Acute disseminated encephalomyelitis

Updates on an inflammatory CNS syndrome

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ABSTRACT

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating CNS disorder with predilection to early childhood. ADEM is generally considered a monophasic disease. However, recurrent ADEM has been described and defined as multiphasic disseminated encephalomyelitis. ADEM often occurs postinfectiously, although a causal relationship has never been established. ADEM and multiple sclerosis are currently viewed as distinct entities, generally distinguishable even at disease onset. However, pathologic studies have demonstrated transitional cases of yet unclear significance. ADEM is clinically defined by acute polyfocal neurologic deficits including encephalopathy. MRI typically demonstrates reversible, ill-defined white matter lesions of the brain and often also the spinal cord, along with frequent involvement of thalami and basal ganglia. CSF analysis may reveal a mild pleocytosis and elevated protein, but is generally negative for intrathecal oligoclonal immunoglobulin G synthesis. In the absence of a specific diagnostic test, ADEM is considered a diagnosis of exclusion, and ADEM mimics, especially those requiring a different treatment approach, have to be carefully ruled out. The role of biomarkers, including autoantibodies like anti–myelin oligodendrocyte glycoprotein, in the pathogenesis and diagnosis of ADEM is currently under debate. Based on the presumed autoimmune etiology of ADEM, the current treatment approach consists of early immunotherapy. Outcome of ADEM in pediatric patients is generally favorable, but cognitive deficits have been reported even in the absence of other neurologic sequelae. This review summarizes the current knowledge on epidemiology, pathology, clinical presentation, neuroimaging features, CSF findings, differential diagnosis, therapy, and outcome, with a focus on recent advances and controversies. ***Neurology*® 2016;87 (Suppl 2):S38–S45**

GLOSSARY

ADEM = acute disseminated encephalomyelitis; **ADEM-ON** = acute disseminated encephalomyelitis followed by optic neuritis; **AHL** = acute hemorrhagic leukoencephalopathy; **IgG** = immunoglobulin G; **IPMSSG** = International Pediatric Multiple Sclerosis Study Group; **MDEM** = multiphasic disseminated encephalomyelitis; **MOG** = myelin oligodendrocyte glycoprotein; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorders; **OCB** = oligoclonal band.

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating CNS disorder, characterized clinically by new-onset polyfocal neurologic symptoms including encephalopathy, coupled with neuroimaging evidence of multifocal demyelination. ADEM is classically considered a monophasic illness, with highest incidence in early childhood. The first descriptions of an ADEM-like disorder with recognition of a temporal relationship to infections (especially smallpox and measles) date back to the 18th century.[1] Over a century later, an association of ADEM with vaccines, notably rabies, was reported. Mortality rates were high (up to 30% for ADEM following measles infection), and neurologic sequelae frequent.[2,3] Successful immunization programs for measles, mumps, and rubella and the development of vaccines devoid of neural elements led to a marked decrease of ADEM following those events. However, ADEM continues to be among the most frequent demyelinating disorders in childhood.[4,5] Immunotherapy is considered standard of care and may contribute to faster recovery

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and improved outcomes as compared to historic reports, although clear-cut evidence for this assumption is lacking.

We review epidemiologic, pathological, clinical, and neuroimaging findings of ADEM, with updates on diagnostic criteria, differential diagnostic workup, and treatment strategies.

DEFINITIONS ADEM has historically been an umbrella term for noninfectious acute inflammatory demyelinating events of the CNS, particularly occurring in children. Until recently, the definition of ADEM varied widely, leading to differences in the phenotypes reported. In 2007, the International Pediatric Multiple Sclerosis Study Group (IPMSSG) proposed consensus definitions for pediatric acquired demyelinating disorders of the CNS to improve consistency in terminology.[6] In 2013, the original definitions were updated.[7] ADEM remains a diagnosis of exclusion, always necessitating thorough consideration of alternate diagnoses. Beyond this, the new ADEM criteria require the following:

1. A first polyfocal clinical CNS event with presumed inflammatory demyelinating cause
2. Encephalopathy (alteration in consciousness or behavior unexplained by fever, systemic illness, or postictal symptoms)
3. Brain MRI abnormalities consistent with demyelination during the acute (3 months) phase
4. No new clinical or MRI findings 3 months or more after the clinical onset

The clinical symptoms and radiologic findings of ADEM can fluctuate in severity and evolve in the first 3 months after onset. Accordingly, a second event is defined as the development of new symptoms more than 3 months after the start of the incident illness. Data to support the biological rationale for the 3-month requirement are needed.

