently in females, rarely observed in children and adolescents [57]	Non-specific in pediatric age though seizures are the most frequent signs at onset; other neurological signs are alteration of consciousness, behavioral changes, motor deficits, cerebellar signs and dystonia [58]	High serum levels of anti-thyroid peroxidase antibodies (higher than in children affected by thyroiditis): a level >60 UI/mL in the presence of an acute neurological sign is diagnostic [58]	Brain lesions observed in 50% of subjects, heterogeneous with diffuse white matter abnormalities and meningeal enhancement; EEG shows generalized slowing without a characteristic pattern [59]	Responsive to high dose intravenous corticosteroids; unfortunately, only 55% of patients have a complete recovery [60]; frequent relapses cause cognitive impairment [61]; plasma exchange and IVIG have been effective in some cases [62]	Familial history of autoimmune diseases; patients typically have hypothyroidism, but more than 40% have a normal thyroid function; some patients may develop hyperthyroidism [63]
Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis	The exact prevalence and incidence of the disease is unknown; patients are younger than 18 years in 40% of the cases; this is the leading cause of autoimmune encephalitis in children; female sex is prevalently involved [64]	The disease progresses from a specific viral-like prodromal phase (reported in up to 86% of patients) followed within a few days or weeks by seizures, abnormal movements, focal neurological deficits, and behavior or personality changes; visual or auditory hallucinations are common; autonomic dysfunction occurs less frequently in children [65]	The target antigen of patients' antibodies is the NR1 subunit of the NMDAR; a comparison of anti-NMDAR antibody levels in serum and CSF indicates the presence of intrathecal synthesis and correlates with outcome [66]; the application of these antibodies into cultures of hippocampal neurons results in a significant decrease of postsynaptic NMDAR clusters, that is reversed after antibody removal [67]	Brain MRI is often normal or shows cortical and subcortical T2-fluid-attenuated inversion recovery signal abnormalities, sometimes with transient cortical–meningeal enhancement; in children the frequency of MRI abnormalities is less than in adults; EEG shows infrequent epileptic activity, but frequent slow disorganized activity [68]	Treatment is based on first-line immunotherapy (i.e., corticosteroids, IVIG and/or plasma exchange); second--line therapies (i.e., rituximab alone or combined with cyclophosphamide) are adopted in cases of unsatisfactory response to first-line drugs (from 30% to 40% of patients) [69]; children with neoplasms have more frequent full recovery and less relapses than those without; minimal residual deficits might persist in 25% of patients; moderate or severe disability occurs in 10% of children; the mortality rate is 8–10% [65]	Ovarian or testicular teratoma (70%); the disease also occurs in patients without neoplasms [64]
Limbic encephalitis	This form is often associated with neoplasms; in children this disease is exceptional and rarely diagnosed in subjects less than 18 years [70]	The main initial signs in young patients are impaired consciousness and rapidly developing seizures; this onset is different from that in adulthood, which usually demonstrates a subacute loss of short-term memory or psychiatric signs; antecedent febrile illnesses are common in children, suggesting a considerable influence of infections in its pathogenesis [70]	A sub-classification is possible by the presence of specific neuronal antibodies, including onconeural antibodies that target intracellular antigens (anti-Hu, anti-Yo, anti-Ri, anti-Ma1/2) and autoantibodies that are directed against cell surface antigens (anti-LGI1, anti-AMPA, anti-GABA) [71]; paraneoplastic encephalitides are mainly T cell-mediated and antibodies are only markers of immune reactivity expressed by the tumor; in the non-paraneoplastic conditions, the antibodies to neuronal membrane receptors and ion channels are frequently involved [72]	Brain MRI indicates signal abnormalities in hippocampus, amygdala and claustrum, mesial temporal hyperintensity on T2-weighted imaging; childhood limbic encephalitis probably involves not only the limbic system, but also the basal ganglia, brainstem and neocortex; EEG shows different abnormalities: the most frequent one is a diffuse and general slowing [73]	Differentiation between autoimmune and paraneoplastic limbic encephalitis is important because the former often responds well to immunotherapy; high-dose corticosteroids or IVIG are considered the first-line agents; patients with antibodies to membranous antigens also benefit from plasma exchange; improvement is observed in 70% of cases; most patients have normal intellectual outcome after recovery; neurologic sequelae include residual epilepsy, psychiatric disorders and memory impairment [74]	Malignancy is often recognized in combination with this encephalitis [75,76]
Rasmussen encephalitis	Affects mostly children or young adults; a German	There are three clinical stages: prodromal phase	Anti-GluR3 autoantibodies can be found in some	Most patients show unilateral enlargement of the	Immunosuppressive or immunomodulatory	Specific associations are not reported in the medical literature

Table 1 (*continued*)

