CNS pathology
Third year medical students 2020

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Lectures 5 and 6: Myelin diseases of the PNS and CNS

This is an e learning lecture

Please Do the following

- 1. Watch the videos about this lecture on the e learning site,(5 short videos)
- 2. Read this slide.
- 3.Write down any questions you have.
- 4. Do the related activities.(available on the elearnig site)
- 5. We will have a discussion session about these lectures and there will be a chance for students' presentations.

ILOS

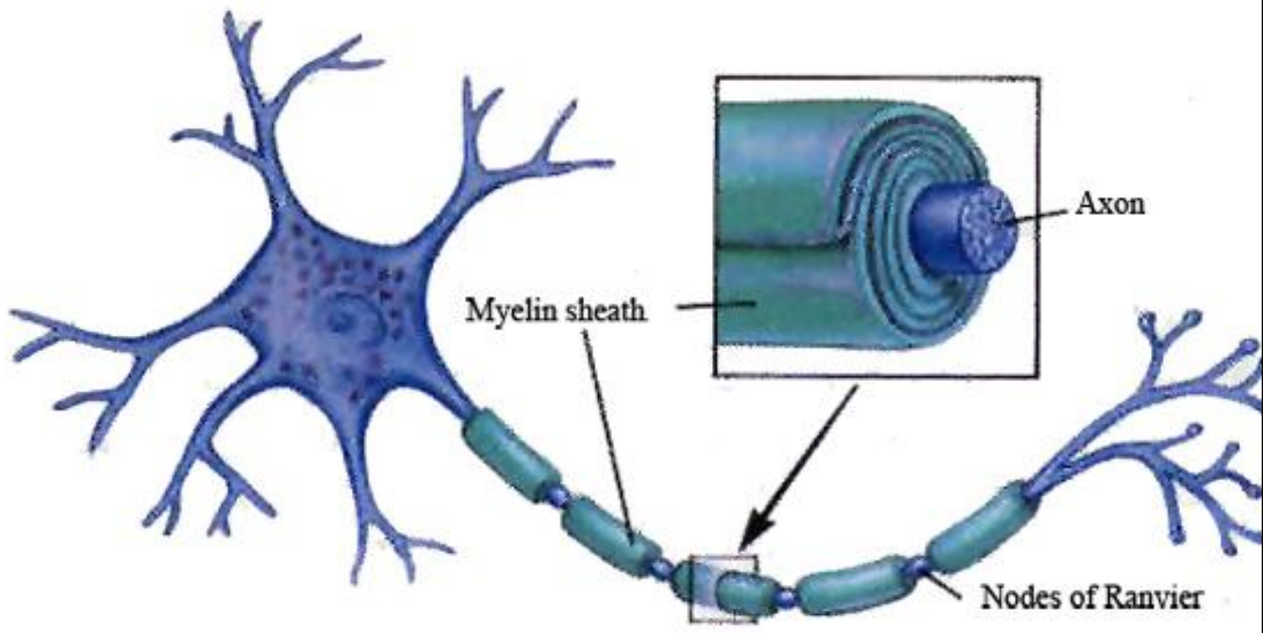
- 1. Understand differences and similarities between diseases of myelin in the CNS and PNS.
- 2. Understand the difference between demyelinating and dysmyelinating diseases
- 3. know the epidemiology, pathogenesis and clinical and morphological features of multiple sclerosis
- 4.Have a brief idea of other demyelinating diseases
- 5. Understand the concept of dysmyelinating diseases and their clinical presentation.
- 6. List causes of demyelinating diseases in the PNS.
- 7. In depth understanding of diabetic neuropathy.

What is myelin?

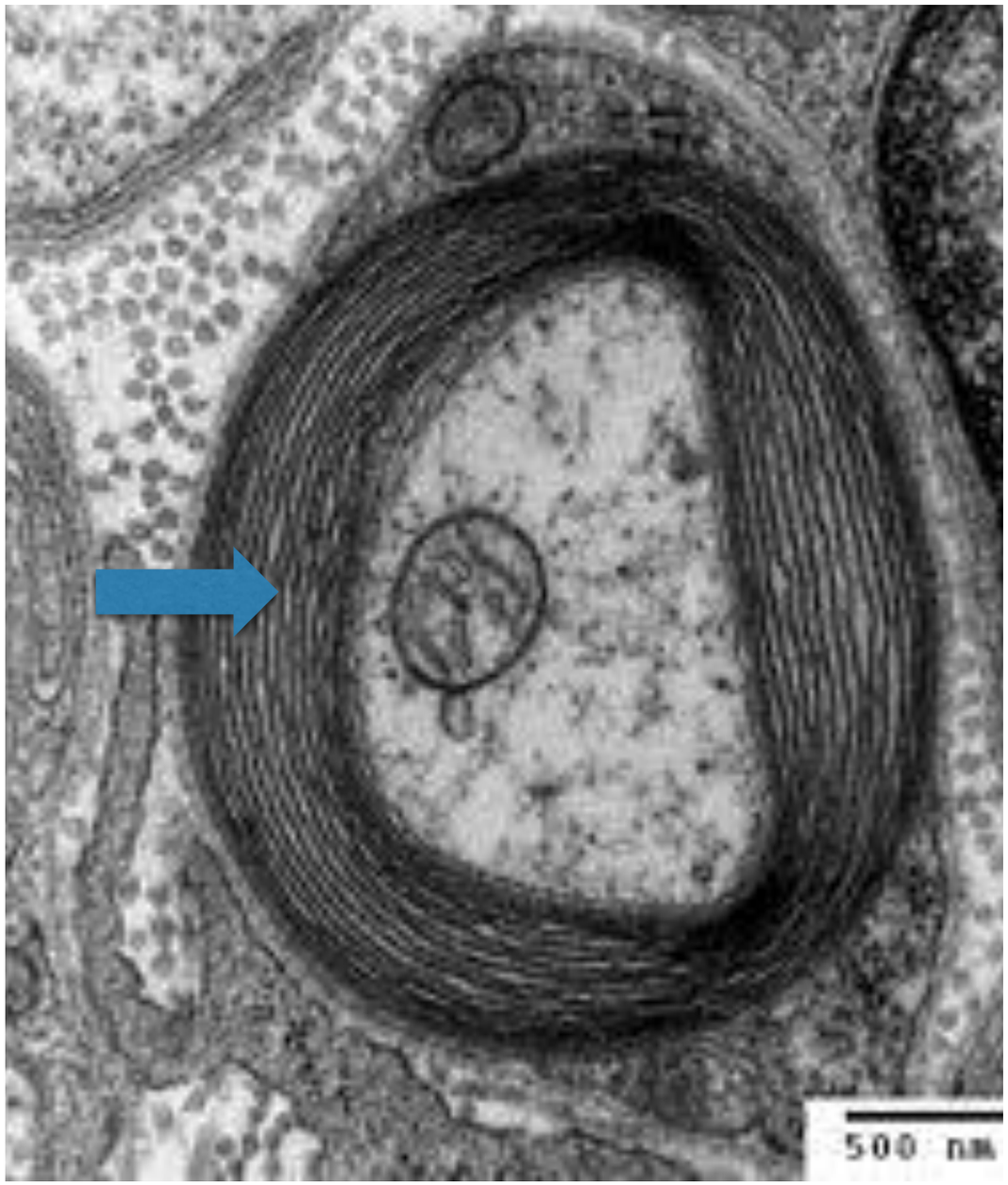
- Myelin is a *protein-lipid complex* that is wrapped around the axons.
- Function: allows rapid propagation of signals.
- Composition: layers of plasma membranes assembled by ***oligodendrocytes (CNS) or Schwann cells (PNS)***
- Myelinated axons are the predominant component of white matter.

