

CNS pathology

Third year medical students

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Lecture 4: Myelin diseases of the CNS

ILOS

- 1. to understand differences and similarities between diseases of myelin in CNS and PNS.
- 2. to understand the difference between demyelinating and dysmyelinating diseases
- 3. to know the epidemiology, pathogenesis and clinical and morphological features of multiple sclerosis
- 4. To have a brief idea of other demyelinating diseases, mainly post infectious demyelination, neuromyelitis optica, and central pontine myelinolysis
- 5. To understand the concept of dysmyelinating diseases and their clinical presentation.

Introduction

- in the previous lectures, we discussed diseases of the PNS and we talked about demyelination in the PNS.
- As you might, or might not, remember, we said that demyelinating neuropathies of the PNS are less common than axonal neuropathies, and are caused mainly by inherited conditions or by autoimmune destruction of myelin. We also said that myelin can be restored from Schwann cells, so demyelinating diseases are potentially reversible.
- Demyelinating diseases of the CNS are similar to demyelination of PNS in the sense that they have **similar causes (inheritance and autoimmune destruction) and in that they are potentially reversible.**
- However, remember that **myelin in the CNS is produced from oligodendrocytes**, so myelin structure is different between CNS and PNS, which means **demyelination of CNS will not affect the nerves of PNS and vice versa.**

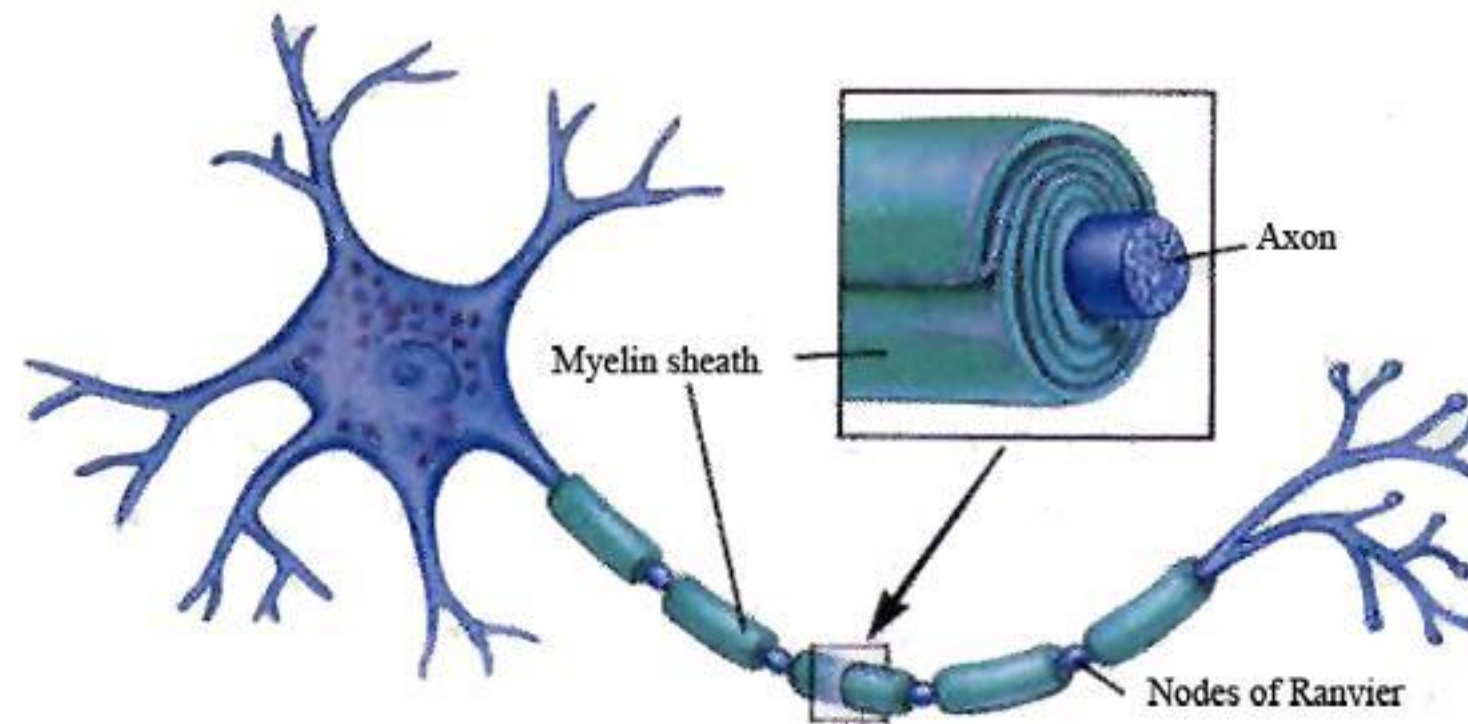
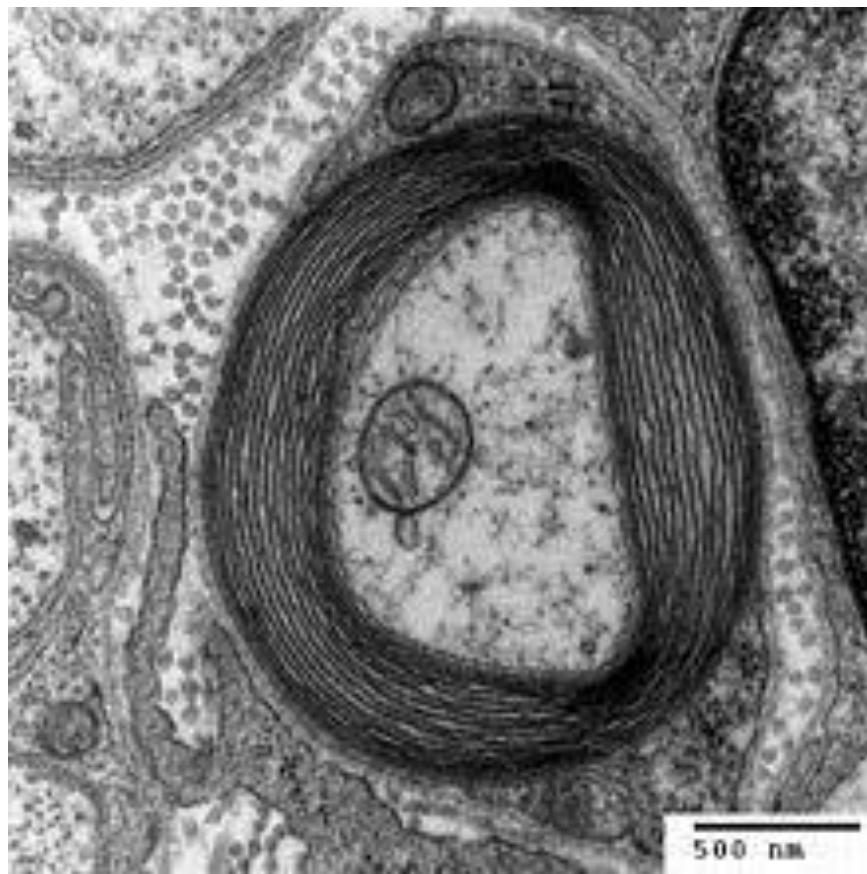
What is myelin?

