CNS pathology 2025
Lecture 3: Myelin diseases of the CNS

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Myelin diseases of the CNS

- 1. **Multiple sclerosis (MS**), where there is autoimmune destruction of myelin. This is the most common type
- 2. **Neuromeylitis optica :** also autoimmune but affects mainly optic nerve and spinal cord.
- 3.**Post infectious demyelination.**
- 4.**Central pontine myelinolysis.**

Multiple sclerosis

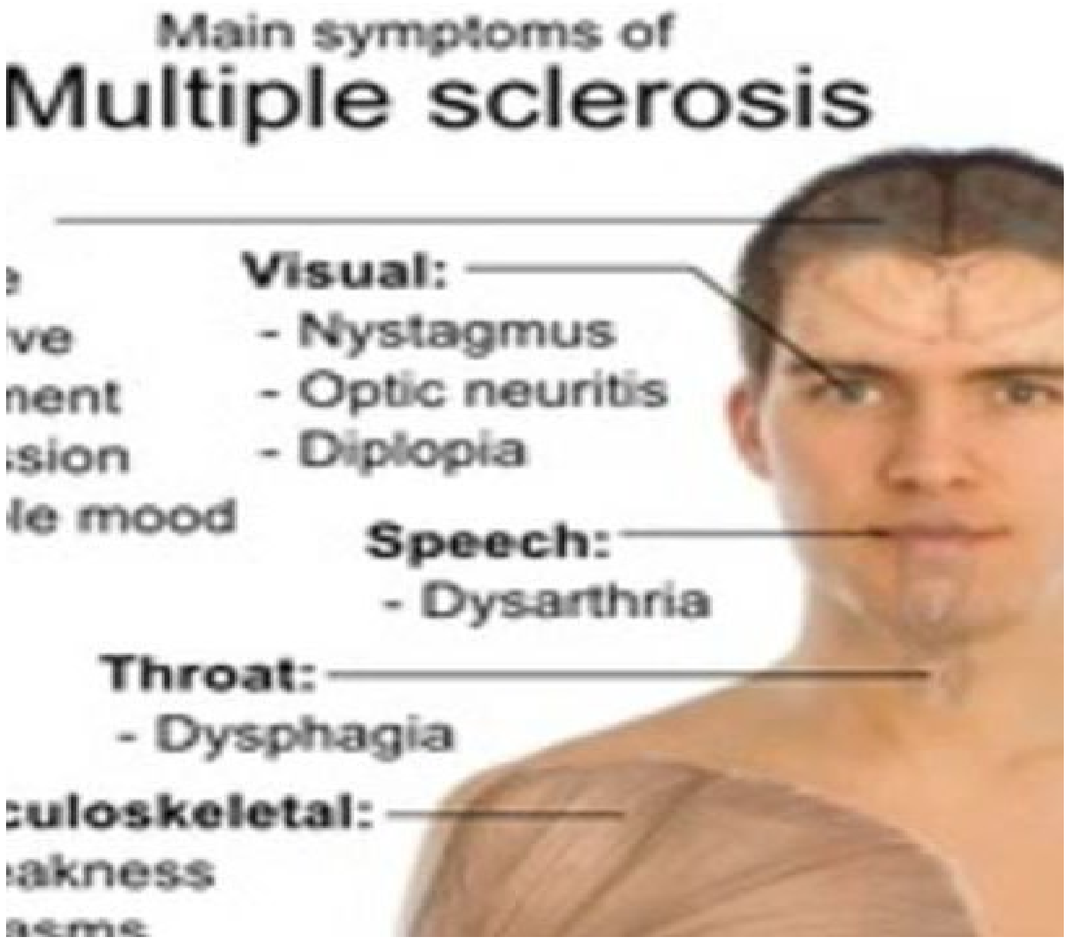
- Is an autoimmune demyelinating disease
- Defined as: *Episodes* of neurologic deficits **separated in time** which are attributed to **white matter lesions** that are s**eparated in space**

