MULTIPLE SCLEROSIS

ROBBINS PAGE 832

OBJECTIVES:

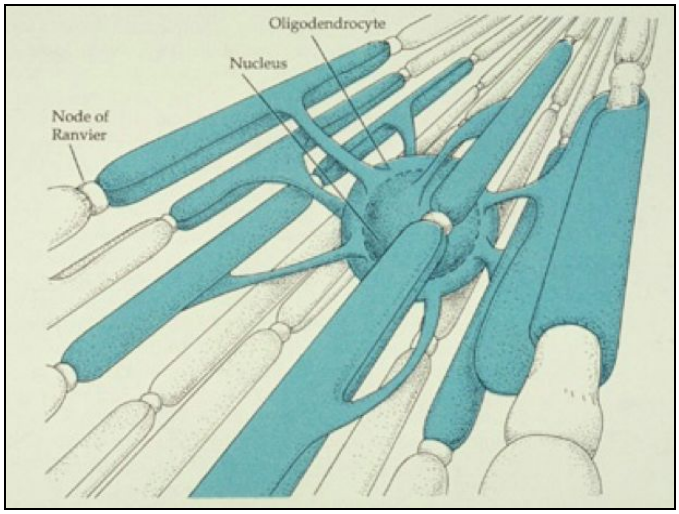
- Appreciate the critical role of myelin in maintaining the integrity of the CNS system.
- Understand the pathogenesis and the clinic-pathological features of multiple sclerosis as the classical and the commonest example of CNS demyelinating diseases.

Important note: **Please check out this link before viewing the file to know if there are any additions or changes. The same link will be used for all of our work: Pathology Edit**

Red: Important
Grey: Extra notes

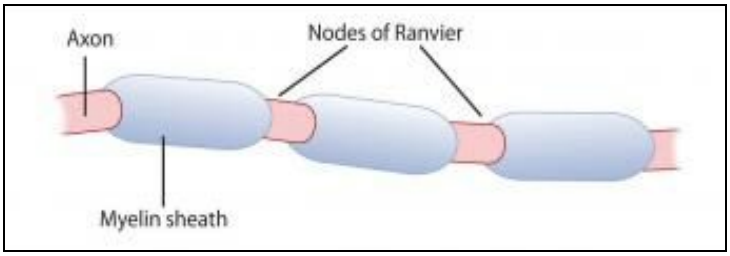
Myelin.

Within the CNS, axons are tightly ensheathed by myelin. which consists of multiple layers of the specialized plasma membrane formed by **oligodendrocytes**. Myelinated axons are dominant in the **white matter**; therefore, most diseases of myelin are primarily **white matter disorders**.



What is the function of myelin?

Improving the speed and efficiency of conduction.



- Segments of axon that ensheathed by myelin→ internodes.
- Gaps between segments → Nodes of Ranvier.

Myelin differences between CNS and PNS:

peripheral nerves	Central nerves
Myelin made by **Schwann cells**	Myelin made by **oligodendrocytes**
One Schwann cell → one internode	Single oligodendrocyte → Many internodes

Most diseases of CNS myelin do not significantly involve the peripheral nerves, and vice versa. Why?
Because specialized proteins and lipids that form myelin in PNS are different from those on CNS.

