Disseminated encephalomyelitis in children

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Abstract

The advent of MRI has contributed to increase the interest and awareness in childhood white matter disorders. A major priority is to distinguish transient and self-limited demyelinating syndromes like disseminated encephalomyelitis (DEM), from life-long diseases like multiple sclerosis (MS). However, the term DEM has been inconsistently applied across studies due to the lack of clear clinical and neuroimaging diagnostic criteria. The present review summarizes the available literature on DEM in children, outlines the main clinical and neuroimaging features at presentation, pathogenesis and outcome, and its differentiation from other conditions with acute impact in the CNS. The recently proposed clinical definitions for monophasic disseminated encephalomyelitis and its relapsing variants are discussed, and controversies surrounding the diagnosis of MS in children are addressed.
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1. Introduction

Disseminated encephalomyelitis (DEM) is an immune-mediated inflammatory disorder of the central nervous system (CNS), characterized by a widespread demyelination that predominantly involves the white matter of the brain and spinal cord. The condition is usually preceded by a viral infection o vaccination, and the presenting features include an acute encephalopathy with multifocal neurological signs and deficits [1–4]. In the absence of specific biological markers the diagnosis of DEM is still based on the clinical and radiological features.

The lack of uniform definitions and clear clinical and neuroimaging diagnostic criteria has led that different conditions being classified as DEM. Although disseminated encephalomyelitis usually has a monophasic course (ADEM), recurrent (RDEM) and multiphasic forms (MDEM) have been reported, raising diagnostic difficulties in distinguishing these cases from multiple sclerosis (MS). The diagnostic differentiation between DEM and MS is important for prognostic reasons and treatment decision. The purpose of this review is to summarize literature data on the clinical and magnetic resonance imaging (MRI) features, pathogenesis and outcome of paediatric DEM. Particular attention on recurrent and multiphasic variants of DEM and its differences from MS are also provided.

2. Epidemiology

DEM is relatively frequent in children, probably due to the higher frequency of immunizations and primary exposure to antigens. The diagnosis of DEM is often made in the setting of a defined viral illness or vaccination. Although there appears to be no gender predominance in DEM [5,6], a male predominance has been described in two paediatric cohorts, with reported female:male ratios of 0.6 [7] and 0.8 [8] as opposed to a 2:1 female preponderance frequently described for MS. The mean age at DEM presentation reported in recently published paediatric cohorts ranges from 5 to 8 years [5,8–10].

A seasonal distribution in the winter and spring months has been reported in two studies [6,7]. A recent study conducted in San Diego County, USA estimated the mean incidence of DEM as 0.4/100,000/year among persons less than 20 years of age living in that region [6]. Five percent of these patients

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had received a vaccination within 1 month prior to the DEM event, and 93% reported signs of infection in the preceding 21 days. In contrast with these findings, the number of reported paediatric DEM patients per year in a study conducted in Germany was very low, with only nine children with DEM per year and 44 new paediatric MS cases per year [11]. Despite the lack of clear worldwide studies on epidemiology and distribution of DEM, the reported geographical differences in incidence are important to be considered and could be influenced by environmental triggering factors [11].

The disorder may be classified as either post-vaccinal or post-infectious DEM; however, absence of clear precedent event has been reported in 26% of patients [8]. Rare cases have been described following organ transplantation [12–16]. Post-infectious forms of DEM typically begin within 2–21 days after an infectious event. Different viral agents, including influenza virus [17], enterovirus, measles [18,19], mumps [20], rubella [19], varicella-zoster, Epstein Barr virus [21], cytomegalovirus, herpes simplex virus [22,23], Hepatitis A virus [24], and coxsackie virus [25] have been associated with DEM [26,27]. Bacterial triggers include *Mycoplasma pneumoniae* [28], *Borrelia burgdorferi* [29], Leptospira, and beta-haemolytic Streptococcus [30,31]. The only epidemiologically and pathologically proven association between vaccination and DEM is with the Semple form of the antirabies vaccine [3,32–39]. Other immunizations that have been temporally related to DEM include Hepatitis B, pertussis, diphtheria, measles, mumps, rubella, pneumococcus, varicella, influenza, Japanese encephalitis, and polio [6,8,19,35–39]. Nevertheless, DEM associated with vaccines may be related to contamination with host animal myelin antigens from CNS culture tissue, as it was identified in certain viral strains of rabies (Semple) and Japanese B encephalitis vaccines [32,40]. The development of modern formulations based on recombinant proteins has dramatically lowered the incidence of vaccine-related DEM [41].