Myelin in the CNS

- Note that myelin is composed of layers of plasma membrane wrapped around the axons.

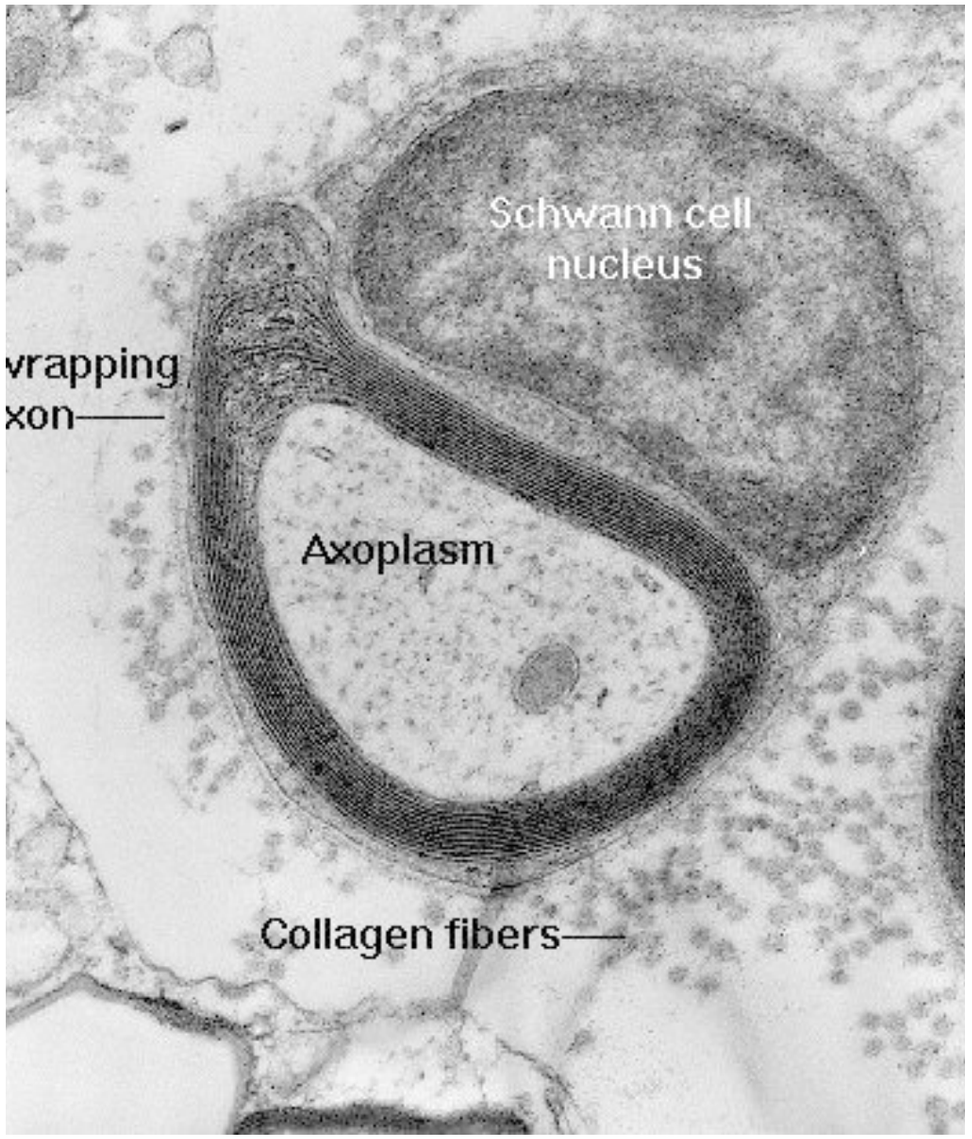


- Myelin in this electron microscopic picture appears as layers of plasma membrane wrapped around the axon.