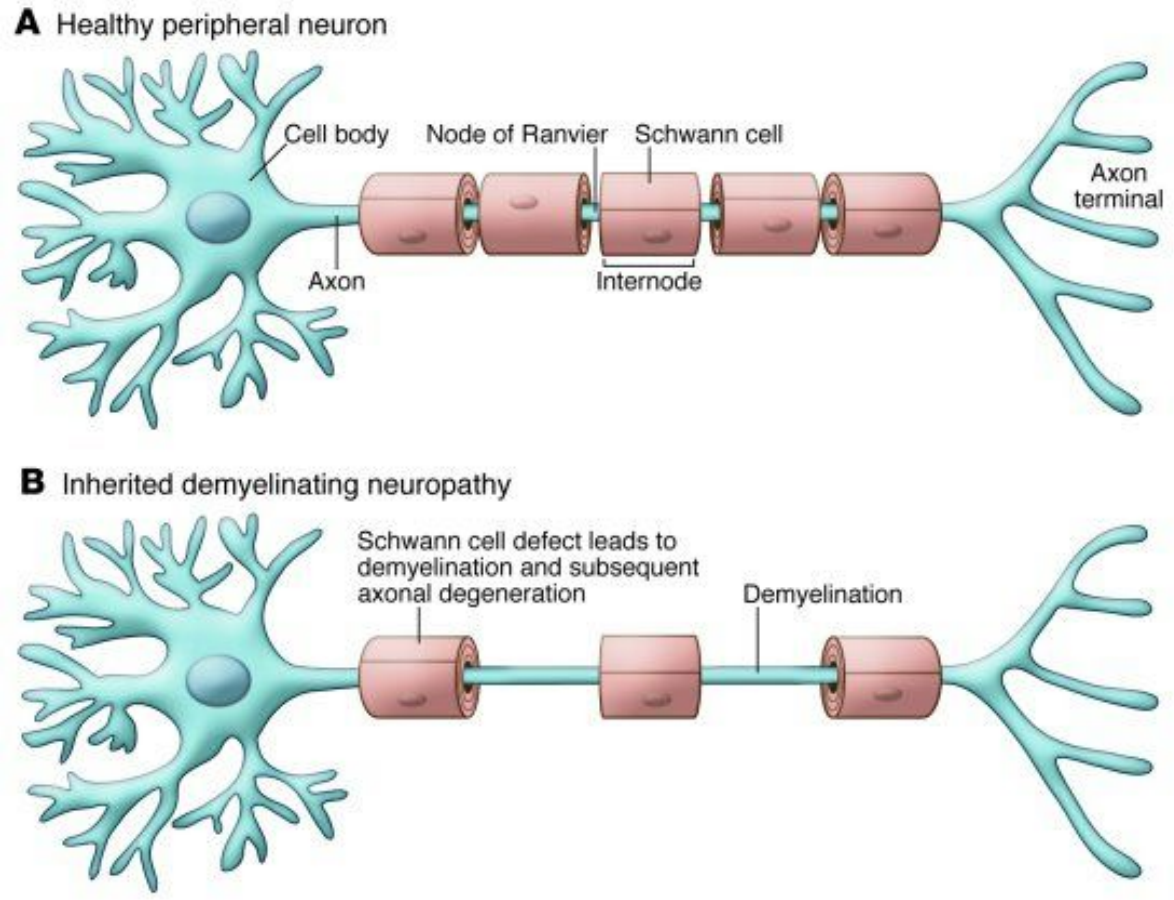
The natural history of demyelinating diseases is determined by → the *limited capacity of the CNS to regenerate normal myelin* and by the degree of secondary damage to axons that occurs as the disease runs its course.

What does that mean? At the beginning of the disease symptoms will appear mild, then they will stop for a period of time (no symptoms = **Remission**). After that there will be residual symptoms (**Relapses**) & they will worsen because the CNS capacity for regeneration destructed myline is limited (also it Takes a long time for regenerate).

مثلا الشخص المصاب تظهر لديه أعراض عصبية متنوعة، في البداية تكون خفيفة (مثال رؤية ضبابية).. بعد فترة يعود نظره طبيعي و هي الفترة الفاصلة ما بين انتكاسات المرض.. ثم تعود له الأعراض مرة أخرى لكنها في كل انتكاسه تكون أقوى من قبل (مثال تعود الرؤية الضبابية ويكون معها أعراض جديدة أخرى مثل صعوبة البلع).

