CNS pathology
Diseases of Myelin

Dr Heyam Awad

MD, FRCPath

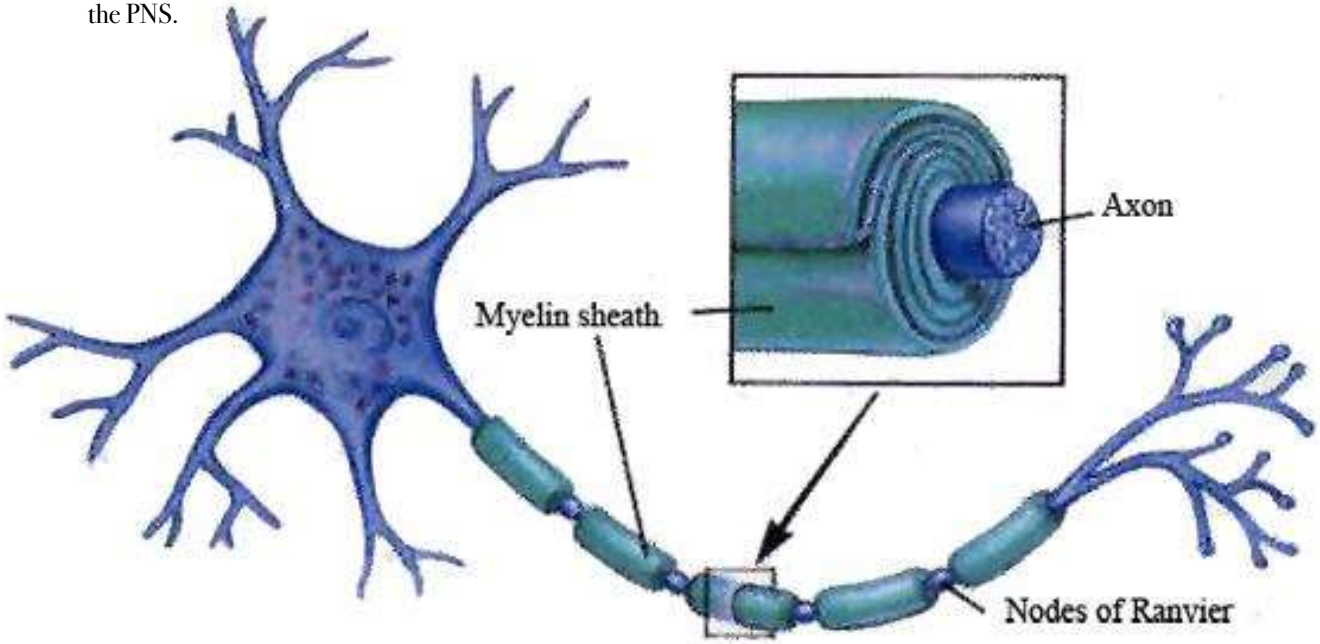
What is myelin?

- 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 in the CNS and Schwann cells in the PNS Made of proteins and lipids, from the plasma membrane of the corresponding cells.
- Myelinated axons are the predominant component of white matter.

