Acute disseminated encephalomyelitis (ADEM) is a monophasic autoimmune demyelinating disease of the central nervous system that typically follows a febrile infection or a vaccination. Children are predominantly affected. A plethora of viral and bacterial pathogens and a number of vaccinations have been associated with ADEM. Experimental animal studies indicate that both primary and secondary autoimmune responses contribute to central nervous system inflammation and subsequent demyelination. The clinical diagnosis of ADEM is strongly suggested by a close temporal relationship between an infectious incident or an immunization and the onset of leukoencephalopathic neurological symptoms. Paraclinical tests may support the diagnosis. Particularly helpful are acute signs of newly developed extensive, multifocal, subcortical white matter abnormalities on magnetic resonance images of the brain. The cerebrospinal fluid may disclose a mild lymphocytic pleocytosis and elevated albumin levels. Oligoclonal bands are not always present in ADEM and, if so, may be transient. The major differential diagnosis of ADEM is multiple sclerosis. Treatment options for ADEM consist of anti-inflammatory and immunosuppressive agents. In general, the disease is self-limiting and the prognostic outcome favorable. In the absence of widely accepted clinical or paraclinical diagnostic guidelines, a number of recently conducted observational case series have substantially broadened our understanding about the clinical phenotype, diagnosis, and prognosis of ADEM.

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Acute disseminated encephalomyelitis (ADEM) is considered a monophasic demyelinating disease of the central nervous system (CNS). Young and adolescent children are most commonly affected. The estimated incidence is 0.8 per 100,000 population per year. Numerous cases among adults and even elderly patients have been reported, too; however, the incidence may be considerably lower. In contrast with cases of multiple sclerosis (MS), there appears to be no sex preponderance in ADEM. In about 50% to 75% of all cases, the clinical onset of disease is preceded by viral or bacterial infections, mostly nonspecific upper respiratory tract infections (Table 1). Acute disseminated encephalomyelitis may also develop following a vaccination (postimmunization encephalomyelitis) (Table 1). Although ADEM is a relatively rare disorder, it is becoming increasingly relevant for several reasons. First, vaccination schedules, particularly for children, have expanded over the past years; second, ADEM may result in permanent neurological disability that is often acquired very early in life.

Vaccination-associated ADEM is most frequently observed after measles, mumps, or rubella vaccinations. However, it has also been reported after polio and Euro-
pean tick-borne encephalitis vaccinations.30,33 It is of note that the incidence of a measles vaccination–associated ADEM is about 10 to 20 per 100,000 vaccinated individuals and thus considerably lower than the incidence of ADEM after a wild-type measles encephalitis (100 per 100,000 infected individuals) (Table 1).

A number of infectious agents, mainly viruses, have been associated with ADEM and are summarized in Table 1. Clinical signs and symptoms of ADEM may manifest themselves parainfectiously or postinfectiously. Typically, there is a latency of 7 to 14 days between a febrile illness and the onset of neurological symptoms. In the case of vaccination-associated ADEM, this latency period may be longer. The recognition of the temporal association between a vaccination or infection and the appearance of neurological signs and symptoms is critical yet unequivocally complex. The Collaborating Center for Reference and Research on Viral Hepatitis of the World Health Organization (Geneva, Switzerland), for instance, has deemed a maximal period of 3 months to diagnose a vaccination-associated ADEM. Such a long lag period may be helpful for the recognition of vaccination-associated ADEM because individual vaccinations are often separated by months and even years and can be easily identified in careful history taking. In contrast, a widely accepted general rule for the latent period between infections and the occurrence of ADEM has not been firmly established. One reason for this may be that it is statistically challenging to establish a causal link between a febrile illness and neurological sequelae. In children who were diagnosed with ADEM, a history of a febrile event can be established in 50% to 75% of all cases.2,3,5,34