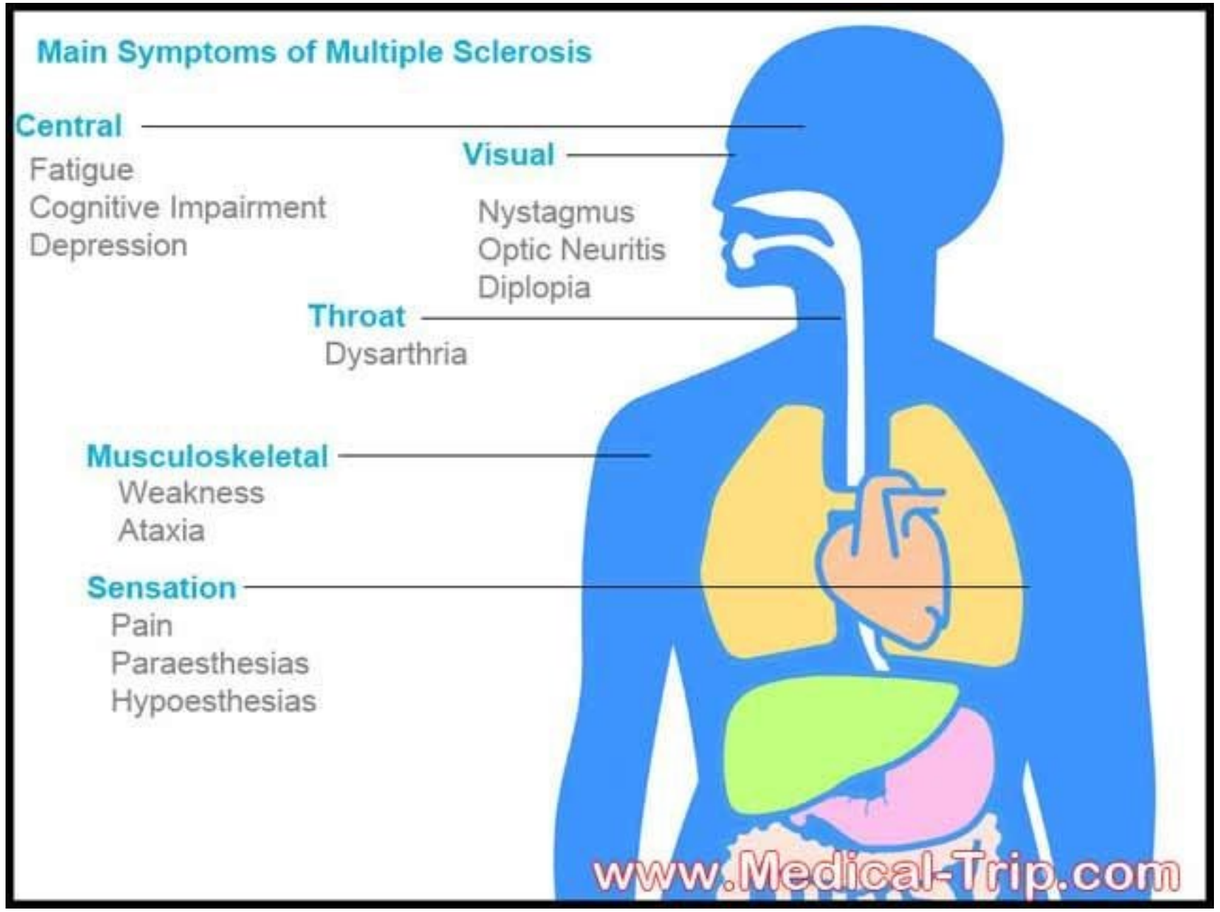
Epidemiology

- 1 per 1000 persons in USA and Europe
- Incidence is believed to be increasing.
- Female : male ratio is 2:1 (all autoimmune diseases are commoner in women)
- Manifests at any age (usually 20-40), but onset in childhood or after 50 is rare.

