### Pathology

NMO lesions affect both white and gray matter and are located mainly in the spinal cord and optic nerves. In the brain, they are most common in the hypothalamus and around the fourth ventricle. NMO lesions center on blood vessels, where IgG, IgM, and complement activation products are seen. The vessels are abnormally thickened and hyalinized. Active NMO lesions show infiltration by mononuclear cells (lymphocytes, monocytes), neutrophils, and eosinophils. Older lesions display demyelination, axon loss, and death of oligodendroglia and neurons. In vitro and animal studies indicate that AQP4-IgG itself is pathogenic, causing complement- and antibody-mediated damage.

### Treatment

Acute relapses are treated with high-dose corticosteroids. If these are not effective, plasma exchange is usually tried.

Because NMO is a rare disease, large multi-center randomized, controlled trials of disease modifying therapies are lacking. Several short case series have pointed toward possible efficacy of azathioprine plus prednisone, rituximab, and mycophenolate mofetil for prevention of future attacks (level C). Eculizumab, a monoclonal antibody that inhibits the complement cascade, was used in a small open-label trial in AQP4-IgG positive NMO patients. Over one year, 85% had no relapses and no patient progressed in disability (level B). Of note, beta-interferons are not effective for NMO and may actually increase the rate of attacks.

### Prognosis

The necrotic nature of NMO results in worse outcomes than MS. Seropositive NMO patients tend to have more frequent and severe relapses than AQP4-IgG negative patients. Death can be a consequence and is often due to respiratory failure. The death rate in a retrospective study covering 1950-1997 was over 30%. Less than 10% mortality was reported in a more recent retrospective study of Caucasian NMO patients.

## ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis (ADEM) is an acute, inflammatory, presumed immune-mediated disorder of the CNS that is encountered primarily in children but may occur in adults. An antecedent viral infection, or occasionally a vaccination, is common. ADEM presents with multifocal neurologic symptoms and signs. These can include encephalopathy, which may manifest as reduced level of consciousness (even coma), or as behavioral changes (e.g. confusion or irritability). Fever is common. Seizures, optic neuritis, and spinal cord involvement can all occur. Males and females are about equally affected. ADEM is usually monophasic, although relapsing ADEM has been described. On MRI, both white and gray matter CNS regions are affected. Gray matter involvement can include the basal ganglia, a region not typically affected in MS. The periventricular white matter region is often spared, unlike MS. When present, enhancement with gadolinium occurs in all lesions simultaneously. CSF often shows pleocytosis and an elevated protein, but no infection. Findings typical of MS, such as oligoclonal bands, are not usual. No randomized prospective treatment trials for acute disseminated encephalomyelitis are reported. Intravenous methylprednisolone followed by a prednisone taper is typically administered, and the response is usually good (level D). Over 80% of cases recover well. As ADEM is only rarely recurrent, long-term immunomodulatory/immunosuppressive therapy is not indicated. A rare hemorrhagic form of ADEM (Weston Hurst syndrome) is more severe and can lead to death or severe disability.

## ACUTE TRANSVERSE MYELITIS

Transverse myelitis (TM) is an inflammatory spinal cord syndrome presenting with abrupt or subacute onset of motor and/or sensory loss below a specific spinal level. Control of bladder and bowel is often affected, as is autonomic function below the level. Back pain and paresthesias may be prominent. Many cases of acute TM are idiopathic, but treatable causes must be ruled out. An urgent MRI with and without gadolinium should be obtained to look for compressive etiologies needing immediate treatment. After a compressive etiology has been ruled out, a lumbar puncture to assess CSF for cell count, glucose, and protein, and cultures and PCRs for infectious causes should be done. The usual tests for MS should be performed, and CSF should be analyzed for evidence of neoplastic etiology. Serum AQP4-IgG, paraneoplastic panels and chest CT should be considered. CSF may also be tested for NMO-IgG, angiotensin converting enzyme, and paraneoplastic antibodies when no etiology is forthcoming.

Acute TM can be the presenting episode for MS (where the TM is generally incomplete and asymmetric) or NMO (where the TM affects ≥3 spinal cord segments). Acute TM can also be caused by spinal cord infarction due to occlusion of the anterior spinal artery. Infections by viruses can cause acute or subacute TM. The most common viruses associated with acute TM are varicella zoster, herpes virus type 2, and cytomegalovirus. The retroviruses HTLV-I and HIV can each cause a myelopathy that is usually subacute. West Nile virus can cause a myelopathy that resembles poliomyelitis, with flaccid paralysis due to infection and death of anterior horn cells. Subacute TM may be caused by vitamin B12 or copper deficiency, or infiltrating or compressive syndromes such as tumors or abscesses. Nitrous oxide anesthesia can precipitate an acute onset myelopathy in the case of borderline vitamin B12 deficiency. Rheumatologic disorders such as Sjögren's disease, systemic lupus erythematosus, and Behçet's disease can all cause TM. Paraneoplastic syndromes associated with anti-CRMP-5 and anti-amphiphysin can cause a tract-specific myelopathy. The history and physical examination should be performed with these disorders in mind.

Treatment is determined by the most likely etiology. Idiopathic TM is treated much like TM in MS or NMO, with intravenous methylprednisolone at 500 mg to 1000 mg/day, usually followed by a short oral prednisone taper (evidence level D). When response to intravenous methylprednisolone is suboptimal, plasma exchange should be considered.

## IDIOPATHIC ACUTE OPTIC NEURITIS

Inflammatory demyelinating optic neuritis can occur as part of MS or NMO, or as an idiopathic entity. Classically, optic neuritis presents over hours with loss of vision together with pain exacerbated by eye movement. Vision loss may range from subclinical to frank blindness. Color vision and contrast sensitivity are disproportionately affected. On examination, a relative afferent