### Table 1. Infectious Pathogens and Vaccines Associated With ADEM

<table>
<thead>
<tr>
<th>Source</th>
<th>Pathogen or Vaccine</th>
<th>Study and Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeh et al8</td>
<td>Coronavirus</td>
<td>CR, 15-year-old boy, CSF-PCR and serum titters positive</td>
</tr>
<tr>
<td>David et al9</td>
<td>Coxsackie B</td>
<td>CR, 8-year-old boy</td>
</tr>
<tr>
<td>Yamamoto et al10</td>
<td>Dengue virus</td>
<td>CR, 58-year-old man</td>
</tr>
<tr>
<td>Fujimoto et al11</td>
<td>Epstein-Barr virus</td>
<td>Case studies of ADEM in Epstein-Barr virus</td>
</tr>
<tr>
<td>Tan et al12, Sacconi et al13</td>
<td>Hepatitis virus (A and C)</td>
<td>CRs, children and adults</td>
</tr>
<tr>
<td>Kaji et al14</td>
<td>Herpes simplex virus</td>
<td>Case series; ~10% developed ADEM after herpes simplex virus CNS infections</td>
</tr>
<tr>
<td>Silver et al15</td>
<td>HIV</td>
<td>CRs, biotopic neuropathologic abnormalities discussed</td>
</tr>
<tr>
<td>Kamei et al16</td>
<td>Human herpesvirus 6</td>
<td>CR, 19-month-old boy</td>
</tr>
<tr>
<td>Fenichel17</td>
<td>Measles</td>
<td>100/100,000 with high mortality</td>
</tr>
<tr>
<td>Sonmez et al18</td>
<td>Mumps</td>
<td>CRs with parainfectious myelitis and brainstem encephalitis</td>
</tr>
<tr>
<td>Voudris et al19</td>
<td>Parainfluenza viruses</td>
<td>CRs, 1 after bone-marrow transplant</td>
</tr>
<tr>
<td>Fenichel17</td>
<td>Rubella virus</td>
<td>1/10,000 to 1/20,000</td>
</tr>
<tr>
<td>Miller et al20</td>
<td>Varicella-zoster virus</td>
<td>1/10,000 to 1/20,000</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Assen21</td>
<td>Borrelia burgdorferi</td>
<td>CR, 45-year-old man, postmortem neuropathologic abnormalities discussed</td>
</tr>
<tr>
<td>Heick and Skriver22</td>
<td>Chlamydia</td>
<td>CR, 18-year-old woman; tracheal swap PCR and serum IgM positive</td>
</tr>
<tr>
<td>Spiker et al23</td>
<td>Legionella</td>
<td>CRs, children and adults</td>
</tr>
<tr>
<td>Riedel et al14</td>
<td>Mycoplasma pneumoniae</td>
<td>CRs, children and adults</td>
</tr>
<tr>
<td>Wei and Baumann25</td>
<td>Rickettsia rickettsii</td>
<td>CR, 7-year-old boy with Rocky Mountain spotted fever after tick bite</td>
</tr>
<tr>
<td>Dale et al26</td>
<td>Streptococcus</td>
<td>Case series with basal ganglia involvement and specific autoantibodies</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koibuchi et al27</td>
<td>Plasmodium vivax</td>
<td>CRs</td>
</tr>
<tr>
<td><strong>Vaccinations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hynson et al28</td>
<td>Hepatitis B</td>
<td>2 Cases of 31 patients were vaccinated 3-6 weeks prior to onset of ADEM</td>
</tr>
<tr>
<td>Plesner et al29</td>
<td>Japanese B encephalitis</td>
<td>Certain vaccines propagated in mouse brains; incidences up to 0.2/100,000 background encephalitis*</td>
</tr>
<tr>
<td>Fenichel30</td>
<td>Japanese B encephalitis</td>
<td>0.1/100,000 for live measles vaccination; this is compared with 0.2-0.3/100,000 background encephalitis*</td>
</tr>
<tr>
<td>Nalini31</td>
<td>Mumps</td>
<td>Strain-dependent 0.06-1.4/100,000*</td>
</tr>
<tr>
<td>Fenichel32</td>
<td>Pertussis</td>
<td>0.9/100,000 for DPT-triple vaccine*</td>
</tr>
<tr>
<td>Ozawa et al20</td>
<td>Polio</td>
<td>CR, 6-year-old girl; oral vaccination 4 years prior; at onset, polio virus culture positive from pharyngeal swab and CSF</td>
</tr>
<tr>
<td>Hemachudha et al33</td>
<td>Rabies</td>
<td>Sample-type (attenuated live virus, propagated in rabbit or goat CNS tissue cultures); up to 1/600</td>
</tr>
<tr>
<td>Fenichel34</td>
<td>Rubella</td>
<td>No complications reported for newer vaccines produced in human diploid cells</td>
</tr>
<tr>
<td>Bolukbasi and Ozmenoglu35</td>
<td>Tetanus</td>
<td>Reports of isolated myelitis and optic neuritis</td>
</tr>
<tr>
<td>Schattenfroh36</td>
<td>Tick-borne encephalitis</td>
<td>CR, 35-year-old man</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; CNS, central nervous system; CR, case report; DPT, diphtheria, pertussis, and tetanus; PCR, polymerase chain reaction.

