Revised & Approved

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04

Pathology

(Multiple Sclerosis)

439

Color index

- Important
- Doctor's note
- Extra info
- Main text

" اللهم لا سهل الا ماجعلته سهلا و انت تجعل الحزن إذا شئت سهلا "

Objective

01 Appreciate the critical role of myelin in maintaining the integrity of the CNS system

02 Understand the pathogenesis and the clinic-pathological features of multiple sclerosis as the classical and the commonest example of CNS demyelinating diseases

Overview

Multiple Sclerosis

- Myelin Definition
- The differences between myelin in CNS and PNS
- Primary Demyelinating disease general classification
- MS definition
- MS pathogenesis
- MS morphology
- MS clinical features
- CNS finding

Myelin

❖ Myelin: is an electrical insulator that allows rapid propagation of neural impulses.

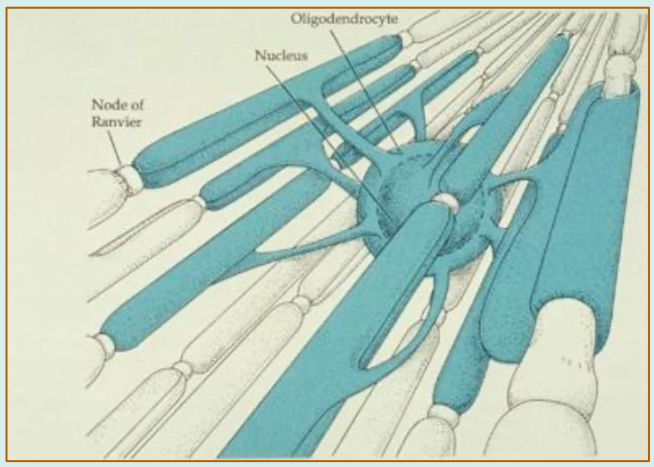
❖ Myelin consists of multiple layers of the specialized plasma membrane of **oligodendrocytes** (in the CNS), with most of the cytoplasm excluded.

❖ 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.

How does it form?

❖ An oligodendrocyte extends processes toward many different axons and wraps a segment of roughly a few hundred microns of axon.

❖ Each of these segments is called an internode, and the gaps between internodes are known as **nodes of Ranvier**.



Myelin differences between CNS and PNS:

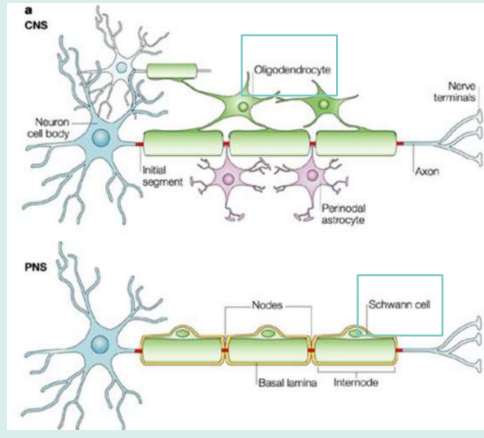
(The myelin in peripheral nerves is similar to the myelin in the CNS)
BUT :

CNS	PNS
- Myelin made by **oligodendrocytes**.	- Myelin is made by **Schwann cell**
- Many internodes comes from a single oligodendrocyte.	- Each cell contributes to only one internode.

Most diseases of CNS myelin do not significantly involve the peripheral nerves, and vice versa, Why?

Because specialized proteins and lipids that form myelin are different from those in CNS.

Natural history of a disease: The course of events that occurs from acquiring the disease until resolution or death, without treatment.



❖ **The natural history of demyelinating diseases is determined by:**

➢ The limited capacity of the CNS to regenerate normal myelin.

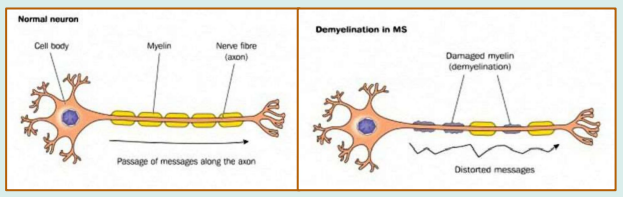
➢ The degree of secondary damage to axons that occurs as the disease runs its course.

