Demyelinating diseases

- What are demyelinating diseases?
  Demyelinating diseases: loss of myelin sheaths with relative preservation of the axon
  Neurological deficits due to the effects of myelin loss on the transmission of electrical impulses along axons Several pathologic disorders can cause myelin loss:
  - immune-mediated destruction of myelin
  - infections
  - inherited disorders (may affect myelin: termed leukodystrophies)

- what is Multiple Sclerosis (MS)?
  It is an autoimmune-mediated destruction of myelin sheaths in the brain and spinal cord.
  It is 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. Variable course of disease. Characterized by periods of relapse and remission that can last from weeks to years.

- what is the epidemiology of MS?
  - MS is the most common demyelinating disease. It affects 1 in 1000 individuals in the US and Europe.
  - It affects women twice as much as men.
  - It can be diagnosed at any age but less often in childhood or after the age of 50. 90-95% between 20-40 years old.
  - Attributed to both genetic predispositions and environmental factors:
    - **Genetic predispositions:**
      - DR haplotype of HLA gene: HLA-DRB1 *1501 haplotype: 3-fold increase in risk of MS (s found only in 25-35% of cases)
      - mutations in other genes involved in the immune system.
      - Individuals with an affected 1st degree relative have a 15-fold increased risk for MS, and individuals with a homozygote twin are at 150-fold risk. However only in about 20% of cases there’s a familial predisposition, most are sporadic.
    - **Environmental**: there’s a geographic distribution where most

MS cases are away from the equator suggesting a role of Vit. D (immune modulator). There's controversy about the possible role of EBV infection but no reliable data. Cigarette smoking. All inflammatory events can contribute.

- What are the different forms of MS?
  - **relapsing-remitting form**: is the most common (80%) there's a fast (days-weeks) development of neurological deficits followed by a slower and gradual remission that can be total or partial
  - **primarily progressive form** (20%): there's continuous progression of the disease from the appearance.
  - **secondary progressive form**: continuous progression of the disease over a longer period of time than in 1ry.
  - **progressive-relapsing form**: progressive attacks that lead faster to disability

- What is the pathogenesis of Multiple Sclerosis (MS)?
  The disease is initiated by the activation of helper T cells. In particular Th1: secretes IFNy→ activates macrophages, and Th17: recruits leukocytes. The leukocyte activation and secretion of inflammatory cytokines is believed to be the cause of the lesions. After that there's a (poor) attempt of re-myelination by oligodendrocytes, and the formation of **multiple sclerotic plaques.**

  Two main phases: Autoimmune attack (start), and Axonal damage (progression)
  1. The BBB endothelial cells acquires inflammatory phenotype (express adhesion molecules and MHC class 2 in response to inflammatory cytokines)
  2. Binding of activated T lymphocyte to BBB
  3. Transmigration through endothelial barrier and perivascular space: immune cells cause destruction of collagen by the release of metalloproteinases, which allows them to cross the BBB and spread to the white matter. Th cells activate macrophages and glia cells to synthesize NO and osteopontin (MS inflammatory stage)
  4. Immune attack:
     1. NO, ROS, anti-myelin antibodies (B cells), activated complement and TNFa help to damage and fragment myelin. Phagocytosis of debris by macrophages
  5. Altered regulation of the immune response
     Osteopontin stimulates Th1 → IFNy, IL-12 (activates macrophages→ ROS) and suppresses Th2 (e.g.IL-10)

6. Demyelination: formation of focal areas of demylinization on the myelin sheaths significant alterations in the conduction of electrical stimuli along the axons
7. Axonal damage
    - Oligodendrocytes and damaged neurons release glutamate (neurotransmitter) excitotoxicity
8. Re-myelination
    - astrocytes and other inflammatory cells release neurotrophic factors to induce remyelination by oligodendrocytes.
9. Sclerotic cicatricial reaction mediated by astrocytes: re-myelination is effective in the early stages of the disease; less effective in later stages fibrosclerosis and irreversible neuronal damage
10. Permanent damage: anatomo-pathological lesions (sclerotic plaques)

- what are the morphological findings of MS?
  MS lesions (plaques) are found in the white matter (but also in the gray matter, where myelinated fibers run through it)
    - periventricular area, corpus callosum, cerebellum, optic nerves, chiasm and spinal cord.

- Types of lesions
    - Acute active lesions: irregular margins, myelin infiltration of lymphocytes and macrophages (containing products of the sheath degradation), axonal damage but conservation, loss of oligodendrocytes, poor astroglial response
    - Chronic active lesions: sharper margins, large external area rich in macrophages (mainly in the internal area) and products of advanced myelin degradation, evident axonal damage
    - Slow expansion lesions: inactive central area surrounded by activated microglia and some macrophages at the edge
    - Chronic inactive lesions: net margin, myelin absence, scarce oligodendrocytes, macrophages and microglia cells but strong sclerotic cicatricial reaction (sclerosis) due to astroglial activation

- what are the signs and symptoms of MS?
  Different from person to person, as the disease may affect different parts of the white matter at different times, however certain patterns are more common.
    - cerebral cortex: motor paralysis, ataxia (lack of balance and

coordination) sensory and cognitive disorders
    - optic nerve: optic neuritis (unilateral visual impairment), retrobulbar neuritis (inflammation of the optic nerve)
    - brainstem: ophthalmoplegia (paralysis of the eye muscles), dysphagia
    - spinal cord motor: sensory and sphincter disorders
    - CSF increase in protein content; IgG increase due to B lymphocyte proliferation in the CNS

    - Two characteristic (but not specific) clinical signs of multiple sclerosis:
        1. **Uhthoff sign**: aggravation of existing symptoms due to exposure to higher than usual ambient temperatures
        2. Lhermitte sign: a sensation of electric shock that runs through the spine and legs following flexion or, more rarely, in extension of the neck

- what is the treatment for MS?
  Not curative.
  Drugs capable of affecting the mechanisms underlying the disease by modifying their course
    - Inmunomodulators:
        - Interferon b1
        - Glatiramer acetate
        - Natalizumab
    - Immunosuppressants:
        - mitoxantrone
        - many others are used in clinical practice: e.g. azathioprine and cyclophosphamide