CNS lecture 4

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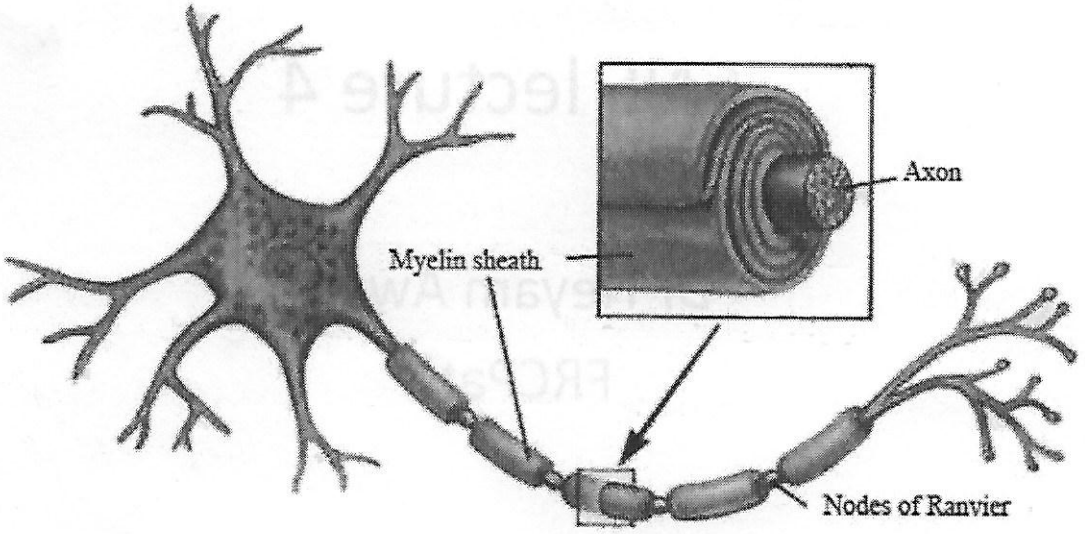
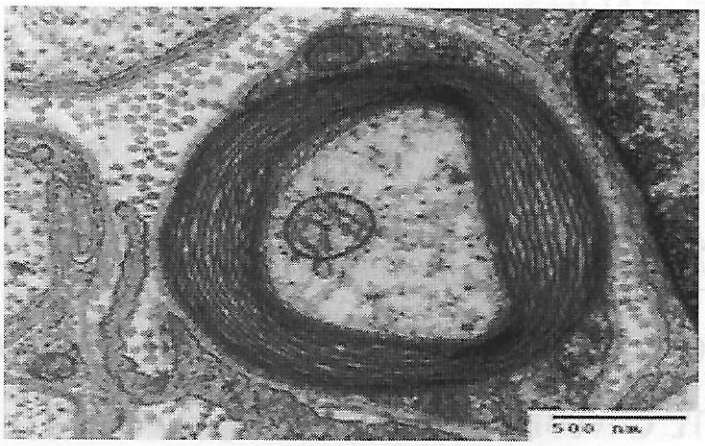
Diseases of Myelin

- Myelin: protein-lipid complex that is wrapped around the axons.
- Function: allows rapid propagation of signals.
- Composition: layers of plasma membranes ↓ assembled by oligodendrocytes (CNS) wrapping around axons
- Myelinated axons are the predominant component of white matter.

Functions of myelin:
① Speeds up nerve impulse transmission
② Electrical insulation → protection from external electrical charges



EM myelin → layers of membrane wrapping around axons



- Myelin diseases of CNS do not affect myelin of peripheral nerves.
- WHY???