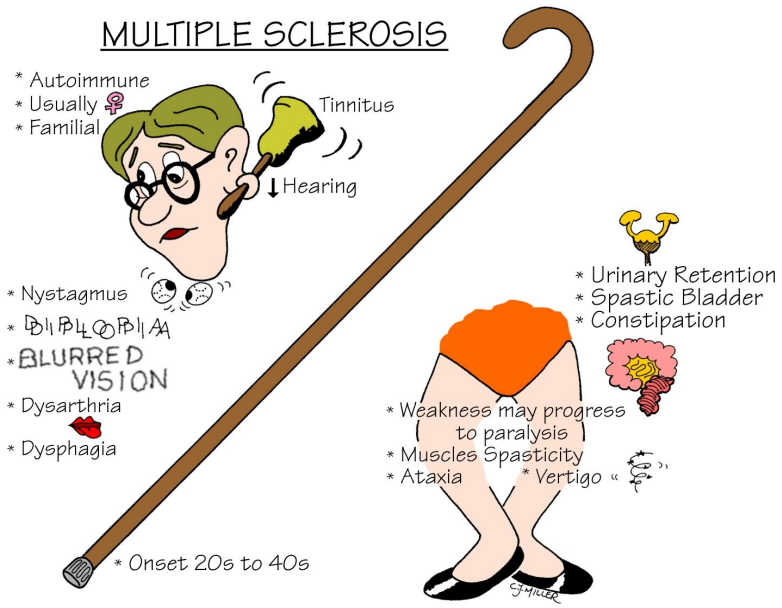
Primary Demyelinating disease.

Demyelinating diseases	Dysmyelinating diseases (Leukodystrophy)
Acquired conditions characterized **destruction** of normal myelin or oligodendrocyte	Myelin is **not formed** properly or has **abnormal turnover** kinetics
Immune-mediated injury: ● Multiple sclerosis. ● Viral infection of oligodendrocytes as in **progressive multifocal leukoencephalopathy.** ● Drugs and other toxic agents.	**Mutations affecting:** ● Proteins required for formation of myelin. Or ● Mutations that affect the synthesis or degradation of myelin lipids.



- Decreased conduction velocity or block
- Destablization of axonal cytoskeleton
- Remodelling of internodal membrane
- Progressive axonal loss

Multiple sclerosis.



MS is an **autoimmune demyelinating disorder.** It is the most common demyelinating disorder.

Prevalence: 1 per 1000 persons in most of the United States and Europe.

Incidence: Becomes clinically apparent **at any age** (common in young adult 20-30) but it's rare in childhood & >50 years. **Women** more affected.

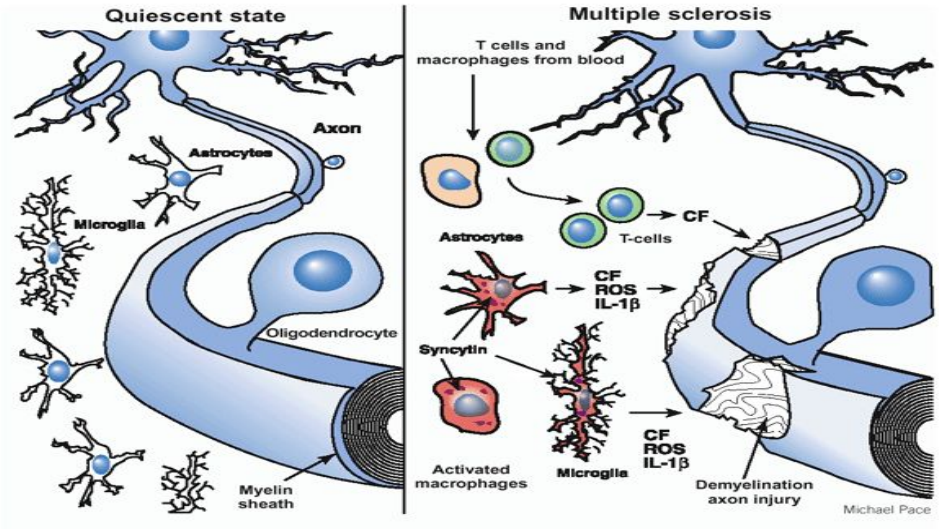
Characterized by: Distinct episodes of neurologic deficits, separated in time (Remission and Relapsing), attributable[1] to white matter lesions that are separated in space (Random).

