CNS pathology
Third year medical students

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FRCPath

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Lecture 5
Diseases of myelin

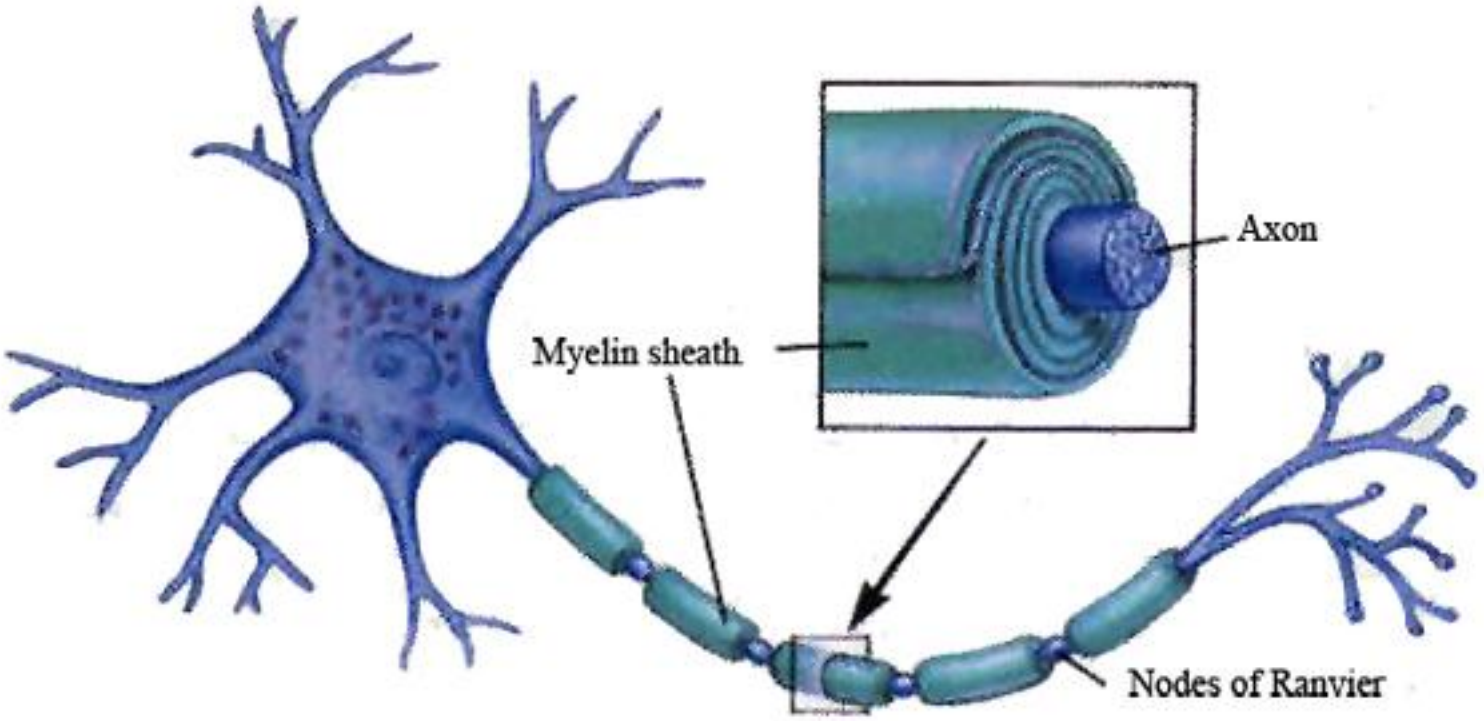
ILOS:

- 1. understand the difference between CNS myelin and peripheral nerves' myelin.
- 2. understand the difference between demyelinating and dysmylinating diseases and their pathogenesis
- 3. in depth understanding of MS in terms of pathogenesis, morphology, epidemiology, clinical picture..
- 4. to have an idea about other demyelinating diseases and their causes.