3. Clinical presentation

DEM is classically described as a monophasic disorder which typically begins within 2 days to 4 weeks after a clinically evident infection or vaccination. The typical symptoms and signs of DEM include a rapid onset encephalopathy associated with a combination of multifocal neurological deficits, leading to hospitalization within a week. A prodromal phase with fever, malaise, headache, nausea, and vomiting may be observed shortly before the development of meningeal signs and drowsiness. The clinical course is rapidly progressive and usually develops over hours to maximum deficits within days (mean, 4.5 days) [8].

The initial neurological features are heterogeneous and related to the distribution of demyelinating lesions within the CNS. The most prevalent neurological symptoms and signs described in recently reported paediatric series are unilateral or bilateral pyramidal signs (60–95%), acute hemiplegia (76%), ataxia (18–65%), cranial nerve involvement (22–45%), visual loss due to optic neuritis (7–23%), seizures (13–35%), spinal cord involvement (24%), impairment of speech [slow, slurred or aphasia] (5–21%), and hemiparesthesias (2–3%) in different combination, with the invariable involvement of mental status, ranging from lethargy to coma [5–10,42–45]. Seizures are mainly seen in children younger than 5 years of age. One study has documented prolonged focal motor seizures going on to status epilepticus in 70% of their younger patients [8].

A unique childhood DEM phenotype was recently reported in association with group A-beta haemolytic streptococcal infection. Ten children between the ages of 3–14 years developed a clinically typical DEM presentation but with a prominent dystonic extrapyramidal syndrome (70%) or behavioral disorder such as emotional lability or inappropriate speech (50%). The syndrome followed an acute pharyngitis but was distinct from rheumatic fever or Sydenham's chorea and was associated with elevated antibasal ganglia antibodies and abnormal basal ganglia imaging [31].

There is a wide variation in the severity of the illness. DEM can present as a subtle disease, with non-specific irritability, headache or somnolence lasting more than 1 day, or may show a rapid progression of symptoms and signs to coma and decerebrate rigidity [26]. Respiratory failure secondary to brainstem involvement or severe impaired consciousness occurs in 11–16% of cases [8,26]. Clinically relevant features of paediatric DEM are summarized in Table 1.

Table 1
Clinically relevant features of monophasic DEM (ADEM)

Age at onset	Childhood (median 5–8 years of age)[a]
Clinical presentation	Frequent preceding infection or vaccination Headache, fever Acute–subacute encephalopathy, in combination with multifocal deficits Pyramidal syndrome Cerebellar ataxia Brainstem involvement
Cerebrospinal fluid	Variable pleocytosis Oligoclonal banding 0–29%[b]
MRI features	Large, multifocal, poor marginated lesions Bilateral subcortical white matter Bilateral deep grey matter (thalamus, basal ganglia) Absence of previous demyelinating lesions
Clinical follow-up	Improvement; there may be residual deficits
MRI follow-up	Complete or partial resolution of lesions Absence of new clinically silent lesions

[a] Median ages from [5,8–11].
[b] Median frequencies of positive oligoclonal bands from [5,8,9,11].

4. Neuroimaging features

The diagnostic hallmark of DEM is the demonstration of inflammatory-demyelinating white matter lesions. MRI is the most sensitive paraclinical test to show these abnormalities, which are most frequently identified on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences as patchy, heterogeneous and poorly marginated areas of increased signal intensity. Lesions are typically large, multiple, and asymmetric, involving the white matter of cerebral hemispheres, cerebellum, brainstem and spinal cord [26,46]. The deep gray matter of the thalami and basal ganglia are frequently involved in a typically symmetrical pattern [8,47]. The white matter lesions in children tend to involve the subcortical and central white matter; nevertheless involvement of the periventricular white matter has been described in 30–60% of cases [7,9,26]. Lesions confined to the corpus callosum are less common. However, large demyelinating lesions of the adjacent white matter may extend into the corpus callosum and cross into the contralateral hemisphere. In a study of 31 children diagnosed with DEM, 90% had lesions in the supratentorial white matter, 29% in the corpus callosum, and 61% had gray matter involvement [9].