Risk factors:

- **15-fold higher** (**in a first degree relative.)**
- **Monozygotic twins**[2] are approximately **25%**, with a much lower rate for **dizygotic twins**[3].
- A significant fraction of the genetic risk for MS is attributable to **HLA-DR-2.**

Pathogenesis:

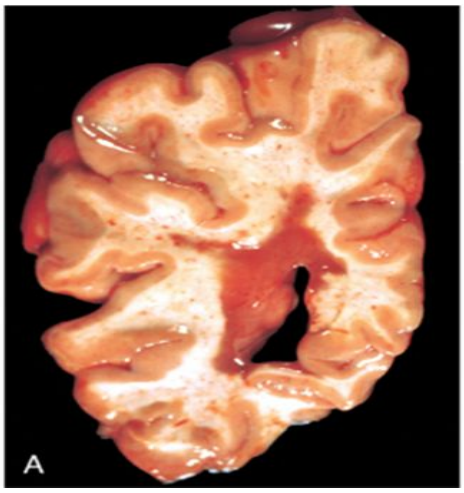
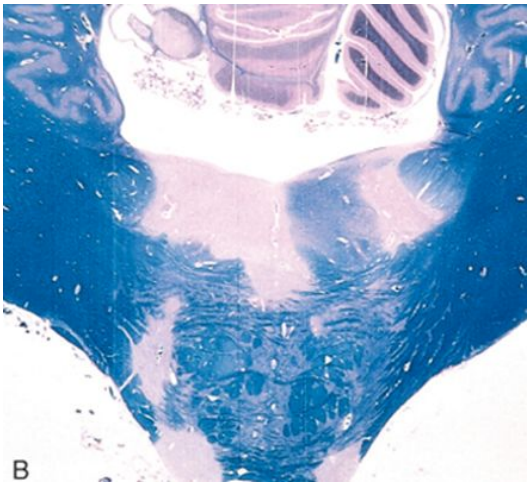
Combination of **environmental** (such as infection) & **genetic factors** that result in a loss of tolerance of self proteins (antigen) → **Antigen presenting Cell comes and activates T-helper (CD4)** → secret cytokines IL2 and IL7 → T cell cross BBB → **Type IV hypersensitivity** → infiltrate of lymphocytes, macrophages,B Cells and plasma cells produce antibody → demyelination, axonal loss and sometimes even leading to neuronal death.



[1] بسبب
[2] التوأم المتشابه
[3] التوأم المختلف

Experimental autoimmune encephalomyelitis (EAE) is the most commonly used experimental model for the human inflammatory demyelinating disease, multiple sclerosis (MS). EAE is a complex condition in which the interaction between a variety of **immunopathological** and **neuropathological** mechanisms leads to an approximation of the key pathological features of MS: inflammation, demyelination, axonal loss and gliosis.

Morphology:

Gross appearance	Microscopic level
	
Multiple, well-circumscribed, slightly depressed, glassy, **gray-tan**, irregularly shaped lesions, this known as **plaques**. (In white matter)	The lesions have sharply defined borders. - (This is special stain for MS: **Luxol fast blue (LFB)**)

We can see plaques in:

- **Usually in ventricles.**
- **Optic nerves and chiasm[4].**
- **Brain stem.**
- **Ascending and descending fiber tracts.**
- **Cerebellum.**
- **Spinal Cord.**

In an active plaque there is:

- Ongoing myelin breakdown
- Abundant **macrophages** containing myelin debris.
- Lymphocytes and monocytes are present, mostly as perivascular cuffs.
- Axons are relatively preserved, but they may be reduced in number.

[4] decussation or crossing of two fibrous bundles, such as tendons, nerves, or tracts.

In inactive plaques (quiescent):

- NO inflammation.
- No myelin.
- Astrocytic proliferation.
- Gliosis are prominent.
- Decrease oligodendrocytes.