Primary Demyelinating disease general classification

***De*myelination disease**	***Dys*myelination disease** The other general term is **Leukodystrophy** which stands for a group of diseases that affect the CNS
Acquired conditions characterized by preferential damage to **previously normal myelin.** Commonly result from **immune-mediated injury**: ❖ Multiple Sclerosis. ❖ Viral infection of oligodendrocytes **as in progressive multifocal Leukoencephalopathy.** Or it can result from : ❖ Drugs and other toxic agents.	**Myelin is not formed properly** or has abnormal turnover kinetics. Associated with mutations affecting: ❖ The proteins required for formation of normal myelin. ❖ Synthesis or degradation of myelin lipids.

Helpful introductory video :)

Multiple sclerosis



Definition	❖ MS is an autoimmune demyelinating disorder characterized by **distinct episodes** (the patient is normal then suddenly deteriorate) of neurologic deficits, **separated in time (relapse** "episodes of new symptoms" **& remission** "episodes of recovery"**)**, attributable to white matter lesions that are separated in space.
Epidemiology	❖ The disease becomes clinically apparent at any age, although an onset in childhood or after the age 50 years is relatively rare ❖ Women are affected twice as often as men ❖ The most common demyelinating disorders (prevalence of 1 per 1000 persons in the United States and Europe).
Marker	❖ In most individuals with MS the illness shows a **relapsing and remitting episodes of neurologic deficits** ❖ The consequence of this pattern of relapsing-remitting disease is the gradual, often stepwise, accumulation of increasing neurologic deficits (CNS symptoms) ❖ 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 ❖ 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 ❖ MS is characterized by the presence of demyelination out of proportion to axonal loss, some injury to axons does occur.

Risk factors

01 15-fold higher when the disease is present in a first-degree relative.

02 The concordance rate for monozygotic twins is approximately 25%, with a much lower rate for dizygotic twins. Roughly 150-fold higher with an affected monozygotic twin.

03 A significant fraction of the genetic risk for MS is attributable to certain HLA DR2 (HLA-DRB1*1501 allele) variants. Brings with it a roughly 3-fold increase in the risk for MS.

04 Other genetic loci include the IL-2 and IL-7 receptor genes and other genes encoding proteins involved in immune response

Pathogenesis

- As any other autoimmune diseases, MS pathogenesis is not well understood.
- The lesions of MS are caused by an **autoimmune response** directed against components of the myelin sheath.
- like other autoimmune diseases, MS is caused by a combination of **environmental** like psychological trauma and **genetic** factors that result in a loss of tolerance to self proteins (in this case, myelin antigens)..
- While MS is characterized by the presence of demyelination out of proportion to axonal loss, some injury to axons does occur

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- In view of the prominence of chronic inflammatory cells within and around MS plaques as well as the genetic evidence, immune-mediated myelin destruction is thought to have a central role in MS. Evidence from human studies as well as from Experimental autoimmune encephalomyelitis is an animal model of MS in which demyelination and inflammation occur after immunization of animals with myelin protein,
- 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
- or certain peptides from myelin proteins—has suggested that a range of immune cells contribute to lesion development in MS .
- **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 the injury to myelin.
- There is also evidence for important contributions from **CD8+ T cells and B cells.**

Initiation of disease by **TH1** and **TH17** that react against myelin and secrete cytokines.

↓

TH1 cells secrete IFN-γ, which activates macrophages, TH17 help recruiting leukocytes

↓

B lymphocytes and antibodies also play an important, but poorly defined

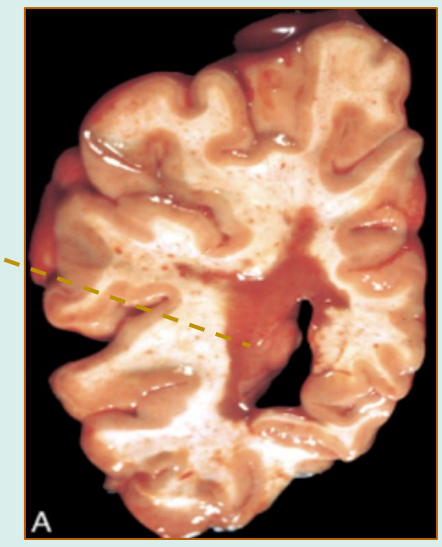
↓

Toxic effects of lymphocytes , macrophages, and their secretions can initiate the process of axonal injury sometimes leading to neuronal death

Morphology

01 Gross appearance:

- MS is a white matter disease



- Affected areas show:

Well circumscribed, Slightly depressed, Glassy, Grey tan, Irregularly shaped lesions.