Table 1 ADEM and its convergence with relapsing demyelinating disorders

Diagnosis	Clinical criteria
ADEM, monophasic[7]	Single polyfocal CNS event with encephalopathy and presumed inflammatory demyelination and no new disease activity (clinical or MRI) >3 months after onset
ADEM, multiphasic[7]	ADEM followed at >3 months by second ADEM episode, but no further ADEM or non-ADEM demyelinating events
ADEM-MS[7]	ADEM followed at >3 months by non-ADEM demyelinating relapse and new MRI lesions meeting criteria for dissemination in space[8]
ADEM-NMOSD[9]	ADEM followed at >3 months by events including optic neuritis, longitudinally extensive transverse myelitis, or area postrema syndrome, meeting MRI requirements according to revised NMOSD criteria[9]
ADEM-ON	ADEM, MDEM, or multiple ADEM attacks followed by optic neuritis

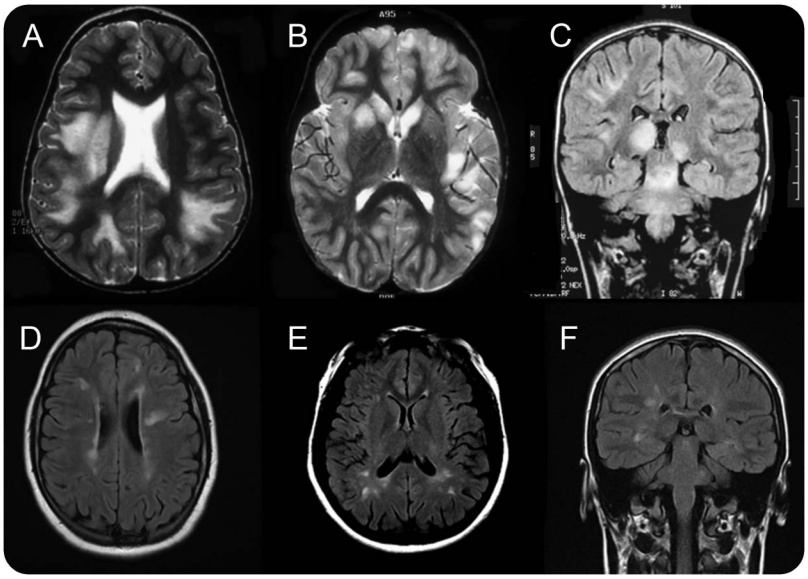
Abbreviations: ADEM = acute disseminated encephalomyelitis; MDEM = multiphasic disseminated encephalomyelitis; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis.

Nonmonophasic ADEM. A small but important subset of patients with ADEM will subsequently be diagnosed with relapsing disorders, including neuromyelitis optica spectrum disorders (NMOSD) and multiple sclerosis (MS). We currently have insufficient diagnostic technologies to reliably distinguish this subset from the majority of patients with ADEM for whom the disease course is monophasic (table 1).

The category of recurrent ADEM was eliminated in the 2013 criteria, and replaced by the term multiphasic disseminated encephalomyelitis (MDEM), describing 2 episodes consistent with ADEM, separated by at least 3 months. A third ADEM-like event is no longer consistent with MDEM, but indicates a chronic relapsing demyelinating disorder, often leading to a diagnosis of ADEM followed by optic neuritis (ADEM-ON), NMOSD, or possibly MS.[10–12] A positive serum anti-aquaporin-4 immunoglobulin G (IgG) titer facilitates a diagnosis of NMOSD.[9,12] As per the 2013 IPMSSG criteria, a relapse after an initial ADEM event may lead to a diagnosis of MS if it is nonencephalopathic, occurs more than 3 months after the ADEM manifestation, and is associated with new MRI findings consistent with the 2010 revised McDonald MS criteria for dissemination in space.[7,8] Since the publication of the 2013 IPMSSG definitions, there has been increasing interest in the role of myelin oligodendrocyte glycoprotein (MOG) antibody response in immune-mediated CNS disorders.[13] Based on recent publications, ADEM-ON has been introduced as a new relapsing clinical phenotype associated with anti-MOG antibodies.[10] Of note, the MRI of patients with ADEM-ON demonstrates resolution of previous ADEM lesions without new T2 or contrast-enhancing lesions (apart from the optic nerve) at the time of optic neuritis attacks, thereby not fulfilling MS MRI criteria for dissemination in space.[10] Taken together, these studies identified similar clinical and radiologic features in a MOG-IgG-positive subpopulation of patients with ADEM, and MOG-IgG seropositivity has been reported to plead against a diagnosis of MS in several independent recent studies.[13–15] However, the exact role of MOG antibodies is controversial.