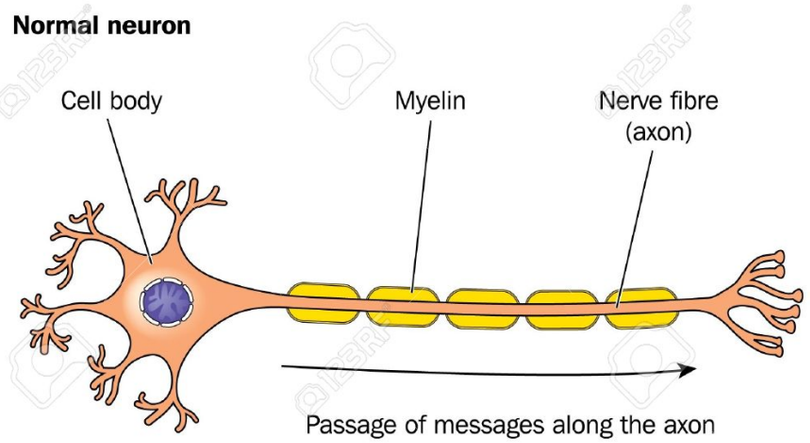


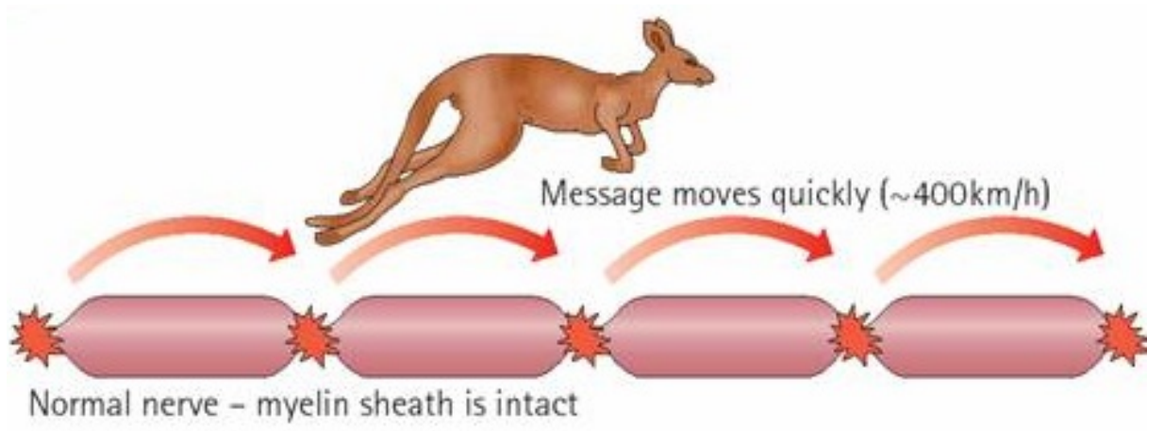
Myelin in the PNS

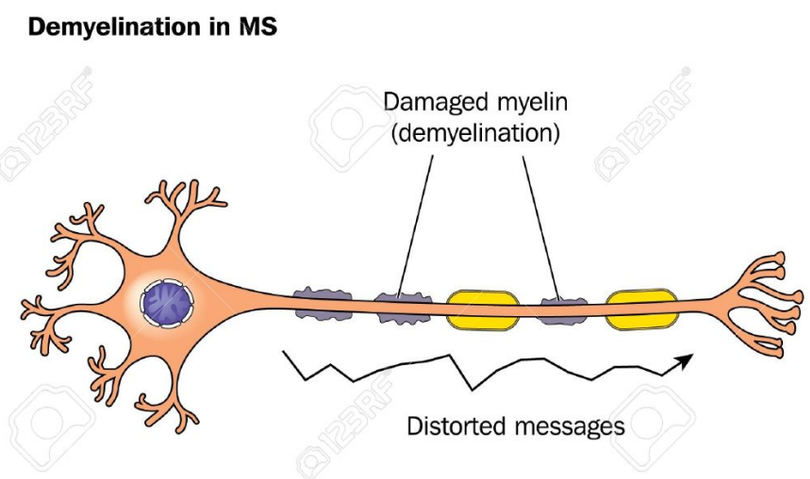
- As this EM picture shows, the part of neuron distal to the cell body has an axon (axoplasm and its surroundings in the pic) and a myelin sheath formed from Schwann cells.

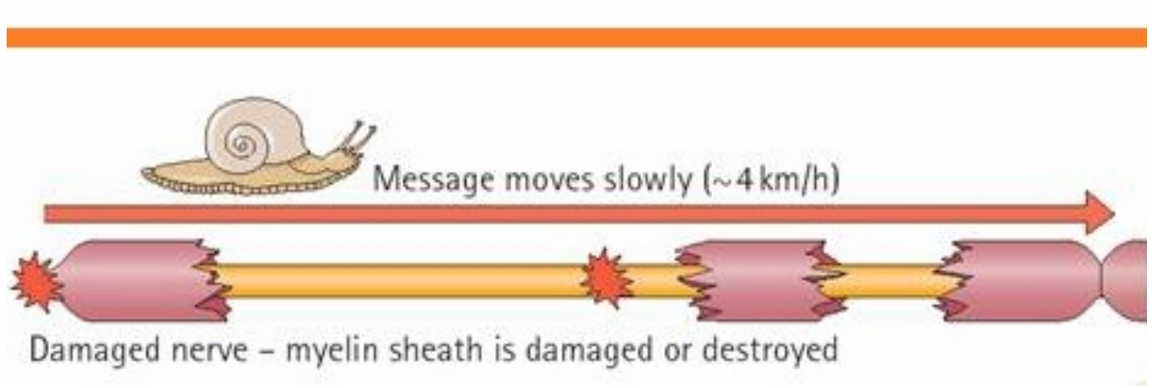


Function of myelin: to insulate axons and allows quick transmission of neural signals









Diseases of myelin in the CNS

- There are two types of myelin disorders in the CNS
- 1. **de**myelinating 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. **dys**myelinating 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. **Neuromeylitis optica :** also autoimmune but affects mainly optic nerve and spinal cord.
- 3.**Post infectious demyelination.**
- 4.**Central pontine myelinolysis.**