*Acute disseminated encephalomyelitis was not explicitly stated; mostly the clinical terms encephalopathy or encephalitis were used. Most of these studies were conducted before the advent of magnetic resonance imaging. Hence, the actual ADEM incidence may be even lower.
cause children are diagnosed with a viral infection 4 to 6 times per year on average, the medical history at any time would be positive in this regard between 33% and 50% of the time. Thus, unless the latency period for a postinfectious ADEM is defined significantly shorter than 30 days, a causal link between a febrile event and ADEM itself cannot easily be established.

PATHOGENETIC CONCEPTS

Overwhelming experimental data indicate that both primary autoimmune responses and immune responses secondary to an infection may contribute to CNS inflammation with subsequent demyelination. Two animal models closely resemble ADEM clinically and histopathologically.

First, experimental autoimmune encephalomyelitis is widely used to study underlying disease mechanisms of ADEM.35 After immunization with CNS homogenate or encephalitogenic myelin peptides emulsified in Freund complete adjuvant, susceptible animals present with a monophasic disease with tetraparesis, weight loss, and incontinence. Histopathologically, inflammatory demyelinating lesions are detectable in the brains and spinal cords of affected animals.

Second, Theiler murine encephalomyelitis, which was established as an animal model in the 1930s, has been used to specifically study infectious and parainfectious mechanisms that may contribute to the pathogenesis of ADEM.36 Susceptible mouse strains present with subacute encephalitis and extensive demyelination after direct inoculation of a cerebral hemisphere with the Theiler murine encephalomyelitis virus. The disease seems to be triggered by a major histocompatibility complex class 1 restricted CD8+ T-cell response against viral epitopes, whereas ongoing inflammation is sustained by major histocompatibility complex class 2 restricted CD4+ T-cell responses against myelin determinants.

Extensive research with these animal models has led to the development of 2 current pathogenic concepts. The inflammatory cascade concept implies a direct CNS infection with a neurotropic pathogen, resulting in CNS tissue damage and systemic leakage of CNS-confined autoantigens into the systemic circulation through a disintegrated blood-brain barrier. These autoantigens, once processed in systemic lymphatic organs, will lead to tolerance breakdown and to a self-reactive and encephalitogenic T-cell response. Such activated T cells are capable of invading the CNS and perpetuating CNS inflammation even further.

The molecular mimicry concept proposes a structural or partial amino-acid sequence homology between the inoculated pathogen and myelin proteins of the host.37 This structural homology is not sufficient for a pathogen to be recognized as “self,” which would result in immunotolerance. Antigen-presenting cells such as B cells or dendritic cells process the pathogen at the site of inoculation, leading to T-cell activation. Activated T cells may in turn cross-activate antigen-specific B cells. Both activated T cells and B cells are quite capable of entering the CNS for routine immune surveillance. Thus, even after clearance of the pathogen, these antigen-specific cells may encounter the homologue myelin protein during their physiologic surveilllance of the CNS. They may become reactivated by local antigen-presenting cells such as microglia, causing an inflammatory immune reaction against the presumed foreign antigen; thus, the initially physiological immune response leads to detrimental autoimmunity.