- Myelin is a *protein-lipid complex* that is wrapped around the axons.
- Function: allows rapid propagation of signals.
- Composition: layers of plasma membranes

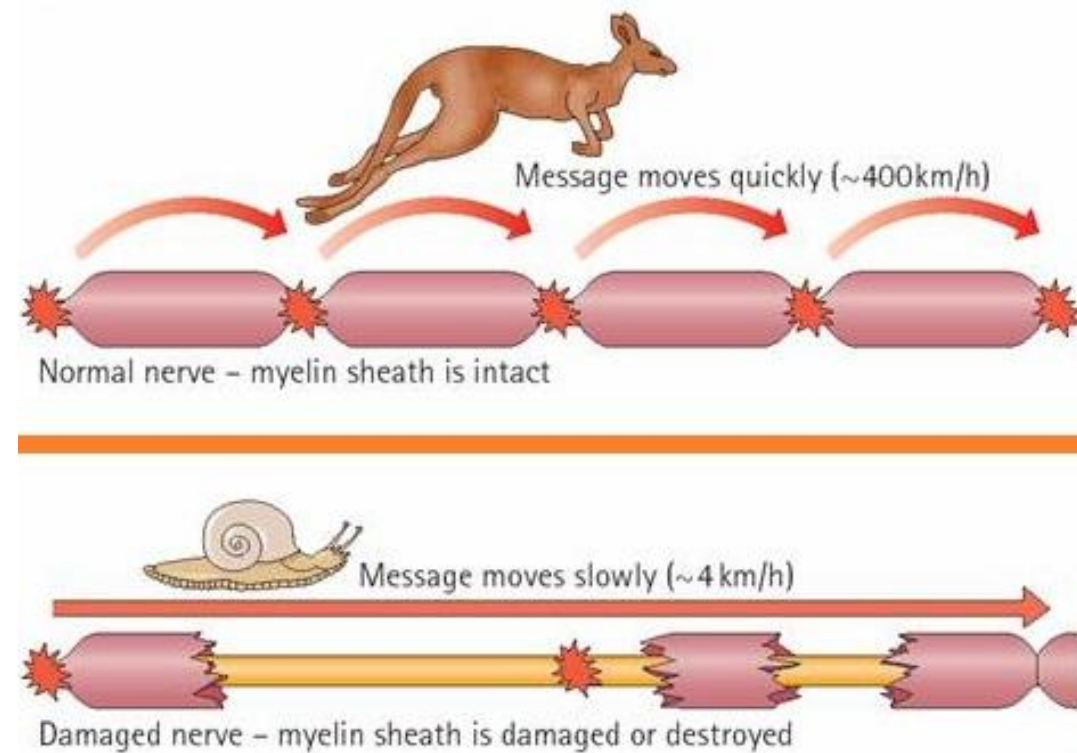
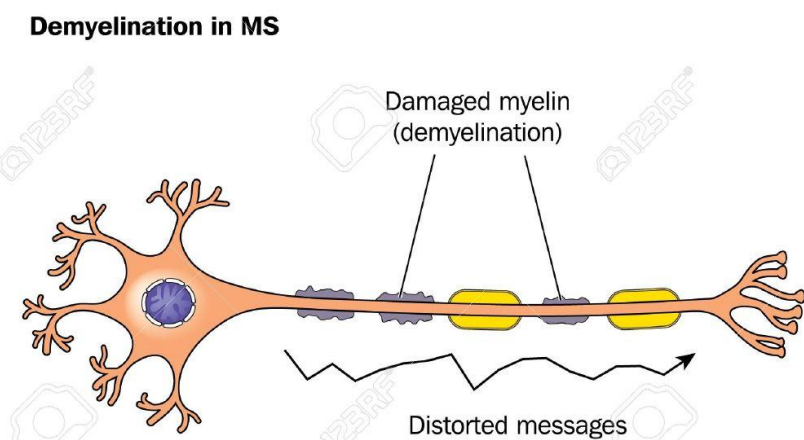
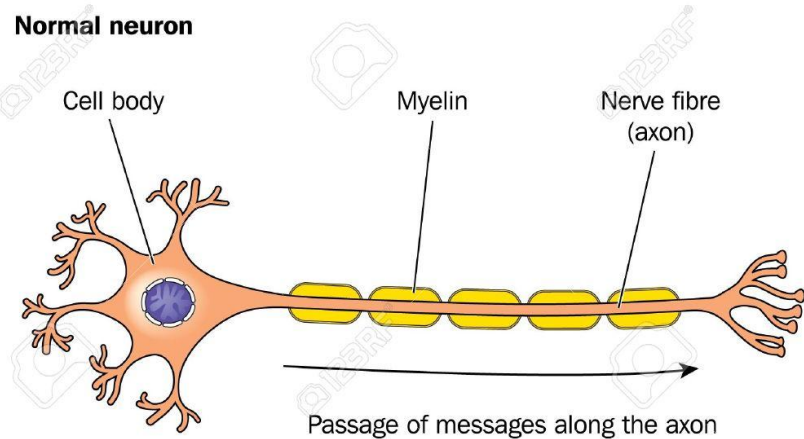
assembled by oligodendrocytes (CNS)

- Myelinated axons are the predominant component of white matter.