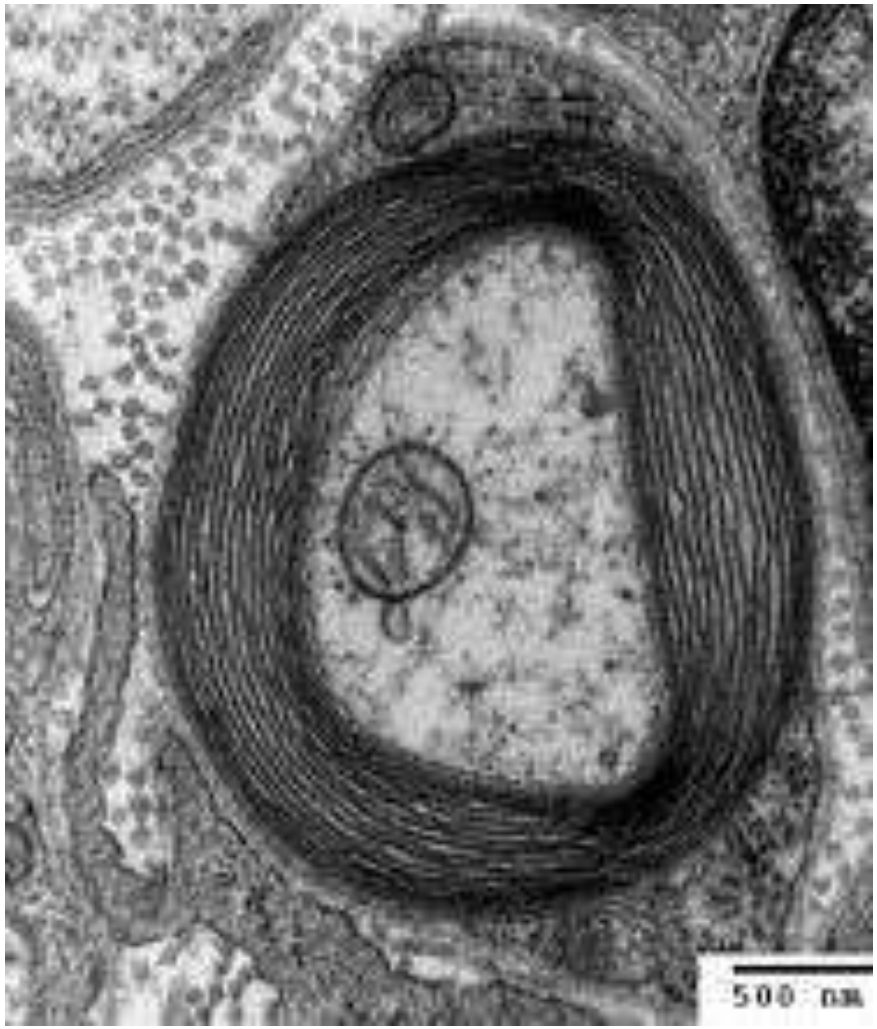
Myelin in the CNS

Myelin is made of layers of the plasma membrane wrapped around the axons, derived form oligodendrocytes in the CNS, and from Schwann cells in the PNS, which shows us that the myelin composition in the CNS is different than that of the PNS.
Thus, the diseases of myelin in the CNS are different from diseases of myelin in the PNS, even autoimmunity targets differ, i.e. a protein targeted in the CNS may not lead to similar attacks in the PNS.

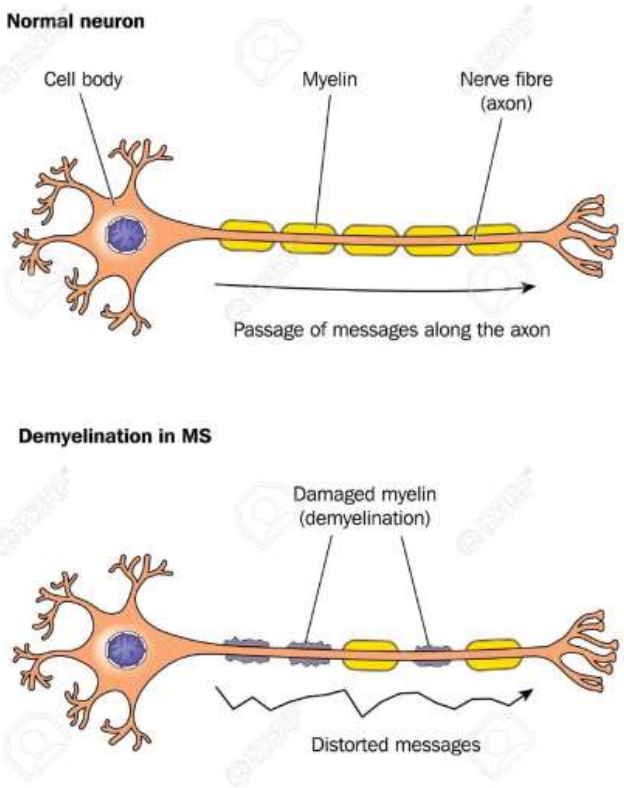
Disease of myelin in the CNS are divided into:
1) Demyelinating diseases: Born right, gone wrong. There is an environmental factor destroying the formerly normal myelin. However, most of these diseases have a genetic predisposition.
2) Dysmyelinating diseases: Inherited diseases, either in myelin proteins or in the turnover of myelin (enzymatic dysfunction).

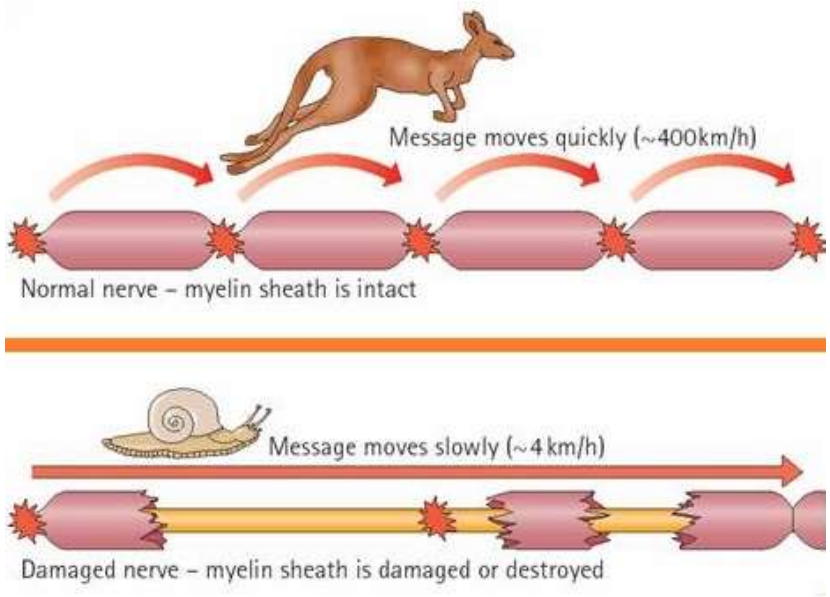


- Myelin in this electron microscopic picture appears as layers of plasma membrane wrapped around the axon.



