sphingosine-1-phosphate receptor antagonists to sequester lymphocytes in secondary lymphoid organs; (3) estriol to induce a pregnancy-like state; (4) molecules to promote remyelination; and (4) bone marrow transplantation.

CLINICAL VARIANTS OF MS

Acute MS (*Marburg's variant*) is a fulminant demyelinating process that in some cases progresses inexorably to death within 1–2 years. Typically, there are no remissions. When acute MS presents as a solitary, usually cavitary, lesion, a brain tumor is often suspected. In such cases, a brain biopsy is usually required to establish the diagnosis. An antibody-mediated process appears to be responsible for most cases. Marburg's variant does not seem to follow infection or vaccination, and it is unclear whether this syndrome represents an extreme form of MS or another disease altogether. No controlled trials of therapy exist; high-dose glucocorticoids, plasma exchange, and cyclophosphamide have been tried, with uncertain benefit.

NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO; Devic's disease) is an aggressive inflammatory disorder characterized by recurrent attacks of ON and myelitis (Table 458-7). NMO is more frequent in women than men (>3:1), typically begins in childhood or early adulthood but can arise at any age, and is uncommon in whites compared with individuals of Asian and African ancestry. Attacks of ON can be bilateral (rare in MS) or unilateral; myelitis can be severe and transverse (rare in MS) and is typically longitudinally extensive, involving three or more contiguous vertebral segments. Also in contrast to MS, progressive symptoms do not occur in NMO. The brain MRI was earlier thought to be normal in NMO, but it is now recognized that in approximately half of cases, there are lesions involving the hypothalamus causing an endocrinopathy; the lower brainstem presenting as intractable hiccoughs or vomiting from involvement of the area postrema in the lower medulla; or the cerebral hemispheres producing focal symptoms, encephalopathy, or seizures. Large MRI lesions in the cerebral hemispheres can be asymptomatic, sometimes have a "cloud-like" appearance and, unlike MS lesions, are often not destructive, and can resolve completely. Spinal cord MRI lesions typically consist of focal enhancing areas of swelling and tissue destruction, extending over three or more spinal cord segments, and on axial sequences, these are centered on the gray matter of the cord. CSF findings include pleocytosis greater than that observed in MS, with neutrophils and eosinophils present in some cases; OCBs are uncommon, occurring in fewer than 30% of NMO patients. The pathology of NMO is a distinctive astrocytopathy with inflammation, a loss of astrocytes, and an absence of staining of the water channel protein aquaporin-4 by immunohistochemistry, plus thickened blood vessel walls, demyelination, and deposition of antibody and complement.

NMO is best understood as a syndrome with diverse causes. Up to 40% of patients have a systemic autoimmune disorder, often systemic lupus erythematosus, Sjögren's syndrome, perinuclear antineutrophil cytoplasmic antibody (p-ANCA)–associated vasculitis, myasthenia gravis, Hashimoto's thyroiditis, or mixed connective tissue disease. In others, onset may be associated with acute infection with VZV, EBV, HIV, or tuberculosis. Rare cases appear to be paraneoplastic and associated with breast, lung, or other cancers. NMO is often idiopathic, however. NMO is usually disabling over time; in one series, respiratory failure from cervical myelitis was present in one-third of patients, and 8 years after onset, 60% of patients were blind and more than half had permanent paralysis of one or more limbs.

A highly specific autoantibody directed against aquaporin-4 is present in the sera of approximately two-thirds of patients with a clinical diagnosis of NMO. Seropositive patients have a very high risk for future relapses; more than half will relapse within 1 year if untreated. Aquaporin-4 is localized to the foot processes of astrocytes in close apposition to endothelial surfaces, as well as at paranodal regions near nodes of Ranvier. It is likely that aquaporin-4 antibodies are pathogenic, as passive transfer of antibodies from NMO patients into laboratory animals reproduce histologic features of the disease.

When MS affects individuals of African or Asian ancestry, there is a propensity for demyelinating lesions to involve predominantly the optic nerve and spinal cord, an MS subtype termed *opticospinal MS*. Interestingly, some individuals with opticospinal MS are seropositive for aquaporin-4 antibodies, suggesting that such cases represent an NMO spectrum disorder.

TABLE 458-7 DIAGNOSTIC CRITERIA FOR NEUROMYELITIS OPTICA

Required:

1. Optic neuritis
2. Acute transverse myelitis

Supportive (2 of 3 criteria required):

1. Longitudinally extensive cord lesion extending over 3 or more vertebral segments
2. Brain magnetic resonance imaging normal or not meeting criteria for multiple sclerosis
3. Aquaporin-4 seropositivity

Source: Adapted from DM Wingerchuk et al: Neurology 66:1485, 2006.

TREATMENT NEUROMYELITIS OPTICA

Disease-modifying therapies have not been rigorously studied in NMO. Acute attacks of NMO are usually treated with high-dose glucocorticoids (solumedrol 1–2 g/d for 5–10 days followed by a prednisone taper). Plasma exchange (typically 7 qod exchanges of 1.5 plasma volumes) has also been used empirically for acute episodes that fail to respond to glucocorticoids. Given the unfavorable natural history of untreated NMO, prophylaxis against relapses is recommended for most patients using one of the following regimens: mycophenylate mofetil (250 mg bid gradually increasing to 1000 mg bid); B cell depletion with anti-CD20 monoclonal antibody (rituximab); or a combination of glucocorticoids (500 mg IV methylprednisolone daily for 5 days; then oral prednisone 1 mg/kg per day for 2 months, followed by slow taper) plus azathioprine (2 mg/kg per day started on week 3). Available evidence suggests that use of IFN-β is ineffective and paradoxically may increase the risk of NMO relapses.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis (ADEM) has a monophasic course and is most frequently associated with an antecedent infection (postinfectious encephalomyelitis); approximately 5% of ADEM cases follow immunization (postvaccinal encephalomyelitis). ADEM is far more common in children than adults, and many adult cases initially thought to represent ADEM subsequently experience late relapses qualifying as either MS or another chronic inflammatory disorder such as vasculitis, sarcoid, or lymphoma. The hallmark of ADEM is the presence of widely scattered small foci of perivenular inflammation and demyelination, in contrast to larger confluent demyelinating 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. An ADEM-like illness rarely follows vaccination with live measles vaccine (1–2 in 10^6 immunizations). 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, EBV, HHV-6, HIV, other viruses, and *Mycoplasma pneumoniae*. Some patients may have a nonspecific upper respiratory infection or no known antecedent illness. In addition to measles, postvaccinal encephalomyelitis may also follow the administration