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
Central
Fatigue
Cognitive Impairment
Depression
Visual
Nystagmus
Optic Neuritis
Diplopia
Throat
Dysarthria
Musculoskeletal
Weakness
Ataxia
Sensation
Pain
Paraesthesias
Hypoesthesias
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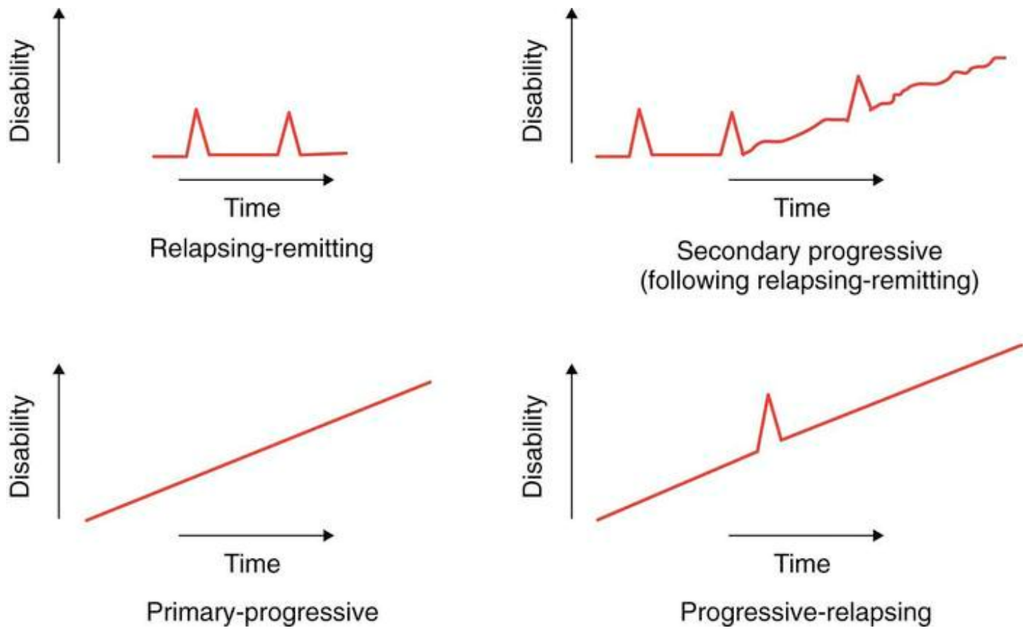
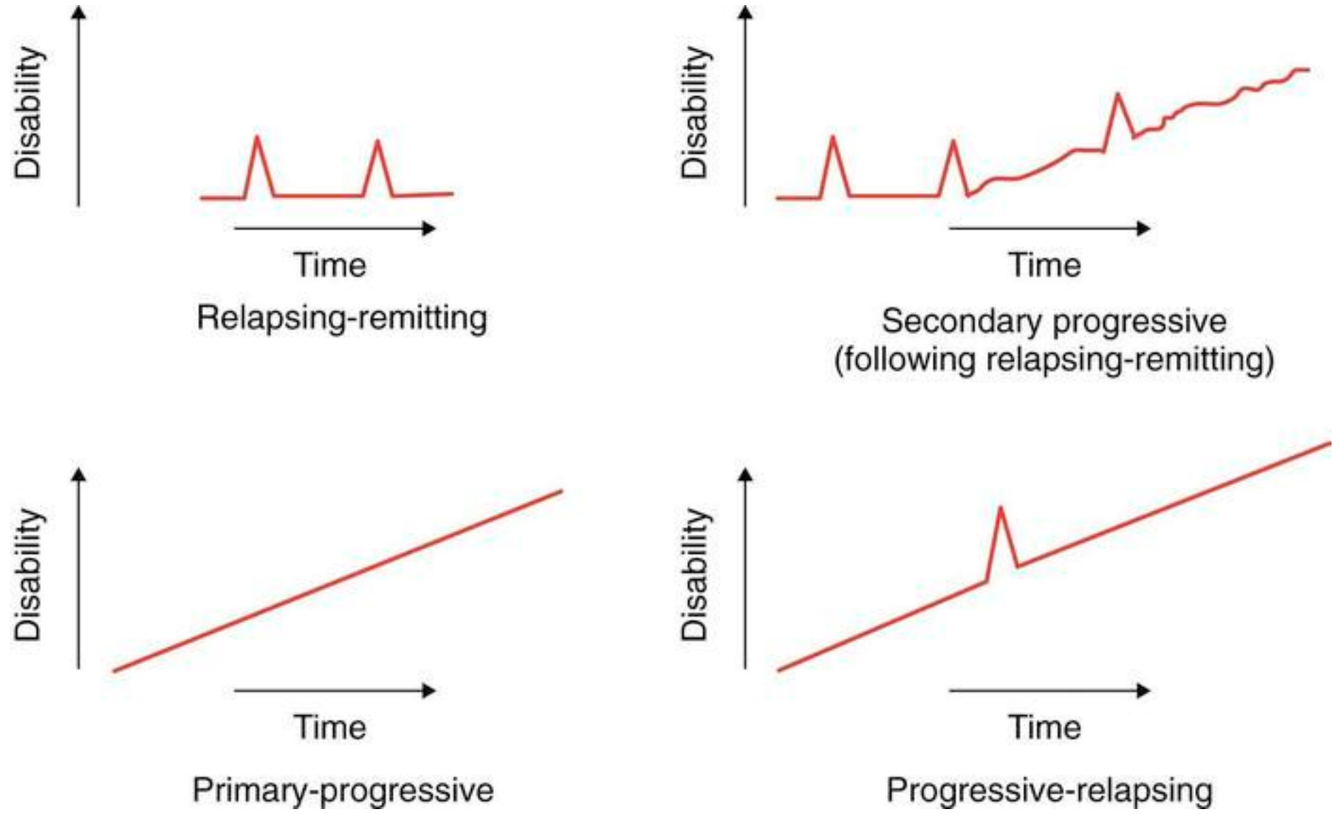
Clinical course