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





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. **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**

Meaning affects different locations in different episodes. May be sensory, may be motor.

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.

- Autoimmune, so:
  - More in women
  - Runs in families (seen in twins!)

- Has genetic predisposition

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.

-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.

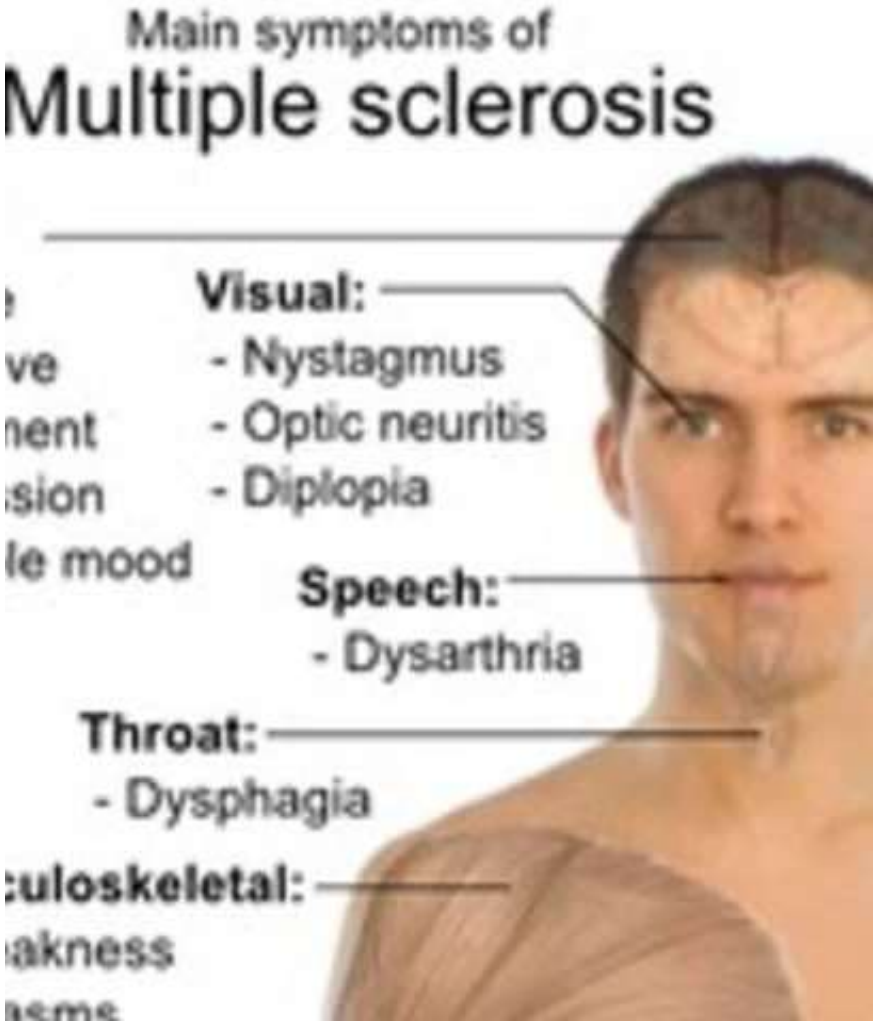
-The most frequent presentation was weakness (30.8%), followed by optic neuritis (20.1%), sensory impairment (19.6%), and ataxia (14.3%).