Five patterns of cerebral involvement have been proposed to describe the MRI findings in DEM [8,48]: (a) *DEM with small lesions* (less than 5 mm); (b) *DEM with large, confluent or tumefactive lesions*, with frequent extensive perilesional edema and mass effect; (c) *DEM with additional symmetric bithalamic involvement*; (d) *acute hemorrhagic encephalomyelitis* (*AHEM*), when some evidence of haemorrhage can be identified into the large demyelinating lesions and (e) *DEM with a pseudo-leukodystrophic pattern*, with a diffuse, bilateral, symmetric and usually non-enhanced white matter involvement [49]. The MRI pattern does not appear to correlate with any particular outcome or disability, as observed in a large paediatric cohort [8] since most lesions tend to resolve on follow-up imaging studies [50]. However, this classification may be useful when considering the differential diagnosis of DEM (see Section 8).

Spinal cord involvement in DEM has been described in 11–28% [5,8–10,42]. The typical spinal cord lesion is large, swollen, showing variable enhancement and predominantly affects the thoracic region.

The reported frequency of gadolinium enhancing lesions on T1-weighted sequences is quite variable in DEM (8–100%), depending on the stage of inflammation [8,9,47,51–54]. The pattern of enhancement is also variable; complete or incomplete ring-shaped, nodular, gyral or spotty patterns have been described [54–56]. Meningeal enhancement of the brain or spinal cord is unusual.

Complete resolution of white matter abnormalities on sequential follow-up MRI scanning has been described in 37–75% of DEM patients, and partial resolution in 25–53% of patients [5,8,51,53,57]. The development of new, clinically silent lesions on serial MRI studies is not compatible with the diagnosis of DEM, and is one of the most powerful predictors of future MS diagnosis.

5. Relapsing forms of DEM

A monophasic clinical course is usually described in and identified with ADEM. Nevertheless, cases of DEM showing recurrences had been known since 1932, when van Bogaert published a case classified as "ADEM with relapses" [58]. Several studies have described relapsing episodes in paediatric cohorts with DEM, occurring at different rates: 1/18 (5.5%) [7]; 1/14 (7%) [59]; 8/84 (10%) [8]; 4/31 (13%) [9]; 7/46 (15%) [10]; 24/132 (18%) [60]; 7/35 (20%) [5]; 9/42 (21%) [6]; 5/21 (24%) [61]. The inter-study variability of the relapsing rates may be influenced by the different clinical definitions and neuroimaging diagnostic criteria for DEM and relapses used in these studies. In addition, the mean follow-up reported in some of these series varied from 18 months [9] to 6.6 years [8].

A variety of terms has been used in the scientific literature to describe children who experience a subsequent event after an initial ADEM illness. Recurrent, relapsing, pseudo relapsing, bi- or multiphasic DEM have all been applied as to whether relapses required a monofocal or multifocal presentation, a specific interval from the first event (less than 4 to more than 8 weeks), same or different neurological deficits, and finally MRI lesions as either in the same or different brain regions [5,8,61–70], leading to remarkable confusion. However, the terms recurrent (RDEM) and multiphasic (MDEM) had already been well defined by Poser [71]. Recurrent DEM as an initial ADEM event followed by a new one, reproducing the original clinical syndrome, completely or in part [61,72,73]. Multiphasic DEM as an initial episode of ADEM followed by bouts of clinical syndromes different from the original one. The clinical concept of relapses of an acute condition like ADEM received support from reports of chronic relapsing experimental encephalomyelitis [46,74].

To date, there are no clear clinical or radiological parameters that predict which patients with DEM will relapse. One recent study [60] focused on the prognostic factors for relapse in children with DEM. An increased risk of relapse was associated with optic neuritis at first attack (hazard ratio, 5.23; 95% CI, 2–13.65), familial history of CNS inflammatory demyelination (7.79; 1.54–39.5), Barkhof MS criteria on first MRI study (2.52; 1.04–6.12) and with no neurological sequelae after first attack (3.79; 1.12–12.85). But although these relapsing cases might have a final diagnosis of MS, 15 of the 24 ADEM patients with a second event were polysymptomatic, and five of them had changes in mental state, suggesting that these five cases were more probably instances of multiphasic DEM. Additionally, several follow-up studies with a considerable time of follow-up reported only one relapse in most children with MDEM [6–10], distinguishing the demyelinating pro-

cess as self-limited and not associated with a lifelong disorder.