Clinical Features:

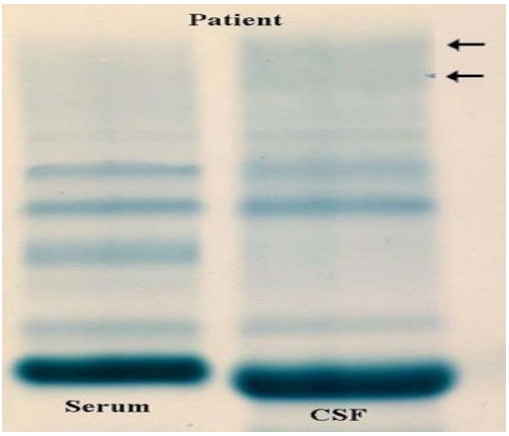
MS lesions can occur anywhere in the CNS → may induce a wide range of clinical manifestations.

1. Unilateral **visual impairment** (due to involvement of the optic nerve "optic neuritis").
   → When this occurs as 1st event, 10% - 50% develop full-blown MS (fully developed).
2. Produces cranial nerve signs and ataxia, and can disrupt conjugate eye movements. (involvement of the brain stem)
3. Motor and sensory impairment (due Spinal cord lesions) which lead to:
   - Loss of sensation and weakness of muscle.
   - Bladder and sexual dysfunction.

CSF findings shows:

- **Mildly elevated protein level** (myelin is destroyed so myelin basic proteins will be present in CSF)
- Increased proportion of **γ-globulin**.
- In one-third of cases there is **moderate pleocytosis**[5] (increased WBC count in CSF).
- Most MS patients show **oligoclonal bands**[6].

Oligoclonal bands are proteins called immunoglobulins. The presence of these proteins indicates inflammation of the central nervous system. These antibodies constitute as a marker of MS activity.