The course of the diseases is variable:

- 1. relapsing remitting means the patient will have symptoms (relapses) separated by periods of complete remission (normal, no symptoms)
- 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 some time 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!



NOTE: usually diseases of myelin do not affect axons, 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.

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

Pathogenesis

- 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 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.

Pathogenesis 1/2

- 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 secretes interferon gamma which activates macrophages
- T helper 17 recruits white blood cells.
- The activated leukocytes produce chemicals that destroy myelin.

Pathogenesis 2/2

-CD 8 T lymphocytes + B lymphocytes might also play a role in myelin destruction.

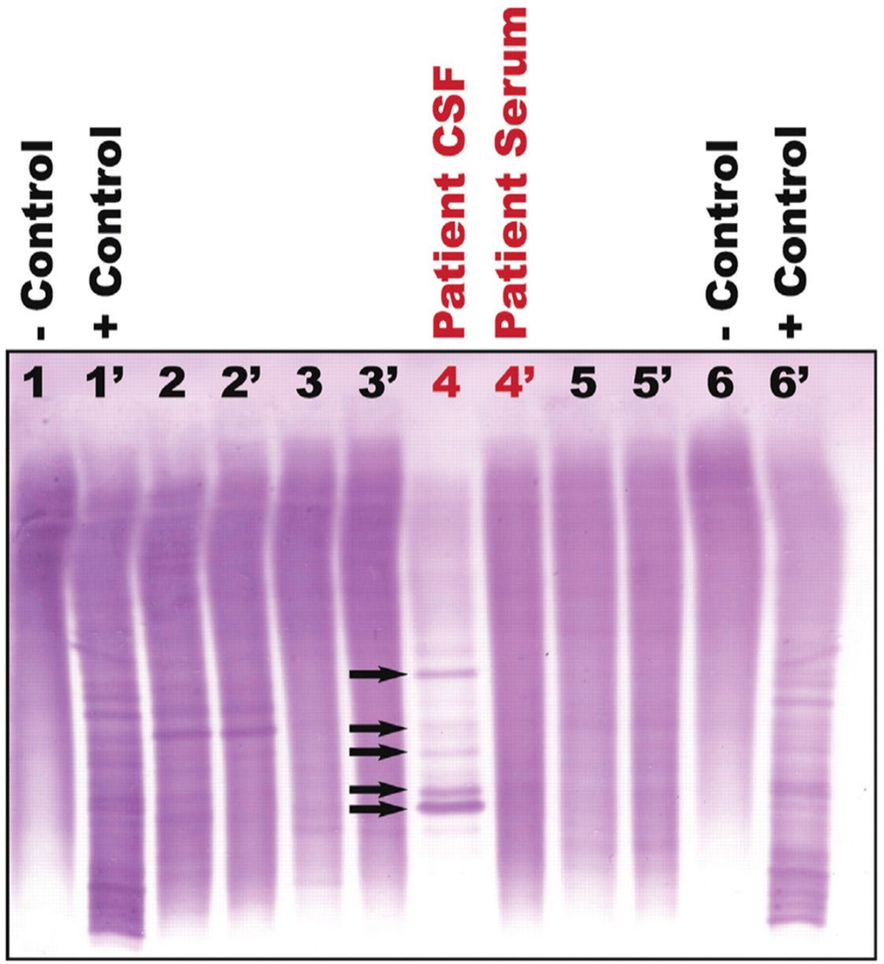
-In addition to demyelination; axonal damage can occur secondary to toxic effects from lymphocytes, macrophages and the chemicals they secrete.