Myelin

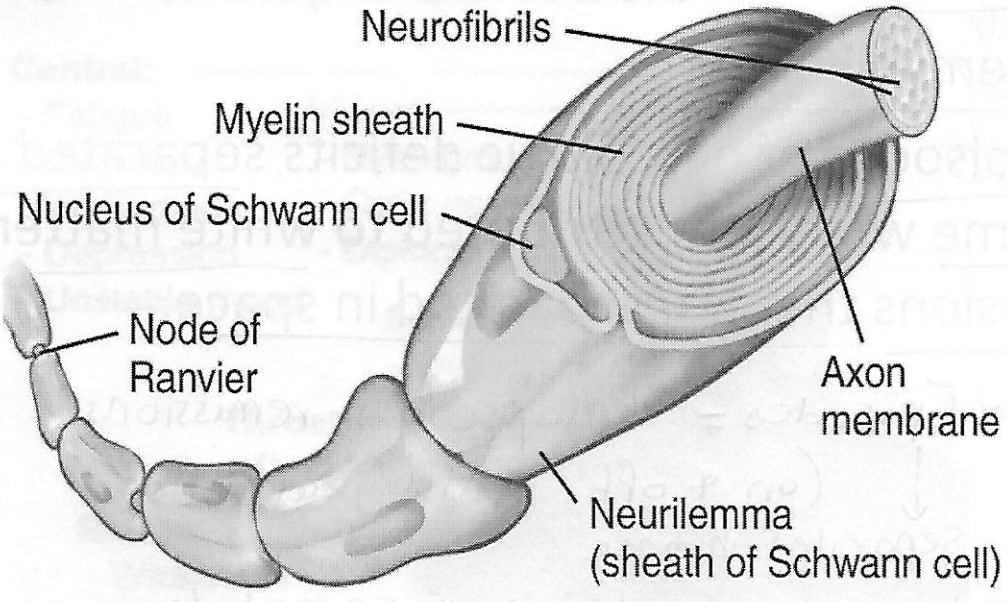
CNS → made by Oligodendrocytes

PNS → made by Schwann cells

different cells → so different components

Myelin in peripheral nerves

→ by Schwann cells



Primary diseases of myelin

→ 2 types

① **Demyelinating diseases** : acquired conditions where there is damage to previously normal myelinated axons due to [1] autoimmune destruction, [2] viral infections, [3] drugs, [4] toxins.

} → destruction is due to an exogenous agent

Most common type: multiple sclerosis

② **Dysmyelinating diseases = leukodystrophy**

myelin not formed properly or has abnormal (rapid) turnover kinetics, result from mutation disrupting function of proteins the form myelin.

⇒ congenital / familial

✳ Multiple sclerosis

- Autoimmune → AI destruction of myelin
- Demyelinating
- Episodes of neurologic deficits separated in time which are attributed to white matter lesions that are separated in space.

* Episodes = relapses + remissions (on + off neurological deficits)
  ↓ separated in time

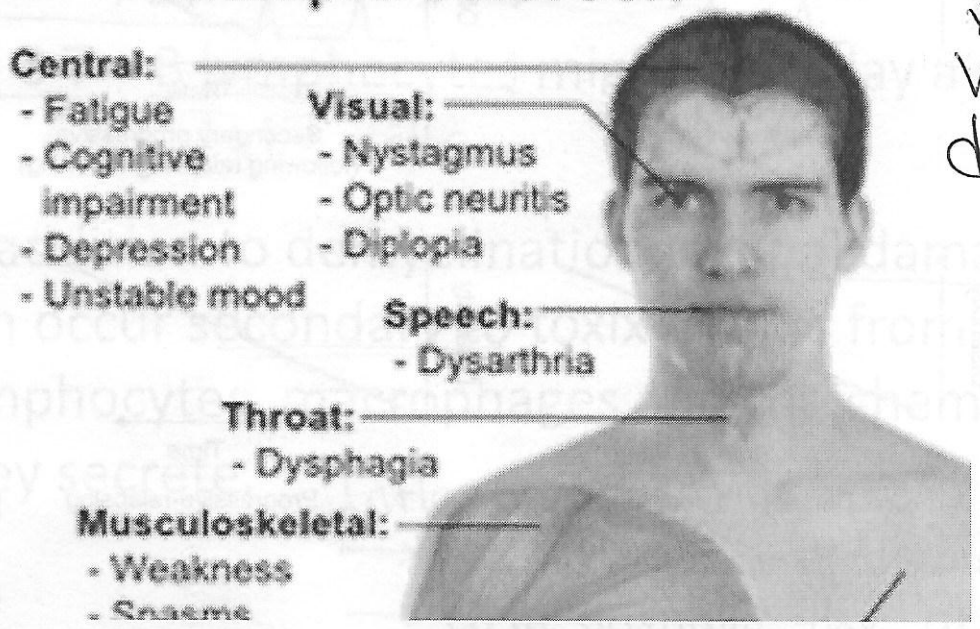
Due to * White matter lesions = several lesions in axons + myelin (not necessarily close to each other)
  ↓ separated in space