EPIDEMIOLOGY Population-based studies show the incidence of ADEM to be 0.3–0.6 per 100,000 per year.[16,17] Nationwide surveys of ADEM in Germany, Canada, and Great Britain report incidences of 0.1–0.3 per 100,000 children per year.[4,5,18] Incidences were higher in the northwest than in the south of the United States, possibly secondary to a geographic distribution similar to that of MS, with an increase in

Figure Representative images demonstrate typical MRI appearances of acute disseminated encephalomyelitis (ADEM) (A-C) and multiple sclerosis (MS) (D-F)



T2-weighted images from a patient with ADEM show bilateral diffuse, multifocal, poorly marginated, large asymmetric lesions of the white matter, basal ganglia, and cortical gray matter (A, B); coronal fluid-attenuated inversion recovery (FLAIR) image demonstrates asymmetric involvement of the thalami (C). FLAIR images from a patient with MS demonstrate multifocal, asymmetric, mostly well-defined ovoid lesions of the white matter, with periventricular predominance and sparing of the basal ganglia, on axial (D, E) and coronal (F) views.

incidence with increasing distance from the equator.[19] The median age at presentation of ADEM is 5–8 years, with male predominance.[18,20] The risk of post-immunization ADEM is significantly lower than the risk of developing ADEM following the infection itself.[21] Considering the frequency of vaccinations and infections in young children, with up to 8 episodes of upper respiratory tract infections per year considered as normal, a chronologic association between a vaccination or an infection and ADEM does not prove causality.

Table 2 MRI characteristics in ADEM vs MS

MRI characteristics	ADEM: Typical	MS: Typical
Deep gray matter and cortical involvement	Yes	No
Bilateral diffuse lesions	Yes	No
Poorly marginated lesions	Yes	No
Large globular lesions	Yes	No
Periventricular pattern of lesions	No	Yes
Lesions perpendicular to long axis of corpus callosum	No	Yes
Ovoid lesions	No	Yes
Lesions confined to corpus callosum	No	Yes
Sole presence of well-defined lesions	No	Yes
Black holes (on T1 sequence)	No	Yes

Abbreviations: ADEM = acute disseminated encephalomyelitis; MS = multiple sclerosis.

PATHOLOGY The hallmark of ADEM pathology consists of perivenular sleeves of demyelination associated with inflammatory infiltrates of myelin-laden macrophages, T and B lymphocytes, occasional plasma cells, and granulocytes.[22] Lesions are of similar histologic age, and may demonstrate acute axonal injury. Larger areas of demyelination are a consequence of coalescence of numerous perivenous demyelinating lesions.[22] In contrast, MS lesions are characterized by confluent demyelination associated with sheets of macrophage infiltration admixed with reactive astrocytes in completely demyelinated regions. However, transitional cases of both perivenous and confluent demyelination in the same patient have been described, suggesting a potential for misclassification even with biopsy.[22] ADEM is the only disorder, aside from MS, in which the full spectrum of cortical lesions can be identified, including subpial demyelinated lesions and intracortical lesions.[22] A pattern of cortical microglial activation distinct from MS, characterized by multifocal microglial aggregates, not associated with cortical demyelination, can also be found in ADEM. These diffuse cortical microglial alterations may represent the pathologic substrate of the depressed level of consciousness typically observed in patients with ADEM.[22]

Whether acute hemorrhagic leukoencephalopathy (AHL) is a separate disease entity or a hyperacute severe variant of ADEM remains controversial. AHL lesions are characterized by the presence of hemorrhages, vessel fibrinoid necrosis, perivascular exudation, edema, and granulocyte infiltration, with perivascular demyelination and reactive astrocytosis typically seen later in disease evolution. A recent report of a fulminant case of AHL revealed perivenular hemorrhages, edema, and granulocytes in the absence of demyelination.[23] Perivascular astrocytes demonstrated dystrophic and swollen processes, suggesting astrocytic damage may be an early event that precedes demyelination in AHL.