Myelin



Function of myelin: to insulate axons and allows quick transmission of neural signals



Diseases of myelin in the CNS

There are two types of myelin diseases in the CNS:

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 in this group is : multiple sclerosis

2. dysmyelinating diseases = leukodystrophies . These are inherited diseases where myelin is not formed properly or has abnormal turnover kinetics , resulting from a *mutation* disrupting function of proteins that form myelin

Demyelinating diseases

- in this group of disorders, the patient develops acquired destruction of myelin.
- main types are:
 - 1. **Multiple sclerosis (MS)**, where there is autoimmune destruction of myelin. this is the most common type in this group.
 - 2. **Neuromyelitis optica** : also autoimmune but affects mainly optic nerve and spinal cord.
 - 3. **post infectious demyelination**
 - 4. **Central pontine myelinolysis**

Multiple sclerosis

- Is an autoimmune demyelinating disease
- Defined as: *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
- Incidence is believed to be increasing.
- Female : male ratio is 2:1
- Manifests at any age (usually 20-40), but onset in childhood or after 50 is rare.

What's the situation in Jordan?

A study: 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.

Continue

- 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.
- The most frequent presentation was weakness (30.8%), followed by optic neuritis (20.1%), sensory impairment (19.6%), and ataxia (14.3%).
- Family history of MS was found in 9.4% of the cases.

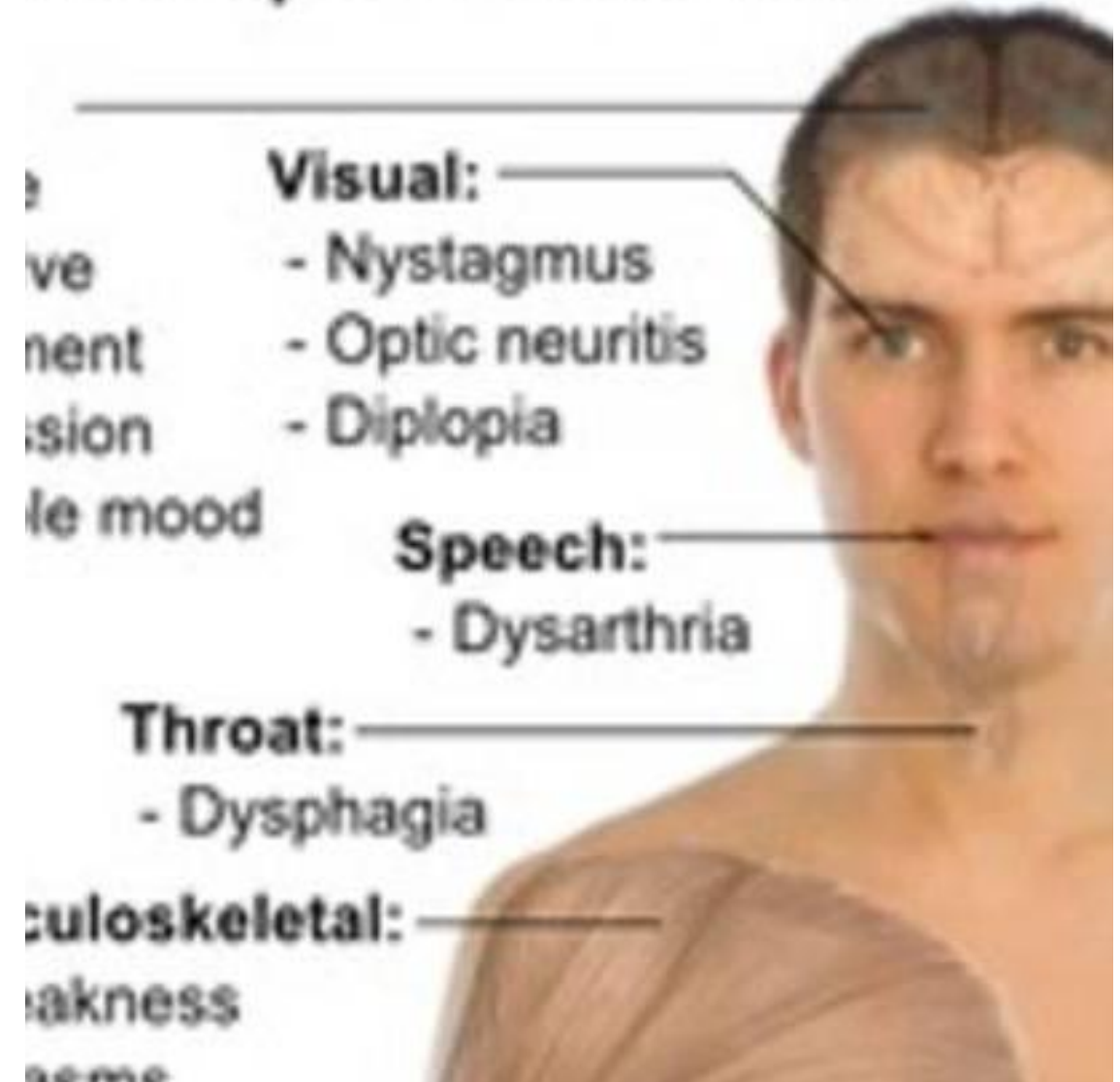
notes on the previous study

- Prevalence in Jordan according to this study is less than in USA (1:1000 USA, compared to around 0.4 per 1000 in Jordan.(
- Mean age of onset similar to that in the West (20-40 years(
- Female to male ratio in USA 2:1. in Jordan study it is !! 6.7:1
- Why this difference in female: male ratio?.. Possible explanations: sample not representative, they might have included optic neuritis in the cases (in optic neuritis females are much more affected than males) or it might be a true difference... more studies needed to be sure.