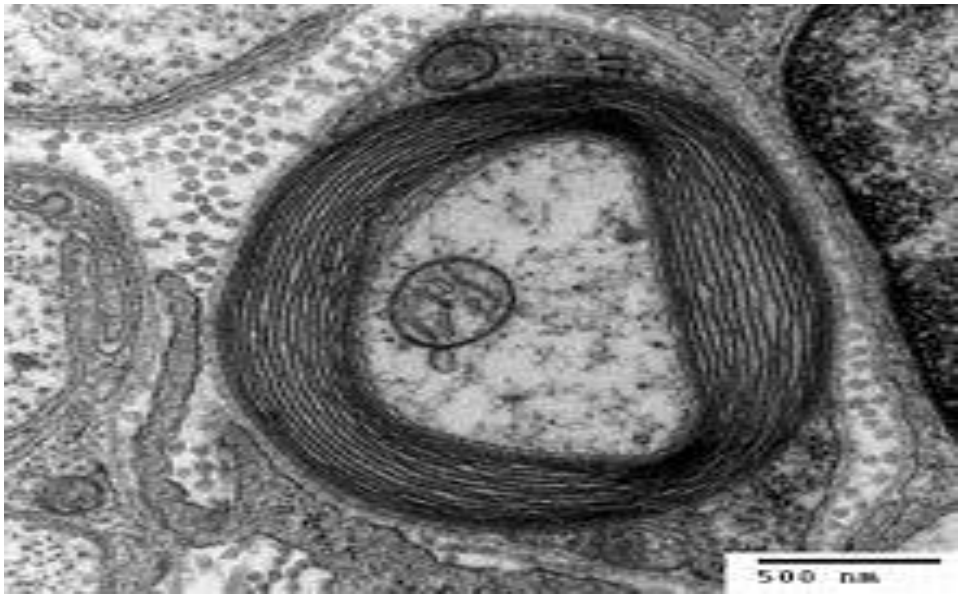
Diseases of Myelin

- 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)
- Myelinated axons are the predominant component of white matter.

oligodendrocyte

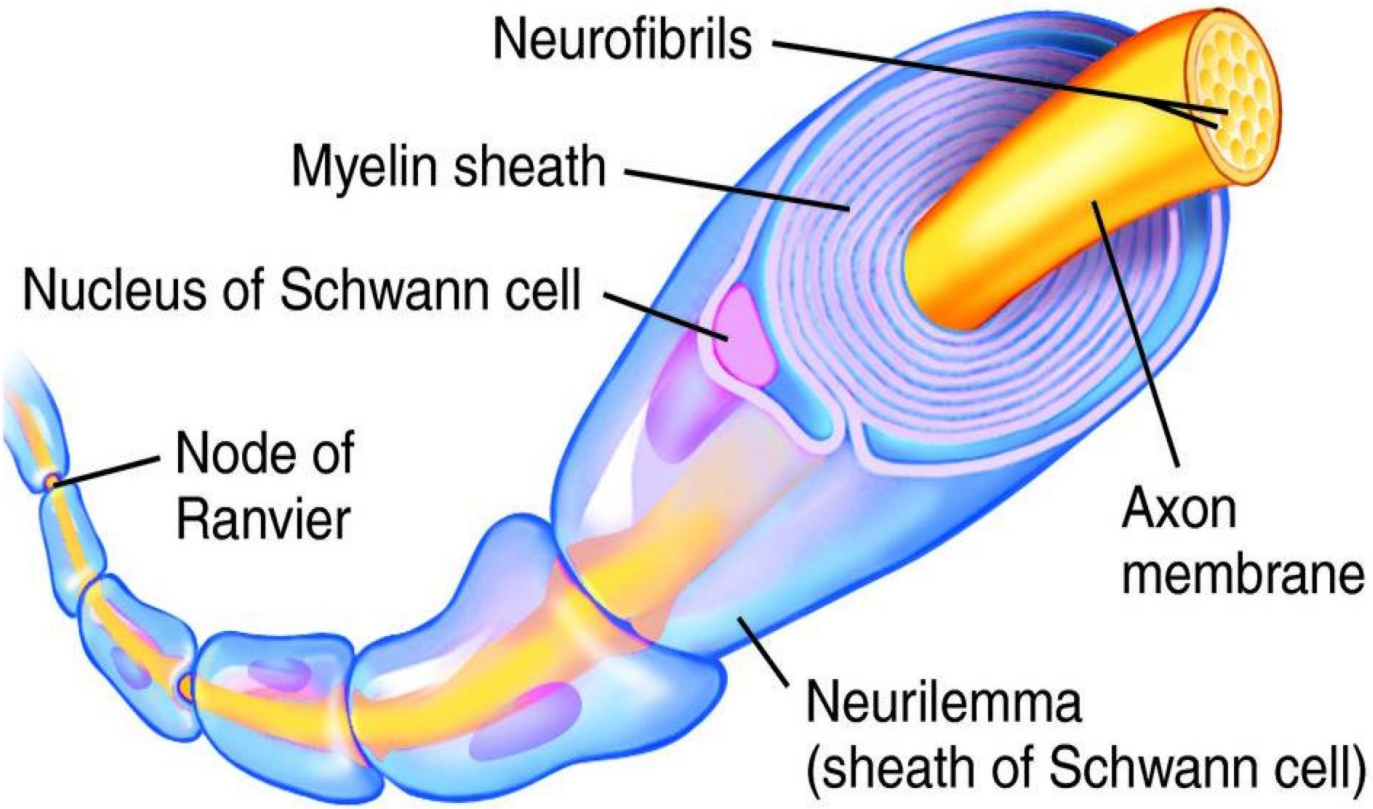


EM myelin



- Myelin diseases of CNS do not affect myelin of peripheral nerves.
- Because Schwann cells are the source of myelin in peripheral nerves.. So different specialized proteins and lipids are involved in myelin formation.