Multiple sclerosis

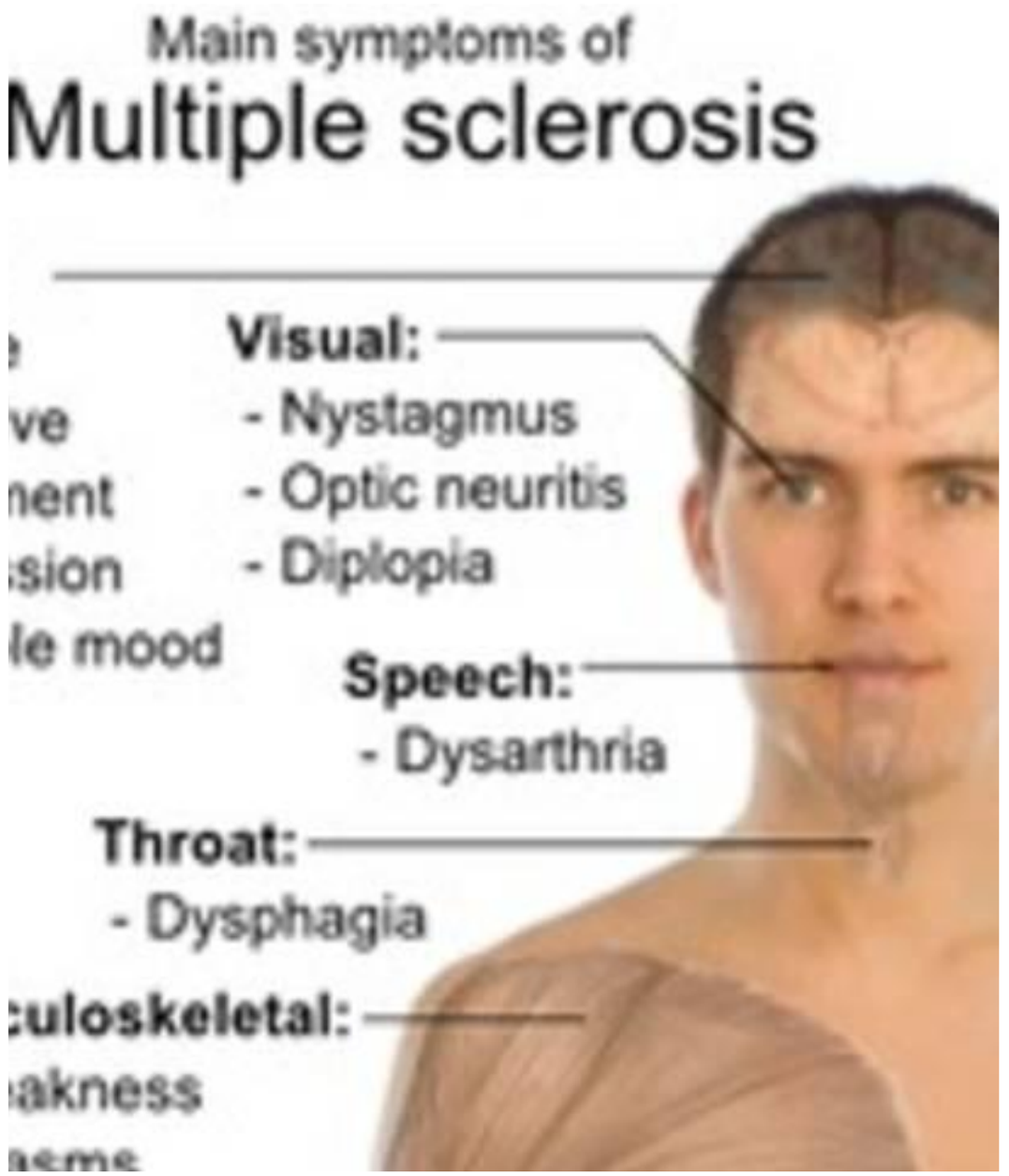
- Is an autoimmune demyelinating disease
- Defined as: *Episodes* of neurologic deficits **separated in time** which are attributed to **white matter lesions** that are s**eparated in space**

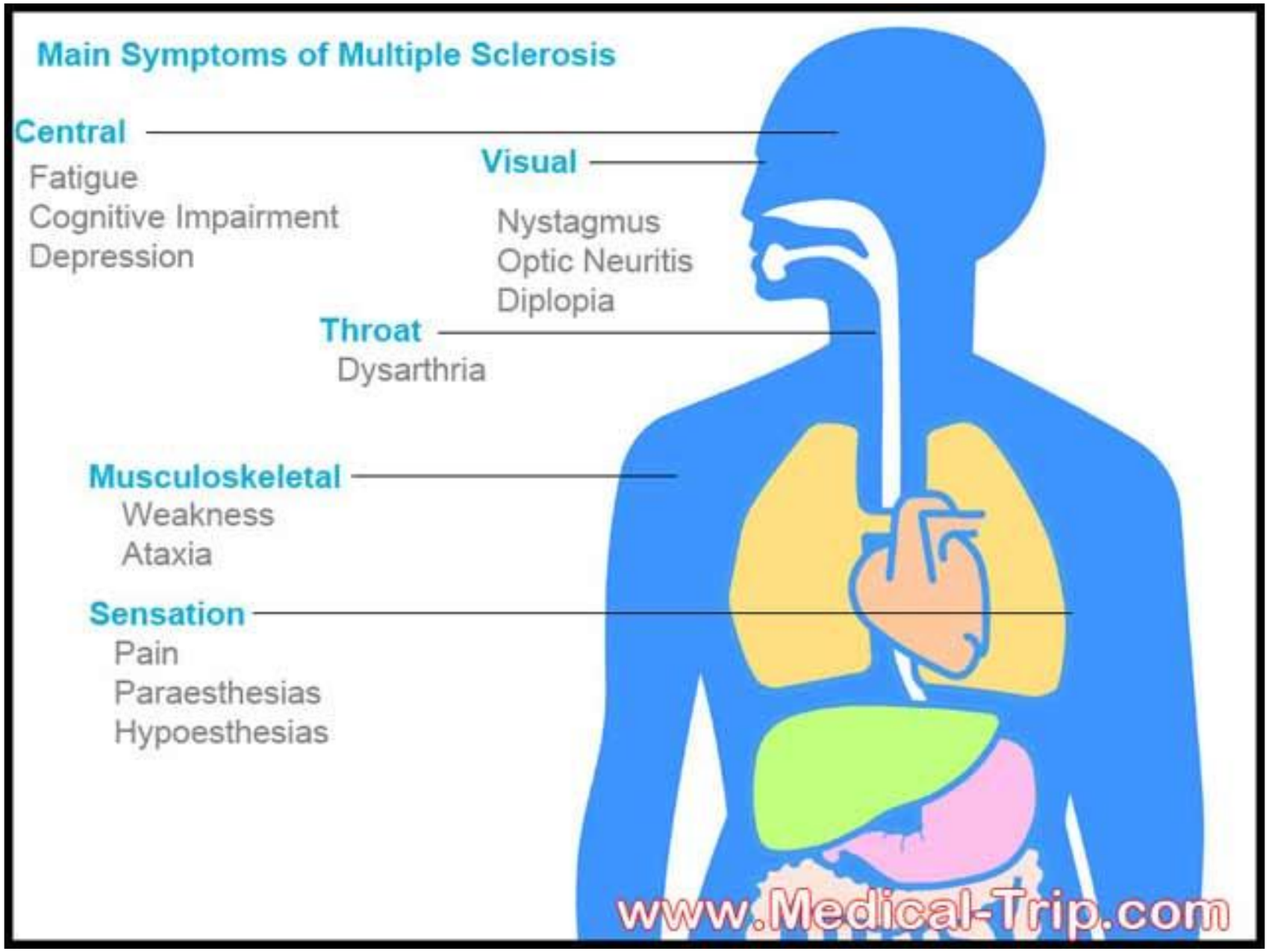
Epidemiology

- 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.