- 1 per 1000 persons in USA and Europe
- Female : male ratio is 2:1

Relapsing and remitting episodes of neurologic deficit variable clinical course.

symptoms

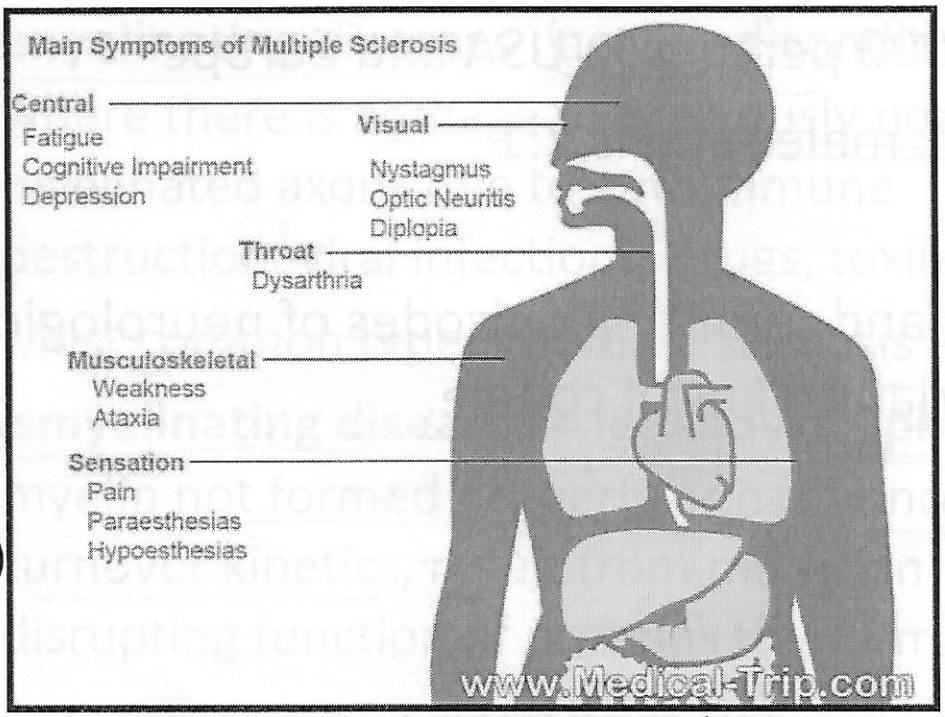
The neurological deficits depend on which axons are affected ⇓ very diverse



Temporary ← symptoms → 3 main functions affected:

↳ if there is remission

since only myelin destroyed not axons (myelin can regenerate)



① Ocular/visual: range from diplopia to blindness

② Cognitive

③ Motor (dysphagia, weakness, etc..