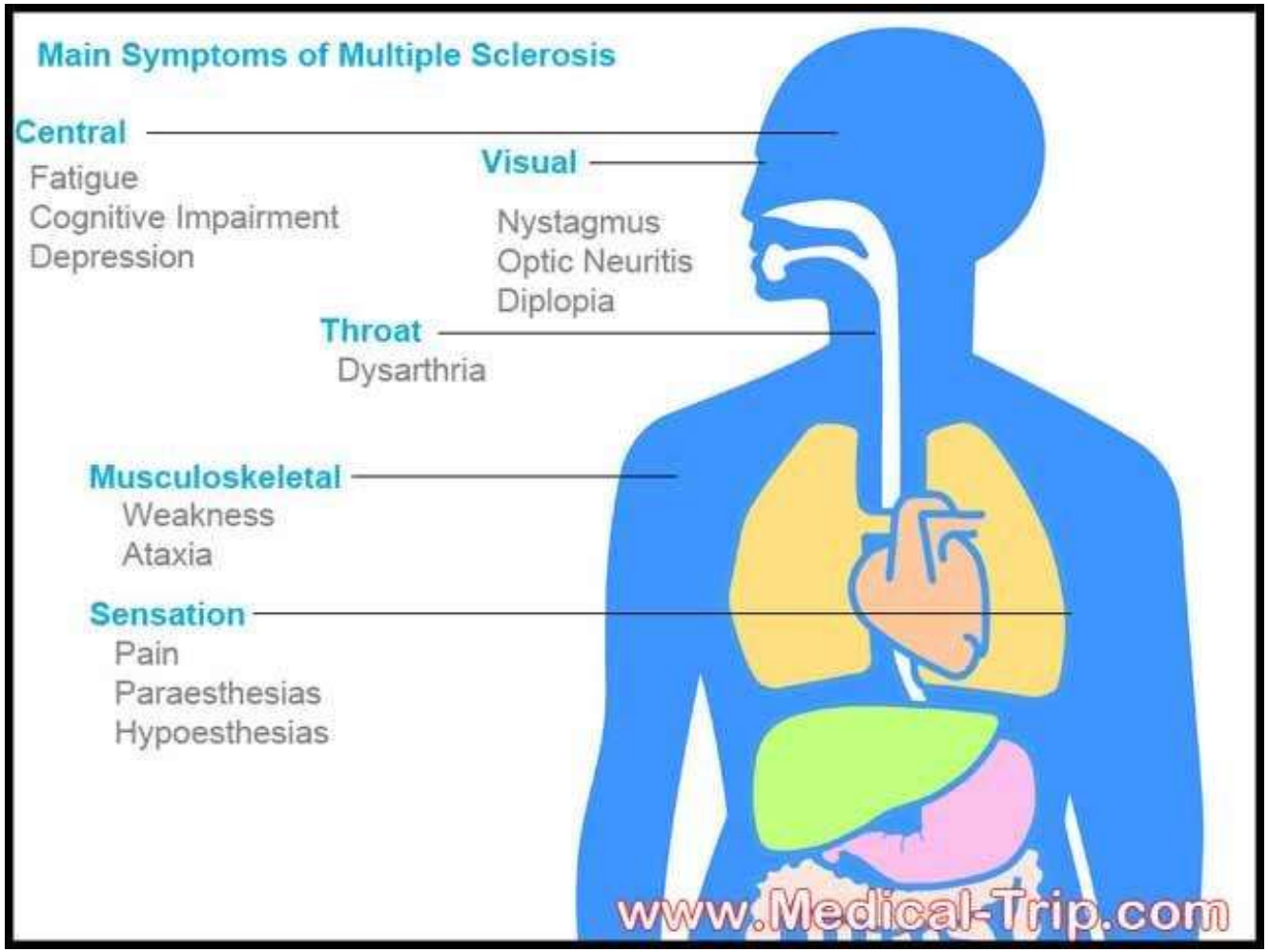
-Family history of MS was found in 9.4% of the cases.

May be important.

clinical presentation

- Signs and symptoms depend on the location of the lesion.
- the clinical presentation is variable. Depends on which nerves are affected, may be sensory, may be motor.
- 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
www.Medical-Trip.com

Clinical course

- The course of the diseases is variable:

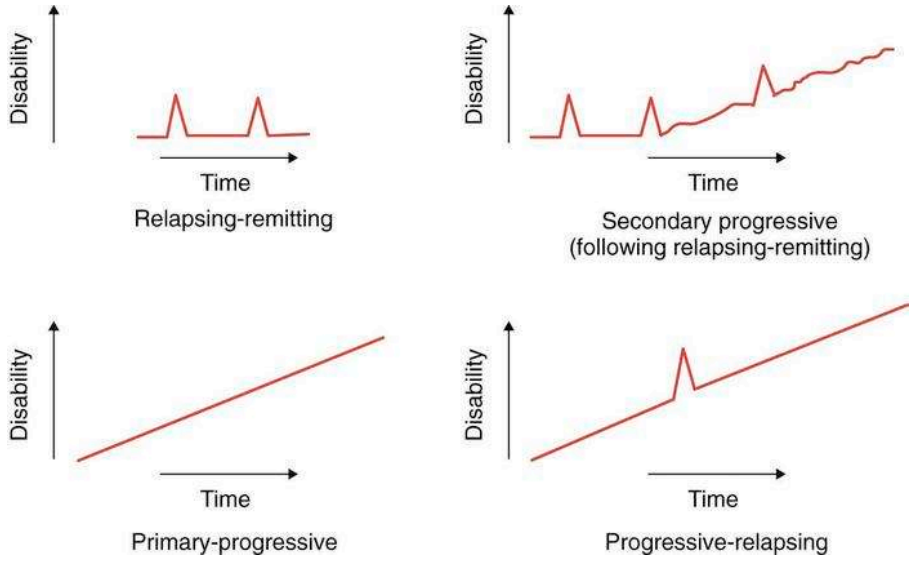
Most common:

