Overview:
Grossly, myelin is the material that makes white matter white. In the Central Nervous System, myelin is made by oligodendroglial cells. If you examine a portion of the CNS and notice that an area that should be white is, instead, pale gray or tan, it usually means the myelin is missing. Absence of myelin may come about in several ways:

1. Improper synthesis, turnover or maintenance of myelin – Leukodystrophies
2. Infection that targets oligodendroglia – Progressive Multifocal Leukoencephalopathy
3. Chronic or repeated episodes of mild ischemia – hypertensive subcortical leukoencephalopathy (“Binswanger’s disease”)
4. Central Pontine Myelinolysis, also known as Osmotic Demyelination Disorder
5. Destruction of myelin and oligos by idiopathic, presumed autoimmune demyelination:
   Multiple Sclerosis (MS – see below)
   Neuromyelitis Optica (NMO; Devic’s Disease
   Acute Diffuse Encephalomyelitis (ADEM)
   Acute Necrotizing Hemorrhagic Encephalomyelitis (ANHE), also known as Acute Hemorrhagic Leukoencephalitis (AHLE)

**Neuromyelitis optica (NMO; Devic’s disease)** is an autoimmune disorder that was once regarded as a variant of MS. It involves simultaneous attacks of demyelination in the optic nerves and the spinal cord. Patients have antibodies against Aquaporin 4, the major water channel in astrocytes, and Aquaporin 4 is depleted in demyelinated areas. MS patients do not have these antibodies. For a brief, informative discussion of this fascinating disease, see the NINDS information page: https://www.ninds.nih.gov/Disorders/All-Disorders/Neuromyelitis-Optica-Information-Page

**Acute Diffuse Encephalomyelitis (ADEM)** is a rare, monophasic demyelinating disorder that typically follows a viral infection or, occasionally, an immunization. Symptoms appear about two weeks later, and the course is fairly rapid. About 20% of patients die, but the rest recover, usually without residual deficits. The lesions are diffuse and mostly perivenular, and resemble those seen in animals that have been immunized with myelin components (experimental allergic encephalomyelitis; EAE).

**Acute Necrotizing Hemorrhagic Encephalomyelitis (ANHE)**, also called Acute Hemorrhagic Leukoencephalitis (AHLE), is a more severe, fulminant disorder that is usually fatal. Like ADEM, it usually follows a viral infection, particularly a URI. Lesions are perivenular, as in ADEM, and there is also focal necrosis of the vessels, resulting in extravasation of blood, thus “hemorrhagic.” Patients who recover may have significant deficits due to necrosis of brain tissue.

**Multiple Sclerosis** is by far the most common demyelinating disease:

Clinical Features:
- Onset is most common in young adults; peak age of incidence is 20-40 years
- Women are much more commonly affected than men (~2:1)
- Usually there is MRI evidence of several lesions present by the time of the first symptoms.
MS is a chronic, episodic and/or progressive disease, usually beginning with a “relapsing-remitting” course of attacks followed by recovery. Over time, many patients experience a transformation to a continuous progression of symptoms without intervening episodes of improvement, followed by a more progressive cumulative disability. If this transformation occurs, the disease state is known as “Secondary Progressive” MS. If the patient experiences continuous symptom progression from the outset, without intervening remissions, the disorder is referred to as “Primary” Progressive MS.

Lesions and symptomatic attacks are “separated by time and space”- both occurrence and location are unpredictable. Symptoms are variable, depending on the anatomic site of lesions. The most common symptoms involve the visual system (optic nerve) and long tracts in the spinal cord. These are areas where a small lesion can have the most noticeable effects. Clinical findings do not always parallel disease activity. In fact, the first few lesions may not be clinically apparent until one of them occurs in a vulnerable area. Typically, the first time a patient presents with symptoms, an MRI scan will reveal other lesions that occurred earlier and didn’t come to medical attention. Symptoms usually improve (“remit”), then may recur in a subsequent attack (relapse). There may not be complete remission, and gradually, with more episodes, the deficits become permanent and cumulative.

Cumulative effects are graded using the Expanded Disability Status Scale (EDSS):

**Note:** Don’t memorize the EDSS, but be aware that there are objective criteria used to grade the severity of a patient’s MS and the cumulative progression of the disease. These criteria, along with MRI data, are also used to assess the effectiveness of treatments.

0 - Normal neurological exam
1.0 - No disability, minimal signs in one of 8 Functional Systems (pyramidal, cerebellar, brainstem, sensory, bowel & bladder, visual, cerebral, other).
2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).
3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.
4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest 500 meters.
5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (usual FS equivalents are one grade
6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5 - Constant bilateral assistance needed to walk 20 meters
7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to a wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5 – Unable to take more than a few steps; restricted to wheelchair, may need aid in transferring; may need motorized wheelchair

8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed much of the day, retains many self-care functions; generally has effective use of arms

9.0 - Helpless bed patient: can communicate and eat

9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow

10.0 - Death due to MS.

Pathologic Findings:
-Multiple lesions (plaques) of demyelination in the white matter, which tend to follow the course of small veins and do not respect tracts or functional system boundaries
-Lesions may also be in the gray matter or overlap the gray-white junction, not sparing the subcortical U fibers in the cerebrum (which are relatively spared in leukodystrophies).
Plaques are
often periventricular, and commonly extend into the corpus callosum.
-Plaques are sharply demarcated and variable in size.
-In early lesions there is loss of myelin and oligodendroglia with many macrophages. The large number of perivascular lymphocytes in a “young” plaque is evidence of an immune reaction.
-Although there is relative sparing of axons in a plaque, loss of axons and neurons does occur, this may happen early, and may proceed continuously, even without “attacks,” contributing to cumulative disability, cognitive impairment and brain atrophy.

