Acute Disseminated Encephalomyelitis in a 4-Year-Old Girl

Julie M. Faulkner, MD
Patrick L. Carolan, MD

Acute disseminated encephalomyelitis (ADEM) is an acute demyelinating disorder of the central nervous system (CNS) characterized by diffuse neurologic signs and multifocal white matter lesions on neuroimaging. ADEM is most frequently seen in children and young adults, often following infection or immunization. Although characterized by a wide range of neurologic abnormalities, ADEM has a favorable long-term prognosis. We report a case of ADEM in a child presenting with lethargy and ataxia and discuss the clinical, etiologic, diagnostic, and therapeutic aspects of this disease.

CASE PRESENTATION

Patient Presentation

A previously healthy 4-year-old girl presented to the emergency department (ED) with lethargy and ataxia.

History of Present Illness

Earlier in the day, the patient was noted to have an unsteady gait and complained of pain behind her right eye. She was taken to her physician who observed fluid behind a dull right tympanic membrane and a low-grade fever of 38.1°C (100.5°F). Acute otitis media was diagnosed, and she was given a prescription for amoxicillin. The unsteady gait was attributed to vertigo associated with the otitis media. Her family was instructed to return for further evaluation if additional symptoms developed or if her gait worsened or did not improve soon.

The child returned home and soon began complaining of abdominal pain and headache. Six episodes of vomiting followed over the course of the afternoon. By evening, she was more lethargic and unwilling to stand or walk and was brought to the ED.

Past Medical History

Her past medical history included atopic dermatitis and occasional episodes of otitis media. She had several upper respiratory infections and a recent acute enteric illness in the preceding months, but she had been healthy for the last 4 weeks prior to the onset of symptoms described above. Her immunizations were current, with her last series received at age 2 years.

Physical Examination

The patient's vital signs in the ED included a temperature of 38.4°C (101.1°F), heart rate of 128 bpm, respiratory rate of 34 breaths/min, and blood pressure of 99/49 mm Hg. She appeared tired, moderately ill, and somewhat irritable, but she was alert, oriented, and spoke clearly. On physical examination, the right tympanic membrane had decreased mobility without erythema. Her neck was supple with full range of motion. Lung, cardiovascular, and abdominal examinations were unremarkable. Cranial nerves II to XII were intact. Her pupils were equally round and reactive to light. No nystagmus was noted. The funduscopic examination was normal. She was able to visually fix on and follow an object. Neurologic examination revealed normal strength and tone. She had brisk deep tendon reflexes in all 4 extremities. Four to 5 beats of left ankle clonus were noted. She had an equivocal Babinski sign bilaterally. She had an unsteady wide-based gait and appeared to be dragging the left foot somewhat while walking. She had mild dysmetria. Sensation to light touch was intact.

Laboratory and Imaging Studies

Computed tomographic (CT) scan of the head was normal. A lumbar puncture was performed and revealed clear fluid with 3 leukocytes/mm^3, a glucose level of 54 mg/dL, and protein level of 27 mg/dL, all within the normal range. No organisms were seen on gram-stained smear. Myelin basic protein was elevated in the cerebrospinal fluid (CSF) at 34.0 ng/mL (normal range, 0.0–1.4 ng/mL). The IgG level in the CSF was

Dr. Faulkner is a pediatric resident, University of Minnesota School of Medicine, Minneapolis, MN. Dr. Carolan is an adjunct associate professor of pediatrics, family medicine and community health, University of Minnesota School of Medicine, Minneapolis, MN, and attending physician, Department of Pediatric Emergency Medicine, Children's Hospitals and Clinics of Minnesota, Minneapolis, MN.

