complement. Therapies include approaches to reduce the antibody burden, either through plasmapheresis or depletion of B cells with anti-CD20 antibody.

Acute Disseminated Encephalomyelitis and Acute Necrotizing Hemorrhagic Encephalomyelitis

Acute disseminated encephalomyelitis is a diffuse, monophasic demyelinating disease that follows either a viral infection or, rarely, a viral immunization. Symptoms typically develop a week or two after the antecedent infection and include headache, lethargy, and coma rather than focal findings, as seen in MS. The clinical course is rapid, and as many as 20% of those affected die; the remaining patients recover completely.

Acute necrotizing hemorrhagic encephalomyelitis (also known as *acute hemorrhagic leukoencephalitis of Weston Hurst*) is a fulminant syndrome of CNS demyelination, typically affecting young adults and children. The illness is almost invariably preceded by a recent episode of upper respiratory infection, most often of unknown cause. The disease is fatal in many patients, with significant deficits present in most survivors.

MORPHOLOGY

In acute disseminated encephalomyelitis, cut sections of brain show only grayish discoloration around white-matter vessels. On microscopic examination, myelin loss with relative preservation of axons can be found throughout the white matter. In the early stages, neutrophils are found within the lesions; later, mononuclear infiltrates predominate. The breakdown of myelin is associated with the accumulation of lipid-laden macrophages. In contrast to MS, all lesions appear similar, consistent with the clinically monophasic nature of the disorder.

Acute necrotizing hemorrhagic encephalomyelitis shows histologic similarities with acute disseminated encephalomyelitis, including a perivenular distribution of demyelination throughout the CNS (sometimes producing confluent lesions). However, the damage is more severe and includes destruction of small blood vessels, disseminated necrosis of white and gray matter with acute hemorrhage, fibrin deposition, and abundant neutrophils. Scattered lymphocytes are seen in foci of demyelination.

The lesions of acute disseminated encephalomyelitis are similar to those induced by immunization of animals with myelin components or with early rabies vaccines that had been prepared from brains of infected animals. This has led to the suggestion that acute disseminated encephalomyelitis is an acute autoimmune reaction to myelin and that acute necrotizing hemorrhagic encephalomyelitis is a hyperacute variant, but inciting antigens have yet to be identified.

Central Pontine Myelinolysis

Central pontine myelinolysis is an acute disorder characterized by loss of myelin in the basis pontis and portions of the pontine tegmentum, typically in a roughly symmetric pattern. It most commonly arises 2 to 6 days after rapid correction of hyponatremia, although it can also be associated with other severe electrolyte disturbances or osmolar imbalances and may also be known as *osmotic demyelination disorder*. It appears that rapid increases in osmolality damage oligodendrocytes through uncertain mechanisms. Inflammation is absent from the lesions, and neurons and axons are well preserved. Because of the synchronous onset of damage, all lesions appear to be at the same stage of myelin loss and reaction. Although originally described in the pons, extra-pontine lesions with similar appearance and apparent etiology may also occur.

While it can involve most parts of the brain, periventricular and subpial regions are spared, and it is extremely rare for the process to extend below the pontomedullary junction. The clinical presentation of pontine lesions is that of a rapidly evolving quadriplegia, which may be fatal or lead to severe long-term deficits, including the "locked-in" syndrome, in which patients are fully conscious yet unresponsive. It is imperative that hyponatremia be corrected slowly and carefully in order to prevent this tragic complication.

KEY CONCEPTS

Demyelinating Diseases

- Because of the critical role of myelin in nerve conduction, diseases of myelin can lead to widespread and severe neurologic deficits.
- Demyelinating diseases show evidence of breakdown and destruction of previously normal myelin, often by inflammatory processes. Secondary injury to axons typically emerges over time as well.
- Multiple sclerosis, an autoimmune demyelinating disease, is the most common disorder of myelin, affecting young adults. It often pursues a relapsing-remitting course, with eventual progressive accumulation of neurologic deficits.
- Other, less common forms of immune-mediated demyelination often follow infections and are more acute illnesses.

Neurodegenerative Diseases

Neurodegenerative diseases are disorders characterized by the progressive loss of neurons, typically affecting groups of neurons with functional relationships even if they are not immediately adjacent. Thus, different diseases tend to involve particular neural systems and therefore have relatively stereotypic presenting signs and symptoms. Recent genetic and molecular studies have shaped the current classification of neurodegenerative diseases, in part from the recognition that there are many shared features.

The pathologic process that is common across most of the neurodegenerative diseases is the accumulation of protein aggregates, which can be used as a morphologic hallmark of the disease (hence the occasional use of the term "proteinopathy"). Protein aggregates may arise because of mutations that alter the protein's conformation or disrupt the pathways involved in processing or