Myelin in peripheral nerves



Primary diseases of myelin

- 1. **demyelinating** diseases : acquired conditions where there is damage to previously normal myelinated axons due to autoimmune destruction, viral infections, drugs, toxins.

  Most common type: multiple sclerosis
- 2. **dysmyelinating diseases = leukodystrophy** myelin not formed properly or has abnormal turnover kinetics , result from mutation disrupting function of proteins that form myelin.

Multiple sclerosis

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

epidemiology

- 1 per 1000 persons in USA and Europe
- Female : male ratio is 2:1
- Manifests at any age (usually 20-40), but onset in childhood or after 50 is rare.

Relapsing and remitting episodes of neurologic deficit variable clinical course.

What about Jordan?

Multiple sclerosis in Jordan: a clinical and epidemiological study

by Khalid El-Salem et al (study from KHCC, JUST and AlBashir)

- 224 patients (165 females, 87%; 59 males, 13%). The mean age of onset was 29.3 years. The prevalence of MS in the city of Amman was 39/100,000. The prevalence of MS in Irbid, north Jordan, was 38/100,000.

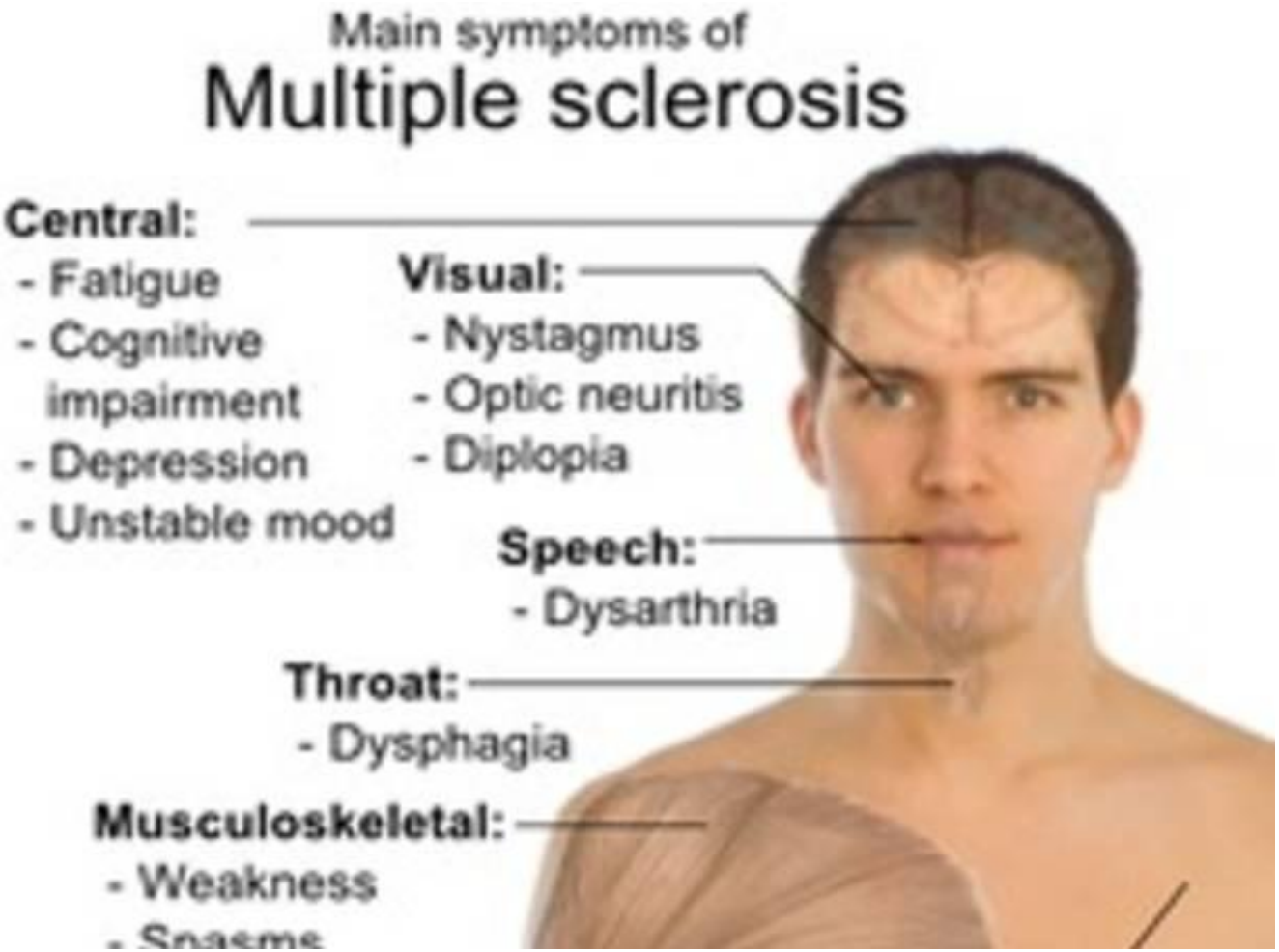
Continuation of the results from the previous study