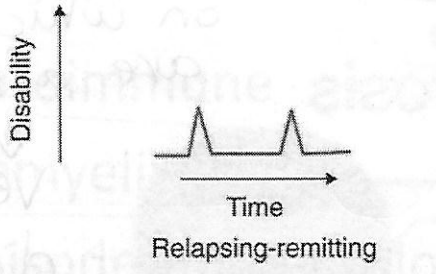
These do not always occur together

Clinical course

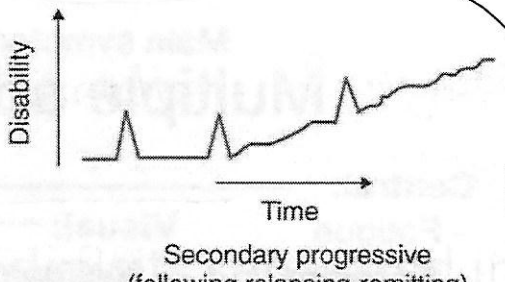
we cannot predict what might happen next

OR

Relapsing and remitting



Relapsing-remitting



Secondary progressive (following relapsing-remitting)

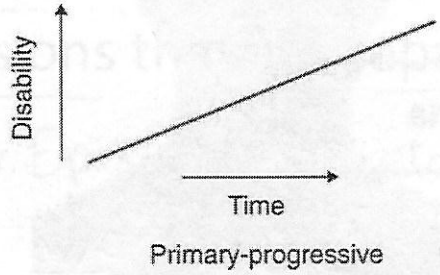
Progressive

↓

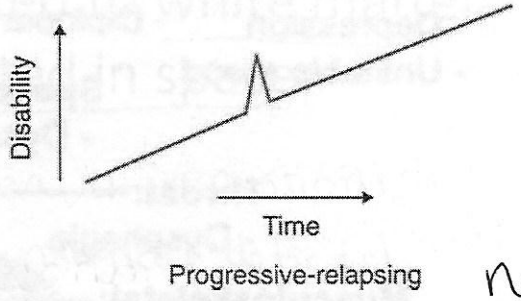
becomes worse with time

↓

neurological problem all life



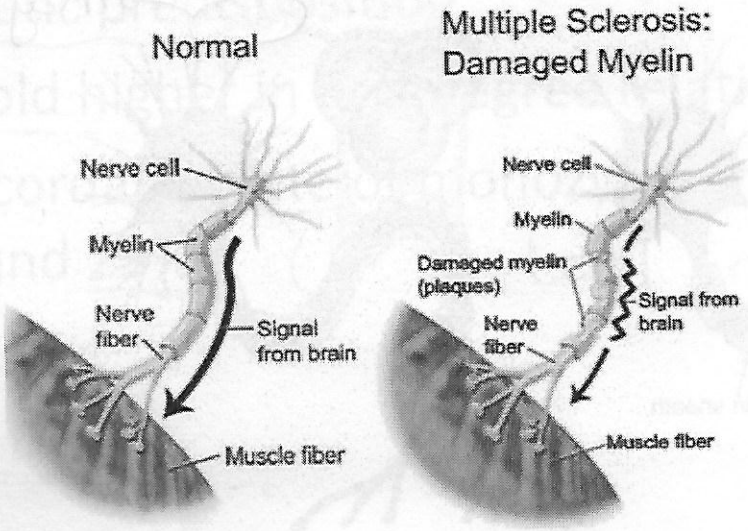
Primary-progressive



Progressive-relapsing

pathogenesis

AI destruction of myelin
↓
Affects signal transmission from brain/ to brain
↓
neurological deficits