- 1, Relapsing remitting means the patient will have symptoms (relapses) separated by periods of complete remission (completely normal)

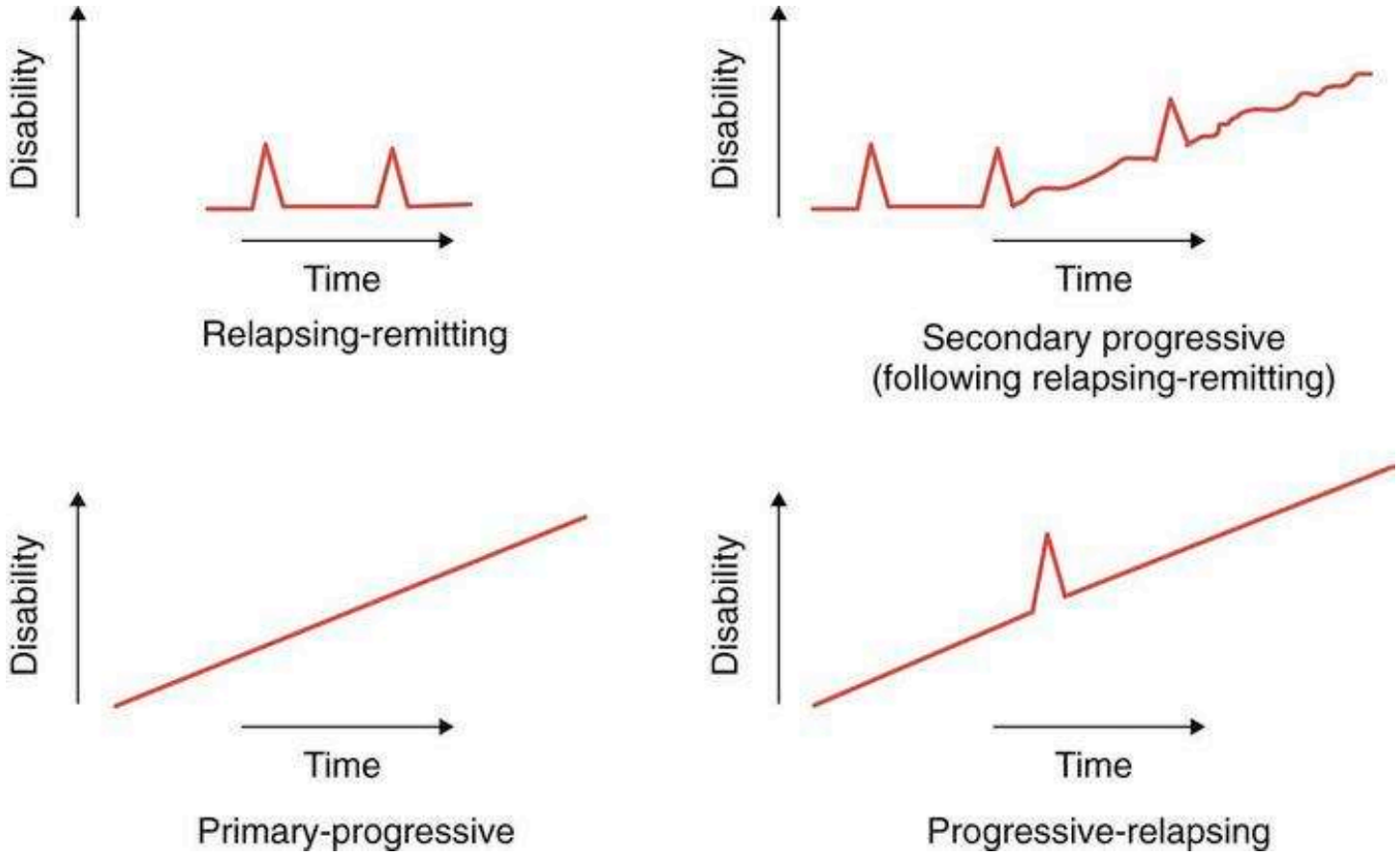
- 2. Primary progressive: when symptoms start, the patient will have symptoms continuously without periods of remission, and the symptoms get worse with time.

- 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: 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. note that it is the inflammation that causes the axonal damage, not the myelin destruction per se.

Inflammatory reaction following the insult, if severe enough to affect axons, no regeneration will occur, as axons cannot be regenerated (myelin can, axons can't).

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)

People are born with their genetic predispositions, but they develop the disease by 20-40 because it seems to have an environmental trigger.