- One evidence that supports the idea that B cells play a role in MS is the presence of **Oligoclonal bands** in the CSF of patients with MS.

Oligoclonal bands

- Oligoclonal bands are IgG (or IgM) bands in CSF. These are detected by a clinical test= protein electrophoresis.
- Protein electrophoresis is a test that detects the presence of protein in fluids. This technique separates proteins according to their size and charge.
- We use the protein electrophoresis method to compare proteins in serum and CSF. This method shows proteins as bands.
- CSF is a filtrate of plasma, so normally CSF has the same serum proteins or even less (large proteins will not be filtrated)
- So: the presence of extra bands in CSF means that these are proteins secreted intrathecally (within the CSF)
- In MS, plasma cells produce IgG (and less frequently IgM), and these will be detected as oligoclonal bands which are not present in serum.

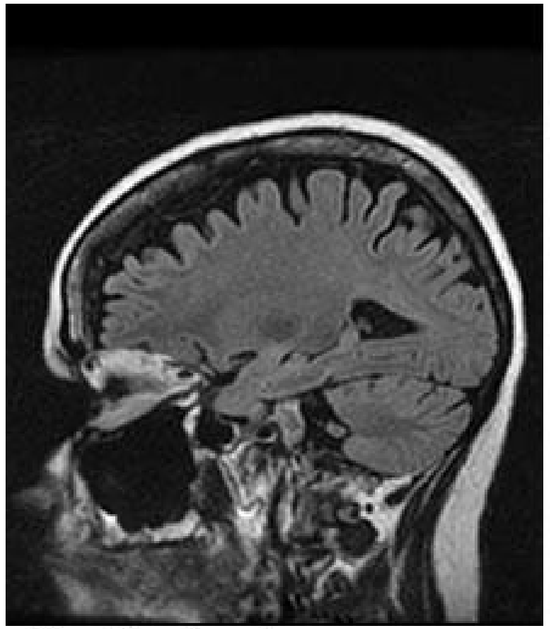
Arrows show bands present in CSF but not serum.



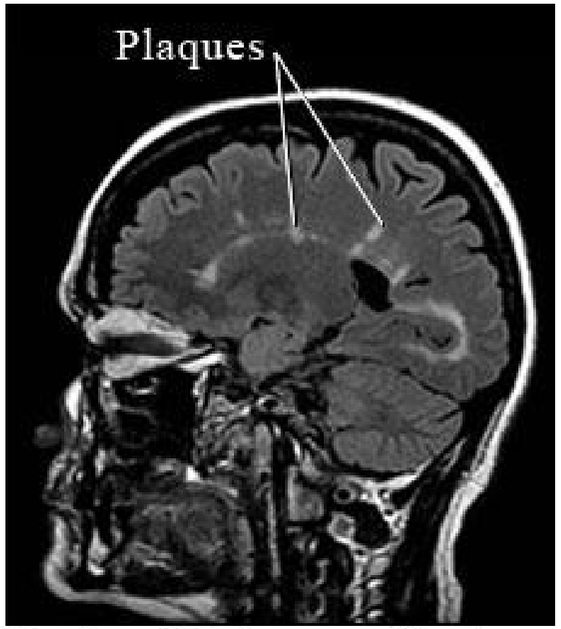
Morphology

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

Neuromyelitis optica

-Inflammatory demyelinating disease affecting mainly the optic nerve and spinal cord .