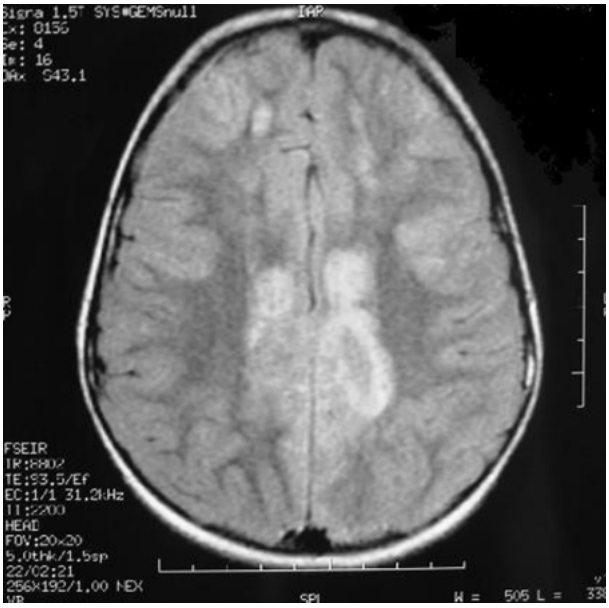

Figure 1. Cranial magnetic resonance image (axial projection) of the case patient, initial presentation, showing multiple areas of T2-weighted and fluid-attenuated inversion recovery signal enhancement, suggesting multifocal demyelination.

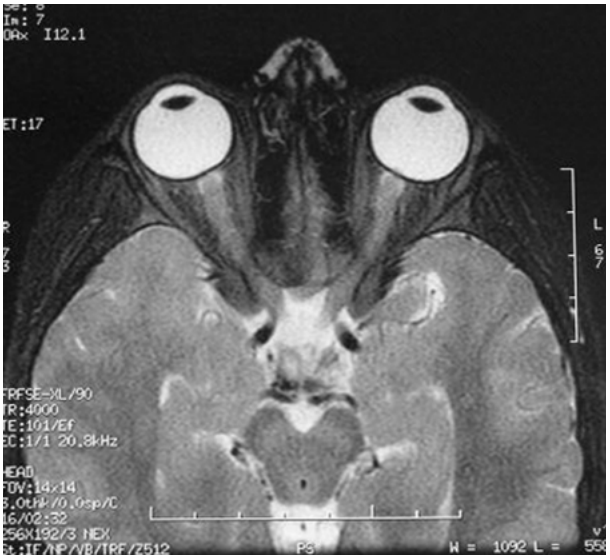

Figure 2. Cranial magnetic resonance image (axial projection) of the case patient, subsequent presentation, revealing T2-weighted signal changes involving the optic nerve and extending to the optic chiasm.

normal, and oligoclonal banding was negative. Her leukocyte count was elevated at 33.9 × 10^3/mm^3, with 89% neutrophils and 8% lymphocytes. The erythrocyte sedimentation rate was elevated at 61 mm/h (normal range, 0–20 mm/h) and C-reactive protein (CRP) was elevated at 5.59 mg/dL (normal range, < 0.30 mg/dL). Serum electrolytes and ammonia level were normal, and serum and urine toxicology screens were negative.

Brain magnetic resonance imaging (MRI) revealed numerous foci of increased T2-weighted and fluid-attenuated inversion recovery sequence (FLAIR) intensity throughout the cerebral hemispheres bilaterally, including the parietal lobes, corpus callosum, frontal lobes, right globus pallidus, and the gray matter of the right cerebellar hemisphere (**Figure 1**).

Diagnosis and Initial Treatment

Clinical and MRI findings were most consistent with ADEM, and the patient was started on high-dose intravenous methylprednisolone (30 mg/kg daily). After 2 days of steroid therapy, improvement was noted in the patient's gait. Blood and CSF cultures exhibited no growth, and antimicrobial agents that had been started at the time of hospital admission were discontinued. The patient's leukocyte count normalized, the CRP level decreased, and her fever resolved.

On day 3 of her hospitalization, she developed frequent watery diarrhea, which tested positive for rotavirus. A 5-day course of high-dose steroids was administered in total. At this point, her gait was essentially normal and steroids were discontinued. She was discharged in good condition with resolving diarrhea. She was scheduled for a repeat brain MRI in 2 weeks and follow-up with pediatric neurology.

Clinical Course

A few days following discharge, the patient began experiencing intermittent headaches, myalgia, and malaise. She complained of visual abnormalities, including poor color vision and decreased visual acuity. She was readmitted 8 days after discharge from her first hospitalization. Funduscopic examination revealed pale optic nerves bilaterally with some blurring of the optic disc margins, consistent with optic neuritis. Repeat brain MRI revealed interval development of bilateral optic neuritis involving the prechiasmatic optic nerves. The prechiasmatic optic nerves were mildly enlarged and demonstrated heterogeneous high signal on T2-weighted images and irregular enhancement on postgadolinium images with poor definition of the margins of both optic nerves, suggesting adjacent inflammatory changes (**Figure 2**). Previously seen lesions of signal abnormality involving the gray and white matter of both cerebral hemispheres as well as the cerebellar hemisphere were significantly improved.