The final outcome of children with definite MDEM has been described in detail in two paediatric cohorts with considerable follow-up. In one study, no impairment was observed in 86% of multiphasic patients [5]. Similarly, eight children with MDEM, who remained relapse-free after a follow-up of 3–16 years (mean 8.2 years), had a median DSS score of 1 (range 0–2.5) at last visit [8]. Serial brain-spinal MRI performed in these children revealed complete or almost complete resolution of demyelinating lesions, and absence of new clinically silent lesions (Fig. 1G and H). Interestingly, relapses in this paediatric subgroup of MDEM were more commonly spontaneous (87%), whereas the first demyelinating episode had been associated with a previous infection in 60% of children [8].

6. Proposed definitions

The International Paediatric MS Study Group has recently proposed operational definitions for acquired CNS demyelinating disorders of childhood, including the monophasic and relapsing forms of DEM [48,75]:

(1) *Acute disseminated encephalomyelitis* (*ADEM*): A first clinical event with a polysymptomatic encephalopathy, of acute or subacute onset, showing focal or multifocal hyperintense lesions predominantly affecting the CNS white matter; no evidence of previous destructive white matter changes should be present and no history of a previous clinical episode with features of a demyelinating event. If a relapse takes place within 4 weeks of tapering steroid treatment or within the first 3 months from the initial event, this early relapse is considered temporally related to the same acute monophasic condition and would replace the terms "steroid dependent ADEM" or "pseudo relapsing ADEM".
(2) *Recurrent disseminated encephalomyelitis* (*RDEM*): New demyelinating event fulfilling diagnostic criteria for ADEM, occurring at least 3 months after the initial event and at least 4 weeks after completing steroid therapy, but showing the same clinical presentation and affecting the same areas on MRI as the initial episode.
(3) *Multiphasic disseminated encephalomyelitis* (*MDEM*): Refers to one or more DEM relapses, including encephalopathy and multifocal deficits, but involving new areas of the CNS on MRI and neurologic exam (Fig. 1A–F). Relapses take place at least 3 months after initial DEM attack and at least 4 weeks after completing steroid therapy.

7. DEM and MS

It is acknowledged that a proportion of children with DEM may develop MS [5,6,42]. However, it remains unclear what proportion of children who present an acute DEM event will be later diagnosed with MS, since numbers from published studies vary from 9.5 [6] to 29% [42]. And it is also unclear if DEM and MS are two distinct clinical disorders or part of a disease spectrum [76].

In the definition proposed by the International Pediatric MS Study Group [75], MS in children requires multiple episodes of CNS demyelination separated in time and space, as specified for adults [77,78] but including patients under 10 years of age. The MRI findings can be used to meet the dissemination in space requirement and to satisfy criteria for dissemination in time following the initial clinical event, if the McDonald MRI criteria are applied [78].

But it should be noted that in the special circumstance of a child whose initial clinical event was classified as DEM, a second demyelinating event not meeting DEM criteria is considered not enough for a definite diagnosis of MS and additional evidence of further dissemination in time is required, either on MRI with emergence of new lesions at least 3 months or a new clinical attack (Fig. 2). Although this statement remains controversial, it seems justifiable to avoid establishing prematurely the diagnosis of MS in children with DEM who relapse, and to extend the clinical and MRI follow-up instead of initiating early immunomodulatory treatment.

The KIDMUS study group examined children with a first demyelinating event, including CIS and DEM, and reported that overall, 57% developed MS as defined by two demyelinating events [42], and 29% of children with an initial DEM event developed MS. When the diagnosis of DEM was further redefined to include "change in mental status" as a diagnostic criterion, 18% of children were found to develop MS after a mean follow-up of 5.4 years [60]. A recent study examined the clinical presentation and disease course of paediatric MS with onset before the age of 10 years, and a polysymptomatic acute encephalopathy (ADEM-like phenotype) was the most frequent clinical presentation observed in 40% of children [79].

8. Differential diagnosis

The presence of an acute encephalopathy and disseminated demyelination of the CNS in a child represent a diagnostic challenge. Many inflammatory and non-inflammatory disorders may have a similar clinical and radiological presentation and should be considered in the diagnostic evaluation. The most frequently considered disorders in the differential diagnosis of paediatric DEM are summarized in Table 2.

