Myelin diseases of the CNS

2. Dysmyelinating diseases (leukodystrophies):

• Inherited diseases where myelin is not formed properly or has abnormal turnover kinetics.

• Caused by mutations in myelin proteins or the enzymes responsible for myelin turnover (balance between destruction and synthesis).

• Affected children are normal at birth but start loosing developmental milestones during infancy and childhood.

• They might have deterioration in motor skills, spasticity, ataxia...

-These diseases are progressive and fatal.

1.Demyelinating diseases:

• Acquired conditions where there is damage to previously normal myelinated axons due to autoimmune destruction, viral infections, drugs, toxins.

• Main types are:

1) Multiple sclerosis (MS):

• Autoimmune disease (all autoimmune diseases are commoner in women).

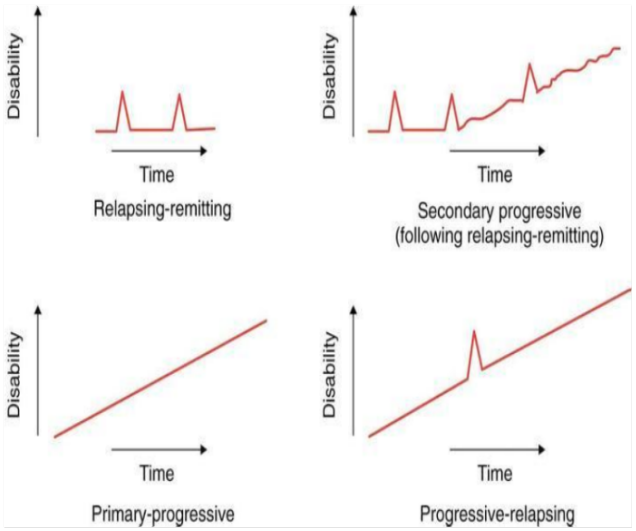
• Episodes of neurologic deficits separated in time which are attributed to white matter lesions that are separated in space.

• The clinical presentation is variable.

• The symptoms are reversible but the disease can recur. When it recurs the symptoms might differ from the initial ones.

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

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 sometime changes to pattern 2.
4. Progressive relapsing: like in 2, but at times symptoms get even worse.



Natural history of multiple sclerosis is defined by: 1. the limited capacity of the CNS to regenerate normal myelin(less efficient than in the PNS)

2. the secondary damage to axons that might occur after repeated relapses.

-usually diseases of myelin do not affect axons,but with repeated attacks ⟶
Inflammation causes the axonal damage, not the myelin destruction
• There is loss of tolerance of self-proteins in the myelin sheath.
Genetic predisposition: ⟶ 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:
-CD4 T lymphocytes play a major role (react against myelin antigens and secrete Cytokines), especially T helper 1 (secretes interferon gamma which activates Macrophages) and T helper 17 (recruits white blood cells).
-CD 8 T lymphocytes + B lymphocytes might also play a role in myelin destruction.
- One evidence that supports the idea that B cells play a role in MS is the presence of Oligoclonal bands : IgG "or IgM" bands in CSF which are not normally present in serum., detected by protein electrophoresis {separates proteins according to their size and charge}.
• 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)
Morphology : White matter disorder. Commonly seen near ventricles, optic nerves and chiasm, brain stem, cerebellum and spinal cord.
• Multiple well circumscribed slightly depressed lesions= plaques "grossly firmer than normal white matter(SCLEROTIC)".
-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.
- B cell depletion therapies improve symptoms dramatically in MS.
2)Neuromyelitis optica:
-Inflammatory demyelinating disease affecting mainly the optic nerve and spinal cord .
-Antibodies to aquaporin-4 (integral membrane protein that conduct water through the cell membrane) are diagnostic .
• In neuromyelitis optica, myelin destruction is caused be antibodies secreted from B cells, whereas in MS, the destruction is mainly due to cellular immunity.

3)Post infectious demyelination:

-Demyelination after viral infection but it is not due to direct effect of the virus.

• Pathogen associated antigens cross react with myelin antigens.

-Acute, monophasic, and usually more severe than MS.

Types → Acute necrotizing haemorrhagic encephalomyelitis : dangerous and fatal.

↓

ACUTE DISSMINAING ENCEPHALITIS: Non-localizing symptoms(symptoms that cannot be attributed to a specific site in the brain.(so, nonspecific symptoms)

• Rapid progression , fatal in 20% of cases • Survivals: complete recovery

4)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(should be corrected at a rate of no more than 8-12 mmol/L of sodium per day).

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

- Causes rapid quadriplegia and can cause locked in syndrome.

• The primary function of the pons is to act as a motor relay center>>> That's why diseases of the pons affect the motor function and can result in paralysis.

Locked in syndrome

-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.

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

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