clinical presentation

- Signs and symptoms depend on the location of the lesion .
- the clinical presentation is variable.
- Patients might have any of the symptoms. the symptoms are reversible but the disease can recur. When it recurs the symptoms might differ from the initial ones.

Main symptoms of Multiple sclerosis



Main Symptoms of Multiple Sclerosis

Central

Fatigue
Cognitive Impairment
Depression

Visual

Nystagmus
Optic Neuritis
Diplopia

Throat

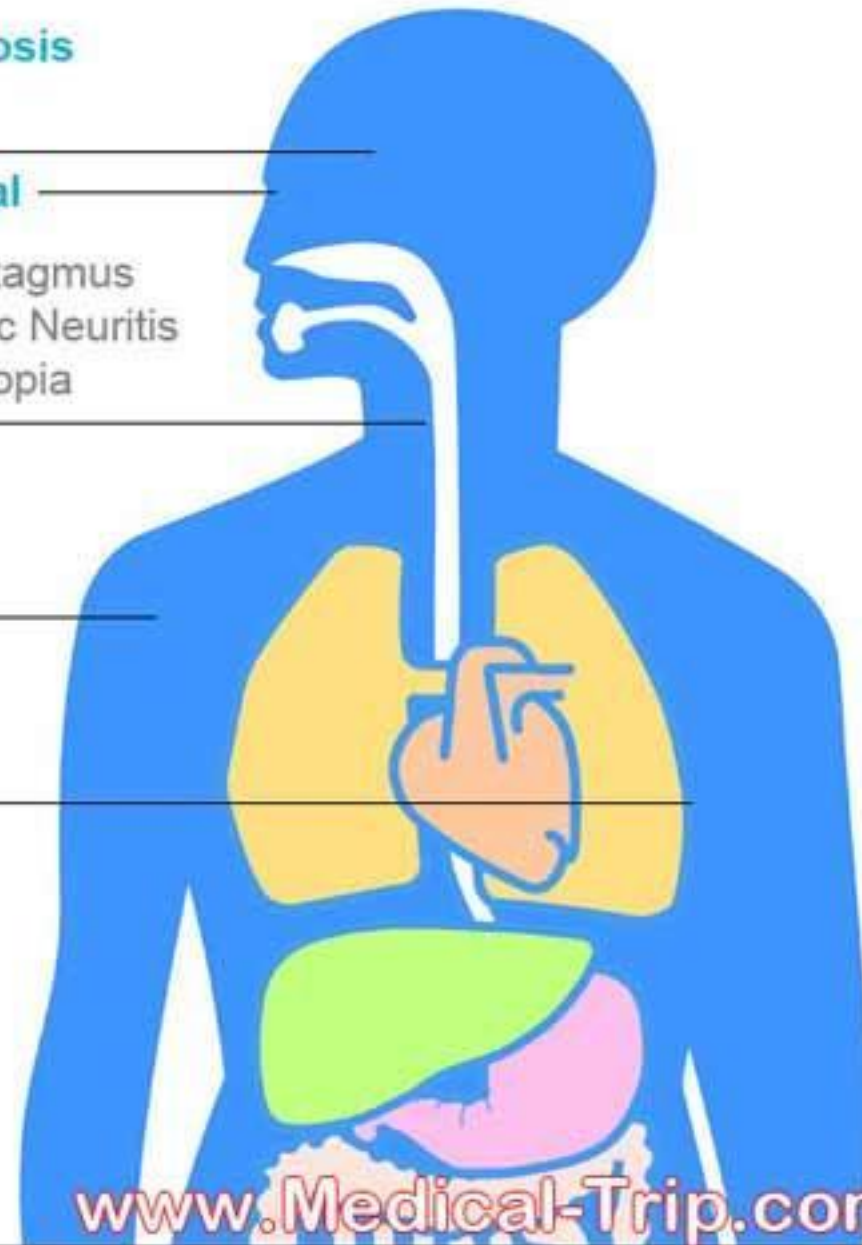
Dysarthria

Musculoskeletal

Weakness
Ataxia

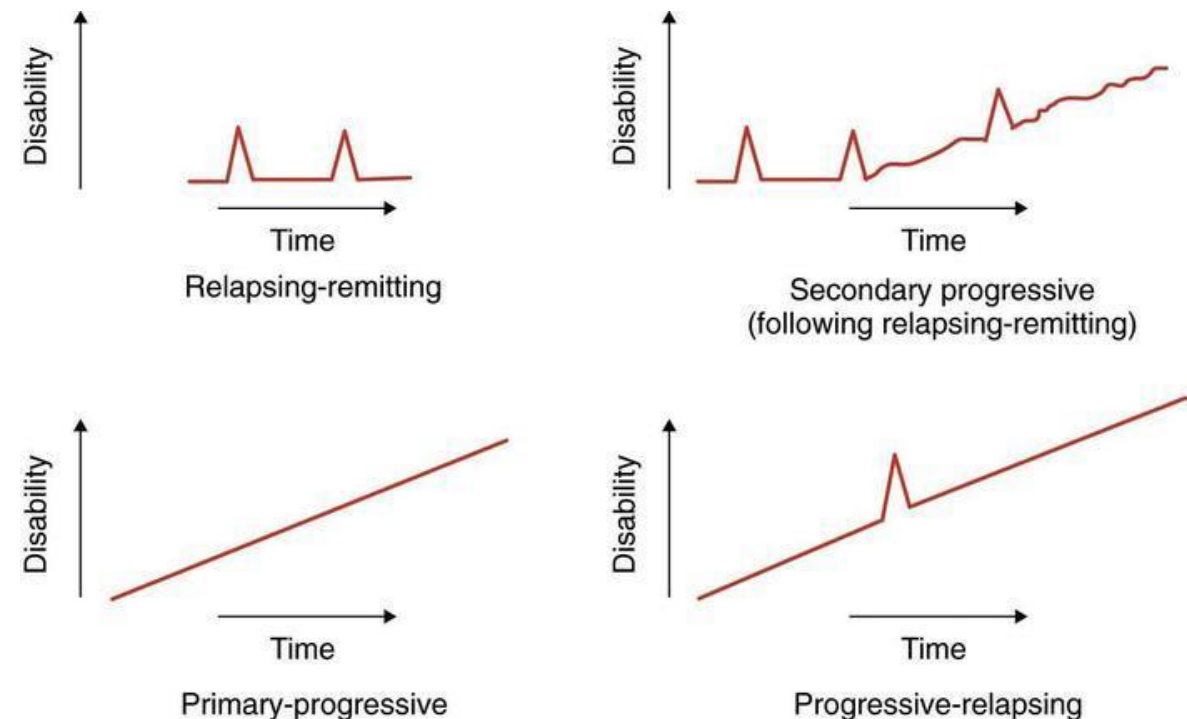
Sensation

Pain
Paraesthesias
Hypoesthesias

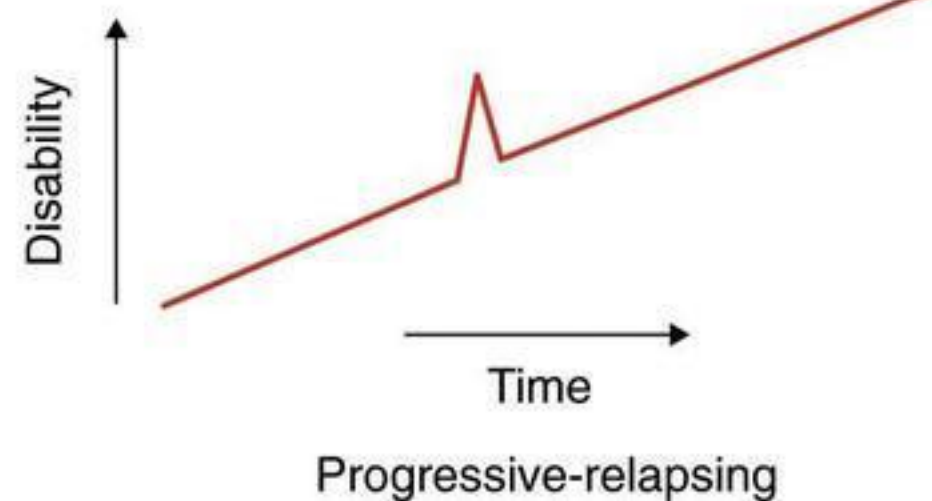
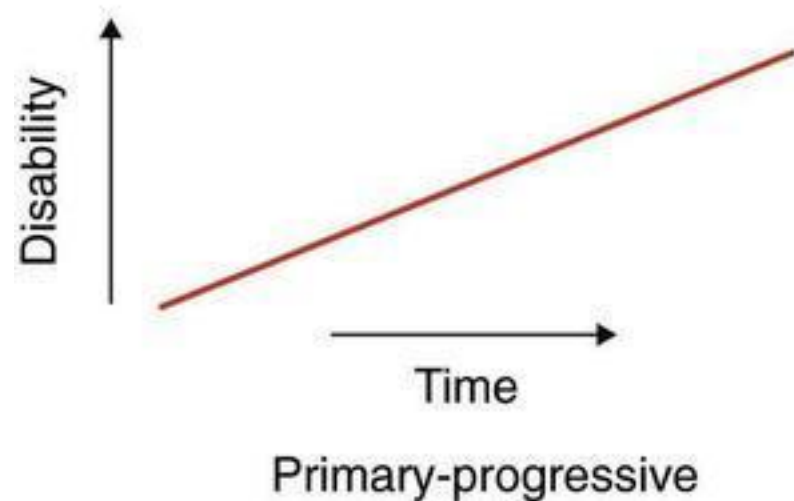
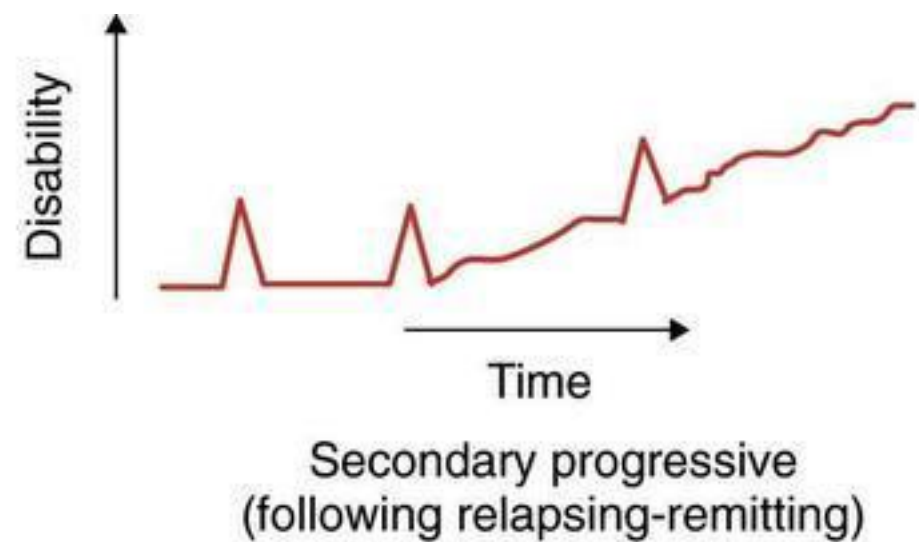
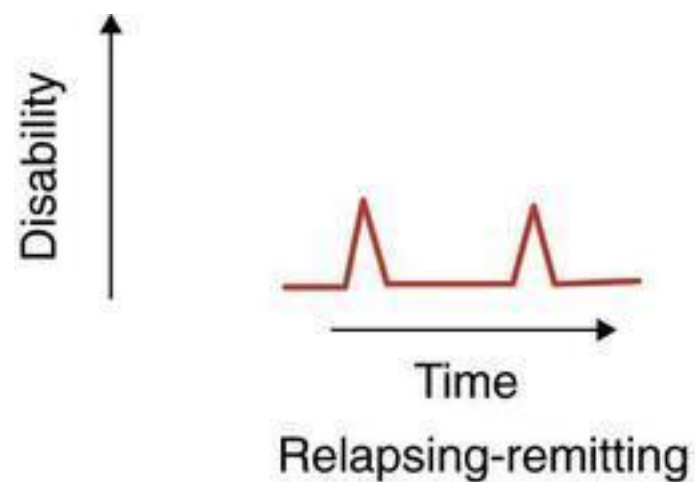