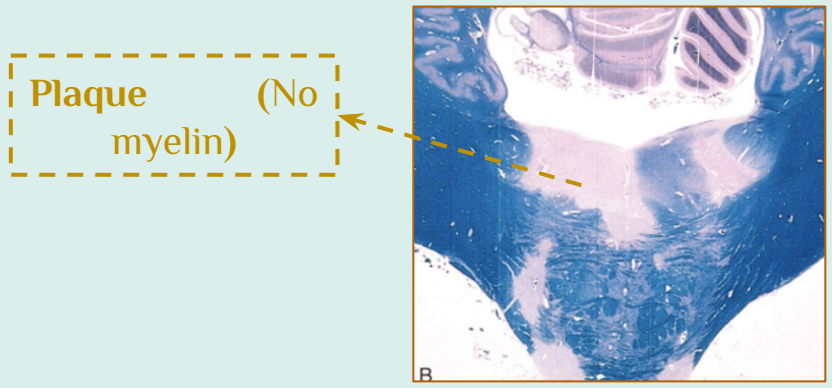
- These lesions are called (**Plaques**).

- They occur beside ventricles and they are frequent in:

Optic nerves chiasm, Brain stem, Ascending and Descending fiber tracts, cerebellum and spinal cord.

02 Microscopic appearance:

- The lesions have sharply defined borders.



Active plaque	Inactive plaques
◆ Ongoing myelin breakdown. ◆ Abundant macrophages containing myelin debris. ◆ Loss of myelin and variable loss of oligodendrocytes. ◆ Lymphocytes , plasma cells and macrophages are present,mostly as **perivascular inflammatory cuffs.** ◆ Axons are relatively preserved, although they may be reduced in number	When plaques become quiescent (Inactive): ◆ The inflammation disappears. ◆ Little to No myelin. ◆ Astrocytic proliferation and **gliosis** are prominent. ◆ Loss of oligodendrocyte and second axonal injury.

Clinical features

certain patterns of neurologic symptoms and signs are commonly observed:

1. **Unilateral visual impairment;**
   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. **Cranial nerve signs and ataxia, and disrupt conjugate eye movements;**
   Due to involvement of **brainstem**.

3. **Motor and sensory impairment of trunk and limbs, spasticity, and difficulties with the voluntary control of the bladder function;**
   Due to **Spinal cord lesions**

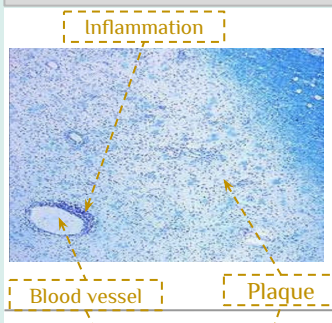
4. **Changes in the cognitive function can be present, but are often much milder than the other finding**

❖ In any given patient, the course of the disease depend on location and severity. 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. Medications are used to control the symptoms only .

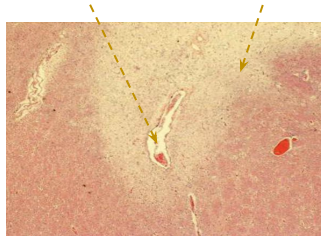
CNS Findings

Microscopic and Radiological findings part was only in the girls slides

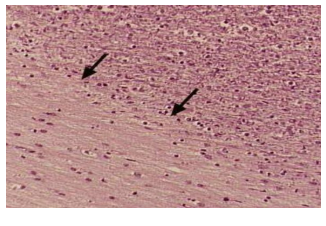
★ Microscopic findings:



- luxol fast blue/PAS myelin stain (early lesion).
- The lesion is centered around a small vein which is surrounded by inflammatory cells
- This is an active plaque due to the presence of inflammatory cells around the blood vessel .



- H&E stained section (long-standing MS).
- An old (inactive) lesion is centered around a vein with very little inflammation.
- Loss of myelin can be seen even without special stains (it is lighter pink than the normal white matter around it).
- Patient has the disease for a long time thus the myelin disappeared.
- No inflammatory cells around the blood vessel so it is an inactive plaque

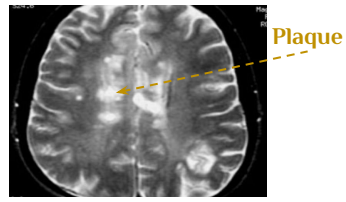


Astrogliosis

- An MS plaque showing a pale plaque almost devoid of myelin.
- There is a decrease in oligodendrocytes and increase in the astrocytic nuclei which is characteristic of old MS lesions.