- The most frequent presentation was weakness (30.8%), followed by optic neuritis (20.1%), sensory impairment (19.6%), and ataxia (14.3%). A relapsing remitting pattern was identified in 90.2% of patients, the rest being primary and secondary progressive, and one patient had a progressive relapsing course. Family history of MS was found in 9.4% of the cases. About 60% of the patients were using interferon beta.

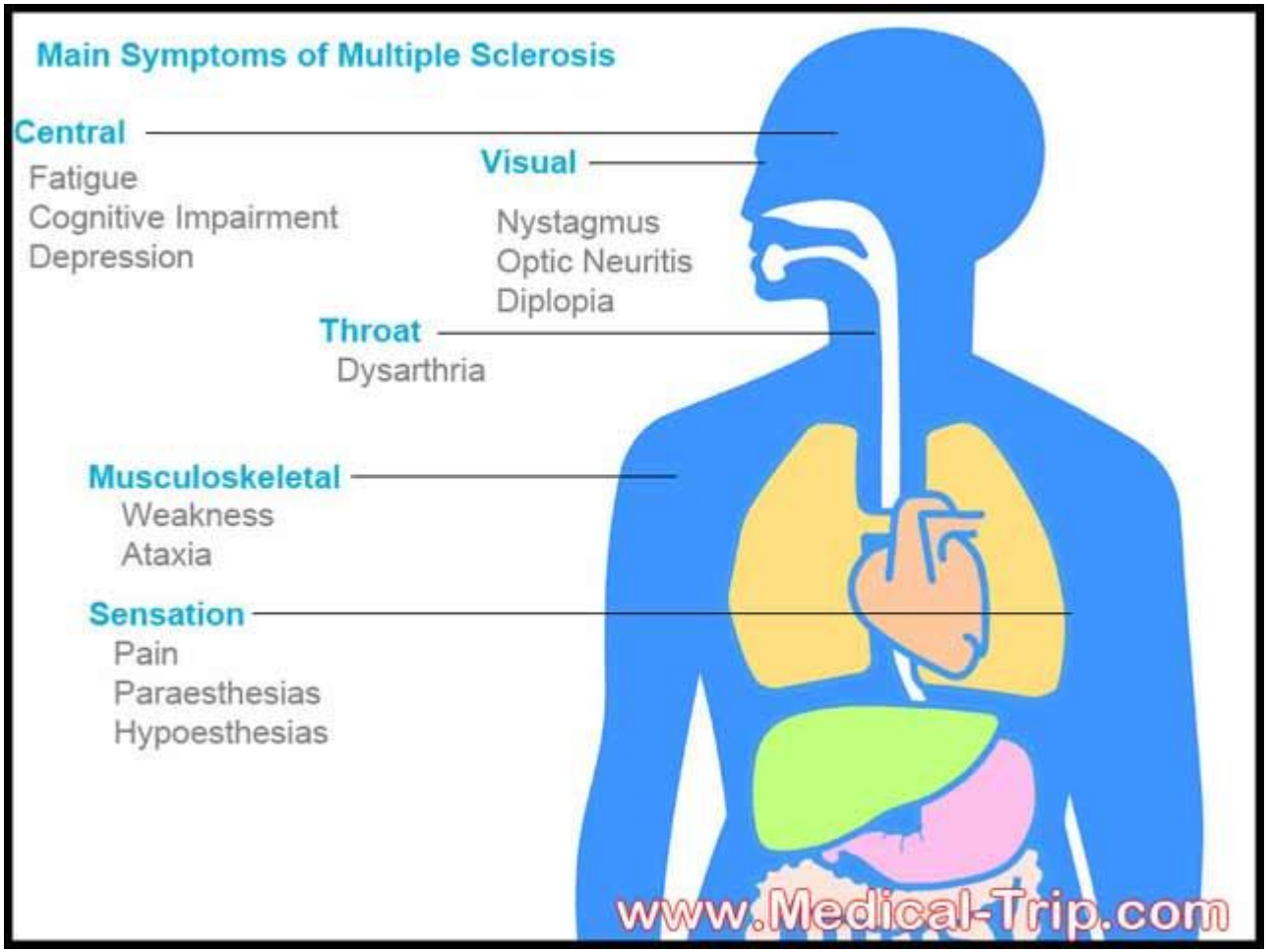
Natural history of MS is determined by

- 1. the limited capacity of the CNS to regenerate normal myelin
- 2. the secondary damage to axons