Genetic predisposition

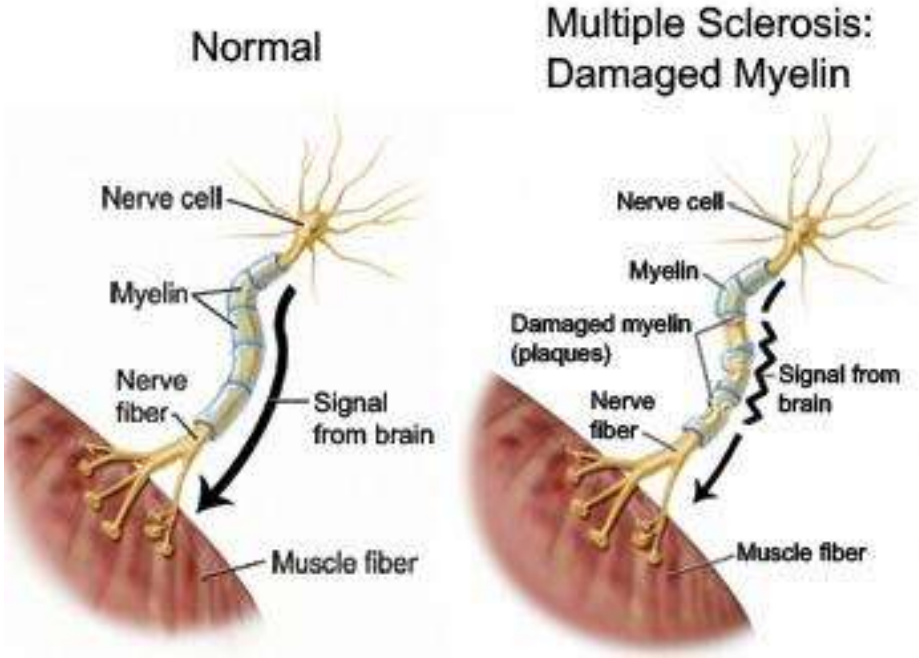
- MS is 15 fold higher in first degree relatives
- Concordance rate of monozygotic twins around 25%
- Association with HLA DR2
- Polymorphism in genes encoding cytokine receptors (IL 2 & IL 7)... these two cytokines control the activation and regulation of T cell mediated immune response.

Not everyone having these genetic susceptibilities will develop diseases, but people with no genetic predisposition won't get the diseases (have genes? = might develop, develop? = definitely have genes, no genes? = definitely won't develop). Important in genetic studies, if genetic variants don't exist in the patient, rule out the disease.

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 1/2

Environmental trigger activates a T-cell response.

- CD4 T lymphocytes play a major role, especially T helper 1 and T helper 17.
- These T cells react against myelin antiges 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.

Pathogenesis 2/2

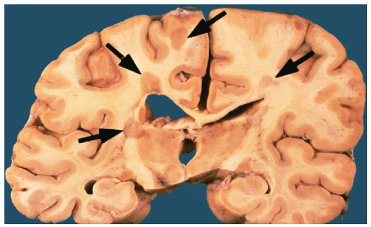
-CD 8 T lymphocytes + B lymphocytes might also play a role in myelin destruction.

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

The main cell implicated in the pathogenesis is CD_4+ T-helper lymphocytes, however, CD8+ and B lymphocytes also play a role.
We knew B lymphocytes are implicated as well because:
1) Monoclonal antibodies are secreted in the CSF by plasma cells in MS, useful in diagnosis, secreted only in the CSF proven by their absence from the plasma (the CSF should be a filtrate of the plasma, if antibodies are only found in the CSF and not in the plasma, that means they were originally secreted in the CSF).
2) Upon performing plasmapheresis, or upon removing B lymphocytes, patients improve.

