Lecture Four

Multiple Sclerosis

432 ***Pathology*** *Team*

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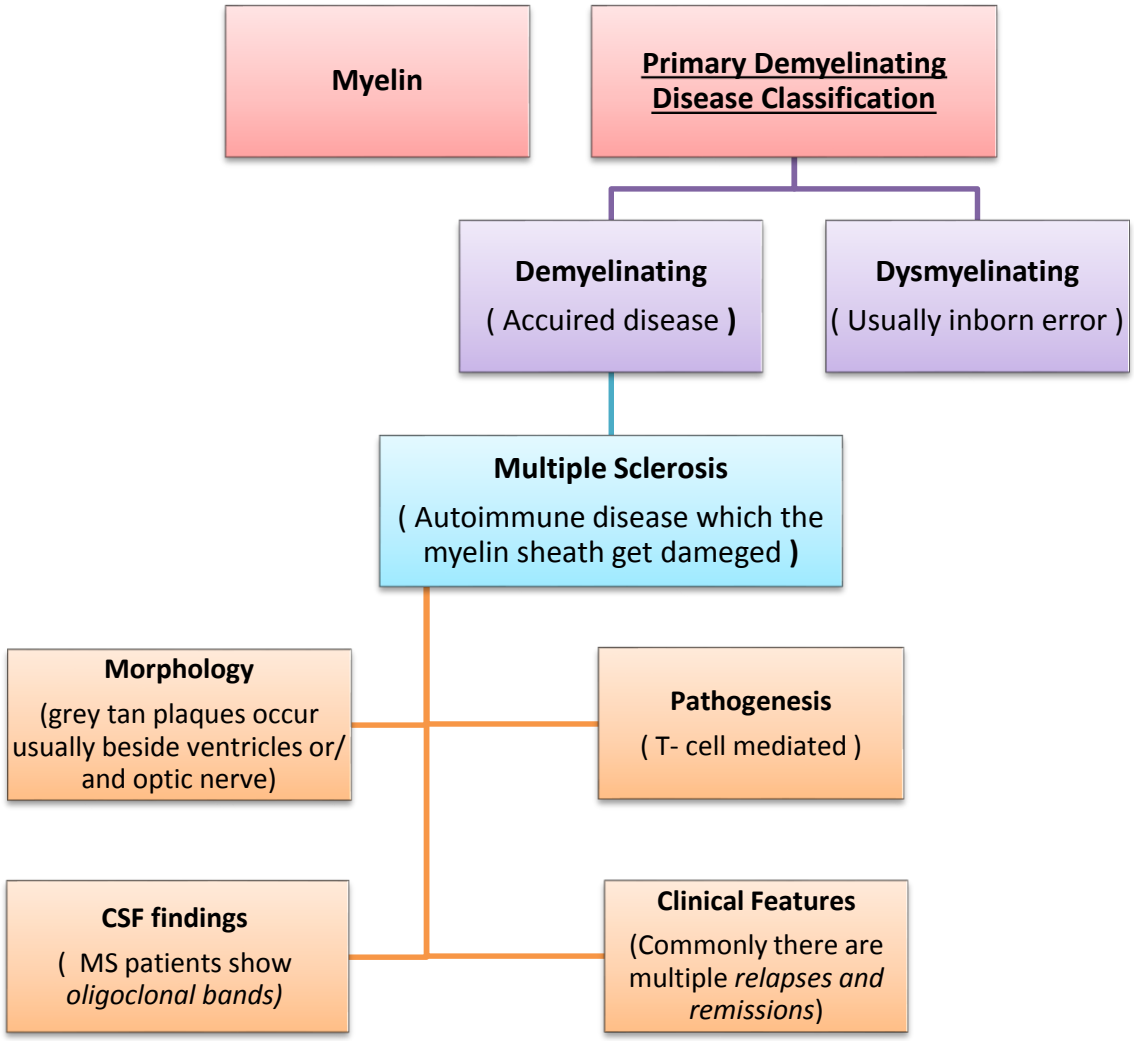
CNS Block

Color Index: female notes are in purple. Male notes are in Blue. Red is important. Orange is explanation.

Multiple Sclerosis

Mind Map:



General Considerations in Multiple Sclerosis

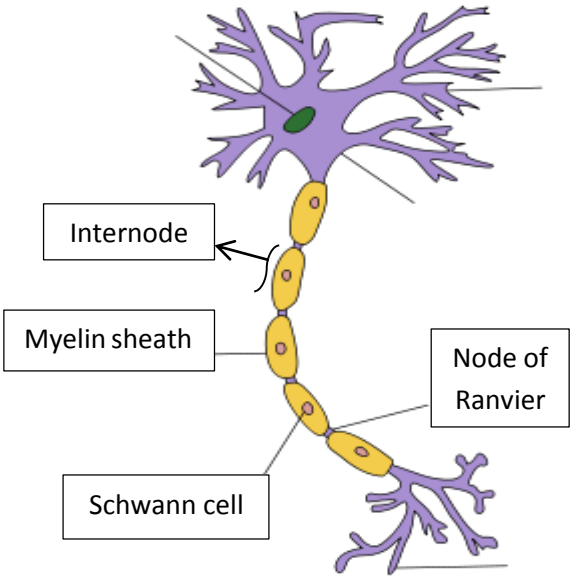
1- Myelin:

Myelin consists of multiple layers of the specialized plasma membrane of oligodendrocytes (in the CNS) around the axon, 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.