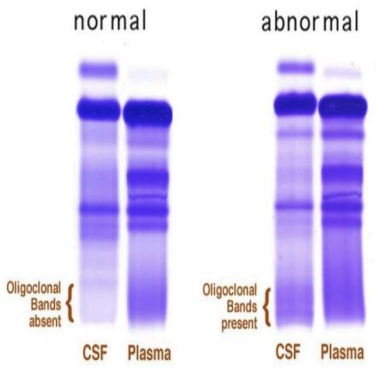
★ Radiological findings:

- Lesions on MRI appear as **bright white spots.**



★ Laboratory findings:

- The CSF shows mildly:



- ❖ Elevated protein levels,Increased **γ-globulin** (IgG) on electrophoresis
- ❖ In 1/3 of cases there is moderate **pleocytosis**(abnormal increase in the amount of lymphocytes in the CSF).
- ❖ **Oligoclonal bands**, representing antibodies directed against a variety of antigenic targets. These antibodies constitute a **marker** for disease activity.

QUIZ!

MCQs

01 | Multiple sclerosis attacks myelin at :			
A) CNS	B) PNS	C) Both A & B	D) Schwann cell
02 | Dysmyelination disease can result from :			
A) Multiple sclerosis	B) Progressive multifocal Leukoencephalopathy	C) Mutations affecting the proteins required for myelin formation	D) Drugs and Toxins
03 | MS is an autoimmune demyelinating disorder characterized by			
A) Attributable to Grey matter	B) Attacking Myelin made by schwann cell	C) Distinct episodes	D) Affecting children
04 | Which factor may play a role in MS?			
A) Environment	B) Viruses	C) Family history	D) All of the above
05 | What are some of the symptoms of MS?			
A) Blurred or double vision	B) Muscle weakness	C) Partial paralysis	D) All of the above
06 | What type of imaging is usually used to see inflammation and damaged areas in the brain?			
A) PET scan	B) MRI scan	C) CAT scan	D) X-ray

MCQs Answer key	01	02	03	04	05	06
	A	C	C	D	D	B

Summary

A 27-year-old Caucasian woman presents to your office complaining of visual disturbances. During physical examination, you note that on lateral gaze, one eye does not adduct and the other eye has nystagmus on abduction. Testing of cerebellar function reveals an intention tremor and you also note decreased sensation on both legs. You obtain CSF fluid via a lumbar puncture and find multiple oligoclonal bands of IgG on electrophoresis. You order an MRI of the brain and refer the patient to a neurologist for further care of her condition.

Multiple sclerosis	
Etiology	Etiology unknown, although **autoimmune**, genetic, and environmental factors have been implicated Incidence increases proportionally with distance from equator and incidence is more common in **HLA-DR2** individuals
Epidemiology	Most often presents in Caucasian **women** between the **ages of 20 and 30**
Pathology	CNS: **Multiple firm plaques** representing **demyelination** within the white matter of the **CNS**, especially in optic nerve, brainstem, and periventricular areas Microscopic plaque: **Depletion of oligodendrocytes**; monocytes, lymphocytes, and lipid-laden macrophages around vessels; **gliosis** and astrocyte proliferation
Clinical manifestation	**Relapsing and remitting course**, but eventually remissions become incomplete; classic **Charcot triad**: nystagmus, scanning speech, and intention tremor; **motor and sensory impairment** of trunk and extremities (hemiparesis, ataxia); **visual impairment** (optic neuritis, retrobulbar neuritis, **internuclear ophthalmoplegia** [on lateral gaze, one eye does not adduct and the abducting eye has nystagmus caused by demyelination of MLF]); urinary/bowel incontinence owing to loss of sphincter control. Lab findings: Lumbar puncture shows mild lymphocytosis and elevated IgG, manifested as **multiple oligoclonal bands** on electrophoresis
Treatment	Corticosteroids and other immunosuppressants

"اللهم علمنا ماينفعنا ، وانفعنا بما علمتنا وزدنا علما يارب العالمين"

Team leaders

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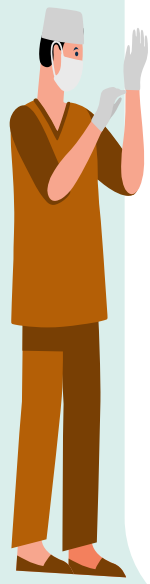

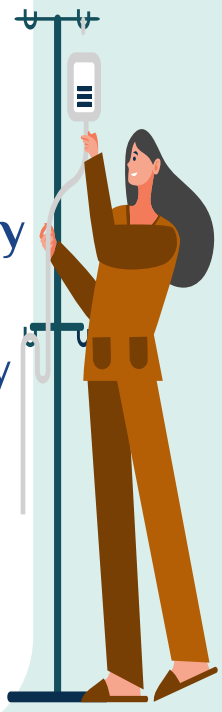

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