**<u>Multiple Sclerosis</u> (Dr. Merchut)**

1. Pathophysiology

Multiple sclerosis (MS) is an **acquired disorder with immune-mediated destruction of normal central nervous system (CNS) myelin** with secondary loss of axons. Such axonal damage may be more predominant and may occur earlier in the course of MS than previously thought. As a **demyelinating** disease, MS is different than the dysmyelinating diseases or leukodystrophies, where abnormal myelin is produced by defective synthesis. Many leukodystrophies are known to be hereditary and often become symptomatic early in life.

Demarcated **white matter plaques** are the classic lesion in MS (Fig. 1), found in the optic nerves, spinal cord, and brain with a periventricular predominance. The immunological pathogenesis of a plaque is complex and not fully understood. An initial step is the penetration of the blood-brain-barrier (the tight junctions linking vascular endothelial cells) by lymphocytes (mostly T-cells) and monocyte-derived macrophages. This begins when adhesion molecules on circulating lymphocytes attach to endothelial receptors. (Natalizumab (Tysabri), a monoclonal antibody which blocks these adhesion molecules, is an effective new treatment for MS but is limited by potentially severe side-effects.) Once inside the brain, the inflammatory cascade escalates with further cytokine and antibody production, ingress and activation of more inflammatory cells, and prominent autoimmune destruction of myelin. At any given time, plaques may be "old" or "new" with varying degrees of inflammation and gliosis or scarring. Plaque formation in different parts of the CNS over time is the basis for the varied clinical symptoms experienced during the course of MS.

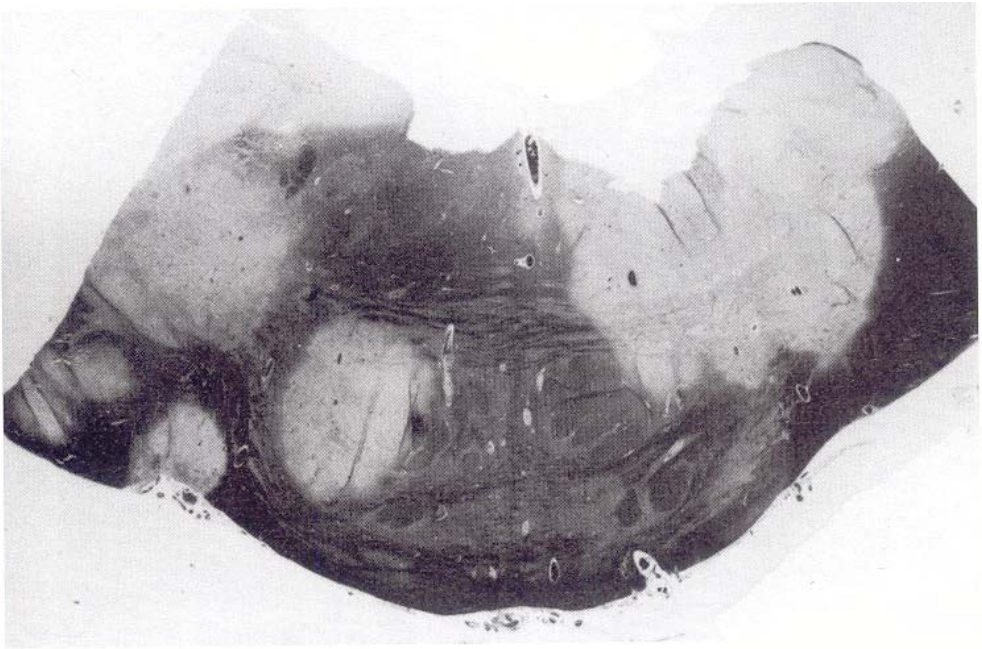

Fig. 1 Low-power, midpontine cross-section, using myelin stain showing multiple sclerosis plaques: well-circumscribed, nonstaining lesions without necrosis or tissue loss. (courtesy of Dr. John M. Lee, Department of Pathology, LUMC)

Within any particular plaque lesion, recovery may vary, but seems to be more favorable earlier in the course of the disease. Clinical signs and symptoms may soon disappear once inflammation has subsided and if only minimal demyelination occurred. Remyelination may be the predominant reparative process in a clinical MS "attack" with a longer recovery period. Some demyelinated axons may develop sodium channels uniformly along their surface, regaining the ability to transmit action potentials, although less efficiently than the saltatory conduction in myelinated axons. The worst scenario involves significant axonal injury and loss, which is the likely explanation for the lack of clinical recovery later in the course of MS, and the development of brain atrophy.