-***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 to be a subtype of MS, but not any more! it is a distinct entity.

Note

Please note: **in neuromyelitis optica, myelin destruction is caused be antibodies** secreted from B cells, whereas in **MS, the destruction is mainly due to cellular immunity** (T helpers and cytotoxic T). However, B cells play a role 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 (doesn't recur), and usually more severe than MS.

There are two types of post infectious demyelination:

1. ACUTE DISSMINAING ENCEPHALITIS

-Symptoms 1-2 weeks after infection

• Non-localizing symptoms: headache, lethargy, coma.

NOTE: Non-localising symptoms means symptoms that cannot be attributed to a specific site in the brain.(so they are nonspecific symptoms)

Localising symptom: A symptom indicating clearly the location of the diseased area.

• Rapid progression , fatal in 20% of cases

• Survivors: complete recovery

2. Acute necrotizing haemorrhagic encephalomyelitis :

- This is more dangerous and fatal.

Central pontine myelinolysis

- **Non immune** process causing edema of oligodendrocytes resulting in separation of myelin from the axons in the pons mainly.

- **Occurs after rapid correction of hyponatremia**

-Edema due to ***sudden change in osmotic pressure*** probably is the cause of the damage

- Causes rapid quadriplegia and can cause locked in syndrome (details later)

- The primary function of the pons is to act as a motor relay center. Many of the descending nerve fibers of various tracts synapse in the region of the pons.

- That’s why diseases of the pons affect the motor function and can result in paralysis.

Central pontine myelinolysis.. continuation

Hyponatremia should be corrected at a rate of no more than 8-12 mmol/L of sodium per day to prevent central pontine myelinolysis.

Locked in syndrome

Locked-in syndrome (LIS) is a condition in which a patient is *aware* but c*annot move or communicate verbally due to complete paralysis* of nearly all voluntary muscles in the body **except for vertical eye movements and blinking.**

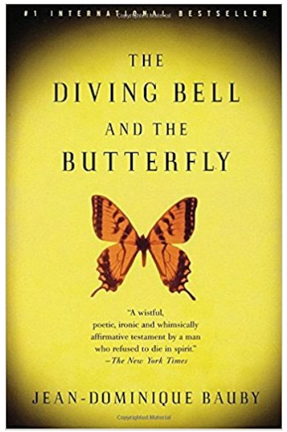
-The individual is **conscious** and sufficiently **intact cognitively to be able to communicate with eye movements.**

-locked-in syndrome is caused by damage in the ventral part of the pons due to pontine infarction, pontine hemorrhage, trauma, central pontine myelinolysis, tumor, or encephalitis.

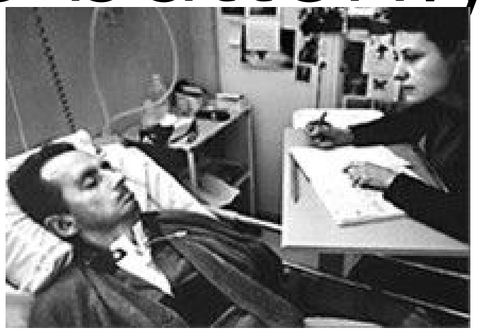
locked in syndrome

The patients have **intact vertical eye movements and blinking** because the supranuclear ocular motor pathways that run dorsally are not affected.

The patient is able to communicate by movement of the eyelids but otherwise is completely immobile.



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 publication.

SUMMARY 1/3

- 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.

Summary 2/3

- 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.
- Neuromyelitis optica is an autoimmune diseases, where myelin is destroyed via antibodies against aquaporine 4. the optic nerve and the spinal cord are the main targets.

SUMMARY 3/3

- 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 patient might die. Survivors retain normal neurological function.
- Central pontine myelinolysis is an iatrogenic diseases 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 quardeplegia and locked in syndrome.

thank you!