CLINICAL PRESENTATION ADEM is characterized by an acute onset of encephalopathy in association with polyfocal neurologic deficits, sometimes preceded by prodromal symptoms (fever, malaise, irritability, somnolence, headache, nausea, and vomiting). The clinical course of ADEM is typically rapidly progressive, with maximal deficits within 2 to 5 days.[20] A severe presentation resulting in admission to an intensive care unit has been reported in 15%–25% of children with ADEM.[24,25] Frequent neurologic manifestations include pyramidal signs, ataxia, acute hemiparesis, optic neuritis or other cranial nerve involvement, seizures, spinal cord syndrome, and impairment of speech. Rarely, respiratory failure

Table 3 Red flags for a diagnosis of ADEM and possible differential diagnoses

	Possible causes
Clinical features atypical for ADEM	
Persistent meningeal signs or headache	Infectious encephalitis, systemic autoimmune disorders (e.g., neurosarcoidosis, SLE), CNS vasculitis
Stroke-like events	CNS vasculitis, antiphospholipid antibody syndrome, mitochondrial diseases (e.g., MELAS, POLG-related disorders)
Recurrent seizures	Infectious or autoimmune encephalitis
Dystonia or parkinsonism	Infectious or autoimmune encephalitis
Neuropsychiatric symptoms	SLE, autoimmune encephalitis
Progressive course	Genetic/metabolic disorders, gliomatosis cerebri, neurosarcoidosis
History of developmental delay or other neurologic abnormalities	Genetic/metabolic disorders
Recurrent encephalopathic events	Genetic/metabolic disorders, systemic autoimmune disorders, autoimmune encephalitis, ANE
CSF features atypical for ADEM	
Cell count >50/mm^3 or neutrophilic predominance or protein >100 mg/dL	CNS infections (e.g., HSV, EBV, enterovirus, West Nile virus, mycoplasma), NMOSD, SLE
Imaging features atypical for ADEM	
Diffuse, symmetric brain lesions	Genetic/metabolic disorders; leukodystrophies, mitochondrial disorders, intoxications (e.g., CO)
Ischemic lesions with restricted diffusion	Stroke, mitochondrial disorders, CNS infections, antiphospholipid antibody syndrome, CNS vasculitis
Mesial temporal lobe lesions	Autoimmune encephalitis

Abbreviations: ADEM = acute disseminated encephalomyelitis; ANE = acute necrotizing encephalopathy; EBV = Epstein-Barr virus; HSV = herpes simplex virus; MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; NMOSD = neuromyelitis optica spectrum disorder; POLG = polymerase gamma; SLE = systemic lupus erythematosus.

occurs due to brainstem involvement. Seizures may develop into status epilepticus.[20,26] Fever and seizures are described more frequently in ADEM compared to other acute demyelinating syndromes. Combined central and peripheral demyelination has been reported,[27–30] but should prompt diligent differential diagnostic workup including screening for other immune-mediated disorders, as well as for leukoencephalopathies of genetic/metabolic origin (e.g., mitochondriopathies, Krabbe disease, X-linked Charcot-Marie-Tooth disease).[31,32]

NEUROIMAGING FEATURES MRI T2-weighted and fluid-attenuated inversion recovery images typically demonstrate multiple hyperintense bilateral, asymmetric patchy and poorly marginated lesions.[20] Usually different sizes of lesions are seen in the same patient.[33] Tumefactive lesions with perilesional edema have been reported.[34] ADEM lesions typically involve the subcortical and central white matter and cortical gray–white matter junction, thalami, basal ganglia, cerebellum, and brainstem.[11,20,33,34] (figure, A–C) Spinal cord involvement has been described in up to 1/3 of patients, often demonstrating large confluent lesions extending over multiple segments, sometimes associated with cord swelling.[20,35] Gadolinium enhancement is reported in up to 30% of patients.[20] Main differentiating features of ADEM compared to MS are periventricular sparing and absence of periventricular ovoid lesions perpendicular to the ventricular edge (Dawson fingers).[34–36] The figure and table 2 summarize MRI characteristics of ADEM vs MS. There are, however, no absolute imaging criteria to differentiate ADEM from MS.