2. The cause of multiple sclerosis

It is unlikely that a single factor is the cause of multiple sclerosis. MS is more common in people born and raised in the temperate latitudes or global zones farther from the equator. This suggests an initiating environmental factor such as viral exposure at a critical time early in life. Although some trends have been found, no single virus type appears to be the solitary trigger of MS. Populations living in temperate zones tend to have lower vitamin D levels than those living in more sun-exposed regions nearer the equator. It has been suggested that low vitamin D levels may enhance the risk of developing MS or increase its severity. Hereditary factors also are important, since the siblings of an MS patient have a twentyfold greater risk of developing MS themselves. There may be a genetic predisposition for autoimmune diseases or MS in particular. In general, it appears that **MS occurs in a genetically susceptible patient exposed to one or more triggering factors (viruses?) that provoke an immune-mediated attack against CNS myelin** from an otherwise normal immune system.

Other immune-mediated CNS disorders bear some similarity to MS. Inflammatory white matter lesions also develop after a viral infection in postinfectious encephalomyelitis, but are monophasic and do not recur later in life. It seems that the viral infection may somehow alter CNS myelin to make it appear "foreign" or that antigenic similarity between virus (or related inflammatory factors) and CNS myelin provokes immunoreactivity to both. Animal models of MS have also been created and studied. Some unique features of MS remain unexplained, such as the confinement of the autoimmune process to the CNS, and its recurrence and persistence over time.

3. Clinical features of multiple sclerosis

MS is **usually a disease of young adults, with its onset between the ages of 20 and 40**. Whenever MS is considered a possibility in older adults, careful questioning and a thorough neurological examination may reveal milder symptoms of MS which occurred earlier in life and spontaneously improved. The female to male patient ratio in MS is almost 2 to 1. After initial symptoms begin the future course of MS is often unpredictable. **The majority, perhaps about 80%, of patients at first have a relapsing-remitting course**, consisting of episodic signs and symptoms, with minimal to no residual neurological deficit. Years later, the recovery from recurrent MS episodes tends to be incomplete or absent in about half of these patients, and neurological deficits accrue as part of the **secondary progressive phase of MS**. The other 20% of diagnosed

MS patients initially have a chronically progressive neurological disorder referred to as primary progressive MS. This subgroup of MS seems to have a different pathogenesis and does not respond well to immunomodulating therapy. In general, most MS patients survive for years despite variable degrees of neurological disability. Their cause of death is more often related to the medical complications associated with significant immobility such as infection, malnutrition, and pulmonary emboli.

The **most common initial signs and symptoms of MS involve the optic nerves or sensory or motor deficits in the lower limbs**. The latter is understandable since the longest white matter tracts in the CNS, functionally related to the lower limbs, are statistically more likely to develop MS plaques. **Optic neuritis** consists of a partial or total loss of vision in one eye, and will be discussed further in the section on Visual, Auditory and Vestibular Systems. Although commonly caused by MS, optic neuritis and the other syndromes described here are not entirely specific for MS and may be caused by other diseases. Blurry vision or diplopia may be due to **internuclear ophthalmoplegia (INO), also known as the medial longitudinal fasciculus (MLF) syndrome**. Paroxysmal jabs of pain on one side of the face may herald **trigeminal neuralgia**. These syndromes are discussed further in the section on Cranial Nerves, Brain Stem Reflexes, and Brain Stem Disorders. MS patients may report an "electric shock" or "tingling" sensation down the spine into the arms or legs provoked by neck flexion. This is **Lhermitte's sign**, caused by "short circuiting" within the posterior columns of the cervical spinal cord due to local demyelination or inflammation from MS plaques, but also caused by vitamin B12 deficiency, or compression of the spinal cord. Other nonspecific deficits include spastic paralysis, ataxia, or sensory deficits in the limbs, as well as bowel and bladder dysfunction and cognitive impairment.