The myelin in peripheral nerves is similar to the myelin in the CNS but:

- Peripheral myelin is made by **Schwann cells**, not oligodendrocytes.
- Each cell in the peripheral nerve contributes to only **one** internode, while in the CNS, **many** internodes comes from a single oligodendrocyte.
- The specialized proteins and lipids are also different.



Because of these differences, most diseases of CNS myelin do not significantly involve the peripheral nerves, and vice versa.

REMEMBER:
Oligodendrocyte: gives myelin in CNS to many axon.
Schwann cell: gives myelin in PNS to one axons (because of its small size it won't be able to give myelin sheath to the axon which is much bigger).

The natural history of demyelinating diseases is determined, in part, by the limited capacity of the CNS to regenerate normal myelin and by the degree of secondary damage to axons that occurs as the disease runs its course.

NOTE: "Natural history of a disease: is the course or prognosis of the disease without treatment"
Function of Myelin is: Insulation & speeds up the transmission of impulses along axons."

2- Primary Demyelinating Disease Classified into:

1) Demyelinating diseases of the CNS:

Acquired conditions characterized by preferential damage to previously **normal** myelin, commonly result from immune-mediated injury. Also viral infection of oligodendrocytes as in progressive multifocal leukoencephalopathy, drugs and other toxic agents.

2) Dysmyelinating diseases of the CNS = (leukodystrophy [common in children] in white matter):

- Myelin is not formed properly or has **abnormal** turnover kinetics "not enough myelin"
- Could be inborn error, (not able to produce myelin)
- Associated with either:
    1. Mutations affecting the **proteins** required for formation of normal myelin.
    2. Mutations that affect the synthesis or degradation of myelin **lipids**.

Multiple Sclerosis

Multiple Sclerosis:

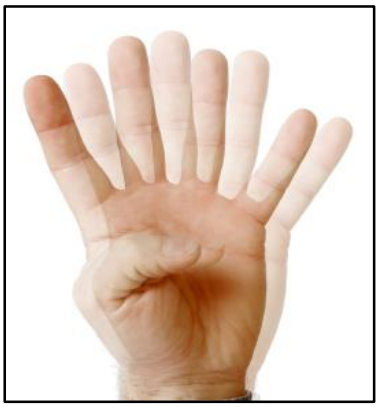
Multiple Sclerosis is an **autoimmune** demyelinating disorder characterized by distinct **episodes** of neurologic deficits, separated in time, attributable to white matter lesions that are separated in space.

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 (young female 20-40yrs, although it is more common in female the prognosis is better than in male patient).

In most individuals with MS the illness shows **relapsing and remitting** episodes of neurologic deficits. 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.



REMEMBER:
The first sign for MS is **double vision** because optic nerve is more frequent to be injured

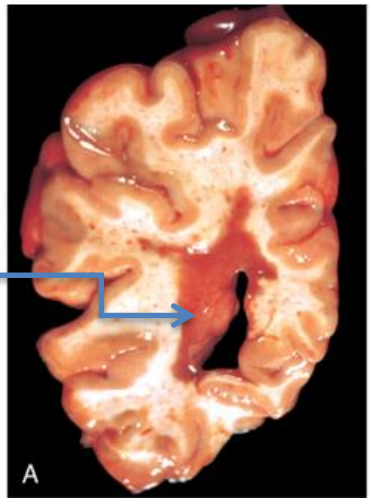
Pathogenesis:

- 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
- The risk of developing MS is 15-fold higher when the disease is present in a **first-degree relative** (genetic predisposing factor).
- The concordance rate for monozygotic twins is approximately 25%, with a much lower rate for dizygotic twins.
- A significant fraction of the genetic risk for MS is attributable to HLA-DR variants, the DR2 allele being the one that most significantly increases the risk for developing MS.
- 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.
- In this model, the lesions are caused by a 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.
- While MS is characterized by the presence of demyelination out of proportion to axonal loss, some injury to axons does occur (MS effect the axons in later stage) and they don't have mental problems
- **Toxic effects** of lymphocytes, macrophages, and their secreted molecules have been implicated in initiating the process of **axonal injury**, sometimes even leading to neuronal death.

NOTE from Robbins: A central role for CD4+T cells has been suggested, with an increase in Th17 and Th1 CD4+ cells thought to be a critical component of injury to myelin.

Multiple Sclerosis Morphology

- MS is a white matter disease
- Affected areas show multiple, well-circumscribed, slightly depressed, glassy, gray-tan, irregularly shaped lesions, termed **plaques**
- They occur beside ventricles and they are frequent in the optic nerves and chiasm, brain stem, ascending and descending fiber tracts, cerebellum and spinal cord.