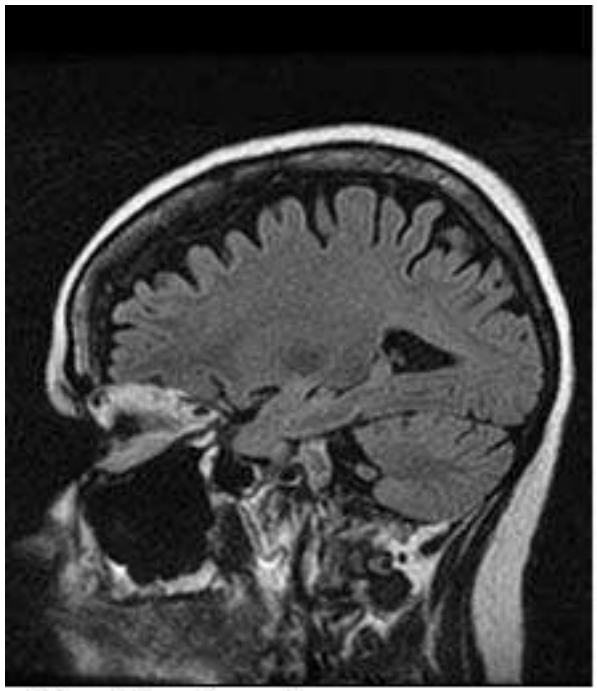
Morphology

White matter disorder

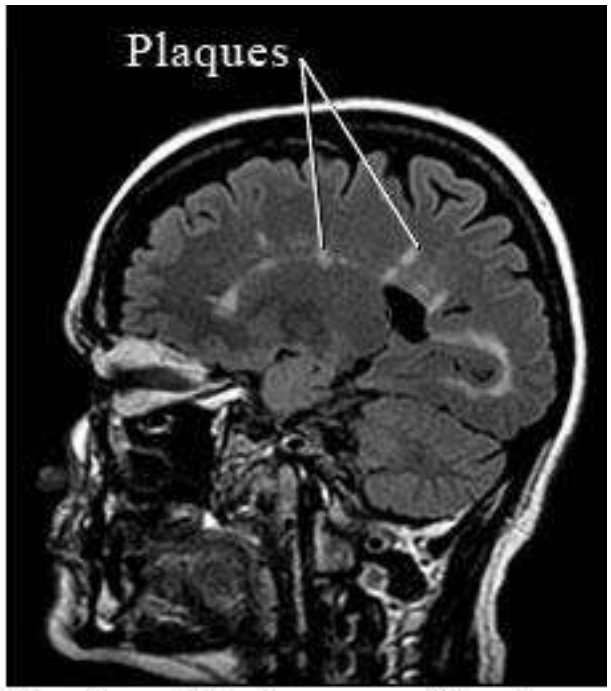


• Multiple well circumscribed slightly depressed grey tan irregularly shaped lesions= plaques

• 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.

+ May see macrophages eating dead myelin.

Neuromyelitis optica

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

-Antibodies to aquaporin-4 are diagnostic . Humoral immunity mediated, T lymphocytes are not involved here.

- (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 optical, 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).

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 (Oligoclonal bands)

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.

This isn't a chronic illness, it involves a single episode, patient either makes it alive or dies.

there are two types of post infectious demyelination

- 1. ACUTE DISSMINAING ENCEPHALITIS

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 :

- This is more dangerous and fatal.

central pontine myelinolysis, caused by nonimmune damage to oligodendrocytes typically after sudden correction of hyponatremia, that may result in a rapidly evolving quadriplegia.

Central pontine myelinolysis

-Lysis here doesn't mean destruction, not autoimmunity or immune reactivity, it means something is separating the myelin from the axon, probably due to changes in osmotic pressures.

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

- **Occurs after rapid correction of hyponatremia**

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

Could very likely be iatrogenic, if a patient has hyponatremia, and it is fixed rapidly, the osmotic pressures change quickly and there'll be edema around the axons separating them from myelin "-lysis."

The result is complete paralysis of all muscles except the nerve responsible for vertical eye movement, causing "locked-in syndrome," the spared nerve passes in the "dorsal pontine," while this disease affects the ventral pontine area.

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.

- **Causes rapid quadriplegia and can cause locked in syndrome**

Note that Locked-in syndrome occurs when the ventral pons is affected, not only due to 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.

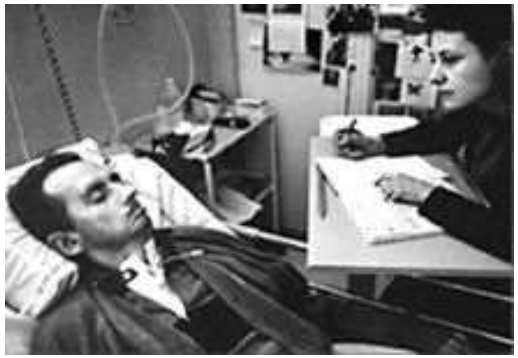
locked in syndrome

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

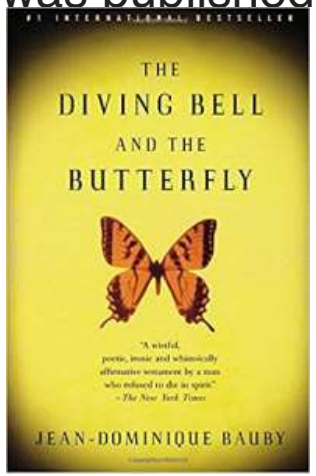
The patient is able to communicate by movement of the eyelids but otherwise is completely immobile.

We must be able to distinguish between Locked-in syndrome, Coma, Brain death, or Vegetative state (where the patient moves but has cognitive impairment).

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, blinkby 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



Dysmyelinating diseases

- Inherited dysmyelinating diseases = leukodystrophies
- • 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...

these diseases are progressive and fatal.

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.

Diseases of myelin in the PNS

- .