An **MS "attack" (or relapse or exacerbation)** lasts at least 24 hours, consisting of the symptoms or signs related to the common or typical events mentioned above, in the absence of fever or infection (2010 revision of the McDonald diagnostic criteria for MS). Any MS patient may appear to have a recurrence of their previous symptoms during an infection, since depolarization and conduction through a remyelinated or "healed" CNS region is impaired by an elevated body core temperature, deemed by some clinicians as a "pseudo-exacerbation."

4. Diagnosis of multiple sclerosis

Since no signs and symptoms or diagnostic test abnormalities are entirely specific for MS, its diagnosis remains a clinical one. Historically the diagnosis consisted of **multiple signs and symptoms disseminated in time and space without a better explanation**. "Disseminated in space" refers to MS lesions in different parts of the CNS. This can be manifest by clinical signs referable to separate anatomical lesions, such as an INO and myelitis of the thoracic spinal cord, or by one or more MRI white matter lesions in at least 2 different typical sites for MS (periventricular, juxtacortical, infratentorial or spinal cord) (2010 McDonald diagnostic criteria for MS). It should be noted that since ischemic infarcts and metastatic tumors may also be multifocal in distribution, any atypical findings for MS should prompt more extensive diagnostic testing (cerebrospinal fluid analysis, evoked potential studies) or a longer period of observation before making a diagnosis of MS. Nowadays **magnetic resonance imaging (MRI) scans of brain and**

**spinal cord have great sensitivity, although less specificity, in detecting small white matter lesions from MS or other disorders** (Figs. 2 and 3). "Disseminated in time" is required for a diagnosis of MS in order to eliminate monophasic mimics of MS like postinfectious encephalomyelitis. The "disseminated in time" criterion may be met if serial MRI scans show subsequent development of additional, asymptomatic white matter lesions at sites unrelated to the initial clinical event. Obviously if a second clinical episode occurs during a period of follow-up, the "disseminated in time" criterion would be met. On any brain MRI scan, enhancement of any white matter lesions indicates recent inflammation (ongoing blood-brain-barrier disruption or leakiness), while other non-enhancing lesions present are considered chronic, or inactive; these white matter lesions would also therefore be "disseminated in time."

Other diagnostic laboratory tests also serve to reveal multiple CNS lesions in a patient suspected of having MS, although again the results themselves are nonspecific and not as sensitive overall as MRI scans. Cerebrospinal fluid (CSF) obtained by lumbar puncture may show features of immunoreactivity not present in the blood and not caused by other CNS conditions such as meningitis. The presence of **oligoclonal bands** in the CSF indicates production of a "few clones" of antibodies in the CNS. In addition, **increased immunoglobulin synthesis in the CSF** may also be detected. An MS patient not in the midst of an active clinical episode may have normal CSF studies, however. Other ancillary tests investigate possible lesions in the visual, auditory and posterior column pathways by recording **evoked potentials**. Computer-averaged cortical responses to visual, auditory or electrical stimuli (the latter delivered to the upper or lower limbs) are recorded. A delayed or absent response suggests a lesion in that system, which may be an MS plaque. For example, a patient with right optic neuritis may have a delayed or absent response (visual evoked potential) over the visual cortex when viewing a flashing pattern with the right eye, but has a normal response when viewing with the left eye.

All in all, the diagnosis of MS is made from several kinds of data---the clinical history and neurological findings plus ancillary testing involving MRI, CSF, and evoked potential recordings---in the absence of a more likely neurological diagnosis. In the case where the diagnosis is unclear, continued clinical observation may be the best option.