Some of the vaccine-associated ADEM cases can be directly attributed to the contamination of the specific vaccine with CNS tissue. This contamination may explain the substantial 0.15% incidence of ADEM after immunization with a live attenuated rabies virus vaccine (Semple vaccine) in developing countries, which is propagated in cultures of rabbit or goat CNS tissue. In this regard, antibodies against myelin antigens are detectable in patients with Semple vaccine–associated ADEM.31 Newer rabies vaccines are propagated in human diploid cells and do not cause this particular adverse effect. A similar mechanism may account for ADEM observed after vaccination against Japanese B encephalitis, where certain vaccine strains are propagated in mouse brains (Table 1).28

CLINICAL PRESENTATION

In recent years, a number of observational studies with relatively large numbers of patients and follow-up time have been conducted. Although the majority of studies focused on children (Table 2), 1 study enrolled adults.7 These studies have greatly enhanced our knowledge of the clinical presentation, diagnosis, and prognosis.

Depending on the focus of the study, 50% to 75% of the patients had a febrile infection—in many cases of the upper respiratory tract—in the 4 weeks preceding the onset of the neurological phenotype (Table 2). Note that many pathogens attributed to the etiology of ADEM may cause upper respiratory tract infections (Table 1). Preceding immunizations were less commonly reported.4,14,38 Neurological signs and symptoms appeared days to weeks after an infection or vaccination, with an average latency of 4 to 13 days.3,5,34 In general, neurological symptoms developed subacutely over a period of days and led to hospitalization within a week.4,5,7,34 Although ataxia,3,5,7,34 altered level of consciousness,3,5,7,34 and brainstem symptoms36,39 are frequently present in both pediatric and adult cases, certain signs and symptoms appear age-related. In childhood ADEM, long-lasting fever5 and headaches2,5,6,39 occur more frequently, but in adult cases, motor and sensory deficits predominate. Despite these empirical observations, clinical discrepancies41,42 should not exclude a priori the diagnosis ADEM in the respective age group. It is noteworthy that a number of authors do not consider monosymptomatic presentations, such as transverse myelitis, pure cerebellar dysfunction, and unilateral (but not bilateral) optic neuritis without radiological abnormalities compatible with ADEM.4,7,34,38,41,44 Classically, however, Bickerstaff encephalitis and postinfectious transverse myelitis are considered subgroups of ADEM, where the inflammation and demyelination appear to be confined to the brainstem or spinal cord, respectively.45,46 Bilateral optic neuritis appears to be associated with chickenpox and has a less polysymptomatic disease course.20 The disseminated necrotizing leukoencephalopathy (Weston-Hurst syndrome, acute necrotizing hemorrhagic en-
The diagnosis ADEM should be readily considered whenever there is a close temporal relation between an infection or a vaccination and the subacute, polysymptomatic onset of neurological deficits attributable to the CNS. In some cases, however, the diagnosis may not be straightforward and may require a variety of additional diagnostic tests.

The most widely applied diagnostic tool is brain magnetic resonance imaging (MRI). For the purpose of clinical outcome trials, some experts consider the diagnosis of ADEM only if the MRI is consistent with disseminated CNS demyelination. This includes, in particular, the detection of widespread, multifocal, or extensive white matter lesions (lesion load >50% of total white matter volume). Lesions in the deep gray matter have also been seen in ADEM. These include areas of the thalamus or the basal ganglia, which often occur bilaterally and are located at the white to gray matter junction.