symptoms


Main symptoms of
Multiple sclerosis
Central:
- Fatigue
- Cognitive impairment
- Depression
- Unstable mood
Visual:
- Nystagmus
- Optic neuritis
- Diplopia
Speech:
- Dysarthria
Throat:
- Dysphagia
Musculoskeletal:
- Weakness
- Spasms

symptoms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Musculoskeletal
Weakness
Ataxia
Sensation
Pain
Paraesthesias
Hypoesthesias
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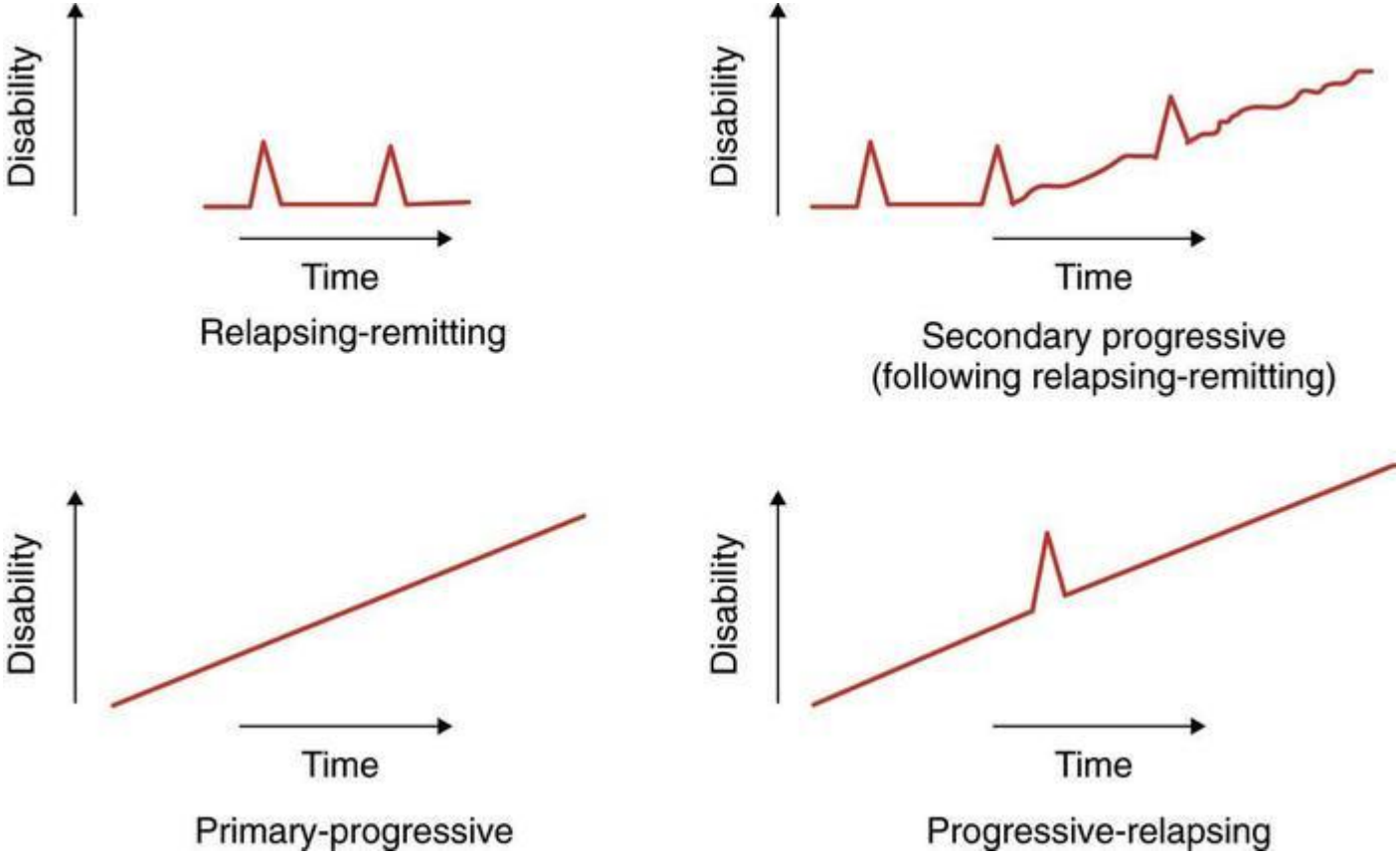
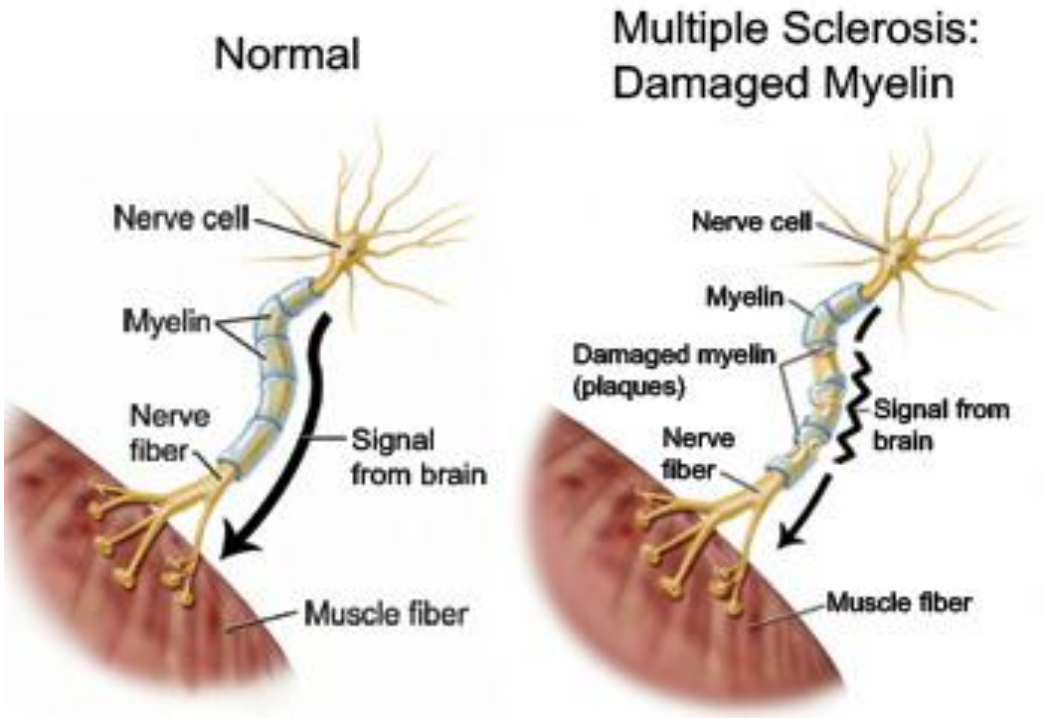
Clinical course