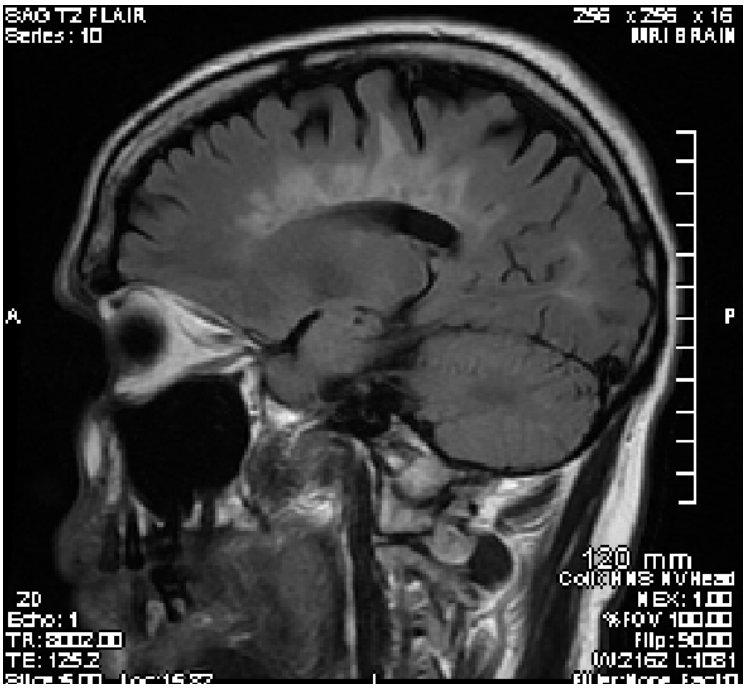


Fig 2. Brain MRI scan (sagittal FLAIR sequence) without contrast, showing high signal MS lesions in the periventricular white matter, radially oriented like “fingers” in the corpus callosum.

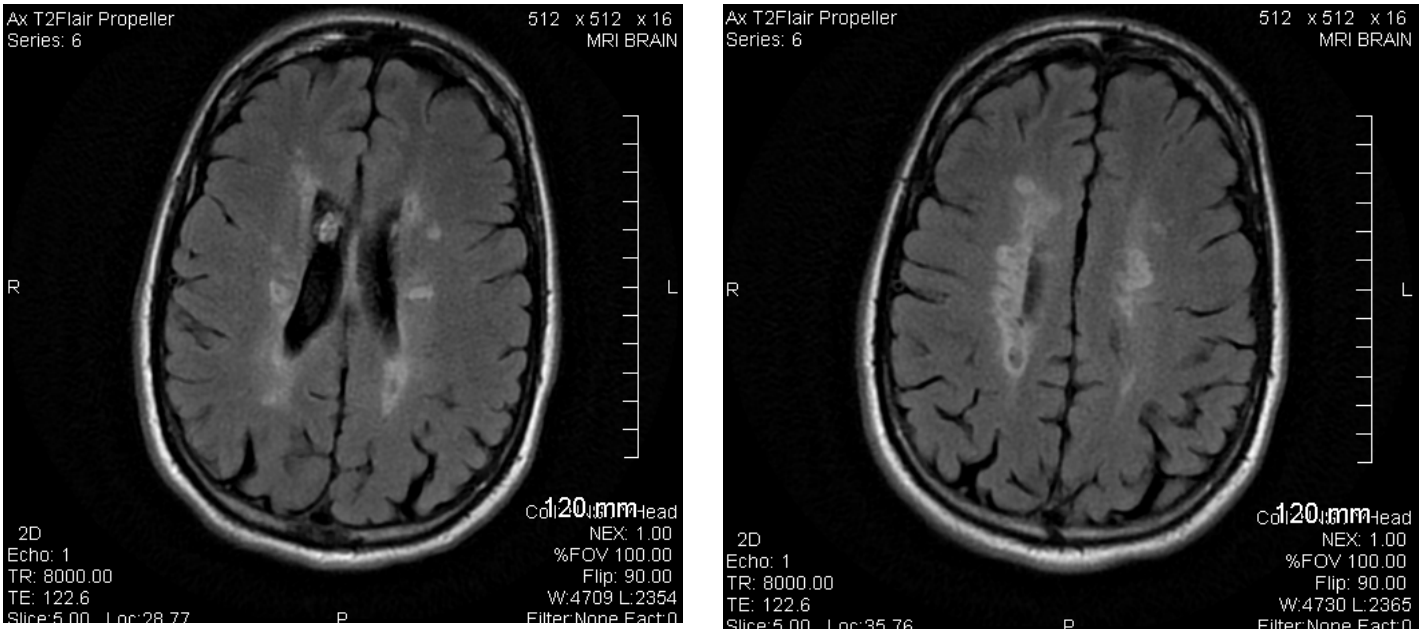


Fig. 3 Brain MRI (axial FLAIR sequence) without contrast, showing high signal MS lesions in the periventricular white matter, some appearing perpendicular to the lateral ventricles.