The exclusion of acute CNS infections should be the first and most important diagnostic clue to be considered by lumbar puncture and further microbiological laboratory tests. A gadolinium-enhanced MRI of the brain and spinal cord should be performed to define the regional distribution and MRI lesion appearance. Brain malignancies, Shilder's dis-
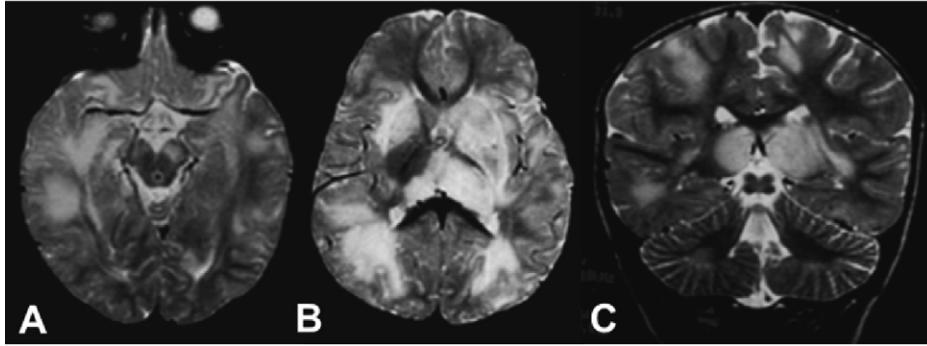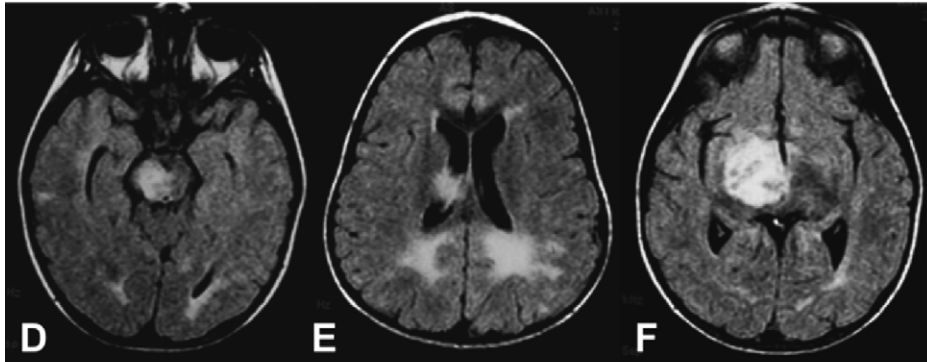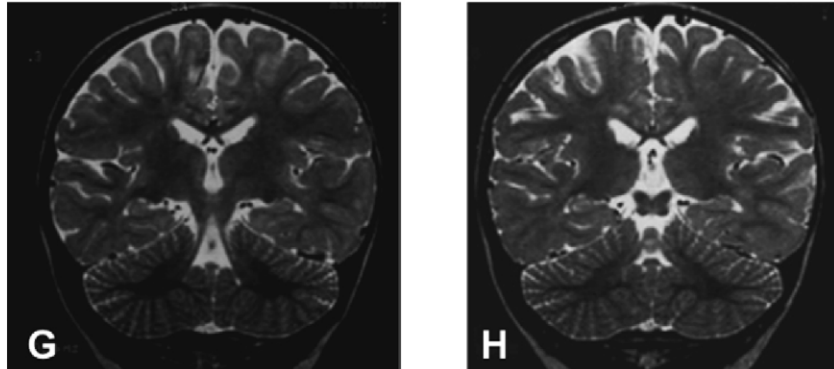
Upper row

Middle row

Lower row

Fig. 1. Illustration of brain lesions in a child with multiphasic disseminated encephalomyelitis (MDEM). A 21-month-old boy became acutely ill with lowered consciousness, ophthalmoplegia and right-sided hemiparesis. The upper row shows axial (A and B) and coronal (C) T2-weighted brain images at presentation, demonstrating an irregular pattern of focal areas of high signal intensity in the mesencephalon (especially on the left), bilateral thalamic and insular regions, and in the periventricular and subcortical white matter. The patient showed gradual clinical improvement with methylprednisolone pulse-therapy, and fully recovered after 3 weeks. Three months after the initial event and 1 month after completing corticosteroid treatment, this boy developed a left-sided hemiparesis, VI and VII cranial nerve involvement and progressive drowsiness, shortly after an upper respiratory viral infection. The middle row shows axial FLAIR series demonstrating signal abnormalities in the mesencephalon (particularly on the right) (D), in the posterior periventricular white matter (E) and a large-tumefactive right lesion with mass effect over the III ventricle (F). This young boy received a second course of methylprednisolone pulse-therapy followed by full clinical recovery. The lower row shows coronal T2-weighted images obtained 1 year after the first event with complete resolution of prior lesions (G and H). This patient has experienced no further relapses during the 9-year follow-up.