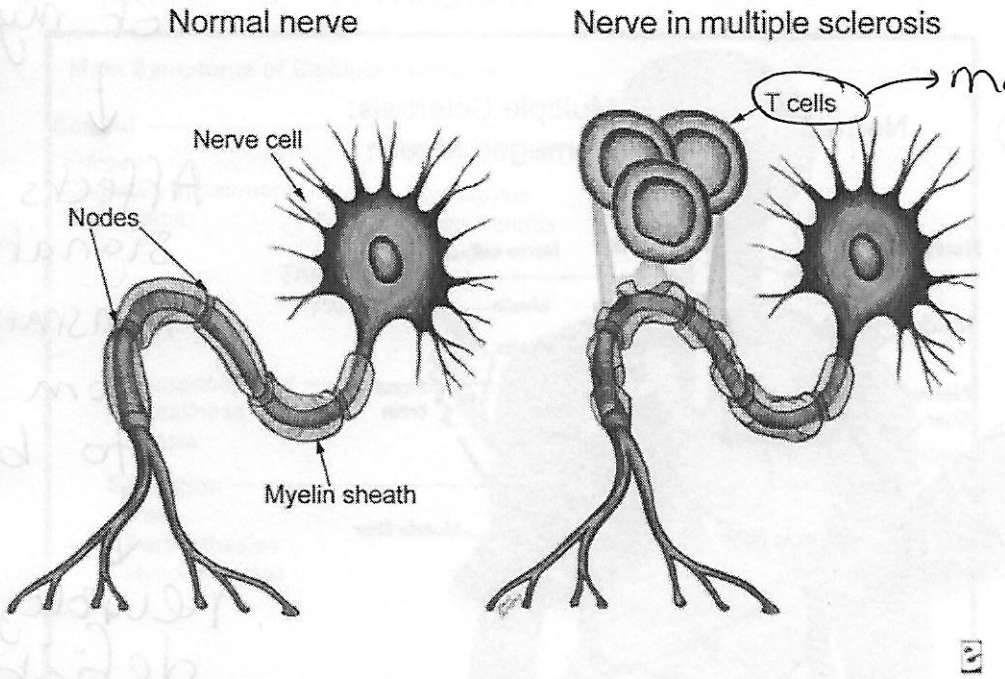


Immune destruction in MS

↳ Main cause of destruction

- CD4 T lymphocytes play a major role.
- CD 8 T + B lymphocytes might also play a role.
  Also T_H17 cells
- In addition to demyelination; axonal damage can occur secondary to toxix effects from lymphocytes, macrophages and the chemicals they secrete.

Inflammatory cells
→ toxic effects and chemicals
→ will damage the axons themselves with time
→ irreversible



pathogenesis

- Autoimmune disease
- Environmental and genetic factors BOTH
- Loss of tolerance to self protein: myelin antigen The antigen provoking the immune response is present within myelin but NOT known
- Initiating agent?? Could be viral infection

First episode can start after a viral infection

Patients have genetic susceptibility → but need an environmental trigger to develop MS

- Genetic predisposition.. evidence:
- 15 fold higher in first degree relatives
- Concordance rate of monozygotic twins around 25% (it is less in dizygotic twins)

- HLA DR2

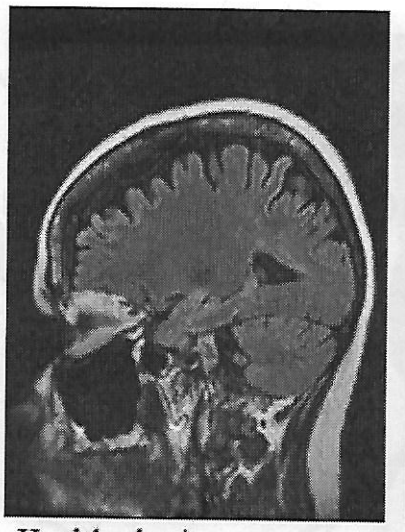
morphology

- White matter disorder
- Multiple well circumscribed slightly depressed grey tan irregularly shaped lesions= plaques
- Commonly seen near ventricles, optic nerves and chiasm, brain stem, cerebellum and spinal cord