5. Treatment of multiple sclerosis

**There is currently no curative treatment of MS**. For any MS attack or exacerbation, however, an associated infection should be sought and treated, while keeping the patient afebrile. Previous MS symptoms may resurface if the body core temperature is increased during fever or physical exertion in hot conditions. Heat impairs or halts the conduction of action potentials in areas of remyelinated or mildly demyelinated axons within the CNS, so **fever control** is important in MS patients. Milder MS attacks involving tingling or numbness do not warrant more aggressive treatment, while episodes of blindness or paralysis may resolve faster if treated with a few days of **intravenous, high-dose corticosteroids, such as methylprednisolone 500-1000 mg/day for 3-5 days, with or without an oral prednisone taper**. Corticosteroids have anti-inflammatory as well as immunosuppressive effects, and are **transiently given for acute MS attacks of significant severity**, not as a continuous or maintenance treatment. Corticosteroids tend to work best early in the course of MS and may not help at all during acute attacks arising after years of MS disease.

In the 1990s **disease-modifying therapy (DMT) with beta-interferon or glatiramer acetate was shown to reduce the severity and frequency of MS attacks and thereby lessen future cumulative neurological disability in some, but not all, patients**. Beta-interferon is a protein which appears to enhance suppressor T-cell function, decreases lymphocyte traffic into the CNS, reduces antigen presentation, and lessens cytokine production. Beta-interferon is synthesized by recombinant DNA technique and is available in several forms: Betaseron (interferon beta-1b injected subcutaneously every other day), Avonex (interferon beta-1a injected intramuscularly weekly), and Rebif (interferon beta-1a injected subcutaneously three times weekly). Glatiramer acetate is a polypeptide resembling myelin basic protein, a byproduct of myelin destruction. It may compete with myelin antigens in binding to antigen-presenting inflammatory cells, and favorably influence lymphocyte activity and cytokine production. Copaxone (glatiramer acetate) is given subcutaneously every day. Many patients experience skin site injection reactions with redness, low-grade fever, malaise and muscle soreness.

Other treatments for MS patients include medications to relieve limb spasticity, pain, paresthesia, and fatigue. Dalfampridine (4-aminopyridine) is an oral potassium channel blocking drug which improves walking speed, presumably by enhancing conduction in demyelinated areas in MS. Bladder, bowel and skin care is important to maintain hygiene and reduce the risk of infection. Appropriate rest, physical therapy, and assistive devices to improve mobility and daily activities are needed as indicated for specific patients.

Management challenges with beta-interferons and glatiramer include intolerable injection site reactions or side-effects, and lack of efficacy, which may arise at variable times after initiation of these DMT. Increases in the frequency or severity of clinical MS attacks, or new, asymptomatic white matter lesions arising on serial brain MRI scans suggest that changing to another DMT should be considered. Several newer DMT are

now available. Natalizumab (Tysabri) is a monoclonal antibody that interferes with the binding of lymphocytes to CNS vascular cell adhesion molecules, stopping these autoimmune cells from breaching the blood-brain-barrier. After showing great clinical benefit, a few patients developed reactivation of latent JC polyomavirus, which fatally infects oligodendrocytes and is untreatable. Any patients given IV infusions of natalizumab are now carefully prescreened and monitored for this complication. Other monoclonal antibody treatments for MS are being developed. Several oral medications are now available, with different mechanisms of action and side-effect profiles, such as fingolimod (Gilenya), teriflunomide (Aubagio) and dimethyl fumarate (Tecfidera)