The patient received a repeat course of high-dose intravenous corticosteroids for 5 days. Brain MRI

performed after 4 days of steroid treatment showed improvement in the inflammatory changes within the optic nerves. Her vision gradually improved and was back to baseline after 5 days of steroid therapy. She was discharged on oral steroids with a 3-week taper and follow-up with neurology and ophthalmology.

Case Resolution

Brain MRI performed 1 week after the oral course of steroids was complete revealed normal optic nerves with only mild enhancement of the prechiasmatic nerves and substantial resolution of the lesions noted on her first MRI, with only minimal residual FLAIR hyperintensity in those regions (**Figure 3**). Six months after her initial presentation, she remained symptom-free.

No infectious agent was clearly identified as the cause of this patient's ADEM. Serologic testing for Epstein-Barr virus (EBV), herpes simplex virus, varicella-zoster virus (VZV), *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Chlamydia trachomatis*, and *Chlamydia psittaci* was negative. Polymerase chain reaction (PCR) was negative for EBV, herpes simplex virus, and VZV in the CSF. Viral cultures of the CSF, including enterovirus, were negative. CSF Lyme titers were negative. She did have an elevated serum titer of human herpesvirus 6 (HHV-6) IgG antibody at 1:1280 (normal, < 1:80), possible evidence of recent past infection. Her CSF was negative for HHV-6 by PCR. HHV-6 IgM or repeat (convalescent) HHV-6 IgG titers were not obtained.

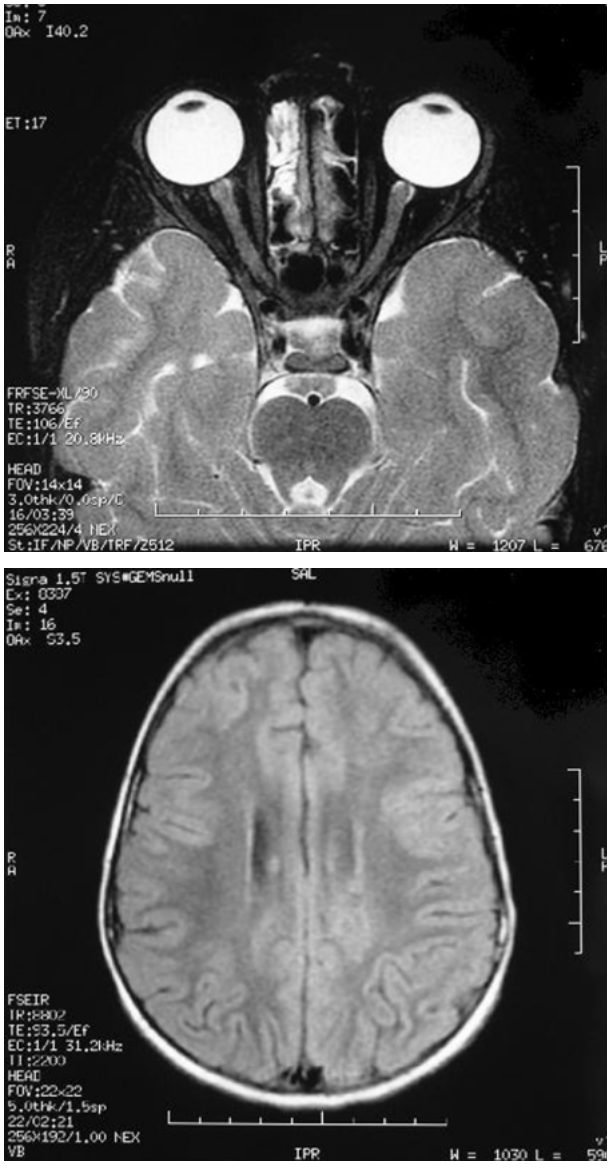

Figure 3. Cranial magnetic resonance images (axial projections) of the case patient obtained 1 week after completion of oral steroid therapy. Near complete resolution of inflammatory demyelination changes is demonstrated in both images, including the prechiasmatic optic pathway (*upper panel*).