pathogenesis



pathogenesis

- Autoimmune disease.
- So there is loss of tolerance of self-proteins in the myelin sheath.
- Genetic and environmental factors play a role in this loss of tolerance.
- Genetic: see next slide !
- Environmental: probably viral infection BUT NOT CERTAIN)

- Genetic predisposition.:
- Disease is 15 fold higher in first degree relatives
- Concordance rate of monozygotic twins around 25%

- Association with HLA DR2
- Polymorphism in genes encoding cytokine receptors (IL 2 & IL 7)… these two cytokines control the activation and regulation of T cell mediated immune response.

note

- The genetic studies done to find associations between MS and genetic variations failed to explain the variations in the clinical course of the disease.

Immune destruction in MS

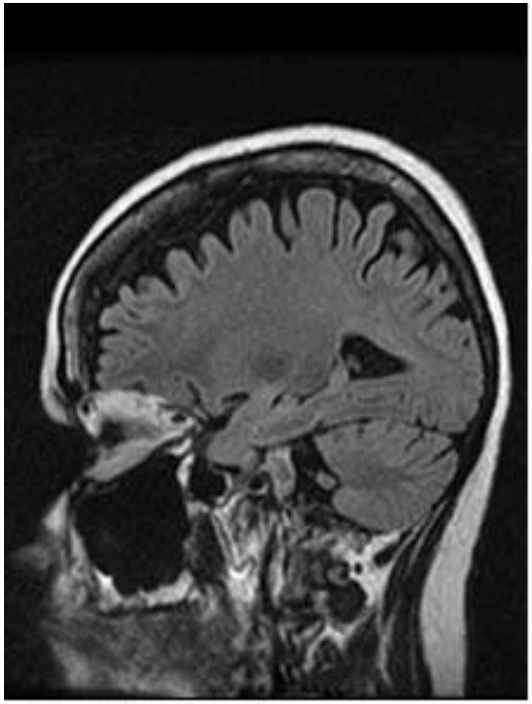
- CD4 T lymphocytes play a major role, especially T helper 1 and T helper 17.
- These T cells react against myelin antigens and secrete cytokines.
- T helper 1 secrete interferon gamma which activates macrophages.
- T helper 17 recruit white blood cells.
- The activated leukocytes produce chemicals that destroy myelin.
- CD 8 T lymphocytes + B lymphocytes might also play a role in myelin destruction.