Clinical course

- the course of the diseases is variable:
- 1, relapsing remitting means the patient will have symptoms (relapses) separated by periods of complete remission (completely normal)
- 2. Primary progressive: when symptoms start, the patient will have symptoms continuously without periods of remission, and the symptoms get worse with time.
- 3. Secondary progressive: disease starts as 1 above, but after sometime changes to pattern 2.
- 4. Progressive relapsing: like in 2, but at times symptoms get even worse.



clinical course: you cannot predict the course of the diseases in different patients. only time will tell!



Outcome

Natural history of MS is determined by

- 1. the **limited capacity of the CNS to regenerate normal myelin**(although myelin can be restored in the CNS, this is less efficient than in the PNS)
- 2. **the secondary damage to axons** that might occur after repeated relapses.

- NOTE: we said previously that diseases of myelin do not affect axons, which is true, but with repeated attacks of autoimmune destruction to myelin, the autoimmune response and associated inflammatory reaction can cause secondary axonal damage, this occurs late in the course of the disease. note that it is the inflammation that causes the axonal damage, not the myelin destruction per se.

Pathogenesis

- MS is an autoimmune disease. like all other autoimmune diseases there is genetic susceptibility and the onset of symptoms is related usually to an environmental trigger like viral infections.
- 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)

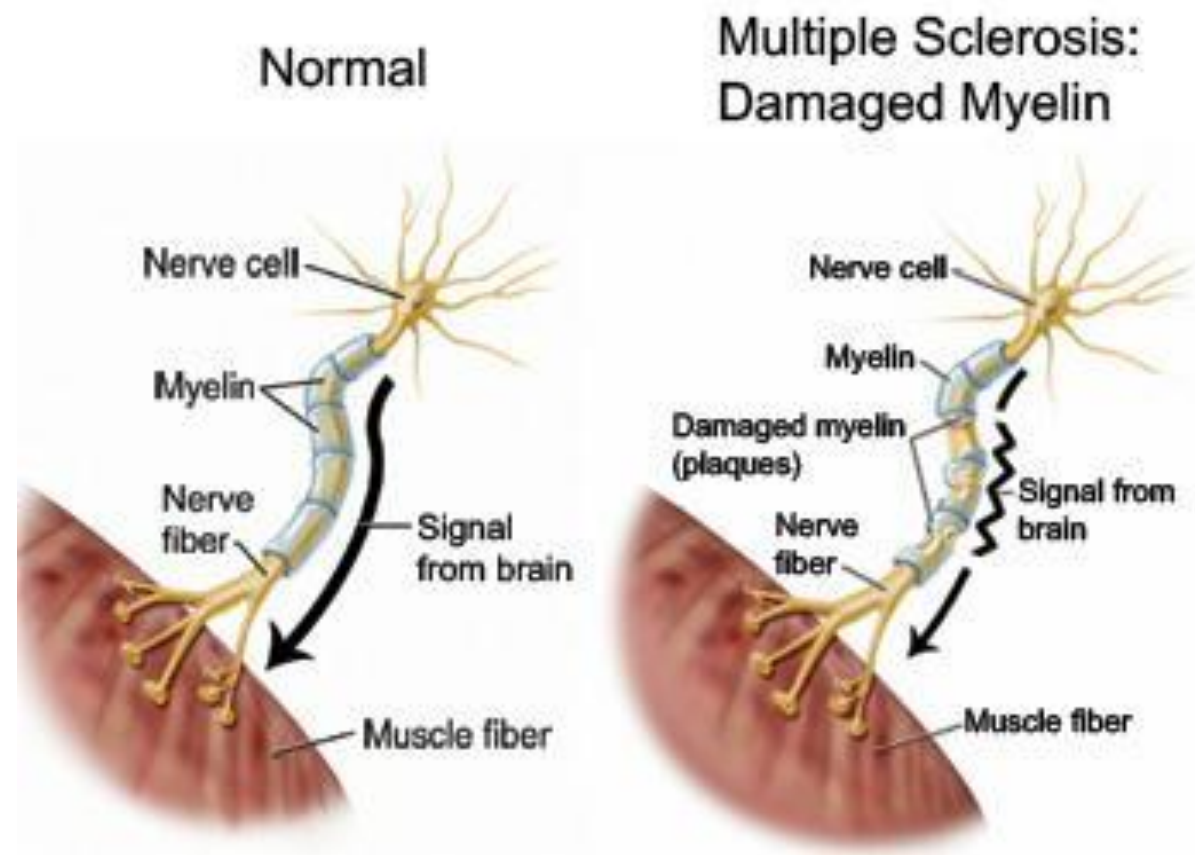
Genetic predisposition

- MS is 15 fold higher in first degree relatives
- Concordance rate of monozygotic twins around %25
- Association with HLA DR 2
- 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 .