Disease	Epidemiology	Clinical features	Antigen or antibody detected	Brain MRI and EEG abnormalities	Response to treatment and long-term outcome	Associations
	study estimated its incidence at 2.4 cases per 10 million people aged 18 years and younger per year [77]; the median age of onset is 6 years, with a range from infancy to adulthood, without sexual or ethnic differences	(nonspecific seizures and hemiplegia), acute phase (frequent seizures, often epilepsia partialis continua, hemiparesis, hemianopsia, cognitive deterioration and aphasia if the dominant hemisphere is affected), residual phase (permanent and stable neurological deficits and continuing seizures) [78]	patients; antibodies against other antigens, such as the alpha-7 nicotinic acetylcholine receptor or Munc-18-1, were also identified in the sera of patients; moreover, cytotoxic T lymphocytes seem to play an important function in the pathogenesis of this encephalitis [79]	ventricular system at brain MRI, T2/FLAIR hyperintense signal in cortical and/or subcortical regions, and ipsilateral atrophy of the head of the caudate nucleus [80]; EEG appears initially normal, then some children develop epileptiform abnormalities	treatments have been employed (i.e., corticosteroids, IVIG, plasmapheresis or protein A immunoabsorption and T-cell inactivating drugs, like tacrolimus and azathioprine); a recent study suggests that treatment with tacrolimus in the early phases gets an improvement of motor and cognitive outcome [81]; surgery still remains the only strategy for seizures by the complete disconnection of the affected hemisphere [78]	
Encephalitis associated with epilepsy	Group of uncommon disorders whose prevalence is still unknown; some cases are reported in subjects between the ages of 1 and 15 years, with a peak incidence at school-age; familial cases have not been reported; the male/female ratio is 3:2 [82]	Various clinical entities, characterized by severe epilepsy with acute or subacute onset, sometimes associated with status epilepticus, followed by drug-resistant partial epilepsy; some authors suggest various acronyms for the condition described: acute encephalitis with refractory repetitive partial seizures (AERRPS), devastating epileptic encephalopathy in school-aged children (DESC), or new-onset refractory status epilepticus (NORSE) [813	The significance of antibody detection in CSF or serum of these patients appears unclear; CNS inflammation and blood–brain barrier disruption could be one of the mechanisms responsible for seizure recurrence [84]	In some patients brain MRI reveals bilateral peri-insular hyperintensity; EEG shows background activity associated with focal or diffuse slow waves and epileptiform abnormalities; seizure onset occurs in most cases in the fronto-temporal and temporal areas [85]	The beneficial effects of corticosteroids and IVIG suggest an immune-mediated pathogenesis; residual symptoms include cognitive impairment, temporal lobe epilepsy and mesial temporal sclerosis [85]	Several associations between epilepsy and immunological diseases have been described, such as systemic lupus erythematosus (in 10–20% of cases) with the presence of anti-phospholipid and anti-cardiolipin antibodies [86]

CNS, central nervous system; CSF cerebral spinal fluid; EEG, electroencephalography; IVIG, intravenous immunoglobulins; MRI, magnetic resonance imaging.

pathogenic mechanisms of disease expression, following molecular mimicry with infectious agents.

- Many clinical features, both neurologic and systemic, can herald the onset of ADEM: encephalopathy, changes in behavior and/or in consciousness of variable severity from lethargy to coma, multifocal or focal central nervous system deficits, such as hemiparesis, ataxia, dystonia, aphasia, diplopia, and dyslexia combined with fever, headache, weakness, and vomiting, in relationship with the different location of ADEM lesions.
- ADEM general course is monophasic in 70–80% of cases, and defined as a first demyelinating or inflammatory clinical event in a previously healthy child with acute onset involving multiple areas of the central nervous system and resolving in a 3-month period.
- Many different immune-mediated encephalitides characterized by diffuse inflammation of brain parenchyma have been also described and should be differentiated from ADEM.
- The most currently used treatment in children with ADEM is immunosuppression because of its presumed autoimmune pathogenesis: intravenous high-dose methylprednisolone, intravenous immunoglobulin as a second line treatment in corticosteroid-resistant or refractory patients, and plasmapheresis have been used with successful results.
- Future studies are needed to identify patients' biologic clues that characterize the subset of ADEM patients with worst outcome as well to optimize treatment strategies using an approach based on the effective risk of neurologic sequelae.

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Incidence and prevalence of systemic lupus erythematosus stratified for year, age, gender and ethnicity: results from a nationwide database

Using the UK Clinical Practice Research Datalink (CPRD), i.e. a longitudinal database of UK general practice records incepted in 1987 and deemed to be representative of the UK population, Rees et al. (**Ann Rheum Dis 2014, E-pub ahead of print 29 sept 2014 doi:10.1136/annrheumdis-2014-206334**) carried out a retrospective cohort study to estimate prevalence and incidence of systemic lupus erythematosus (SLE) in UK over the period 1999-2012. Incidence and prevalence were stratified for year, age, gender and ethnicity.
The Authors found an incidence varying from 5.93/100,000 person-year in 2000 to 4.02/100,000 person/year in 2010 with an annual decline of 1.8% and a progressive increase of prevalence form 64.63/100,000 people in 1999 to 97.04/100,000 people in 2012. Prevalence and incidence were about six fold higher in women compared with men with a peak of incidence in the group of 50-59 years of age. People of Black Caribbean ethnicity had the highest incidence (31.46/100,000 person-year) and prevalence (517.51/100,000 people) rate.

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