DISCUSSION

Epidemiology of ADEM

ADEM has a low incidence, and it is estimated that a hospital-based general pediatrician with access to MRI will probably see 1 case per year.[1] In a review of 360 children diagnosed with ADEM, 60% were boys.[2] Younger children (in the first decade of life) are more commonly affected,[3–5] although ADEM does occur in adults.[6] Some studies have shown a seasonal distribution with peak incidence in winter and spring.[3,4]

The epidemiology of ADEM has changed over time. In the past, ADEM followed infections such as chicken pox, measles, and smallpox. Due to widespread immunization, ADEM in developed countries is now seen most frequently after nonspecific upper respiratory tract infections and acute febrile illnesses.[4]

Etiology

The etiology of ADEM is unknown. Results from animal models indicate that both an infectious mechanism and an autoimmune response may contribute to the demyelination.[7] Myelin autoantigens, such as myelin basic protein, proteolipid protein, and myelin oligodendrocyte protein, may share similar antigenic determinants with those of an infecting pathogen.[8] The body may mount an immune reaction producing antimicrobial antibodies or a cell-mediated response, which cross-reacts with the myelin autoantigens and results in demyelination. Studies have shown that lymphocytes, especially the T helper 2 T cells, have

Table. Etiologic Agents Implicated in Acute Disseminated Encephalomyelitis

Infectious agents
Viruses
Herpes simplex virus[1,4]
HIV[1]
Human herpesvirus 6[1]
Measles[1,4]
Hepatitis A and B[1,4]
Varicella zoster virus[1,4]
Rubella[4]
Mumps[1,4]
Influenza A and B[1,4]
Coxsackievirus[1,4]
Epstein-Barr virus[1,4]
Cytomegalovirus[1,10]
Rotavirus[4,11]
Bacteria
Mycoplasma pneumoniae[1,4,7,12,13]
Group A β-hemolytic streptococcus[1,4,14]
Campylobacter sp.[1,4]
Salmonella sp.[1]
Chlamydia sp., *Legionella* sp.[1,4,13]
Leptospirosis[1]
Borrelia burgdorferi[1]
Rickettsiae[1,4,15]
Immunization
Measles[1]
Rubella[1]
Meningitis A and C[1,16]
Influenza[1]
Japanese B encephalitis[1]
Smallpox[1]
Bacille Calmette-Guérin[1]
Diphtheria[17]
Tetanus[17]
Polio[17]
Hepatitis B[18]
Rabies[1,19]
Idiopathic

Adapted largely from Stonehouse et al[1] and Murthy et al,[4] with additional sources noted.

increased reactivity to myelin basic protein in children with ADEM.[9]

Despite attempts to identify microbial pathogens in patients with ADEM, usually no infectious agent is identified, as was seen with the case patient. Many viruses and bacteria have been associated with ADEM (**Table**). ADEM following immunization is rare but has been reported (Table). Post-immunization ADEM is most commonly associated with measles, mumps, and rubella vaccinations. The incidence is 1 to 2 per million doses of live measles vaccine immunizations, which is 20 times lower than the incidence of ADEM after natural measles virus infection.[20–22]

The case patient developed an enteric infection due to rotavirus during the course of her first hospitalization. Rotavirus has been reported to be associated with ADEM.[4] A report described 2 patients with rotavirus disease and encephalopathy, with MRI findings consistent with ADEM in one of the children.[11] The patient was hospitalized during rotavirus season and may have contracted this virus in the community or hospital, complicating but not causally related to the ADEM.

Patient Presentation

A prodromal phase, beginning 4 to 21 days after the inciting event, often occurs, typically consisting of fever, malaise, myalgia, headache, stiff neck, nausea, and vomiting.[17] The onset of the CNS disorder follows in the next 1 to 20 days,[7] with a rapid progression to peak neurologic dysfunction seen over several days. A characteristic feature of ADEM is multifocal neurologic signs and symptoms, including motor deficits (ataxia, paraparesis, hemiparesis, monoparesis), altered consciousness, sensory deficits, movement disorders, tremors, dysarthria, aphasia, nystagmus, urinary retention or incontinence, cranial neuropathies, optic neuritis, transverse myelitis, and seizures.[18] Occasionally, there may be rapid progression to coma and decerebrate rigidity.[1] Although rare, ADEM can present as a subtle illness in children with poorly explained irritability, headaches, or psychiatric illness.[23,24] A rare hemorrhagic variety known as Weston-Hurst syndrome has also been described.[8]

