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another chronic inflammatory disorder such as vasculitis, sarcoidosis, or lymphoma. Many cases previously thought to represent ADEM are now recognized as MOGAD. The hallmark of ADEM is the presence of widely scattered foci of perivenular inflammation and demyelin ation that can involve both white matter and gray matter structures, in contrast to larger confluent white matter lesions typical of MS. In the most explosive form of ADEM, acute hemorrhagic leukoencephalitis, the lesions are vasculitic and hemorrhagic, and the clinical course is devastating.

Postinfectious encephalomyelitis is most frequently associated with the viral exanthems of childhood. Infection with measles virus is the most common antecedent (1 in 1000 cases). Worldwide, measles encephalomyelitis is still common, although use of the live measles vaccine has dramatically reduced its incidence. In developed countries, ADEM is now most frequently associated with varicella (chickenpox) infections (1 in 4000–10,000 cases). It may also follow infection with rubella, mumps, influenza, parainfluenza, Epstein-Barr virus, human herpesvirus-6, HIV, dengue, Zika, other viruses, and Mycoplasma pneumoniae. Cases have also been described in association with SARSCoV-2 infection. Some patients may have a nonspecific upper respira tory infection or no known antecedent illness. Modern vaccines appear to pose no meaningful risk for ADEM; one large study (Vaccine Safety Datalink) of 24 different vaccines in >9 million individuals (64 million doses in total) revealed no excess risk for ADEM, with the possible exception of Tdap (tetanus, diphtheria, acellular pertussis) vaccine estimated at less than one case per million doses. PART 13 Neurologic Disorders All forms of ADEM presumably result from a cross-reactive immune response to the infectious agent that then triggers an inflam matory demyelinating response. Autoantibodies to MBP and other myelin antigens have been detected in the CSF from some patients with ADEM, and as noted above, ADEM cases with serum or CSF antibod ies against MOG are now considered to be MOGAD. ■ ■CLINICAL MANIFESTATIONS In severe cases, onset is abrupt and progression rapid (hours to days). In postinfectious ADEM, the neurologic syndrome generally begins late in the course of the viral illness as the exanthem is fading. Fever reappears, and headache, meningismus, and lethargy progressing to coma may develop. Seizures are common. Signs of disseminated neu rologic disease are consistently present (e.g., hemiparesis or quadripa resis, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss, and brainstem

involvement). In ADEM due to chicken pox, cerebellar involvement is often conspicuous. CSF protein is mod estly elevated (0.5–1.5 g/L [50–150 mg/dL]). Lymphocytic pleocytosis, generally ≥200 cells/μL, occurs in 80% of patients. Occasional patients have higher counts or a mixed polymorphonuclear-lymphocytic pat tern during the initial days of the illness. Transient CSF oligoclonal banding was reported in a minority of cases. MRI usually reveals extensive changes in the brain and spinal cord, consisting of white matter hyperintensities on T2 and fluid-attenuated inversion recovery (FLAIR) sequences with gadolinium enhancement on T1-weighted sequences. ■ ■DIAGNOSIS The diagnosis is most reliably established when there is a history of a recent infectious illness. In severe cases with predominantly cerebral involvement, acute encephalitis due to infection with herpes simplex or other viruses including HIV may be difficult to exclude; other consid erations include hypercoagulable states including the antiphospholipid antibody syndrome, autoimmune (paraneoplastic) limbic encephalitis, vasculitis, sarcoidosis, primary CNS lymphoma, or metastatic cancer. An explosive presentation of MS can mimic ADEM, and especially in adults, it may not be possible to distinguish these conditions acutely. The simultaneous onset of disseminated symptoms and signs is com mon in ADEM and rare in MS. Similarly, meningismus, encephalopa thy (drowsiness, stupor or coma), and seizures suggest ADEM rather than MS. Unlike MS, in ADEM, optic nerve involvement is generally bilateral and transverse myelopathy complete. MRI findings that favor ADEM include extensive and relatively symmetric white matter

abnormalities, basal ganglia or cortical gray matter lesions, and gado linium enhancement of all abnormal areas. In contrast, OCBs in the CSF are more common in MS. In one study of adult patients initially thought to have ADEM, 30% experienced additional relapses over a follow-up period of 3 years, and they were reclassified as having MS. Other patients initially classified as ADEM are subsequently found to have NMO, MOGAD, or GFAP autoimmunity. Occasional patients with “recurrent ADEM” have also been reported, especially children; however, it is not possible to distinguish this entity from atypical MS. Because of the clinical overlap at presentation between ADEM and MS, it is important that routine surveillance imaging be performed follow ing recovery from ADEM so that subclinical disease activity due to MS can be recognized and treatment for MS initiated. ■ ■TREATMENT Initial therapy is with high-dose glucocorticoids; depending on the response, treatment may need to be continued for 8 weeks. Patients who fail to respond within a few days may benefit from a course of plasma exchange or IV immunoglobulin. The prognosis reflects the severity of the underlying acute illness. In modern case series of pre sumptive ADEM in adults, mortality rates of 5–20% are reported, and many survivors have permanent neurologic sequelae. ■ ■FURTHER READING Banwell B et al: Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. Lancet Neurol 22:268, 2023. Baxter R et al: Acute demyelinating events following vaccines: A casecentered analysis. Clin Infect Dis 63:1456, 2016. Cacciaguerra L et al: Updates in NMOSD and MOGAD diagnosis and treatment: A tale of two central nervous system autoimmune inflammatory disorders. Neurol Clin 42:77, 2024. Cree BAC et al: Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): A double-blind, randomised placebo-controlled phase 2/3 trial. Lancet 394:1352, 2019. Hagbohm C et al: Clinical and neuroimaging phenotypes of autoim mune glial fibrillary acidic protein astrocytopathy: A systematic review and meta-analysis. Eur J Neurol 20:e16284, 2024. Pittock SJ et al: Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N Engl J Med 381:614, 2019. Qin C et al: Single-cell analysis of anti-BCMA CAR T cell therapy in patients with central nervous system autoimmunity. Sci Immunol 9:eadj9730, 2024. Traboulsee A, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica

spectrum disorder: A randomised, doubleblind, multicentre, placebo-controlled phase 3 trial. Lancet Neurol 19:402, 2020. Wingerchuk DM et al: International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85:177, 2015. Section 3 Nerve and Muscle Disorders Anthony A. Amato, Richard J. Barohn

Peripheral Neuropathy Peripheral nerves are composed of sensory, motor, and autonomic elements. Diseases can affect the cell body of a neuron or its periph eral processes, namely the axons or the encasing myelin sheaths. Most peripheral nerves are mixed and contain sensory and motor as well as autonomic fibers. Nerves can be subdivided into three major

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