Thus far, no MRI criteria have been identified that are specific for ADEM. However, a number of investigators have identified 2 specific MRI patterns. Corpus callosum long axis perpendicular lesions (Dawson fingers) and periventricular lesions are more common in MS and are associated with a higher risk to experience a MS-defining relapse. In addition, it is widely accepted that follow-up MRI scans help establish or confirm a diagnosis of ADEM. The interval should not be shorter than 6 months. Whereas ADEM lesions should resolve or remain unchanged, the appearance of new lesions is strongly suggestive of MS. It may also be noteworthy that MRI may be useful to exclude the dissemination in time of CNS demyelination, which points toward a chronic CNS disorder like MS. It is, however, of note...
that the most recent MRI-based diagnostic criteria for MS were not designed for children with CNS demyelinating disease. Because most patients present initially with nonspecific symptoms, such as headaches, fever, and lethargy, a lumbar puncture is typically indicated to rule out acute viral, bacterial, or parasitic meningoencephalitis. The cerebrospinal fluid (CSF) may show a nonspecific lymphocytic pleocytosis and elevation of albumin levels. The median frequency of oligoclonal banding in childhood cases was 12.5% (range, 0-29%) and in the adult cases (37.5-58%). Oligoclonal banding may be present only transiently. This is in sharp contrast with MS and other neuroinflammatory diseases. Occasionally, it is possible to identify the inciting pathogen by specific cell-culture techniques or polymerase chain reaction (PCR) results from the CSF. These PCR results should be interpreted with caution because the prevalence of many neurotropic viruses is extremely high in the general population. Thus, it may be difficult to prove a causative relation of ADEM to a positive PCR test result for an infectious pathogen.

A guided brain biopsy may be considered in cases suspicious of a CNS malignancy, eg, insidious clinical onset with detectable mass effect or an unusual lesion location on MRI. Acute disseminated encephalomyelitis lesions with typical histopathological features can be identified anywhere in the CNS white matter or brainstem. ADEM is characterized by perivascular infiltration with macrophages and T cells. In very early stages, polymorphonuclear granulocytes may be observed. In contrast with MS, in ADEM demyelination remains restricted to the perivascular area, and confluent demyelination is not observed. In the advanced disease stages, astrocyte hyperplasia and gliosis may be present. In the absence of detailed histopathological classification guidelines that would enable the pathologist to unequivocally establish a diagnosis of ADEM, many experts discourage diagnostic biopsies.

DIFFERENTIAL DIAGNOSIS

As discussed earlier in this article, neither the clinical presentation nor paraclinical tests allow a specific and unequivocal diagnosis of ADEM. If in doubt, the diagnosis has to be made by exclusion. The most important and most common differential diagnosis is MS. The following paragraphs outline differential diagnoses, which are reviewed and referenced elsewhere.

Infectious meningoencephalitis of viral, bacterial, or parasitic origin may present with a typical yet not specific MRI appearance and may be diagnosed through specific antibody testing, microbial culture techniques, or direct detection of the pathogen by PCR. Herpes simplex virus encephalitis is a frequent clinical mimic of ADEM, with the initial clinical features being fever, headaches, and confusion. Further diagnostic work-up frequently reveals unilateral or bilateral temporal lobe changes on MRI images with frequent intraparenchymal hemorrhages, a higher CSF pleocytosis than ADEM with a mixture of neutrophils and mononuclear cells in the initial phase of the disease, typical electroencephalographic changes, and elevated antiherpes simplex virus IgM titers.

Antiphospholipid antibody syndrome is increasingly being diagnosed in children, and the initial clinical presentation may be similar to that of ADEM. In addition, ischemic lesions detectable by MRI may be indistinguishable from those seen with ADEM. A history of recurrent arterial or venous thrombosis, fetal loss, and the detection of specific antiphospholipid antibodies and lupus anticoagulants should be indicative of antiphospholipid antibody syndrome.

In primary isolated CNS angiitis, a patient may present with headaches and an acute polysymptomatic neurological phenotype, including an altered mental status. Images on MRI scans of the brain typically show deep brain infarcts that occasionally may mimic white matter lesions. Magnetic resonance angiography or conventional CNS angiography are often useful diagnostic tests because their results are usually within normal limits in ADEM. In some cases, it may ultimately be necessary to obtain a leptomeningeal biopsy to specifically look for vasculitic inflammatory changes.

Vasculitis secondary to rheumatic autoimmune diseases, including systemic lupus erythematosus, may be detected by the presence of specific serum autoantibodies and systemic involvement of multiple organs. Angiography may show pathological vessels but is typically normal in ADEM patients.