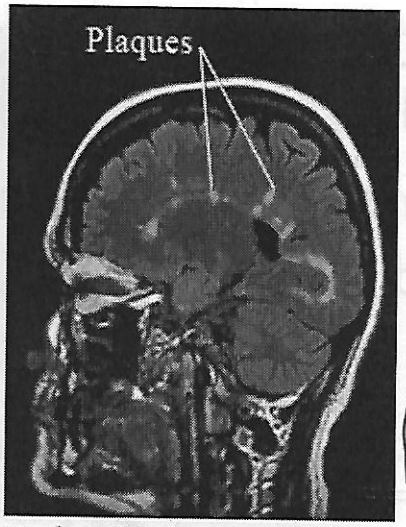
→ optic manifestations are common

white matter becomes depressed and loses its colour → becomes gray macroscopically

plaques



Healthy brain



Brain with damage (lesions or plaques) caused by MS

T-helper cells
↓
Inflammation
↓
Macrophages
↓
Phagocytosis

Plaques → Active → ongoing destruction of myelin by macrophages (phagocytosis actively happening)

Plaques → Quiescent → chronic stage/ inactive

(1)

- Active plaques: ongoing myelin breakdown, macrophages containing myelin debris

Active plaques.. One of four classes

- Type 1: macrophages infiltrating with sharp margins
- 2: like 1 but also complement deposition
- 3: less well defined borders + oligodendrocyte apoptosis
- 4: non- apoptotic oligodendrocyte loss

* Myelin can be regenerated → but if the inflammation reaches the stage of neuronal damage → irrerersible → permanent neurological damage

②
- Quiescent, inactive plaques: inflammation disappears leaving behind little or no myelin
- Astrocytic proliferation and gliosis prominent

Repair

regeneration by glial cells

* Other demyelinating diseses

- 1. post infectious, most common form of these
- 2.Neuromeylitis optica (other than MS)
- 3.Central pontine myelinolysis
- 4.Progressive multifocal leukoencephalopathy

① Post infectious demyelination

*Symptoms of neurological deficit occur 1-2 weeks after infection by a virus (even a mild virus)

- Not due to direct effect of the virus
- Pathogen associated antigens (viral antigens) cross react with myelin antigens.... Provoke autoimmune response against myelin
- Onset: acute, monophasic
  - acute → Sudden
  - monophasic → Occurs one time → no relapses and remissions

Here the triggering agents (viral antigens) are different than MS, but the effects on myelin are the same

Post infecious demyelinating

1. Acute (→ sudden) disseminated (→ more than one part) encephalomyelitis (→ of brain)

- Symptoms 1-2 weeks after infection
- Nonlocalizing symptoms: headache, lethargy, coma
  - → no specific symptoms to certain neurons
  - → mild and disseminating (...
- Rapid progression , fatal in 20% of cases
- Survivals: complete recovery

Post infectious demyelinating

- 2. acute necrotizing hemorrhagic encephalomyelitis: more dangerous
- Children and young adults mostly affected.

② Neuromyelitis optica

- Inflammatory demyelinating disease
- Mainly optic nerve and spinal cord
- Antibodies to aquaporin-4 are diagnostic
- Previously thought a subtype of MS

→ these antibodies are different than those found in MS

③ Central pontine myelinolysis

affects pons mainly

destruction of myelin

- Non-immune process
- Loss of myelin in centre of pons
- Occurs after rapid correction of hyponatremia
- Edema due to sudden change in osmotic pressure probably is the cause of the damage
- Causes rapid quadriplegia

④ Progressive multifocal leukoencephalopathy

- Reactivation of JC virus in the immunocompromised
- JC will be discussed in another lecture!

* leukodystrophies

(congenital) → myelin itself not well-formed or rapid turnover

- Inherited demyelinating diseases
- Most are autosomal recessive, some X linked

Several types

- Lysosomal enzyme, peroxisomal enzymes, or myelin protein mutations

↓ rapid destruction of myelin

morphology

- White matter: grey and translucent with decreased volume (because ↓ myelin + loss of whitish colour of myelin)
- Loss of white matter.. Brain atrophic, ventricles enlarge (secondary)
- Several types of diseases exist, each with a specific mutation