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Demyelinating and Inflammatory Disorders

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INTRODUCTION

In demyelinating CNS disorders, previously normal myelin is lost due to an acquired, typically inflammatory disease. The prototypic CNS demyelinating disorder is multiple sclerosis (MS). Other disorders of this type include neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), acute transverse myelitis (TM), and optic neuritis (ON).

MULTIPLE SCLEROSIS

Definition/Epidemiology

According to the National Multiple Sclerosis Society, MS affects over 2 million people worldwide. It is a presumed autoimmune disorder, although the exact etiology is still not fully understood. MS begins as a relapsing remitting disease in greater than 80% of patients and ultimately becomes progressive in greater than 50% of untreated patients. Patients with progressive MS accumulate neurologic disability, with or without discrete relapses. MS is more common in females, with the current female to male ratio in North America and in Europe estimated at 2-4 : 1. An exception is primary progressive MS (see Clinical Presentation), where the female to male ratio is 1 : 1.

MS is most common in persons of northern European ancestry. Recent genome-wide association studies indicate that many genes affect the risk of MS, although most confer only a small risk of disease (odds ratios less than 1.5). Alleles within the HLA-DR region (DRB1*15:01 > DRB1*13:03 > DRB1*03:01) are the most well-established and confer the greatest risk with odds ratios between 1.5 and 4 for most populations of northern European ancestry.

Environmental factors can also confer risk for MS. Modifiable factors include low vitamin D blood level, high body mass index during adolescence/young adulthood, and smoking cigarettes. Seropositivity to the Epstein Barr virus increases the risk of MS; a symptomatic case of infectious mononucleosis confers greater risk than seropositivity alone. Though relatively high at 1/1000 to 1/500, the incidence of MS appears relatively stable in North America, the United Kingdom, and Europe. Incidence of MS may be increasing in several regions where MS was not previously prevalent, such as Iran, Turkey, Sicily, and South Africa. These reports of increasing incidence may reflect a real increase or just improved recognition and diagnosis.

Pathology

Classically, MS causes demyelinating CNS white matter lesions with relative sparing of axons. The most common pathology of active lesions in white matter is perivascular mononuclear cell infiltration (monocyte/macrophages, lymphocytes), with a variable presence of antibody and activated complement. Acutely active white matter lesions display blood-brain barrier breakdown, which is manifest on MRI by gadolinium enhancement. Despite its categorization as a "white matter disease," gray matter is frequently damaged in MS. Gray matter lesions have been under-recognized because they are difficult to see by MRI, and are often not appreciated pathologically without special stains. Such gray matter lesions may occur in the white matter tracts within deep gray structures such as the thalamus or be within gray matter itself, such as in the cerebral cortex. Cortical gray matter lesions can be subpial, extend into cortex from underlying white matter (leukocortical), or be wholly within the cortex. Cortical lesions are characterized by activated microglia and relatively fewer infiltrating lymphocytes and macrophages when compared with white matter MS lesions. Ectopic lymphoid tissue containing B cells, a finding associated with chronic inflammation, has also been observed in meninges of progressive MS subjects.

Clinical Presentation

MS may manifest with a variety of symptoms and signs. Common presentations include: optic neuritis, diplopia (often caused by internuclear ophthalmoplegia due to a propensity of MS to affect the medial longitudinal fasciculus), TM, brainstem syndromes, sensory disturbances, and weakness. Less frequent presentations include seizures, cognitive problems, bladder control problems, and pain. Clinically isolated syndrome (CIS) refers to a single attack that is likely due to CNS demyelination. CIS may be acute or subacute in onset, and may involve a single or more than one CNS region. CIS presentations may look identical to MS attacks, but a formal diagnosis of MS cannot be made until the occurrence of separation of lesions in time. Ultimately, most CIS patients do develop MS. In one study, over 85% of CIS patients with even one silent abnormality on brain or spinal cord magnetic resonance imaging (MRI) eventually developed clinically definite MS. On the other hand, only about 20% of those without any other MRI abnormalities developed clinically definite MS.