Pathogenesis:
-Probably an autoimmune disorder which may be “triggered” by infection
-Geographic distribution - more common among people who live in temperate zones up to age 15 – Infection? Sunlight? Vitamin D?
-Oligoclonal IgG in CSF is consistent with immune response to infection, although no etiologic agent has been identified.
-Genetic predisposition – 40% concordance in monozygotic twins; specific gene linkages (HLA DR2; single nucleotide polymorphisms have been identified in IL-2 & IL-7 receptor genes)
-Evidence for Immune Mechanisms:
-Serum and CSF cause in vitro demyelination
-Antibodies to myelin and oligodendroglia are present
-Patients’ T cells react against myelin in vitro
-Therapeutic effectiveness of Interferon-beta, natalizumab and other immunosuppressive agents

During the formation of a plaque, activated T-cells and monocytes leave blood vessels and accumulate in brain tissue and perivascular spaces in the plaque area. They may damage tissue either directly or by secretion of pro-inflammatory cytokines.

Several types of T lymphocytes participate in the inflammatory process. In particular, two subsets of “helper” T cells, TH-1 and TH-2, exert opposing influences.
Th-1 cells are referred to as “pro-inflammatory;” because they produce cytokines including interferon gamma, interleukin-2 and Tumor necrosis factor alpha, which promote the inflammatory response, and they stimulate the microglia and macrophages which damage and phagocytize tissue in a developing MS plaque. Recently, TH-17 cells have also been found to play a role in recruitment of leukocytes.

Pro-inflammatory TH-1 cell functions are somewhat counterbalanced by the anti-inflammatory activity of TH-2 cells. They produce cytokines including interleukin-4, interleukin-10, and transforming growth factor-beta, which suppress inflammation and down-regulate
TH-1 cell activity. Th-1 cells predominate in patients who have clinically active MS.

Interferon-beta therapy alters cytokine production by monocytes and favors differentiation and proliferation of anti-inflammatory TH-2 cells.

Interferon-beta was the first of a group of drugs referred to as “Disease-Modifying Therapies.” In general, they have immunomodulatory, anti-inflammatory and immunosuppressive effects. They reduce the number of relapses, improve the MRI appearance, and slow the progression of clinical disability. Not surprisingly, there is considerable evidence of greater effectiveness with early treatment.

Glatiramer Acetate (Copolymer-1; Copaxone) is another effective immunomodulatory therapy in RRMS. It’s exact mechanism(s) of action is(are) unknown, but it appears to promote development of certain TH-2 cells. For many years, interferon-beta and Copaxone were the only effective disease-modifying therapies.

Newer therapies include:

• Natalizumab (Tysabri) – an antibody against cell adhesion molecules that prevents migration of inflammatory cells out of blood vessels. BUT – there are problems: natalizumab is associated with development of Progressive Multifocal Leukoencephalopathy (PML), a viral illness usually seen in immunocompromised persons.

AND – there are now many more treatments available or on the way:

• Fingolimod (Gilenya), has been on the market for about five years and was the first M.S. treatment delivered by a pill. It prevents lymphocyte egress from lymphoid tissues, reducing infiltration into the CNS. It has been shown to reduce relapses by 50% and brain shrinkage by 30%-40%.

• Teriflunamide (Aubagio), was approved by the FDA in September, 2012. It is a pill that can reduce relapses by about 30%

• Dimethyl fumarate (BG-12; Tecfidera), another pill, received FDA approval in March, 2013. It has been used for decades to treat psoriasis. The mechanism of action involves inhibition of pro-inflammatory cytokines and enhancement of anti-inflammatory cytokines, as well as a novel effect of activation of the NRF-2 pathway, which protects cells from oxidative stress. Studies have shown that it reduces relapse rates by 50% and slows progression of the disease, compared with a placebo. Recently, it has been associated with 4 cases of PML in MS patients.

• Alemtuzumab (Lemtrada) is a humanized monoclonal antibody against CD52, an antigen found on the surface of normal and malignant lymphocytes. It has been shown to reduce the number of relapses in patients with relapsing-remitting MS and also delay progression of disability. It was approved in Canada and Europe, and was submitted for US approval in 2012, BUT the FDA declined approval in December, 2013, due to concerns about potential serious side effects and the design of the pivotal clinical trials. The FDA reversed its position and approved the drug in November 2014, but with the suggested restriction that, because of its safety profile, the use of Lemtrada should generally be reserved for patients who have had an inadequate response to 2 or more other treatments.
Most recently (Dec., 2016) Ocrelizumab (Ocrevus), a monoclonal antibody against CD20+ B-cells, was the first treatment to demonstrate effectiveness in Primary Progressive MS. Ocrevus was granted Priority Review Designation by the FDA and was approved March 28, 2017.

**Objectives**

Know about multiple sclerosis, including:
clinical features - characteristic symptoms, risk factors, progression
- morphology and development of lesions– histopathology, distribution, changes over time, relation to symptoms
- laboratory findings
- theories of pathogenesis
- current treatment options

Know the major features of NMO, ADEM and ANHE