

Neuroscience II

Pathology of Demyelinating diseases of the CNS

Dr. Hani Ahmed Alanqar
Consultant of pathology



DEMYELINATING DISEASES

Demyelinating diseases of the CNS are acquired conditions characterized by preferential damage to myelin with relative preservation of axons. The clinical deficits, at least initially, are due to the effect of myelin loss on the transmission of electrical impulses along axons.

Several pathologic processes can cause loss of myelin. These include immune-mediated destruction of myelin (as in multiple sclerosis [MS]) and infections (as in progressive multifocal leukoencephalopathy PML). In addition, inherited disorders may affect synthesis or turnover of myelin components; these are termed leukodystrophies.



Multiple Sclerosis (MS)

MS is an autoimmune demyelinating disorder characterized by distinct episodes of neurologic deficits that are separated in time and are attributable to patchy white matter lesions that are separated in space. It is the most common of the demyelinating disorders, having a prevalence of approximately 1 per 1000 persons in most of the United States and Europe.



The disease may become clinically apparent at any age, although onset in childhood or after 50 years of age is relatively rare. Women are affected twice as often as are men. In most individuals with MS, the clinical course takes the form of relapsing and remitting episodes of variable duration (weeks to months to years) marked by neurologic defects, followed by gradual and partial recovery of neurologic function. The frequency of relapses tends to decrease over time, but there is a steady neurologic deterioration in most affected individuals.



Pathogenesis

MS is caused by an autoimmune response directed against components of the myelin sheath. As in other autoimmune disorders, the pathogenesis of this disease involves both genetic and environmental factors . The incidence of MS is 15-fold higher when the disease is present in a first-degree relative and roughly 150-fold higher with an affected monozygotic twin.

Environmental factors are also important. For example, there is geographic variation in the prevalence of MS, with a higher number of cases diagnosed away from the equator; it has been proposed that this latitude dependence may be related to a low level of vitamin D (an immune system modulator) in people who are not exposed to sunlight during winter.

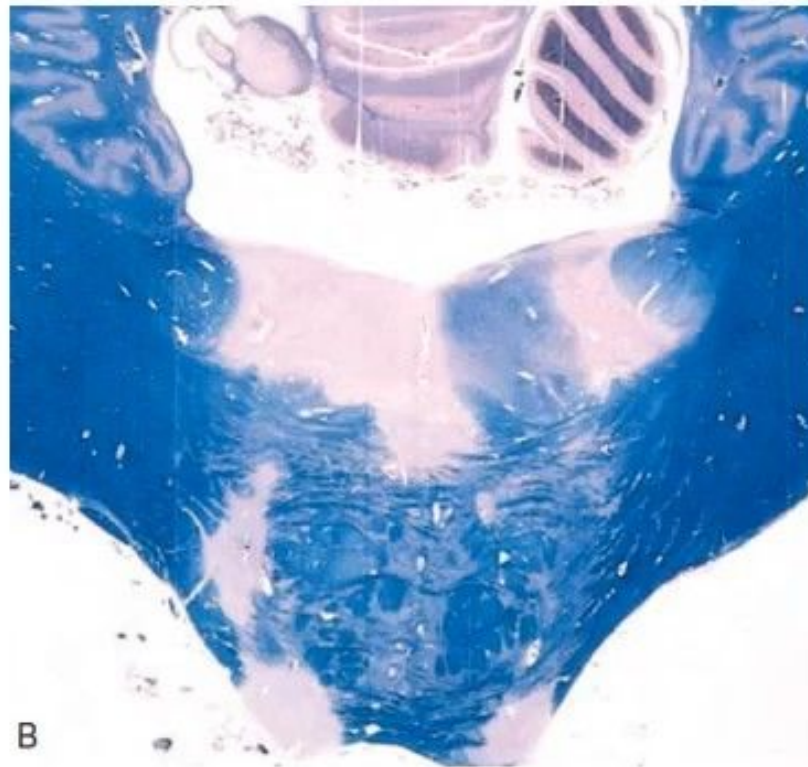


MORPHOLOGY

MS is a white matter disease that is best appreciated in sections of the brain and spinal cord. In the fresh state, the lesions are firmer than the surrounding white matter (“sclerosis”) and appear as well circumscribed, somewhat depressed, glassy, gray-tan, irregularly shaped plaques . The area of demyelination often has sharply defined borders, a feature best appreciated with stains for myelin . The size of lesions varies considerably, from small foci that are only recognizable microscopically to large confluent plaques.

