Multiple sclerosis

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Introduction:

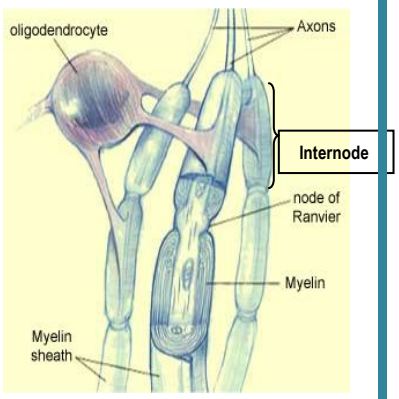
Myelin:

- Myelin consists of multiple layers of the specialized plasma membrane of oligodendrocytes (in the CNS), with most of the cytoplasm excluded.
- Although myelinated axons are present in all areas of the brain, they are the dominant component in the white matter; therefore, most diseases of myelin are primarily white matter disorders.

→*What is the function of myelin?*

The function of myelin sheath is protection and insulation of nerve fibers. This insulation makes the nerve impulses "jump" throughout the nerve fiber, greatly increasing conduction speed.

Each segment of the axon is known as an *internode*, and the gaps between internodes are known as *nodes of Ranvier*



The differences of myelin between CNS and PNS:

	PNS	CNS
Type of cells producing myelin	Schwann cell	oligodendrocyte
Number of segments covered by one cell	one segment "internode"	many internodes
Component	Different components(lipids and proteins)	

← Therefore the diseases affecting the myelin of the CND differs from those of the PNS

Demyelinating and Dysmyelinating disease of the CNS:

	Demyelinating diseases	***Dysmyelinating disease*** (oligodystrophy, *leukodystrophy*) (rare)
cause	acquired (previously normal myelin)	myelin is not formed properly or has abnormal turnover kinetics (congenital)
Result from	• immune-mediated injury (commonly) • Drugs and other toxic agents. • Viral infection of oligodendrocytes as in progressive multifocal leukoencephalopathy which is a type of change associated with the white matter, which includes localized areas of cell death, e.g: In HIV patients, a virus called JC virus (John Cunningham virus) attacks the oligodendrocytes which ultimately leads to damage and loss of myelin sheath.	• mutations affecting the proteins required for formation of normal myelin • mutations that affect the synthesis or degradation of myelin lipids

→What is "natural history of a disease"?

Natural History of a disease is the course of a particular disease if it is not treated or manipulated in any way.

The natural history of demyelinating diseases is determined by:

1. The limited capacity of the CNS to regenerate normal myelin
2. The degree of secondary damage to axons that occurs as the disease runs its course.

Multiple Sclerosis:

MS is an autoimmune demyelinating disorder characterized by *distinct episodes of neurologic deficits, separated in time, attributable to white matter lesions that are separated in space.*

Epidemiology:

- The most common demyelinating disorders (prevalence of 1 per 1000 persons in most of the United States and Europe)
- The disease becomes clinically apparent at any age, although onset in childhood or after age 50 years is relatively rare.
- Women are affected twice as often as men.

Characteristics:

- In most individuals with MS the illness shows **relapse (**presentation of symptoms of a disease, after a period of improvement, mostly new in the case of MS) **and remission (**The period during which the symptoms of a disease decrease temporarily or vanish)
- The frequency of relapses tends to decrease during the course of the illness, but there is a steady neurologic deterioration in a subset of patients.
- Like other autoimmune diseases, MS is believed to be caused by a combination of environmental and genetic factors that result in a

loss of tolerance to self-proteins. Some examples of genetic factors are:

1. In a first-degree relative (parent, sibling, or child) the risk of developing MS is 15-fold higher when the disease is present.
2. The concordance rate for monozygotic twins is approximately 25%, with a much lower rate for twins

Concordance: the presence of a given trait in both members of a pair of twins

Monozygotic twins are twins that develop from one oocyte.

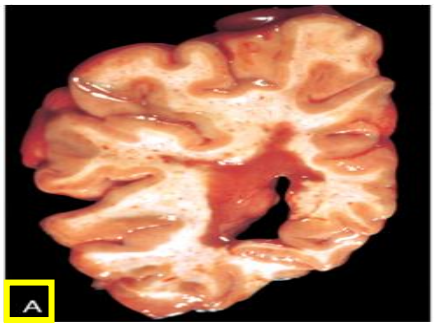
Dizygotic twins are twins that develop from two oocytes

- **Experimental allergic encephalomyelitis** is an animal model of MS in which demyelination and inflammation occur after immunization with myelin, myelin proteins, or certain peptides from myelin proteins.