Pathogenesis



Pathogenesis

- 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=

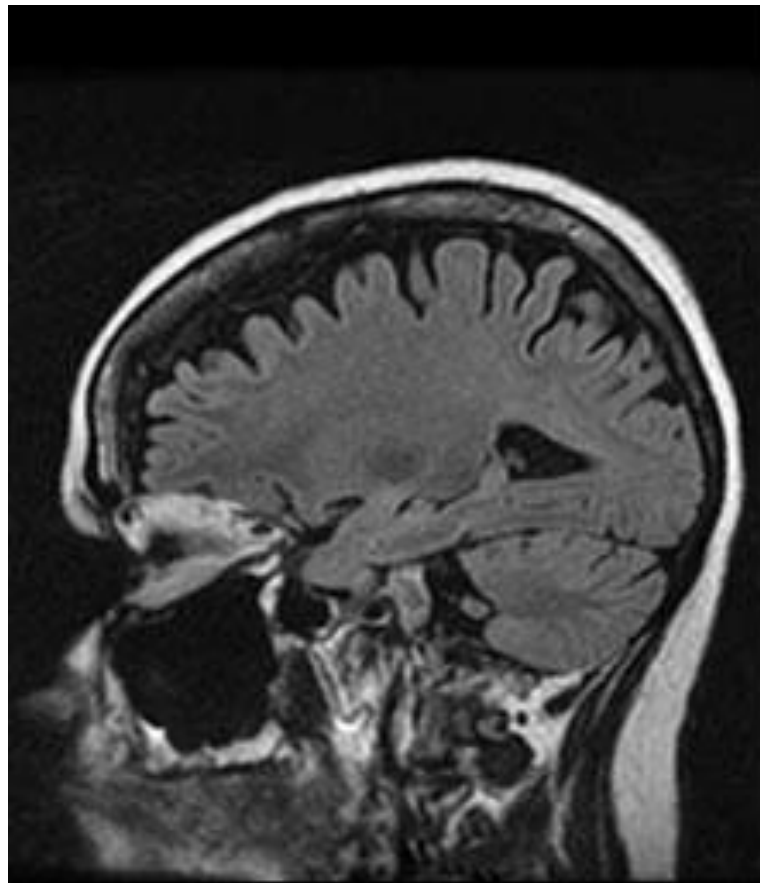
plaques

- These plaques appear grossly firmer than normal white matter (**SCLEROTIC**, hence

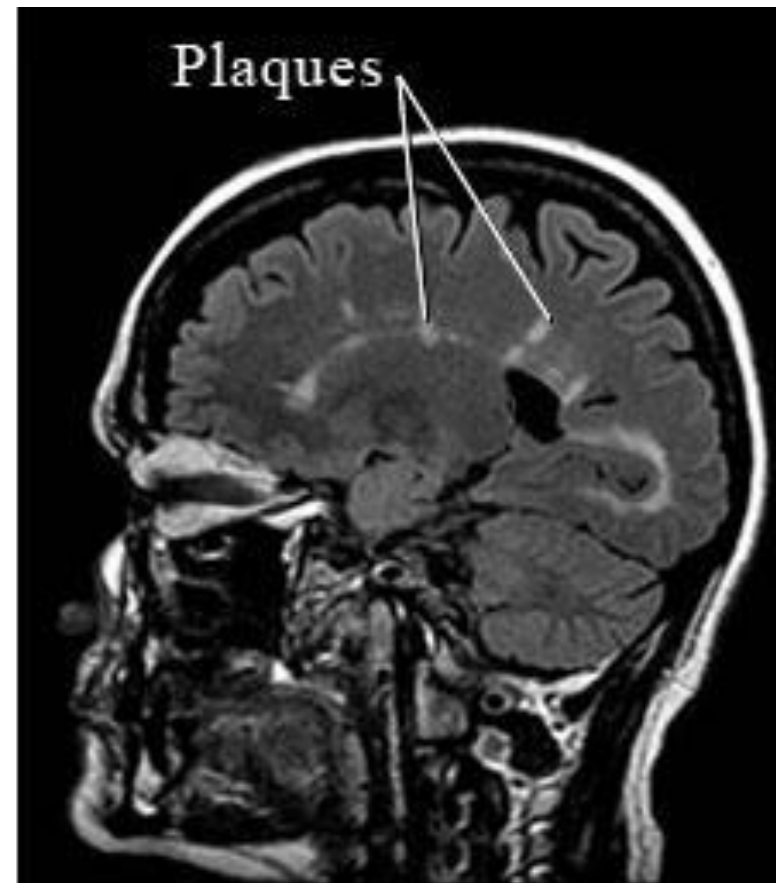
the name: multiple sclerosis)

- Commonly seen near ventricles, optic nerves and chiasm, brain stem, cerebellum

and spinal cord



Healthy brain



Brain with damage (lesions or plaques) caused by MS

Morphology

two types of plaques can be seen

- 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 prominent gliosis.

Neuromyelitis optica

- Inflammatory demyelinating disease
- Mainly optic nerve and spinal cord affected.
- ***Antibodies to aquaporin-4 are diagnostic***

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

-this disease was Previously thought a subtype of MS, but not any more! it is a distinct entity.

Please note: in neuromyelitis optica, myelin destruction is caused by antibodies secreted from B cells, whereas in MS, the destruction is mainly due to cellular immunity (T helpers and cytotoxic).