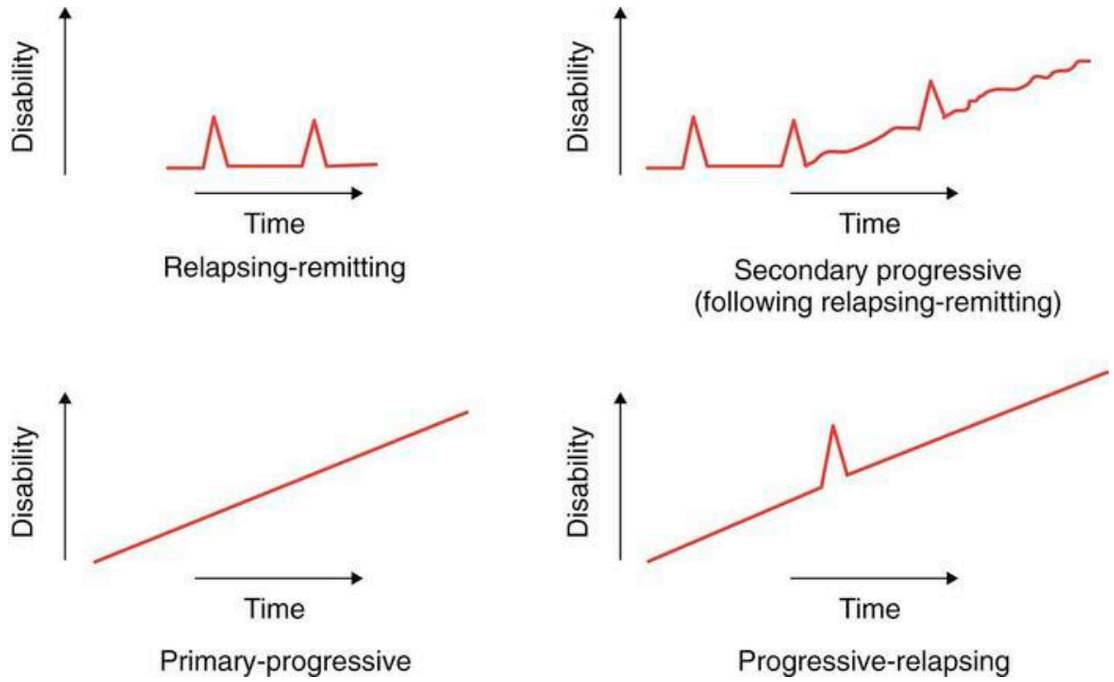



Main Symptoms of Multiple Sclerosis
Central
Fatigue
Cognitive Impairment
Depression
Visual
Nystagmus
Optic Neuritis
Diplopia
Throat
Dysarthria
Musculoskeletal
Weakness
Ataxia
Sensation
Pain
Paraesthesias
Hypoesthesias
www.Medical-Trip.com

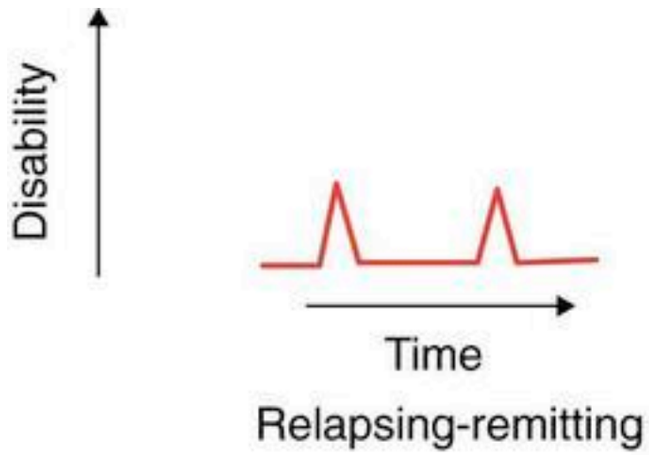
Clinical course

The course of the diseases is variable:

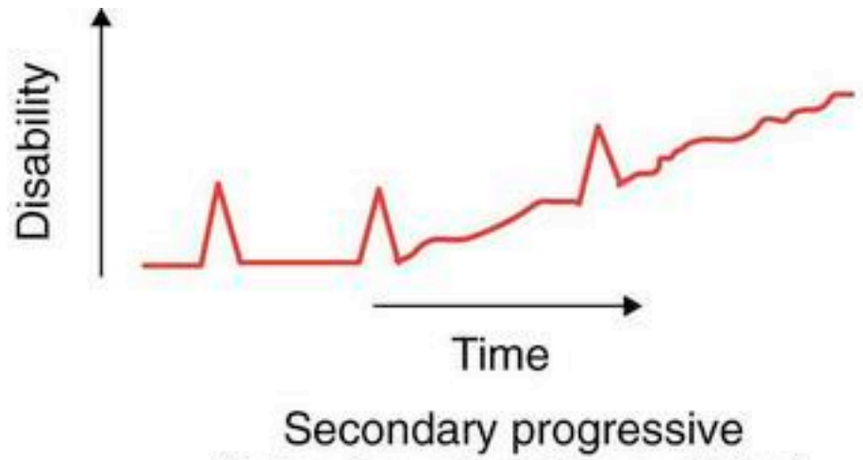
- 1. relapsing remitting means the patient will have symptoms (relapses) separated by periods of complete remission (normal, no symptoms)
- 2. Primary progressive: when symptoms start, the patient will have symptoms continuously without periods of remission, and the symptoms get worse with time.
- 3. Secondary progressive: disease starts as 1 above, but after sometime changes to pattern 2.
- 4. Progressive relapsing: like in 2, but at times symptoms get even worse.