Diagnostic Methods

Children with ADEM often have evidence of inflammation in laboratory studies. Elevation of the leukocyte count, particularly the lymphocyte count, is common. The erythrocyte sedimentation rate and CRP level may also be elevated. CSF findings are typically normal, although in some cases lymphocytosis, elevated protein concentration, and/or elevated pressure may be seen. The glucose level in the CSF is usually normal. Special CSF studies may reveal increased levels of gammaglobulin, IgG, myelin basic protein, and the presence of

oligoclonal bands, although these findings are thought to be nonspecific.[7] Serologic testing for EBV, *Mycoplasma* species, herpes, VZV, influenza A and B, mumps, cytomegalovirus, and rubella is rarely positive.

Electroencephalogram (EEG) abnormalities are common but nonspecific and are not routinely used to diagnose ADEM.[17] An EEG may show an excess of background activity, consistent with encephalopathy or encephalitis. Rarely, an EEG will show focal epileptiform activity.[1]

A head CT is usually normal at onset and is often not helpful in establishing a diagnosis because it usually takes 5 to 14 days for abnormalities to appear.[25] The typical CT scan shows lesions of low attenuation in the subcortical white matter.[17] MRI of the brain usually shows early features of the disseminated CNS demyelination associated with ADEM. MRI T2-weighted and FLAIR images show patchy areas of increased signal intensity.[26] Involvement of the deep and subcortical white matter is almost universal. Lesions may be extensively distributed. Gray matter lesions are seen less frequently and only with the more characteristic white matter lesions. Involvement of the thalami and basal ganglia is a typical finding in ADEM. Spinal cord and brainstem lesions are occasionally seen. Follow-up MRI scans typically show evidence of partial or complete resolution of the lesions.[1]

Differential Diagnosis

Meningitis and encephalitis must be ruled out in a child with fever and CNS findings. Acute cerebellar ataxia, intoxication, Guillain-Barré syndrome, CNS tumors or bleed, head injury, metabolic disturbances, and hydrocephalus may be part of the differential diagnosis based on patient presentation. Findings on MRI can provide useful complementary information to the clinical picture. The MRI findings typical of ADEM, however, may also be seen in multiple sclerosis (MS), vasculitis, subcortical arteriosclerotic leukoencephalopathy, neurosarcoidosis, progressive multifocal leukoencephalopathy, HIV encephalitis, subacute sclerosing panencephalitis, mitochondrial encephalopathy, leukodystrophies, leukoencephalopathies following chemotherapy and radiation, and osmotic myelinolysis.[27]

Treatment

Appropriate viral and bacterial cultures of blood and CSF should be obtained in patients presenting with fever, meningism, acute encephalopathy, and evidence of inflammation in blood and CSF. Consideration should be given for the empiric coverage with antibiotics and/or antivirals pending the results of culture or PCR testing. Both glucocorticoids and intravenous immunoglobulin have been used in the treatment of ADEM.[28] Because the disease is rare, treatment modalities have not been subject to randomized controlled clinical trials.[28] Treatment of ADEM is targeted to suppress a presumed aberrant immune response and typically involves 3 to 5 days of high-dose intravenous methylprednisolone (20–30 mg/kg/d), with or without a following course of oral prednisolone beginning at 2 mg/kg/d and tapering over 4 to 6 weeks depending on clinical response.[1] Despite the lack of case-controlled studies to prove the efficacy of steroids, anecdotal evidence of their benefit is strong.[29] Spontaneous remission occurs, although treatment with steroids is usually considered beneficial in most patients. When steroids fail to stabilize or improve the clinical situation, intravenous gammaglobulins[30–32] or plasmapheresis[33–35] have been beneficial in case reports and small series.

Clinical Course

After beginning treatment, most children have clear improvement over the following days, weeks, and months with no subsequent neurologic impairment. In the past, ADEM was associated with a mortality rate of 25% after measles infection, with major residual neurologic sequelae in 25% to 40% of survivors.[36,37] More recent data from 3 retrospective reviews of children diagnosed with ADEM found 100% survival, with more than 80% of children neurologically normal in follow-up.[3,4,18]