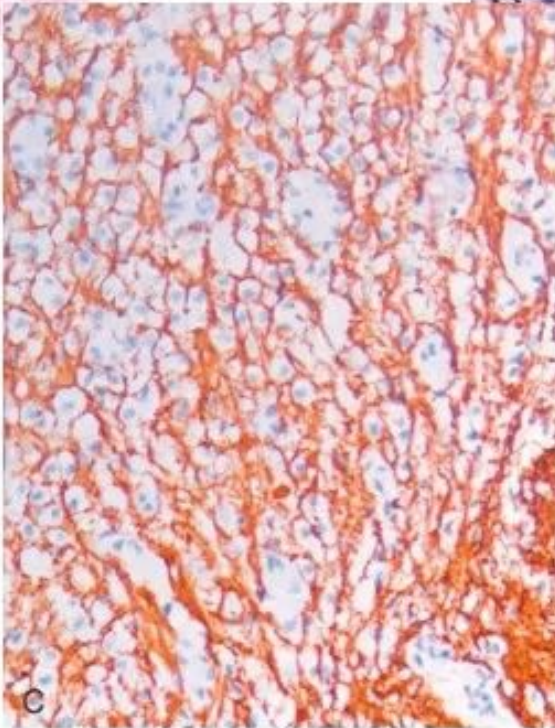
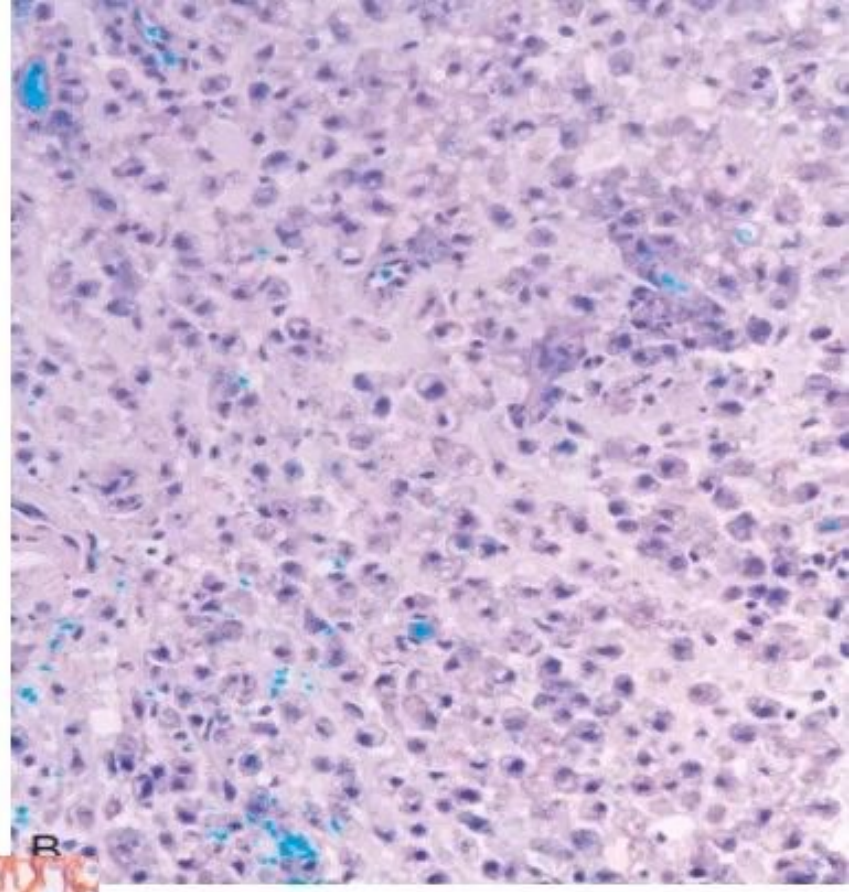
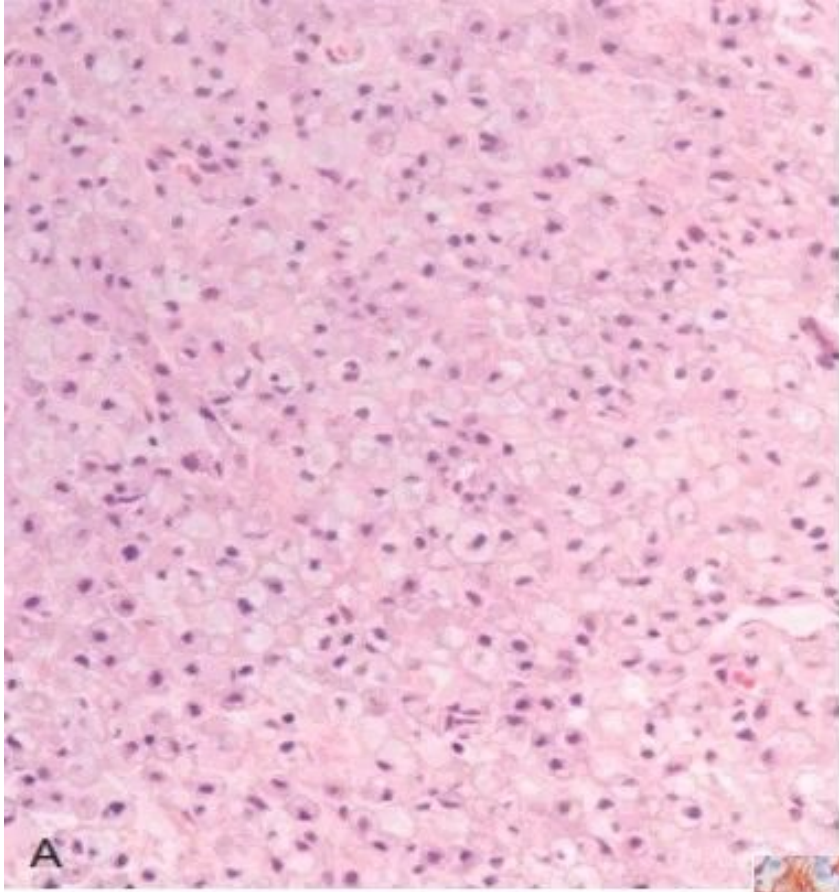