Encephalomyelitis: inflammation of the brain and spinal cord

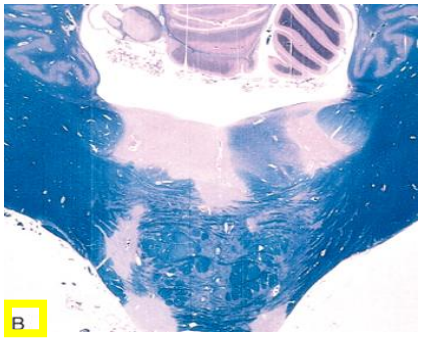
In this model, the lesions are caused by T cell-mediated delayed type hypersensitivity reaction to myelin proteins, and the same immune mechanism is thought to be central to the pathogenesis of MS So multiple sclerosis is thought to be an autoimmune disorder where T cells (cytotoxic) attack the myelin sheath by causing an inflammatory response that may even cause secondary destruction of the axons.

Morphology:



- Slide (A): Affected areas show **plaques** which are one or multiple, well-circumscribed, slightly depressed, glassy, gray-tan, irregularly shaped lesions.
- They occur beside periventriculer areas and they are frequent in the optic nerves - can be the first clinical sign and the most important one- and chiasm, brain stem, ascending and descending fiber tracts, cerebellum and spinal cord.

- Slide (B): The lesions have sharply defined borders at the microscopic level.



- This section of the brainstem is seen by using Luxol fast blue (LFB) s special stain used to see myelin under a light microscope.
- With the stain, the myelin looks blue, and the neurons appear purple.

Stages of a plaque:

1. **active plaque**:
    1. Ongoing myelin breakdown –inflammatory process- with abundant macrophages containing myelin debris
    2. Lymphocytes and monocytes are present, mostly as perivascular cuffs (surrounding the vessels).
    3. Axons are relatively preserved-not injured-, although they may be reduced in number later.
2. **inactive plaques:**
    1. the inflammation mostly disappears, leaving behind little to no myelin
    2. Astrocytic proliferation and gliosis are prominent

Gliosis: A process leading to scars in the central nervous system that involves the production of a dense fibrous network of neuroglia (supporting cells) in areas of damage.

Clinical features of Multiple sclerosis:

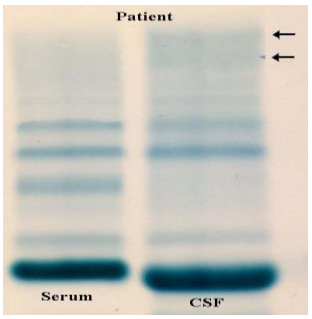
- The course of MS is variable. MS lesions can occur anywhere in the CNS → may induce a wide range of clinical manifestations
- The consequence of this pattern of relapsing-remitting disease is the gradual, often stepwise, accumulation of increasing neurologic deficits
- neurologic symptoms and signs that are commonly observed:
    1. Unilateral visual impairment occurring over the course of a few days is a frequent initial manifestation of MS (due to involvement of the optic nerve (*"optic neuritis, or retrobulbar neuritis"*)
    2. When this occurs as the first event, only a minority (10% to 50%) go on to develop full-blown (mature case) MS.
    3. Involvement of the brain stem produces cranial nerve signs and ataxia (Loss of the ability to coordinate muscular movement) and can disrupt conjugate eye movements.
    4. Spinal cord lesions give rise to motor and sensory impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of bladder function at severe extents.
    5. Changes in cognitive function (such as: mental processes of perception, memory, judgment, and reasoning), can be present, but are often much milder than the other findings

In any individual patient it is hard to predict when the next relapse will occur; most current treatments aim at decreasing the rate and severity of relapses rather than recovering lost function, using immunosuppressant therapies.

Test can be used for diagnosis and estimating the severity:

- Immunoglobulin in the CSF:

- It shows mildly elevated protein level with an increased proportion of γ-globulin
- In one-third of cases there is moderate pleocytosis (The presence of a greater number of cells than normal)
- When the immunoglobulin is examined further, most MS patients show *oligoclonal bands*- suggest inflammation of the central nervous system.-, representing antibodies directed against a variety of antigenic targets



These antibodies constitute a marker for disease activity