ADEM can relapse, with most reported cases occurring after rapid weaning of high-dose steroids.[4] Relapses beyond the first few months of the initial illness may indicate MS, especially if new symptoms develop or new CNS lesions are found on imaging studies. In a large study that followed children initially diagnosed with ADEM for a mean of 9 years, 18% had ADEM relapses and 14% were later diagnosed with MS.[38] Although the onset of MS usually occurs in the third and fourth decades of life, it has been reported in children. In a study of 4632 MS patients, 2.7% had initial manifestations before age 16 years.[39]

The distinction between ADEM and MS cannot be made with absolute certainty at initial presentation. A second attack of MS may occur over a period of months to years in children; therefore, establishing a diagnosis of MS may require prolonged follow-up. There are several differences, however, between ADEM and MS.[3] With ADEM, there is often a prodromal viral illness, fever, and meningism, which is unusual with MS. Ataxia is common in ADEM but rarely a presenting feature in childhood MS. ADEM typically produces

widespread CNS disturbance and alterations in consciousness, which are seldom seen in MS. Unlike ADEM, MS usually presents as a monosymptomatic syndrome, such as optic neuritis or a subacute myelopathy, and typically develops a relapsing-remitting course. The distinction between ADEM and MS is important, as treatments available for relapsing-remitting MS have been shown in randomized trials to alter the natural history of the disease.[40,41]

CONCLUSION

ADEM often presents as an acute polysymptomatic encephalopathy with minimal CSF and CT findings. A history of recent infection or immunization and a MRI scan demonstrating extensive white matter changes aids in the diagnosis. Steroids are generally accepted as beneficial therapy, and long-term prognosis is favorable. ADEM is considered to be a monophasic illness. Relapses beyond the first few months of the initial illness should lead the clinician to consider MS as the diagnosis. **HP**

REFERENCES

1. Stonehouse M, Gupte G, Wassmer E, Whitehouse WP. Acute disseminated encephalomyelitis: recognition in the hands of general paediatricians. Arch Dis Child 2003;88:122–4.
2. Davis LE, Booss J. Acute disseminated encephalomyelitis in children: a changing picture. Pediatr Infect Dis 2003; 22:829–31.
3. Dale RC, de Sousa C, Chong WK, et al. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain 2000;123 Pt 12:2407–22.
4. Murthy SN, Faden HS, Cohen ME, Bakshi R. Acute disseminated encephalomyelitis in children. Pediatrics 2002;110(2 Pt 1):e21.
5. Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. Neurology 2002;59:1224–31.
6. Wang PN, Fuh JL, Liu HC, Wang SJ. Acute disseminated encephalomyelitis in middle-aged or elderly patients. Eur Neurol 1996;36:219–23.
7. Stuve O, Zamvil SS. Pathogenesis, diagnosis, and treatment of acute disseminated encephalomyelitis. Curr Opin Neurol 1999;12:395–401.
8. Fisher RS, Clark AW, Wolinsky JS, et al. Postinfectious leukoencephalitis complicating *Mycoplasma pneumoniae* infection. Arch Neurol 1983;40:109–13.
9. Pohl-Koppe A, Burchett SK, Thiele EA, Hafler DA. Myelin basic protein reactive Th2 T cells are found in acute disseminated encephalomyelitis. J Neuroimmunol 1998;91:19–27.
10. Kanzaki A, Yabuki S. [Acute disseminated encephalomyelitis (ADEM) associated with cytomegalovirus infection—a case report.] [Article in Japanese.] Rinsho Shinkeigaku 1994;34:511–3.
11. Lynch M, Lee B, Azimi P, et al. Rotavirus and central nervous system symptoms: cause or contaminant? Case reports and review. Clin Infect Dis 2001;33:932–8.
12. Yamamoto K, Takayanagi M, Yoshihara Y, et al. Acute disseminated encephalomyelitis associated with *Mycoplasma pneumoniae* infection. Acta Paediatr Jpn 1996;38:46–51.
13. Easterbrook PJ, Smyth EG. Post-infectious encephalomyelitis associated with *Mycoplasma pneumoniae* and *Legionella pneumophila* infection. Postgrad Med J 1992; 68:124–8.
14. Hall MC, Barton LL, Johnson MI. Acute disseminated encephalomyelitis-like syndrome following group A beta-hemolytic streptococcal infection. J Child Neurol 1998;13:354–6.
15. Wei TY, Baumann RJ. Acute disseminated encephalomyelitis after Rocky Mountain spotted fever. Pediatr Neurol 1999;21:503–5.
16. Py MO, Andre C. [Acute disseminated encephalomyelitis and meningococcal A and C vaccine: case report.] [Article in Portuguese.] Arq Neuropsiquiatr 1997;55:632–5.
17. Garg RK. Acute disseminated encephalomyelitis. Postgrad Med J 2003;79:11–7.
18. Hynson JL, Kornberg AJ, Coleman LT, et al. Clinical and neuroradiologic features of acute disseminated encephalomyelitis in children. Neurology 2001;56:1308–12.
19. Apak RA, Kose G, Anlar B, et al. Acute disseminated encephalomyelitis in childhood: report of 10 cases. J Child Neurol 1999;14:198–201.
20. Murthy JM, Yangala R, Meena AK, Jaganmohan Reddy J. Acute disseminated encephalomyelitis: clinical and MRI study from South India. J Neurol Sci 1999;165:133–8.
21. Fenichel GM. Neurological complications of immunization. Ann Neurol 1982;12:119–28.
22. Nalin DR. Mumps, measles, and rubella vaccination and encephalitis [letter]. BMJ 1989;299:1219.
23. Nasr JT, Andriola MR, Coyle PK. ADEM: literature review and case report of acute psychosis presentation. Pediatr Neurol 2000;22:8–18.
24. Patel SP, Friedman RS. Neuropsychiatric features of acute disseminated encephalomyelitis: a review. J Neuropsychiatry Clin Neurosci 1997;9:534–40.
25. Lukes SA, Norman D. Computed tomography in acute disseminated encephalomyelitis. Ann Neurol 1983;13: 567–72.
26. Edwards-Brown MK, Bonnin JM. White matter diseases. In: Atlas SW, editor. Magnetic resonance imaging of the brain and spine. 2nd ed. New York: Raven Press; 1996: 649–706.
27. Triulzi F, Scotti G. Differential diagnosis of multiple sclerosis: contribution of magnetic resonance techniques. J Neurol Neurosurg Psychiatry 1998;64 Suppl 1:S6–14.
28. Deputy SR. The treatment of acute disseminated encephalomyelitis with corticosteroids or intravenous immune globulin: pro article. Pediatr Infect Forum 2003;5:2, 6.
29. Hawley RJ. Early high-dose methylprednisolone in acute