Guillian Barre syndrome

- Is an ***autoimmune neuropathy.*** Causing motor symptoms, acute symmetric ascending paralysis.
- Often follows bacterial viral or mycoplasma infection
- Can follow immunisation or surgery
- most commonly after Campylobacter jejuni, CMV, EBV
- CSF: increased proteins and few WBC Useful in diagnosis.
- **Guillian Barrie has two forms**: demyelinating , which is the predominant form in USA and Europe, and an immune mediated axonal neuropathy which is more common in Asia

Clinical features of Gullian Barre

- Acute symmetric neuromuscular paralysis often begins distally and ascends proximally
- Sensory and autonomic disturbances may also occur
- 5% of patients present with ophthalmoplegia, ataxia and areflexia = if these symptoms exist , it is called Fisher syndrome
- Muscle paralysis may cause respiratory difficulty, which might cause death.
- Autonomic involvement may cause cardiac arrhythmia, hypo or hypertension
- **Neuropathy resolves 2-4 weeks after onset and most patients recover**

Acute disease.

Chronic inflammatory demyelinating polyneuropathy CIDP

- Chronic acquired inflammatory polyneuropathy characterised by symmetric, mixed sensorimotor polyneuropathy that persists for 2 months or more.
- it is immune mediated but usually there is no previous history of infection.
- occurs in patients with other autoimmune diseases and in AIDS patients.

numbness, and pain or tingling sensations. Like Guillain-Barré syndrome, CIDP is immune mediated. But in contrast to Guillain-Barré syndrome, CIDP follows a chronic, relapsing-remitting, or progressive course. It occurs with increased frequency in patients with other immune disorders, such as systemic lupus erythematosus and HIV infection. The peripheral nerves show segments of demy-

Diabetic neuropathy

- Neuropathy is the **most common complication of diabetes**.
- The prevalence of diabetic neuropathy ranges from 7% within 1 year of diagnosis to 50% for those with diabetes for >25 years.
- Risk of developing neuropathy depends on: duration of diabetes, and level of control of blood sugar; the worse the control the higher the possibility of developing neuropathy.

People at risk:
- If long lasting diabetes (10-20 years).
- Uncontrolled diabetics.

- The presence of cardiovascular autonomic neuropathy dramatically shortens the patients' life expectancy.
- Loss of feeling in the lower limbs is a high risk for limb amputation, which occurs in 1–2% of diabetic patients.

Diabetic neuropathy: clinical manifestations

- can manifest as polyneuropathy or mononeuropathy
- Several forms of neuropathy can occur: Sensory, motor, or autonomic.
- 1. **distal symmetric sensorimotor polyneuropathy which is the most common form.** Symptoms include numbness, tingling, and weakness. It can also cause pain. These symptoms usually start in the longest nerves in the body and so first affect the feet and later the hands. This is sometimes called the "**stocking-glove**" pattern.
- 2. **autonomic** neuropathy causing changes in bowel, bladder, or cardiac function Changes in cardiac function due to autonomic neuropathy is the most dangerous, may cause arrhythmias, hypotension, hypertension...
- 3. **Lumbosacral** neuropathy causing pain in lower legs.

Diabetic neuropathy: pathogenesis

- Mechanism of diabetic neuropathies :*unknown*, probably due to nerve ischemia because of small vessel disease

- several theories tried to explain how neuropathy occurs. factors that cause neuropathy include: **microangiopathy** ,longstanding **hyperglycemia** causing a downstream metabolic cascade leads to peripheral nerve injury through an increased flux of the **polyol pathway**, enhanced **glycation end-products** formation, excessive release of **cytokines**, activation of **protein kinase C** and exaggerated **oxidative stress**. All these might damage the nerves.

Doctor's accepted theory: Diabetes causes microangiopathy in the vessels supplying the nerves, leads to ischemia of the nerves, leads to neuropathy.

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.
- 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.

SUMMARY 2/3

- 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.
- 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.
- Dysmyelinating diseases are a group f inherited disorders where children are born normal but develop neurological deficit 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.

Summary 3/3

- Demyelinating neuropathies in the PNS can be acute (Gullian Barre syndrome) or chronic (CIDP)
- Guillian Barre is an acute autoimmune disease occurring after infections or immunisation. it causes symmetric paralysis that starts in lower limbs and ascends. it can cause sensory and autonomous symptoms as well
- Guillian Barre (G-B) is life threatening if respiratory muscles are affected
- G- B can be due to demyelination, but also due to axonal damage which is also autoimmune in nature.
- CIDP is similar to G-B regarding symptoms but is chronic and associated with other autoimmune diseases and HIV. Usually it is not preceded by infection.
- diabetic neuropathy is the most common cause of peripheral neuropathies. it can present as mono or poly neuropathy, can be sensory, motor or auonomic and risk increases with increased detain of diabetes and poor control of blood sugar.

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 olidodendricytes and the cause of demyelination is autoimmunity due to cross reaction
- D. Wrong, neurmyelitis optical is caused by auto antibodies.. not cellular immunity
- E. Correct, quiescent plaques occur during repair phase and contain gloss.. astrocytes are the main cells responsible for this.

thank you!