Central nervous system neoplasia, CNS metastasis of a systemic malignancy, or primary CNS neoplasms typically present with a more insidious onset than ADEM. Some clinical characteristics, however, are similar to those of ADEM, including altered cognition, headaches, and focal neurological signs and symptoms. Additionally, the MRI may resemble one from ADEM in that it may show signs of mass effect and perifocal edema. In many cases, CSF cytological tests, systemic tumor staging (including serum tumor markers and radiological diagnostic workup), and guided brain biopsy may be necessary to ascertain the diagnosis. Another group of patients, those with paraneoplastic syndromes, can also present with cognitive changes, slurred speech, gait instability, and other clinical signs and symptoms. It is believed that in paraneoplastic syndromes, immune responses are directed against certain “onconeural” antigens, which are normal self nervous system antigens expressed ectopically by tumors outside the nervous system. These clinical entities are associated with ovarian cancer, breast cancer, small cell lung cancer, and Hodgkin disease, and they may become clinically apparent before the malignancy itself. The presence-specific paraneoplastic antibodies may guide the diagnosis.

Neurosarcoidosis should also be considered a differential diagnosis of ADEM. However, sarcoidosis is typically a chronic disease, and patients with neurosarcoidosis frequently present with a relapsing-remitting clinical phenotype. Furthermore, systemic organ involvement is frequent in patients with sarcoidosis, and there may be CNS as well as peripheral nervous system involvement. Specific laboratory tests, ie, angiotensin-converting enzyme, lysosome, serum levels of IL-2 receptor, chest x-rays, and bronchial lavage, may be helpful in some cases.

Human immunodeficiency virus–associated encephalopathies, including subacute human immunodeficiency virus encephalitis and progressive multifocal leu-
koencephalopathy, may occasionally also be considered, but clinical symptoms typically develop slower than those of ADEM. The diagnosis is made by a positive test for human immunodeficiency virus and detection of virus in the CSF by means of PCR.

Mitochondrial encephalopathies, such as MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes), may cause recurrent episodes of migraine-like headaches, focal neurological deficits, and signs of encephalopathy during infancy. Affected children typically display failure to thrive and deafness. Magnetic resonance images of CNS white matter frequently show lesions that are compatible with ADEM. Elevated lactate levels, histopathological findings of ragged red fibers in biopsied muscle tissue, and a commercially available test that detects mutations in the mitochondrial tRNA (Leu-UUR) gene confirm the diagnosis.

Adrenoleukodystrophy is caused by an impaired ability to oxidize very-long-chain fatty acids. Inheritance is X-linked, and clinical signs of the cerebral form usually manifest themselves between 5 and 10 years of age. The clinical characteristics of this disorder result from progressive demyelination of the CNS and adrenal cortical failure. The cerebral form of adrenoleukodystrophy is characterized by behavioral changes, focal neurological signs, and seizures. On T2-weighted MRI neuroimages, confluent, bilateral MRI white matter abnormalities are often seen. Elevated long-chain fatty acids in the serum confirm the clinical diagnosis.

Behçet disease is caused by immunocomplex vasculitis and is most common in patients of Mediterranean or Far East decent. The age of onset is between 20 and 40 years, and men are more often affected. The clinical presentation and pathological changes on MRI may mimic those of ADEM with mental alterations, frequent affec-
tions of the brainstem, and disseminated lesions of the white and gray matter on MRI. Behçet disease, however, is defined by relapses, and systemic signs such as ophthalmological or dermatological involvement may be present.

MULTIPHASIC DISSEMINATED ENCEPHALOMYELITIS VS MS

In principle, ADEM is considered a monophasic disease. However, it has been demonstrated that 25% to 33% of ADEM patients will have relapses in the future (Table 2). Despite the effort to improve the diagnostic accuracy a priori, it is still impossible to predict which patients will suffer from recurrent bouts. Two distinct clinical settings have to be discerned.