disseminated encephalomyelitis [letter]. Neurology 1998;51:644–5.
30. Kleiman M, Brunquell P. Acute disseminated encephalomyelitis: response to intravenous immunoglobulin. J Child Neurol 1995;10:481–3.
31. Hahn JS, Siegler DJ, Enzmann D. Intravenous gammaglobulin therapy in recurrent acute disseminated encephalomyelitis. Neurology 1996;46:1173–4.
32. Finsterer J, Grass R, Stollberger C, Mamoli B. Immunoglobulins in acute, parainfectious, disseminated encephalomyelitis. Clin Neuropharmacol 1998;21:258–61.
33. Stricker RB, Miller RG, Kiprov DD. Role of plasmapheresis in acute disseminated (postinfectious) encephalomyelitis. J Clin Apheresis 1992;7:173–9.
34. Kanter DS, Horensky D, Sperling RA, et al. Plasmapheresis in fulminant acute disseminated encephalomyelitis. Neurology 1995;45:824–7.
35. Dodick DW, Silber MH, Noseworthy JH, et al. Acute disseminated encephalomyelitis after accidental injection of a hog vaccine: successful treatment with plasmapheresis. Mayo Clin Proc 1998;73:1193–5.
36. Litvak AM, Sands IJ, Gibel H. Encephalitis complicating measles: report of 56 cases with follow-up studies in 32. Am J Dis Child 1943;65:265–95.
37. Miller HG, Evans MJ. Prognosis in acute disseminated encephalomyelitis; with a note on neuromyelitis optica. Q J Med 1953;22:347–79.
38. Rust RS, Dodson W, Prensky A, et al. Classification and outcome of acute disseminated encephalomyelitis [abstract]. Ann Neurol 1997;42:491.
39. Duquette P, Murray TJ, Pleines J, et al. Multiple sclerosis in childhood: clinical profile in 125 patients. J Pediatr 1987;111:359–63.
40. Johnson KP, Brooks BR, Cohen JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995;45:1268–76.
41. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG) [published erratum appears in Ann Neurol 1996;40:480]. Ann Neurol 1996;39:285–94.