- In addition to demyelination; axonal damage can occur secondary to toxic effects from lymphocytes, macrophages and the chemicals they secrete.

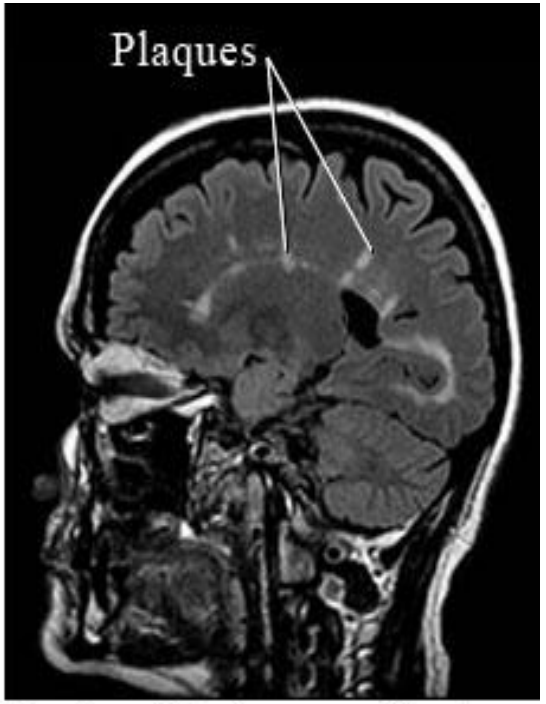
morphology

- White matter disorder
- Multiple well circumscribed slightly depressed grey tan irregularly shaped lesions= plaques
- These plaques appear grossly firmer than normal white matter (SCLEROTIC, hence the name: multiple sclerosis)
- Commonly seen near ventricles, optic nerves and chiasm, brain stem, cerebellum and spinal cord

plaques



Healthy brain



Brain with damage (lesions or plaques) caused by MS

morphology

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

- **Quiescent(inactive plaques**): inflammation disappears leaving behind little or no myelin. Instead there is astrocytic proliferation and gliosis prominent

Other demyelinating diseases

- 1. post infectious, most common form
- 2.Neuromeylitis optica
- 3.Central pontine myelinolysis
- 4.Progressive multifocal leukoencephalopathy

Post infectious demyelination

- Not due to direct effect of the virus
- Pathogen associated antigens cross react with myelin antigens…. Provoke autoimmune response against myelin
- Onset: acute, monophasic

Post infectious demyelinating

1. Acute disseminated encephalomyelitis

- Symptoms 1-2 weeks after infection (rarely after immunization)
- Non-localizing symptoms: headache, lethargy, coma
- Rapid progression , fatal in 20% of cases
- Survivals: complete recovery

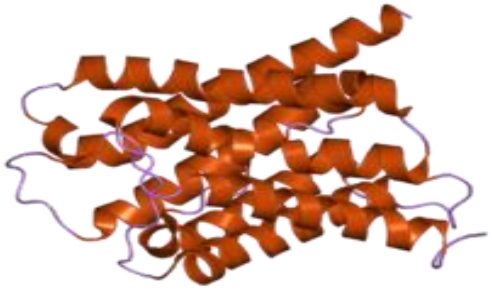
Post infectious demyelinating ..

- 2. acute necrotizing haemorrhagic encephalomyelitis:
- more dangerous, permanent disability can occur.
- Children and young adults mostly affected.

Neuromyelitis optica

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

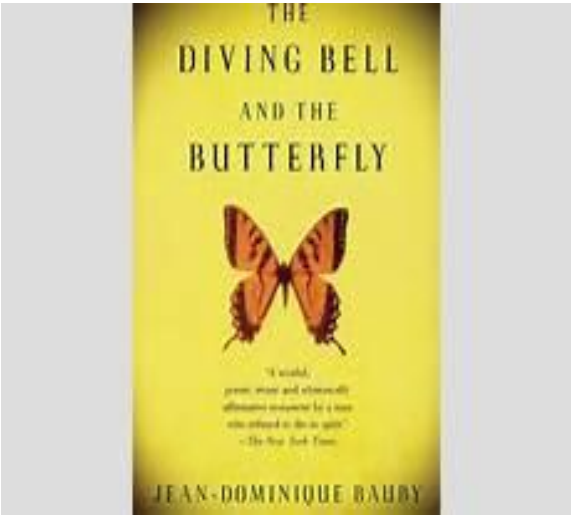
- AQP4 belongs to the aquaporin family of integral membrane proteins that conduct water through the cell membrane.