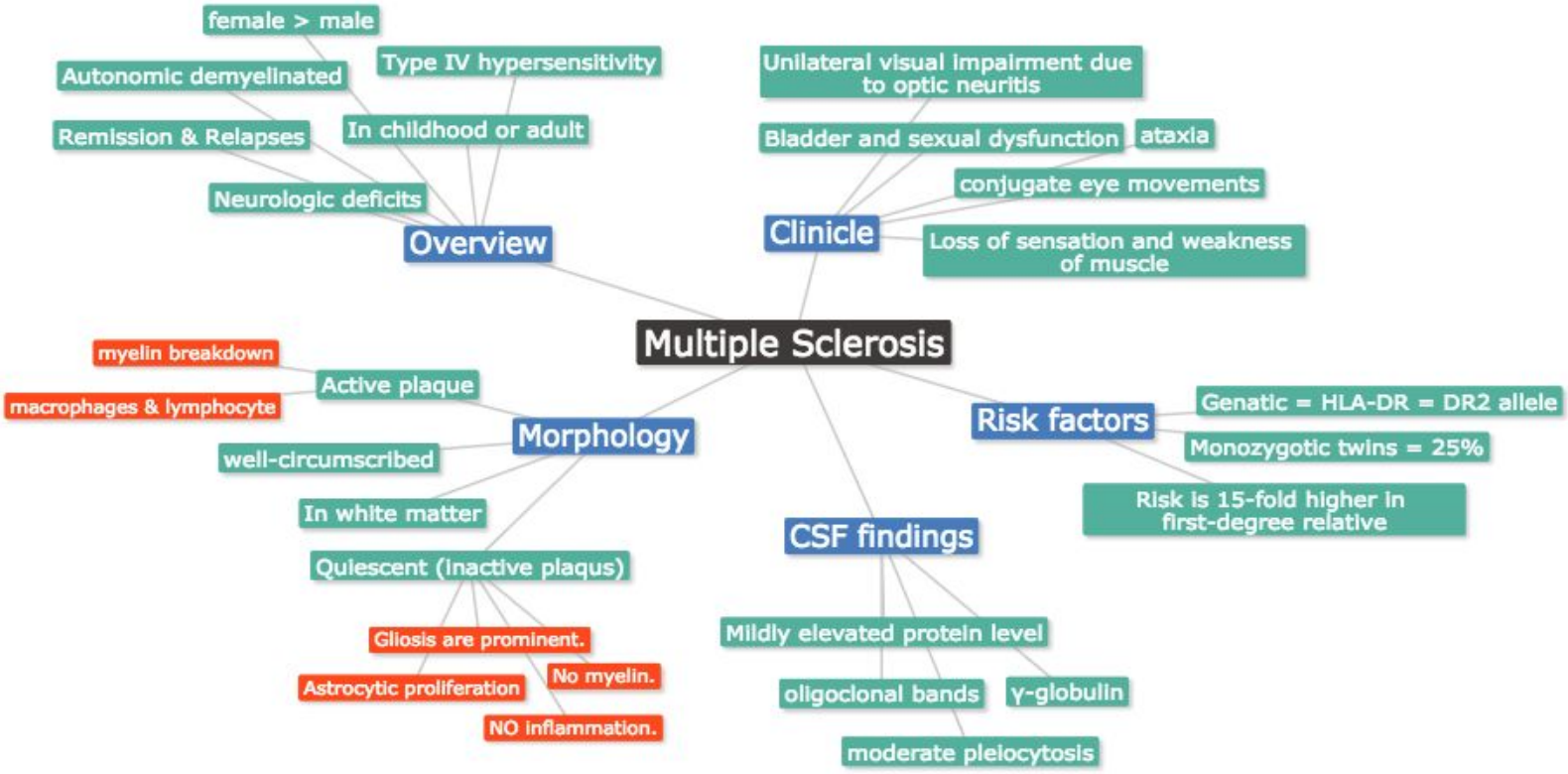


Treatment:

Acute attack by Steroids and long-term treatment (low-progressive) by: Interferon-Beta.

[5] an increase in white blood cells (WBCs)
[6] antibodies directed against a variety of antigenic targets

Summary.



MCQ's.

1. **Multiple Sclerosis usually affects:**

A. Children
B. young Adult
C. old age

Answer : B

2. **MS symptoms may be caused by:**

A. Damage to myelin (the sheath covering the nerve fibers)
B. Damage to axons (the nerve fibers themselves)
C. Both A & B
D. Neither

Answer : C

3. Which of the following is usually not a symptom of MS :

A. Fatigue
B. Walking difficult
C. Problems with eyesight
D. Peripheral nerves

Answer : D

4. MS is strongly associated with :

A. HLA-DR2
B. HLA-DQ
C. HLA-A

Answer : A

5. Although the exact cause of MS is not yet known, which factor may play a role?

A. Environment
B. Viruses
C. Family history
D. All of the above

Answer : D

6. Leukodystrophy Characterized by preferential damage to _____ myelin :

A . not properly formed
B. previously normal
C. abnormal turnover kinetics
D. A & C

Answer : D

7. Demyelinating diseases of CNS Associated with :

A . multiple sclerosis
B. mutations that affect the synthesis or degradation of myelin lipids
C. viral infection
D. neither

Answer : B

8. The concordance rate for dizygotic twins is approximately 25%, with a much lower rate for monozygotic twins :

A. True
B. False

Answer : B

9. MS has worse prognosis in :

A. Men less than women
B. Women less than men
C. Women more than men
D. Neither

Answer : B

10. **CSF findings in MS :**
    A. Absence of Oligoclonal Bands
    B. IgG level will decrease
    C. A & B
    D. Neither

Answer : D

For any suggestions or questions please don't hesitate to contact us on: Pathology434@gmail.com
Twitter: @Pathology434
Ask us: www.ask.fm/Pathology434

Examine yourself in pathology:
http://library.med.utah.edu/WebPath/EXAM/MULTORG/examidx.htm

Good Luck! :)

YOU NEVER KNOW HOW STRONG YOU ARE UNTIL BEING STRONG IS THE ONLY CHOICE YOU HAVE

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