ease, Marburg's variant of MS, and brain abscess should be considered when large focal tumour-like lesions are detected on MRI [80–84]. A lesion pattern with symmetric bithalamic involvement may be seen in children with acute necrotizing encephalopathy, deep cerebral venous thrombosis, hypernatremia and extrapontine myelinolysis, as well as in children with ADEM after Japanese B encephalitis vaccination [85–91]. Lesions in the basal ganglia may be consistent with organic aciduria, infantile bilateral striatal necrosis, *M. pneumoniae* infection, voltage-gated potassium channel antibody associated encephalitis and poststreptococcal ADEM with auto-reactive antibasal ganglia antibodies [31,92–94]. The presence of complete ring-enhanced lesions in the cerebral white matter is unusual in DEM, and brain abscess, tuberculomas, neurocysticercosis, toxoplasmosis and histoplasmosis should be excluded [54,95].
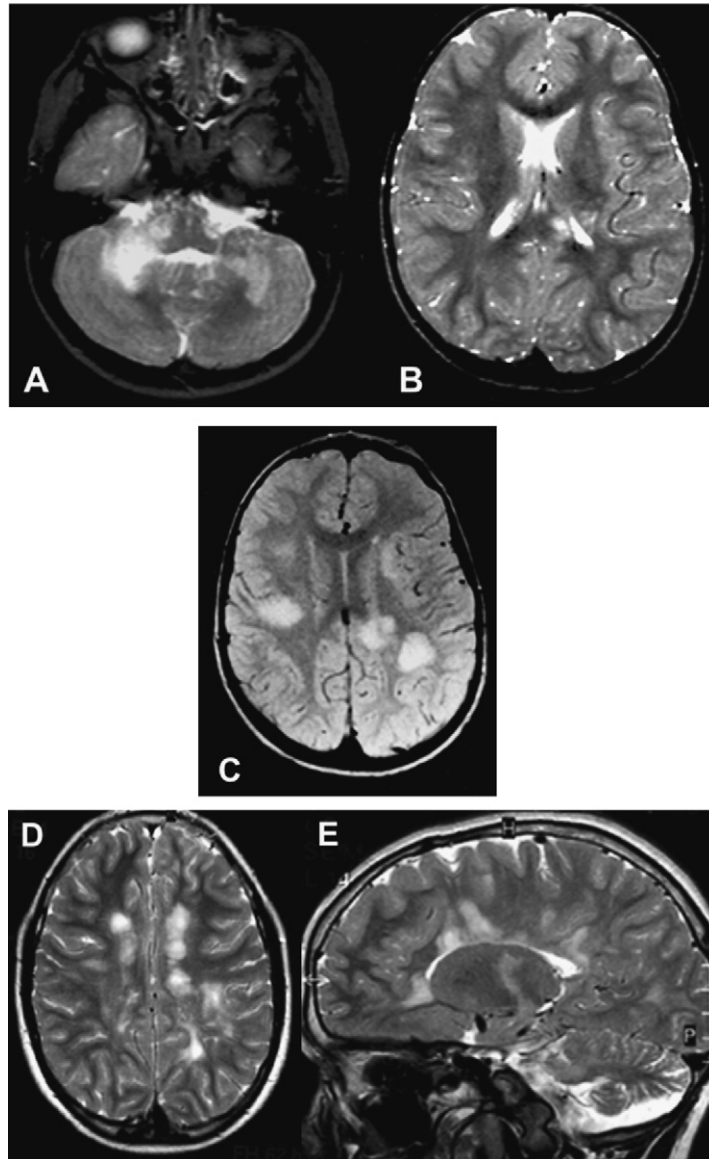
Fig. 2. MRI appearance of multiple sclerosis in a child with ADEM-like onset. A 2-year-old boy developed an acute event with ataxia, right hemiparesis and drowsiness; he was unable to walk in the following 3 days. Axial T2-weighted brain images at presentation (A and B) show bilateral involvement of cerebellar white matter, especially on the right side, with additional areas of high signal in the corpus callosum (splenium) and left internal capsule. The patient fully recovered after corticosteroid treatment. Five months later he had difficulties in swallowing with progressive ataxia. On examination he was alert, with cerebellar ataxia, left hemiparesis and bilateral pyramidal signs. Oligoclonal bands were positive in CSF. A new brain MRI showed bilateral ill-defined lesions in the periventricular and subcortical white matter (C). The boy received methylprednisolone pulse-therapy with good recovery. After a new clinical attack 3 months later the diagnosis of paediatric MS was made and treatment with IFN beta-1a was begun. The last two images (D and E) were obtained 6 years after the first event showing well-defined new lesions, perpendicular to the long axis of the corpus callosum, which positively correlate with the diagnosis of MS.