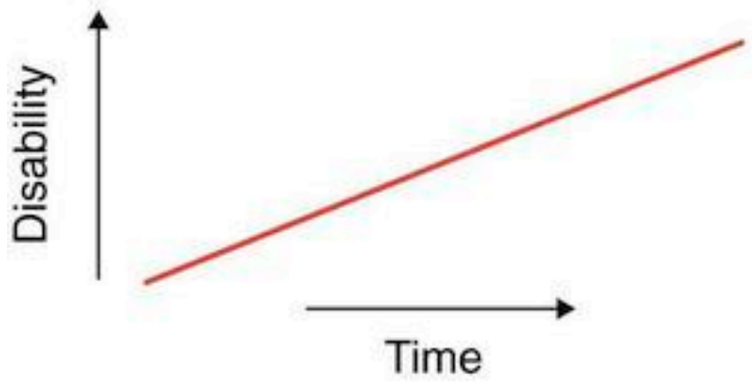
Clinical course: you cannot predict the course of the diseases in different patients. Only time will tell!



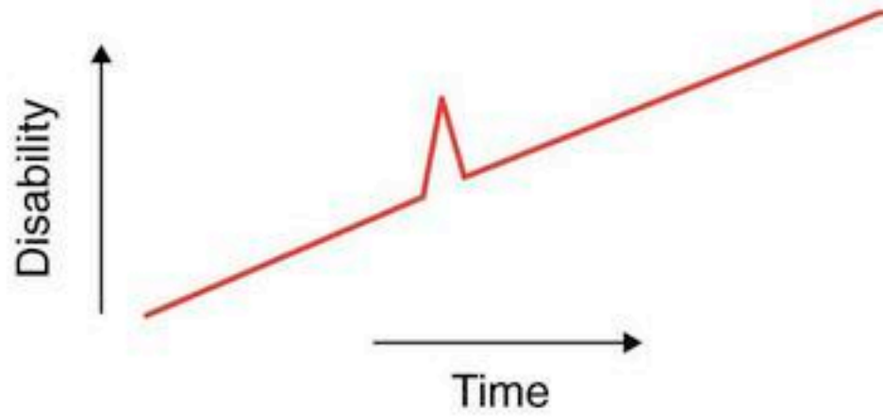
Relapsing-remitting



Secondary progressive
(following relapsing-remitting)



Primary-progressive



Progressive-relapsing

Disease outcome

Natural history of multiple sclerosis is defined 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.

Outcome

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.

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

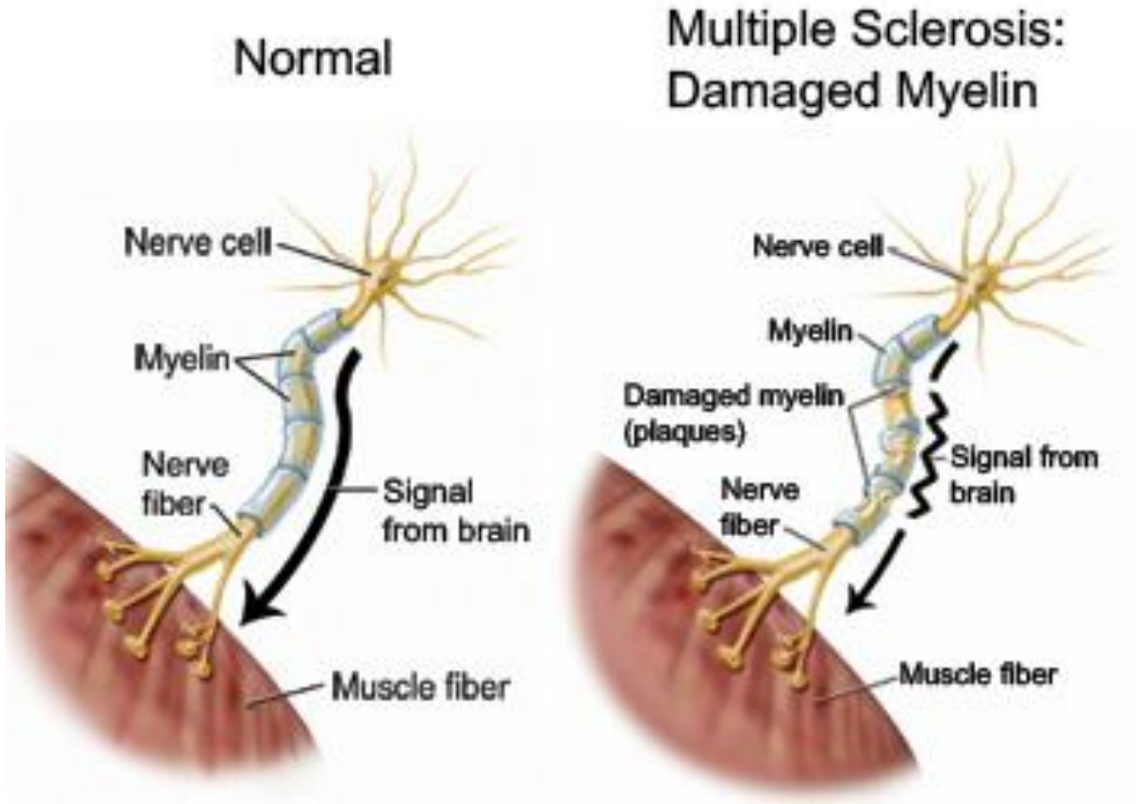
MS is 15 fold higher in first degree relatives

- 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.

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

- 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.