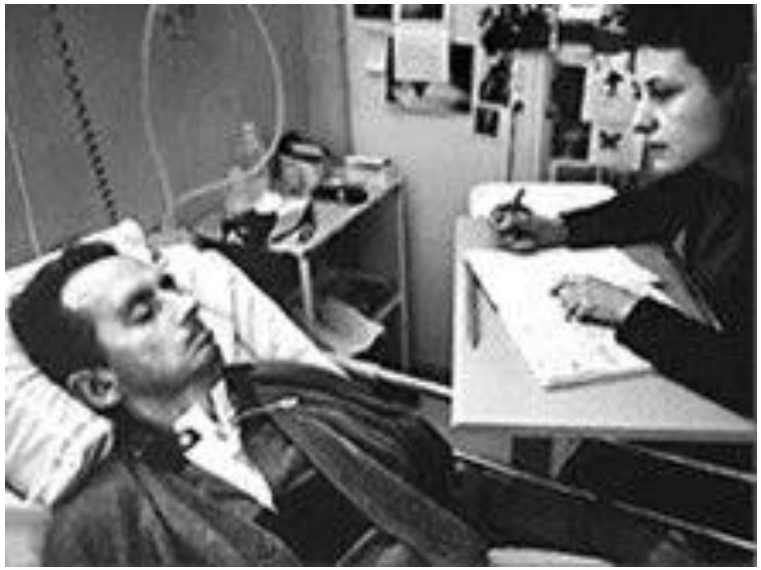


Central pontine myelinolysis

- Non immune process
- Loss of myelin in centre of pons, but also can affect other sites.
- Occurs after rapid correction of hyponatremia or after severe osmolar or electrolyte imbalances.
- Edema due to sudden change in osmotic pressure probably is the cause of the damage
- Hyponatremia should be corrected at a rate of no more than 8-12 mmol/L of sodium per day to prevent central pontine myelinolysis.
- Causes rapid quadriplegia and can cause locked in syndrome

- **Locked-in syndrome** (**LIS**) is a condition in which a patient is aware but cannot move or communicate verbally due to complete paralysis of nearly all voluntary muscles in the body except for vertical eye movements and blinking. The individual is conscious and sufficiently intact cognitively to be able to communicate with eye movements.


THE
DIVING BELL
AND THE
BUTTERFLY
JEAN-DOMINIQUE BAUBY



leukodystrophies

- Inherited dysmyelinating diseases
- Most are autosomal recessive, some X likned.

- Mutations in : Lysosomal enzymes, perixosomal enzymes, or myelin protein.

- Several types of dysmyelinating diseases exist.
- Affected children are normal at birth but start loosing developmental milestones during infancy and childhood.
- They might have deterioration in motor skills, spasticity, ataxia…

morphology

- White matter: grey and translucent with decreased volume
- Loss of white matter.. Brain atrophic, ventricles enlarge

- Several types of diseases exist, each with a specific mutation

Leukodystrophies… DO NOT ATTEMPT TO MEMORIZE!!!

Table 1. Different Types of Leukodystrophies and with Clinical Features

Disorder	Inheritance	Enzymatic defect	Clinical manifestations
Pelizaeus-Merzbacher	X-linked recessive and autosomal dominant	Not identified	Onset in infancy, progressive CNS deterioration
Metachromatic leukodystrophy	Autosomal recessive	Aryl sulfatase A	Most common type of leukodystrophy, onset at one to two years, associated with bouts of fever and abdominal pain, gall bladder dysfunction
Krabbe's disease	Autosomal recessive	Galactocerebrosidase	Also known as globoid cell leukodystrophy, onset at four to six months of age
Adrenoleukodystrophy	X-linked recessive	Defective metabolism of long chain fatty acids	Also known as sudanophilic cerebral sclerosis, onset at 5 to 10 years of age, accompanied by hypoadrenalism
Canavan's disease	Autosomal recessive	Not identified	Onset at two to four months of age, increased water content of brain, questionable defect in mitochondrial function leading to increased plasma membrane permeability to water and cations; children have macrocephaly without evidence of hydrocephalus
Alexander's disease	Autosomal recessive	Mitochondrial defect	Onset within first year of life

Adapted from Tobias JD. *Anaesthetic considerations for the child with leukodystrophy.* Can J Anaesth. 1992;39(4):394–7.


Fun2Video .com
Yes, I did it!
I WILL DO IT
I CAN DO IT
I'LL TRY TO DO IT
HOW DO I DO IT ?
I WANT TO DO IT
I CAN'T DO IT
I WON'T DO IT
WHICH STEP HAVE YOU REACHED TODAY ?