Recurrent episodes of CNS demyelination should raise the potential diagnosis of MS or systemic diseases with CNS involvement, such as systemic connective tissue diseases (systemic lupus erythematosus, neuro-Behçet disease, ANCA-associated vasculitis and antiphospholipid syndrome) [96]. The association of symptomatic or asymptomatic brain lesions and recurrent events of demyelination involving optic nerves and spinal cord has been described in children with neuromyelitis optica (NMO), as recently reported [97,98].

9. Treatment and prognosis

There is no standard therapy for DEM. Corticosteroid treatment is the most widely reported therapy for DEM, typically at high doses. Although there has been great variety in the specific formulations, routes of administration and dosing, most paediatric groups described a high-dose steroid regime using intravenous methylprednisolone (10–30 mg/(kg day) up to maximum dose of 1 g/day) or dexamethasone (1 mg/(kg day)) for 3–5 days [5,8,9,99–101]

Table 2
Diagnostic categories to consider and exclude in children with DEM

CNS infectious conditions
  Viral, bacterial or parasitic meningoencephalitis
  Subacute sclerosing panencephalitis
  HIV-associated encephalopathy:
    Subacute HIV encephalitis
    Opportunistic CNS infections
    Progressive multifocal leukoencephalopathy
  CMV subacute encephalitis

CNS inflammatory-demyelinating disorders
  Postinfectious demyelinating cerebellitis
  Postinfectious demyelinating brainstem encephalitis
  Neuromyelitis optica
  Multiple sclerosis
  Neurosarcoidosis
  Behçet's disease

CNS vascular disorders
  Prothrombotic conditions
  Antiphospholipid antibody syndrome
  Primary isolated CNS angiitis
  Systemic vasculitis with CNS involvement (systemic lupus
  erythematosus)
  Sickle cell anemia
  Susac syndrome
  CADASIL
  Deep sinovenous thrombosis
  Carotid dissection

Intracranial mass lesion
  Gliomatosis cerebri
  Primary CNS lymphoma
  Histiocytosis

Toxic, nutritional and metabolic disorders
  CO poisoning
  Vitamin B12 deficiency
  Folate deficiency
  Mercury poisoning
  Ibuprofen-induced aseptic meningitis
  Post-hypoxic-ischemic newborn leukoencephalopathy
  Central pontine and extrapontine myelinolisis
  Marchiafava-Bignami disease
  Radiation induced leukoencephalopathy
  Mitochondrial encephalopathy with lactic acidosis and stroke like
  episodes (MELAS)
  Organic acidurias
  Inherited leukodystrophies

Miscellaneous
  Reversible posterior leukoencephalopathy
  Recurrent migraine headache
  Hashimoto's encephalopathy

followed by oral prednisone taper for 4–6 weeks. In many studies, full recovery following treatment with methylprednisolone pulse-therapy was reported in 50–90% of children [5,8–10,43].

The use of intravenous immunoglobulin (IVIG) has been reported in several case studies as well, either alone [102,103] or in combination with corticosteroids [100,104]. The usual total dose of IVIG is 1–2 g/kg, administered over 2–5 days [105–107]. Additionally, the use of plasma exchange in

ADEM has been reported in only a small number of severe cases, usually refractory to corticosteroid or IVIG treatment [43,108–113].

With the current use of high-dose corticosteroids, the long-term functional and cognitive prognosis of DEM in children is favorable. The most frequently reported residual problems are focal motor deficits, from mild clumsiness to severe hemiparesis, visual problems to blindness, symptomatic epilepsy, and behavioral and cognitive disturbances [8,114,115].