If relapses occur during anti-inflammatory treatment, they should be regarded as flare-ups of the initially monophasic disease course. This typically occurs while the dose is being tapered or shortly after discontinuation of treatment. In this scenario, the diagnosis of multiphasic disseminated encephalitis (MDEM) should strongly be considered. If, on the other hand, there is a clear dissemination of time and space with regard to the clinical relapse, the diagnosis of MS should be considered. In this instance, the initial event that led to the diagnosis ADEM was most likely a clinically isolated syn-

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TREATMENT

Controlled clinical trials that would meet the type A or type B criteria proposed by the American Academy of Neurology, Saint Paul, Minn, and the MS Council for Clinical Practice Guidelines have not yet been conducted in ADEM. At this time, intravenous high-dose corticosteroids are, based on empirical evidence (type C recommendation), widely accepted as first-line treatment. The aim is to abbreviate the CNS inflammatory reaction as soon as possible and to achieve an accelerated clinical improvement. A number of various other anti-inflammatory and immuno-suppressant therapies may potentially also be effective. Several case studies have reported beneficial effects of plasmapheresis and intravenous immunoglobulin therapies. Immunosuppressive agents, such as mitoxantrone or cyclophosphamide, should be considered as alternative therapies if corticosteroid treatment shows no clinical effect or if relative and absolute contraindications for corticosteroids exist.

As a pragmatic and clinical practical approach, we propose the following treatment scheme. For therapeutic interventions in MS relapses, we propose an initial regime of high-dose intravenous methylprednisolone with a cumulative dose of 3 to 5 g, followed by a prolonged oral prednisolone taper of 3 to 6 weeks. Should a patient not respond adequately to corticosteroids, therapy should be escalated, preferentially with intravenous immunoglobulin (0.4 g/kg of body weight over 5 days). Alternatively, plasma exchange, or apheresis, may be considered. An increase in dosage is recommended if patients do not respond appropriately to the aforementioned therapies.
to be beneficial, at least empirically.14,54,60 Widespread and early use of high-dose steroids has shown early as possible and as aggressive as necessary.14 Persistent, disabling neurological sequelae.59 Second, the ADEM has decreased considerably because of efficient vac-
ted.57,58 In general, treatment should be initiated as early as possible and as aggressive as necessary.14

PROGNOSIS

In the past, the prognosis and long-term outcome for pa-
tients diagnosed with ADEM were considered poor. This has changed dramatically and is attributable primarily to 2 factors. First, the incidence of postinfectious measles ADEM has decreased considerably because of efficient vac-
cinations. Twenty-five percent of ADEM induced by measles infections may be lethal, and an additional 30% to 35% of the surviving patients do not recovery fully and suffer from persistent, disabling neurological sequelae.39 Second, the widespread and early use of high-dose steroids has shown to be beneficial, at least empirically.14,54,60

Nowadays, the long-term prognosis of ADEM in terms of functional and cognitive recovery is favorable (Table 2).61 In several studies, the average time period to recovery was reported to be between 1 and 6 months.4,5 However, cases with a per-acute onset or prolonged disease course were also described.3,4 The outcome was favorable in most cases, ranging between 70% and 90% if minor residual disability was considered (Table 2). However, it should be stressed that the mortality of postinfectious ADEM may still be as high as 5%. Some studies have associated an unfavorable prognosis to a sudden onset and an unusually high severity of the neurological symptoms.

If, as outlined in this article, a patient experiences clinical relapses, the diagnosis of ADEM should be reconsidered in favor of relapsing-remitting MS, which implies a less favorable prognosis.

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Correspondence: Olaf Stüve, MD, Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9036 (olaf.stuve@utsouthwestern.edu).

Author Contributions: Study concept and design: Menge, Nessler, Neuhaus, and Stüve. Acquisition of data: Menge, Nessler, Wiendl, Neuhaus, and Kieseier. Drafting of the manuscript: Menge, Nessler, and Stüve. Critical revision of the manuscript for important intellectual content: Menge, Hemmer, Nessler, Wiendl, Hartung, Kieseier, and Stüve. Obtained funding: Hemmer. Administrative, technical, and material support: Nessler, Neuhaus, and Hartung. Study supervision: Hemmer, Nessler, Wiendl, Hartung, and Stüve.

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