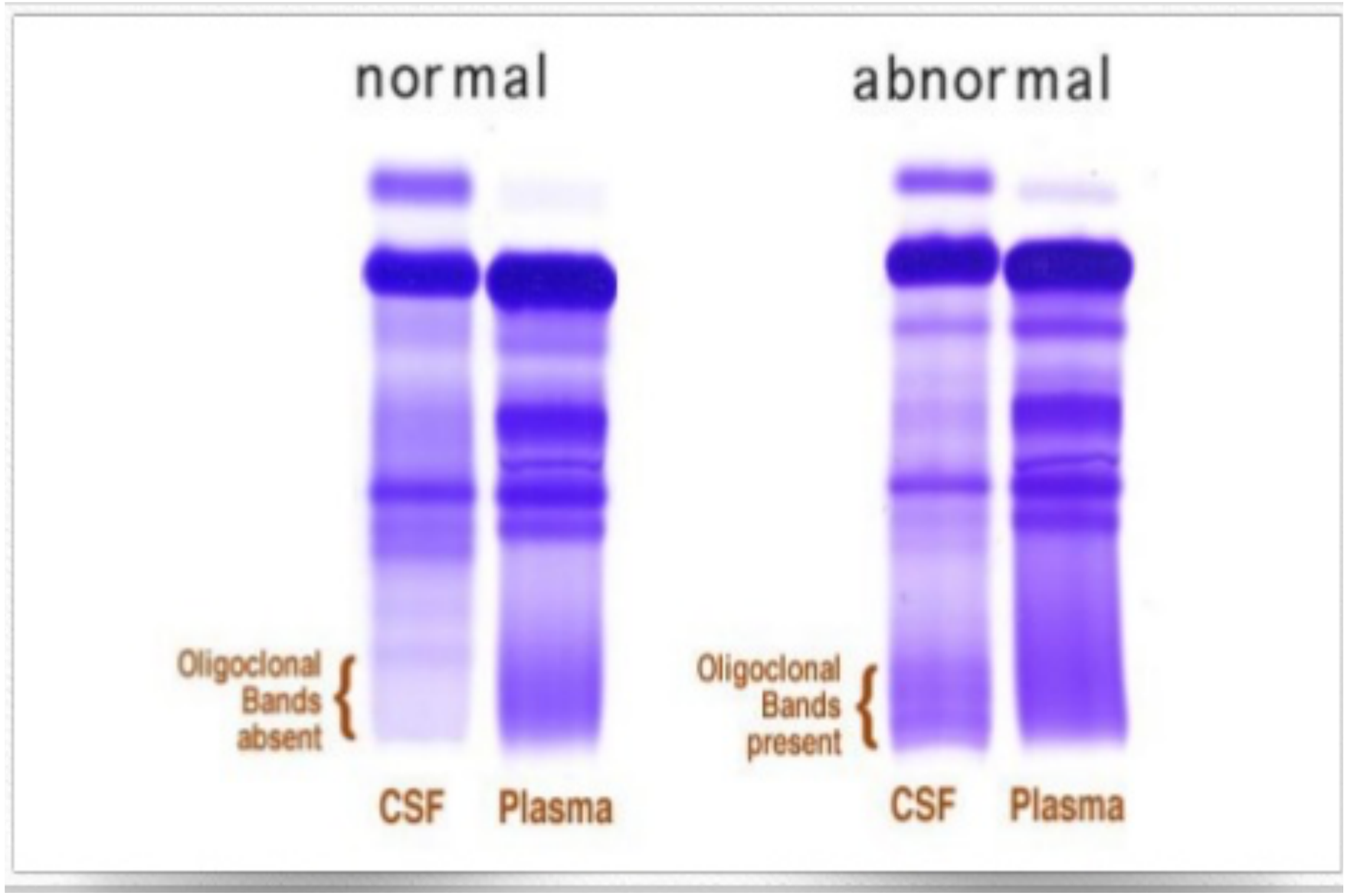
-In addition to demyelination; axonal damage can occur secondary to toxic effects from lymphocytes, macrophages and the chemicals they secrete.

- 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.