Follow-up imaging. Serial MRIs play an important role to confirm the ADEM diagnosis in retrospect. Monophasic ADEM is per definition not associated with the development of new lesions more than 3 months after disease onset.[7] Complete or partial resolution of MRI abnormalities has been described in the majority of patients.[26] The authors suggest reassessing patients with at least 2 additional MRIs (e.g., 3 months and 9–12 months after clinical onset), in order to rule out ongoing disease activity indicating a diagnosis other than ADEM. However, frequency and timing of re-imaging will have to take into account age and clinical characteristics, and may be deferred in asymptomatic young children requiring sedation for their MRIs.

New MRI techniques. There have been conflicting reports of MRI diffusion patterns showing reduced or increased diffusion within ADEM lesions.[37,38] Recently, apparent diffusion coefficient values were found to be increased in the majority (70%) of 17 children with ADEM, consistent with vasogenic edema.[39] Data on magnetic resonance spectroscopy of ADEM are limited. In a single pediatric case report, low levels of *N*-acetylaspartate were measured within lesions, normalizing at follow-up.[40] As opposed to MS, magnetization transfer and diffusion tensor imaging findings measured in normal-appearing brain tissue were not different between ADEM and healthy controls, possibly indicating that the pathologic process of ADEM is sparing normal-appearing brain tissue.[41]

CSF FINDINGS CSF studies in ADEM are notable for their lack of confirmatory features. CSF leukocyte count has been described to be normal in 42%–72% of children with ADEM.[16,20,42–44] Pleocytosis is typically mild, with a high percentage of lymphocytes and monocytes.[44,45] CSF protein is increased (up to 1.1 g/L) in 23%–62% of pediatric patients with ADEM.[16,20,42–44] An elevated CSF IgG index has been reported in 2/54 and 3/13 children in 2 pediatric ADEM cohorts. Of note, none of these patients with elevated IgG indices had CSF oligoclonal bands (OCBs).[20,34] Indeed, most notably, OCBs are a rare phenomenon in children with ADEM diagnosed according to IPMSSG consensus definitions. Out of

Table 4 Differential diagnosis of ADEM guided by MRI

MRI pattern	Diseases
Multifocal white matter lesions	Multiple sclerosis
	Primary CNS vasculitis
	Secondary CNS vasculitis (e.g., CNS lupus, Behçet disease)
	Neurosarcoidosis
	Hashimoto encephalopathy (SREAT)
	Mitochondrial; POLG-related disorders
	Posterior reversible encephalopathy syndrome
Bithalamic orbistriatal lesions	Acute necrotizing encephalopathy, type 1 (OMIM #608033)
	Biotin-thiamine-responsive basal ganglia disease (OMIM #607843)
	Mitochondrial (e.g., Leigh syndrome, OMIM #256000)
	Deep cerebral vein thrombosis
	Japanese encephalitis
	West Nile virus encephalitis
	Epstein-Barr virus encephalitis
	Extrapontine myelinolysis
	Bithalamic glioma
Bilateral and diffuse large white matter lesions	Leukodystrophies
	Toxic leukoencephalopathies
	Hemophagocytic lymphohistiocytosis
	Gliomatosis cerebri
Tumefactive lesions	Astrocytoma
	Lymphoma
	Abscess/infection

Abbreviations: ADEM = acute disseminated encephalomyelitis; MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; POLG = polymerase gamma; SREAT = steroid-responsive encephalopathy associated with autoimmune thyroiditis.

53 patients described in 3 more recent case series, OCBs were only detected in one patient (1.9%).[34,42,43] In cases where CSF OCBs are detected in ADEM, they tend to manifest as mirror bands present in both serum and CSF, and would therefore not be considered as true OCBs per definition, but suggest an antibody production that is not intrathecally restricted.[46] Infectious studies of the CSF are, by definition, negative in ADEM with the caveat that the breadth and sensitivity of current infectious assays remain limited.

DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND WORKUP The diagnosis of ADEM is made on clinical grounds with MRI support. Variable clinical manifestations and lack of specific biological markers imply that the diagnosis requires exclusion of differential diagnoses. The first priority is to rule out potentially treatable CNS infections. The authors recommend gadolinium-enhanced brain and spinal cord MRI, and CSF studies including cell count, protein, lactate, IgG index, and oligoclonal IgG (in CSF and serum), in addition to screening for infectious agents, especially herpes simplex virus, enterovirus, Epstein-Barr virus, and mycoplasma. Bloodwork will typically include complete blood count, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, NMO-IgG, and MOG antibodies. Extensive, specialized testing for alternative disorders is guided by red flags (table 3). An MRI-based approach to the differential diagnosis of ADEM is provided in table 4.

Differentiation of ADEM and MS is of prognostic and therapeutic importance. Children with ADEM are generally younger, and systemic symptoms such as fever, vomiting, meningism, and headache are much more common in ADEM than MS. Intrathecal oligoclonal IgG synthesis is a hallmark of MS, but atypical in ADEM. Disease activity (clinical or MRI) >3 months after ADEM onset points towards a chronic disorder like ADEM-ON, MS, or NMOSD (table 1). Discriminatory MRI features of ADEM and MS are listed in table 2.

TREATMENT There are no randomized studies for the treatment of ADEM. Thus, management of ADEM is based on expert opinions and observational studies.[20,26,47] Despite the lack of conclusive evidence, high-dose corticosteroids are currently widely accepted as first-line therapy.[48] A typical treatment regimen consists of IV methylprednisolone at a dose of 30 mg/kg/d (maximally 1,000 mg/d) for 5 days, followed by an oral taper over 4–6 weeks with a starting dose of prednisone of 1–2 mg/kg/d. An increased risk of relapse was observed with steroid taper of ≤3 weeks.[49] IV immunoglobulin treatment has been described in case reports and small case series, mostly in combination with corticosteroids or as a second-line treatment in steroid-unresponsive ADEM.[50,51] The usual total dose is 2 g/kg, administered over 2–5 days.[47] Plasma exchange is recommended for therapy-refractory patients with fulminant disease, e.g., using 7 exchanges every other day.[47] In single case reports, patients with fulminant ADEM and cerebral edema have been treated with hypothermia or decompressive craniotomy.[52,53]

OUTCOME The majority of children with ADEM are reported to have full recovery. Typically, neurologic improvement is seen within days following initiation of treatment, and recovery to baseline will occur within weeks rather than months.[54] However, mortality rates of 1%–3% have been reported recently,[24,25] and long-term cognitive deficits have been observed, affecting attention, executive function, verbal processing, and

behavior, as well as IQ scores, specifically in children with ADEM before age 5 years.[55,56]

Relapsing ADEM—MDEM—has been reported, although at much lower frequency (<10%) since implementation of the 2007 ADEM criteria. It is currently under debate whether patients with relapsing ADEM represent a distinct group of children with other neuroimmunologic diseases like NMOSD or MOG-antibodies-associated disorders. ADEM as a first manifestation of MS appears to be uncommon, occurring in <10% of patients with ADEM.[20] Predictors of MS following ADEM and other acute demyelinating syndromes are discussed in "Pediatric acquired CNS demyelinating syndromes: Features associated with multiple sclerosis" by Hintzen et al. (p. S67).

CONTROVERSIES AND FUTURE DIRECTIONS

ADEM is possibly not a single specific disease, but an inflammatory CNS syndrome with immune-mediated demyelination and strong predilection to young children. Further delineation of potentially different etiologies for an ADEM presentation, including antibodies to CNS proteins like aquaporin or MOG, will hopefully enhance our understanding of the disease and facilitate treatment decisions. The question whether and how often ADEM can present as the first manifestation of MS is still under debate. In view of the relatively low incidence of ADEM, multicenter studies are required to provide more information with regards to pathogenesis, biomarkers, differential diagnoses, and therapeutic options, with the ultimate goal to promote efficacious and specific treatment approaches in order to optimize long-term outcomes in children with demyelinating disorders.

AUTHOR CONTRIBUTIONS

Daniela Pohl: abstract, treatment, outcome, controversies, and future directions. Gulay Alper: neuroimaging features, differential diagnosis, investigations and workup, tables, figures. Keith van Haren: CSF findings, differential diagnosis, investigations and workup, tables. Andrew Kornberg: epidemiology, differential diagnosis, investigations, and workup. Claudia Lucchinetti: pathology. Silvia Tenembaum: definitions, clinical presentation. Anita L. Belman: introduction. All authors contributed extensively to the editing and consensus-finding process of all sections of the manuscript.

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