Under the Microscope:

1) The lesions have sharply defined borders.

2) **Active plaque** there is evidence of ongoing myelin breakdown with abundant macrophages containing myelin debris. Lymphocytes and monocytes are present, mostly as perivascular cuffs. Axons are relatively preserved, although they may be reduced in number.

3) When plaques become quiescent (**inactive plaques**), the inflammation mostly disappears, leaving behind little to no myelin Instead, astrocytic proliferation and gliosis are prominent.

NOTE: Luxol Fast Blue stain: is a commonly used stain to observe myelin under light microscopy. With the stain, the myelin looks blue, and the neurons appear purple.

Clinical Features:

- The course of MS is variable. MS lesions can occur anywhere in the CNS → may induce a wide range of clinical manifestations
- Commonly there are multiple episodes of new symptoms (*relapses*) followed by episodes of recovery (*remissions*); typically, the recovery is not complete.
- The consequence of this pattern of **relapsing-remitting disease** is the gradual, often stepwise, accumulation of increasing neurologic deficits
- Certain **patterns** of neurologic symptoms and signs are commonly observed:

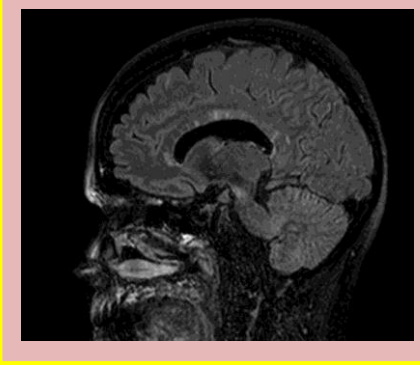
  1- Unilateral **visual impairment** occurring over the course of a few days is a frequent initial manifestation of MS (due to involvement of the optic nerve "*optic neuritis*") when this occurs as the first event, only a minority (10% to 50%) go on to develop full-blown MS.
  2- Involvement of the brain stem produces **cranial nerve signs** and **ataxia**, and can disrupt conjugate eye movements.
  3- **Spinal cord lesions** give rise to motor and sensory impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of bladder function.
  4- Changes in cognitive function 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.

CSF findings

- It shows mildly elevated protein level with an increased proportion of γ-globulin
- In one-third of cases there is moderate **pleiocytosis** (different cell in CSF)
- When the immunoglobulin is examined further, most MS patients show *oligoclonal bands*, representing antibodies directed against a variety of antigenic targets
- These antibodies constitute a marker for disease activity

NOTE: "corpus callosum appears black in CT scan"



NOTE: JC virus or John Cunningham virus (JCV): it usually causes progressive multifocal leukoencephalopathy (PML) which is demyelinating disease.
Most MS patients show oligoclonal bands, while monoclonal band appears in lymphoma patients.

Summary (from Robbins Basic Pathology)

Primary Diseases of Myelin

- **Because of the critical role of myelin in nerve conduction, diseases of myelin can lead to widespread and sever neurological deficits.**
- **Diseases of myelin can be grouped into demyelinating diseases (in which normal myelin is broken down for inappropriate reasons- often by inflammation processes), and dysmyelinating diseases (metabolic disorders that include the leukodysrophies in which myelin structure or its turnover is abnormal).**
- **Multiple sclerosis, an autoimmune demyelinating disease, is the most common disoreder of myelin, affecting young adults. It often pursues a relapsing- remitting course, with eventual progressive accumulation of neurologic deficts.**

Questions from Pathology Recall book

1/ what is the etiology of MS?

Unknown, immune or viral theory postulated but not proven. It is thought to be multifactorial.

2/ what evidence supports the theory of an immune system etiology?

Increased incidence associated with human leukocyte antigen (HLA).

3/ what is increased in the CSF in patients with MS and how is it detected?

Immunoglobulin, seen as multiple oligoclonal bands on electrophoresis.

4/ what are the morphologic changes of MS in the brain and spinal cord?

Multiple focal areas of demyelination known as plaques.

5/ what 3 sites are particularly affected in MS?

Optic nerve, Brainstem, Paraventricular areas.

6/ what cells infiltrate the plaques before reactive gliosis occurs?

Helper CD4+ cells, Cytotoxic CD8+ T lymphocytes, Macrophages

7/ what is the characteristic pattern of the disease?

Periods of exacerbation alternate with long periods of asymptomatic remission, but there is eventual progression to mental deterioration.

(Questions asked by Dr. Hala)

1/ what is the first sign of MS?

A. Double vision C. Ataxia
B. Headache D. Difficulties with the voluntary control of bladder function

2/ whet type of allergy cause of MS?

A. Hypersensitivity Type I C. Hypersensitivity Type II
B. Hypersensitivity Type III D. Hypersensitivity Type IV

3/ what is the most common nerve affected in MS?

A. Trigeminal C. Facial
B. Optic D. Vagus

Answers Box
A
D
B

Helpful video "What is Multiple Sclerosis": http://www.youtube.com/watch?v=qgySDmRRzxY

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us: 432PathologyTeam@gmail.com