Please also note that the role of B cell immunity in MS is not well understood, but B cells definitely play a role, the evidence being

1. Immunoglobulins are found in the CSF of patients with MS
2. B cell depletion therapies improve symptoms dramatically in MS.

Post infectious demyelination

- In this entity there is demyelination occurring after viral infection.

The *demyelination is not due to direct effect of the virus*

- *Pathogen associated antigens cross react with myelin antigens....*

Provoke autoimmune response against myelin

- Onset: acute, monophasic, and usually more severe than MS.

there are two types of post infectious demyelination

1. Acute disseminated encephalomyelitis

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

2. Acute necrotizing haemorrhagic encephalomyelitis:

- more dangerous
- Children and young adults mostly affected.

central pontine myelinolysis

- **Non immune** process causing edema of oligodendrocytes resulting in separation of myelin from the axons.
- Loss of myelin in centre of pons mainly.
- **Occurs after rapid correction of hyponatremia**
-

- 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

-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.**

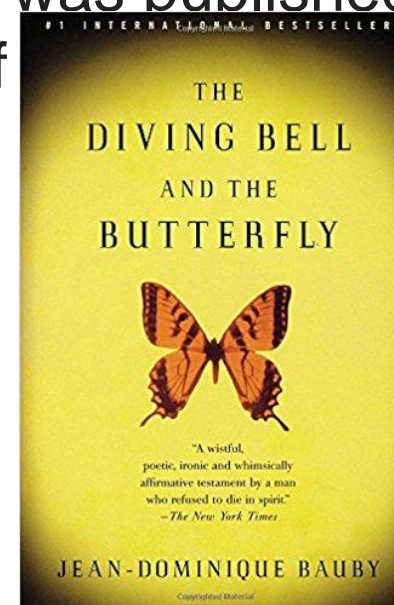
-locked-in syndrome is caused by damage to specific portions of the lower brain and brain stem, with no damage to the upper brain.

The diving bell and the butterfly



A French journalist, [Jean-Dominique Bauby](#) suffered a massive stroke that left him with [locked-in syndrome](#).

He wrote a book by blinking his eye !! his secretary will recite the alphabet and he blinks his eye to tell her the letter he wants.. and letter by letter, blink by blink, they wrote a book about his experience in being locked in and about his life before the stroke. The French edition of the book was published on March 7, 1997. It sold the first 25,000 copies on the day of



Leukodystrophies

Inherited dysmyelinating diseases

- Most are autosomal recessive, some X linked .
- Mutations in :Lysosomal enzymes, peroxisomal enzymes, or myelin protein.

Several types of dysmyelinating diseases exist .

- Affected children are normal at birth but start losing developmental milestones during infancy and childhood .
- They might have deterioration in motor skills, spasticity, ataxia ...

This table is just to give you an idea of the diversity of leukodystrophies.. don't attempt to memorise!!

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.

SUMMARY 1/2

- myelin diseases of the CNS are either inherited (dysmyelinating diseases or leukodystrophies) or acquired (demyelinating)
- Demyelination occurs due to autoimmune destruction of myelin (MS, neuromyelitis optical, post infectious) or due to toxins or chemicals or in iatrogenic settings(central pontine myelinolysis)
- MS is an autoimmune diseases that occurs in genetically susceptible individuals (usually with certain polymorphisms in IL2 and IL 7 receptors) and in association with HLA DR 2.
- Environmental triggers (viral infections) in genetically susceptible individuals start the symptoms.
- T helper 2 is stimulated and recruits macrophages, T helper 17 recruits WBCs. These cause inflammatory damage to myelin.
- the myelin destruction occurs via CD 4 (helper) and CD8 (cytotoxic) T cells. B cells also play a role.
- MS is a white matter diseases, there are sclerotic plaques within the white matter
- Clinical symptoms of MS vary between individuals and clinical course is unpredictable.
- Although MS is a diseases of myelin, with time and with recurrent immune and inflammatory response, axonal damage can occur.

SUMMARY 2/2

- Neuromyelitis optica is an autoimmune disease, where myelin is destroyed via antibodies against aquaporin 4. The optic nerve and the spinal cord are the main targets.
- Post infectious demyelination occurs after viral infections and is caused by autoimmune destruction of myelin due to cross reactivity between viral and myelin proteins.
- Clinical symptoms of post infectious demyelination are more severe than MS and patients might die. Survivors retain normal neurological function.
- Central pontine myelinolysis is an iatrogenic disease occurring due to rapid correction of hyponatremia which causes disturbed osmotic balance and separation of myelin from axons. The main symptoms are related to motor dysfunction and can cause quadriplegia and locked in syndrome.
- Dysmyelinating diseases are a group of inherited disorders where children are born normal but develop neurological deficits with age. In these diseases there are mutations in the myelin kinetics (destruction more than synthesis) or in the myelin proteins themselves. The majority of these are autosomal recessive.

Exam style question

- Which of the following combinations is correct?
- A. IL 2 receptor polymorphisms and better outcome of MS
- B. Central pontine myelinolysis and predominance of sensory symptoms.
- C. Acute disseminating encephalomyelitis and viral infection of oligodendrocytes.
- D. Neuromyelitis optica and cellular autoimmune myelin destruction affecting optic nerve and spinal cord
- E. Quiescent Plaques in MS and astrocyte proliferation.

Explanation of the question

- A. wrong. Genetic changes do not predict outcome or course of diseases in MS
- B. Wrong. the pons is involved mainly in motor function, so in central pontine myelinolysis the symptoms are motor mainly.
- C. Wrong, in both forms of post infectious demyelination, there is no direct infection to oligodendrocytes and the cause of demyelination is autoimmunity due to cross reaction
- D. Wrong, neuromyelitis optical is caused by auto antibodies.. not cellular immunity
- E. Correct, quiescent plaques occur during repair phase and contain glia.. astrocytes are the main cells responsible for this.



thank you!