Even children thought to have full recovery demonstrated subtle neurocognitive deficits in attention, executive function and behavior when reevaluated more than 3 years after DEM [114], although these deficits were not as severe as those reported for paediatric patients with MS [116]. In one study, behavioral and cognitive problems were reported as more prominent in children younger than 5 years at DEM diagnosis [115].

10. Immunopathogenesis

ADEM is characterized histologically by perivenular infiltrates of T cells and macrophages, associated with "sleeves" of demyelination that surround venules [117,118]. A variety of pathological features have been recently described in biopsy and autopsy samples of children with DEM and AHEM. The autopsy of a 5-year-old boy with severe and fatal ADEM grossly described diffuse brain edema, uncal and tonsillar herniation [6], in addition to perivascular lymphocytic infiltrates, fibrin deposition within vascular lumens and adjacent demyelination. Viral inclusion bodies were not seen in HE sections. In contrast, the brain biopsy performed in a 10-year-old girl with severe AHEM, demonstrated perivascular hemorrhagic necrosis with subacute inflammation consisting of macrophages, neurophils and lymphocytes in the subcortical white matter.

Although DEM is typically described as white matter demyelination with relative preservation of axons, axonal damage has been identified in the brain of some patients [119,120].

The precise pathogenesis of DEM is still unclear; however given its histological features, it has been likened to the animal model of experimental autoimmune encephalomyelitis (EAE) and Theiler murine encephalomyelitis. In EAE, animals are immunized with a combination of encephalitogenic myelin proteins or peptides, developing a monophasic syndrome of motor weakness and incontinence, associated with diffuse CNS inflammatory demyelination [121,122]. Viral or bacterial epitopes resembling myelin antigens have the capacity to activate myelin-reactive T cell clones through molecular mimicry [123], and can thereby elicit a CNS-specific autoimmune response. Thus, it has been suggested that preceding infections in DEM may elicit a cross-reactive anti-myelin reaction through a mechanism of molecular mimicry. Another animal model, putatively mimicking postinfectious DEM, is created by direct inocu-

lation of genetically susceptible mice with Theiler murine encephalomyelitis virus (TMEV) (picornavirus), inducing widespread CNS inflammatory demyelination through an immune-mediated reaction primarily involving TMEV-specific CD4 and CD8 T cells [124–127]. The TMEV model highlights the phenomenon of epitope spreading secondary to a destructive CNS viral infection resulting in a secondary autoimmune response and chronic inflammation [128–130]. Although this model superficially bears some resemblance to DEM, the epitope spreading is more likely to be an important phenomenon in chronic inflammatory disorders such as MS. Alternatively, the molecular mimicry hypothesis suggests that structural similarities between the pathogen (viral/vaccine polypeptides) and the host (central or peripheral nerve myelin) are sufficient to induce T cell activation but not sufficient to induce tolerance.

Sequences in myelin basic protein (MBP) have been shown to resemble several viral sequences, and in some cases, cross-reactive T cell responses have been demonstrated. Examples of cross-reactive T cells with MBP antigens include HHV-6 [131], coronavirus [132], influenza virus hemagglutinin [133], and EBV [134]. Proteolipid protein (PLP) shares common sequences with Haemophilus influenza [135] and myelin oligodendrocyte glycoprotein (MOG) mimics Semliki Forest Virus (SFV) peptides [136].

Elevated titers of anti-myelin antibodies in sera from DEM patients have recently been demonstrated as compared to patients with MS or viral encephalitis [137]. A recently published study reported the presence of circulating conformation-dependent autoantibodies to MOG in a subset of children and adults with DEM, but only rarely in adult-onset MS cases [138]. New available data suggest that enhanced T and B cell-myelin responses play a role in the pathogenesis of postinfectious and postvaccinal DEM, including MOG as the prominent target autoantigen. Furthermore, the response of some DEM patients to plasmapheresis or intravenous immunoglobulins reinforces the pathogenic role of these autoantibodies.

11. Conclusions

Due to the lack of an identified biomarker, the diagnostic of DEM is still based on clinical and neuroimaging presenting features. Hence, to conduct appropriate prospective multicenter studies, the use of standardized definitions and a uniform classification system for disseminated and restricted forms of acquired demyelinating disorders in children is mandatory. Prospective studies are much needed in order to identify biologic mechanisms underlying these disorders as well as relevant prognostic indicators of relapse, which may contribute to an early distinction between DEM/MDEM and definite MS in children.

Conflict of interest

None.

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