Plaques commonly occur adjacent to the lateral ventricles and are also frequent in the corpus callosum, optic nerves and chiasm, brainstem, ascending and descending fiber tracts, cerebellum, and spinal cord. Plaques can extend into gray matter because myelinated fibers are present there as well.



Microscopically, in an active plaque, there is ongoing myelin breakdown associated with abundant foamy macrophages ; lymphocytes are also present, mostly as perivascular cuffs, especially at the outer edge of the lesion. Active lesions are often centered on small veins; myelin is usually completely absent , but axons are relatively preserved . In time, astrocytes undergo reactive changes. As lesions become quiescent, the inflammatory cells slowly disappear. Within inactive plaques, there is no macrophage-rich infiltrate, little to no myelin is found, and there is a reduction in the number of oligodendrocyte nuclei; instead, reactive gliosis is prominent. Axons in old gliotic plaques are usually greatly diminished in number.





Clinical Features

Although MS lesions can occur anywhere in the CNS and consequently may induce a wide range of clinical manifestations, certain patterns of neurologic symptoms and signs are more common. Unilateral visual impairment due to involvement of the optic nerve (optic neuritis) is a frequent initial manifestation of MS. However, only a minority of individuals (10% to 50%, depending on the population studied) with an episode of optic neuritis go on to develop MS (which requires multiple episodes to support the diagnosis).

Involvement of the brainstem produces cranial nerve signs (ataxia,). Spinal cord lesions give rise to motor and sensory impairment of trunk and limbs, spasticity, and loss of bladder control. Examination of the CSF in individuals with MS shows a mildly elevated protein level and in one-third of cases a moderate pleocytosis. IgG levels in the CSF are increased,



Neuromyelitis Optica (NMO)

is a syndrome with synchronous (or near-synchronous) bilateral optic neuritis and spinal cord demyelination. Once considered a variant of MS, it is clearly a distinct disorder. NMO has an even greater skewing toward women than MS, is more commonly associated with poor recovery from the first attack, and is often characterized by the presence of aquaporin-4 antibodies, which appear to be pathogenic. Areas of demyelination in NMO show loss of aquaporin-4, the major water channel of astrocytes. White cells (often including neutrophils) are common in the CSF. Within the damaged areas of white matter, there is typically necrosis, an inflammatory infiltrate including neutrophils and eosinophils, and vascular immunoglobulin and complement deposition. Acute attacks are treated with glucocorticoids or plasma exchange, while long-term treatments include agents that decrease antibody titers (e.g., by depleting B cells) or that inhibit complement



Acute Disseminated Encephalomyelitis and Acute Necrotizing Hemorrhagic Encephalomyelitis

Acute disseminated encephalomyelitis is a diffuse, monophasic demyelinating disease that follows a viral infection or, rarely, a viral immunization. Symptoms typically develop 1 or 2 weeks after the antecedent event and include headache, lethargy, and coma rather than focal findings, as seen in MS; in contrast to MS, all brain lesions appear similar, consistent with the clinically monophasic nature of the disorder. The clinical course is rapid, and as many as 20% of those affected die; the remaining patients usually recover completely.



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Acute necrotizing hemorrhagic encephalomyelitis (also known as acute hemorrhagic leukoencephalitis or Weston Hurst disease) 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. This disorder shows histologic similarities with acute disseminated encephalomyelitis; however, the damage is more severe. The disease is fatal in many patients, with significant deficits present in most survivors.



Central Pontine Myelinolysis

Is an acute disorder characterized by loss of myelin in the base of the pons 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 is clinically known as osmotic demyelination syndrome. 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.