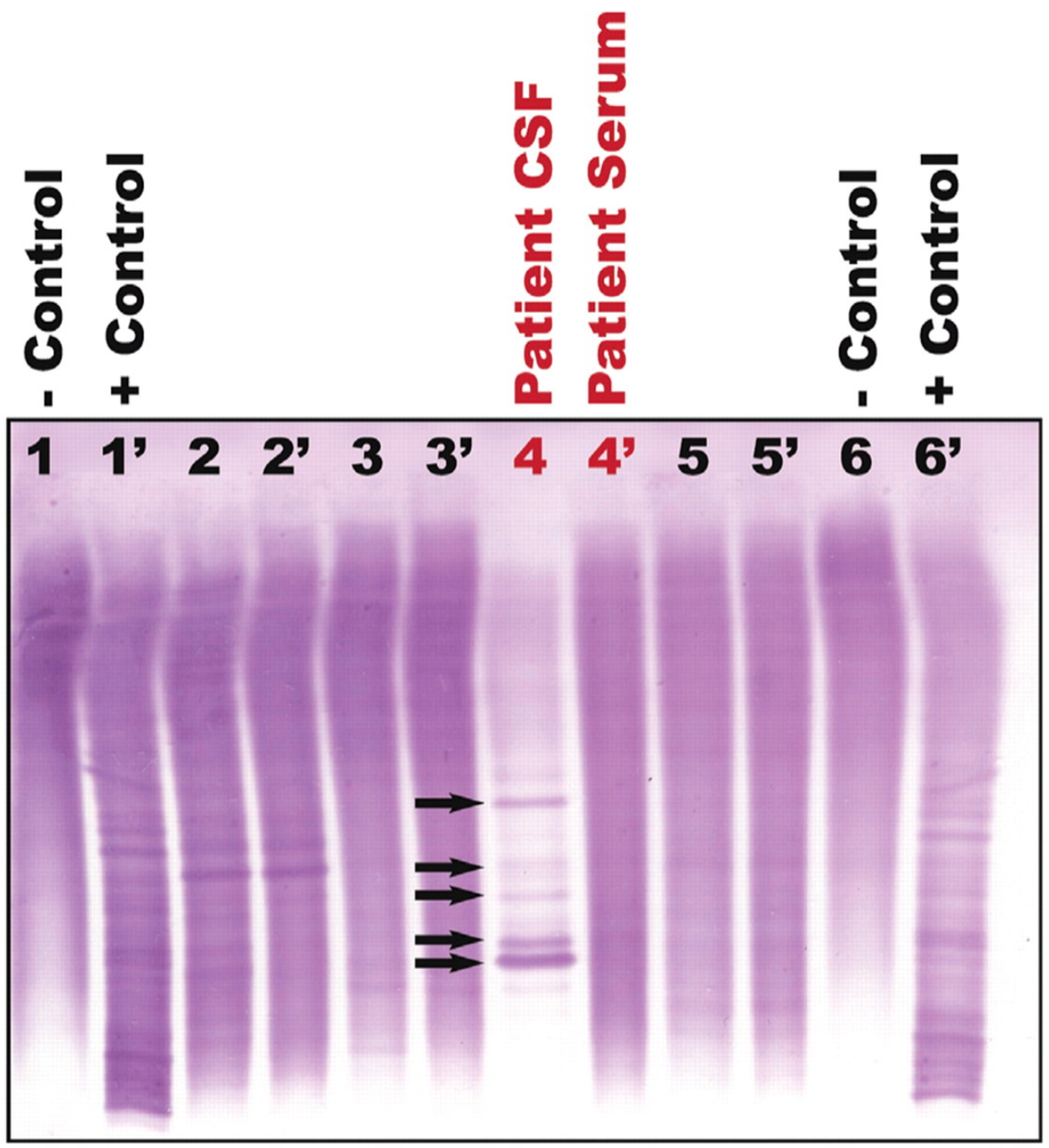
Oligoclonal bands

- 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.

Oligo-clonal bands in the CSF are used to diagnose MS



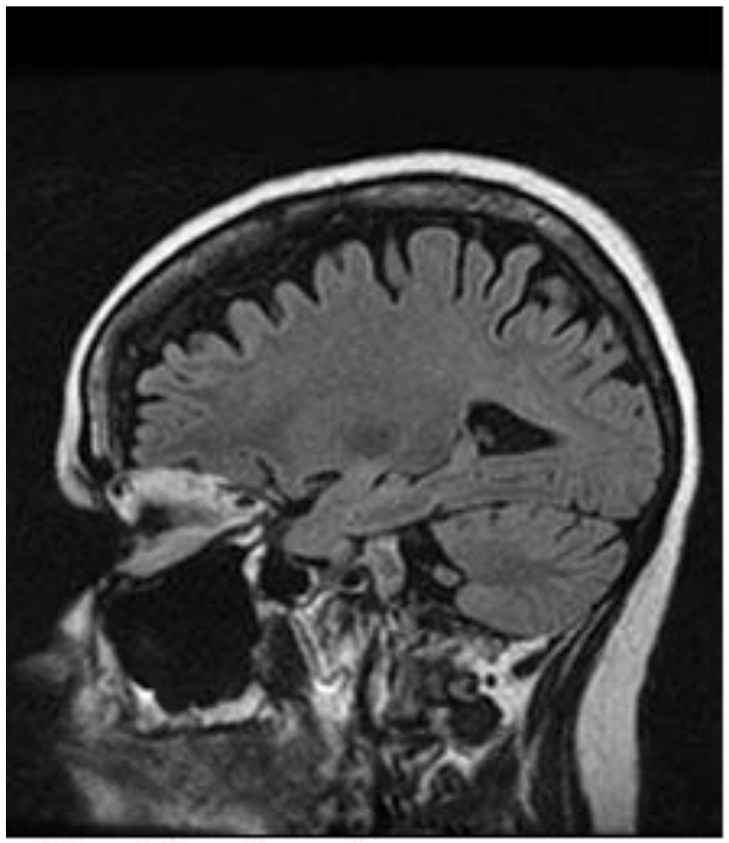
Arrows show bands present in CSF but not serum.



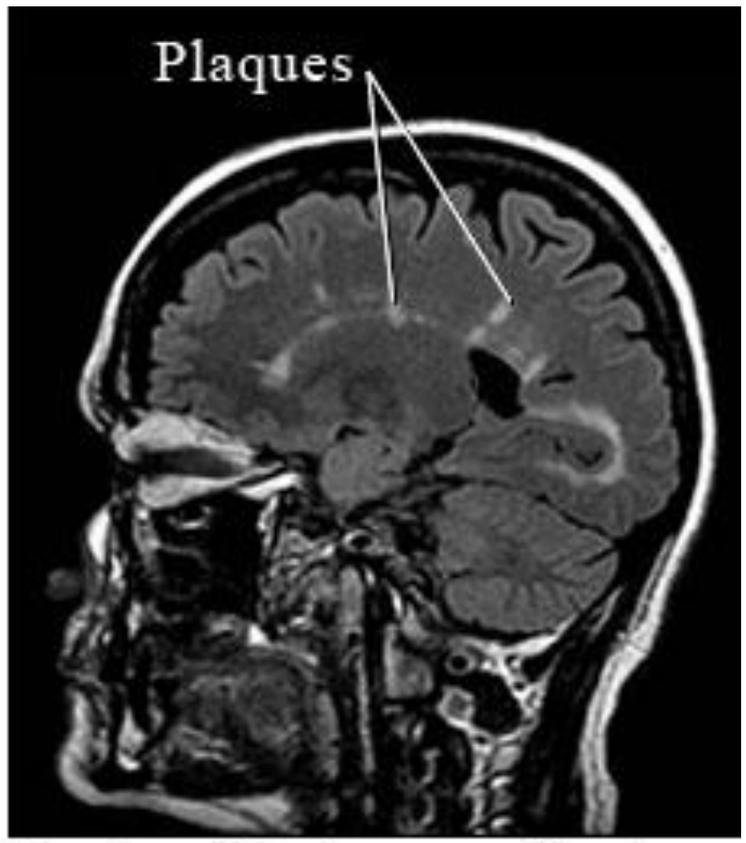
Morphology

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

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 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 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 T).

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.

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
- Survivals: 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 ***<u>sudden change in osmotic pressure</u>*** 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.**

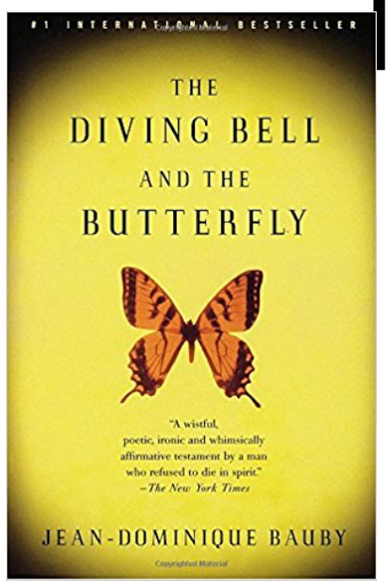
-locked-in syndrome is caused by damage in the ventral part of the pons due to pontine infarction, pontine hemorrhage, trauma, central pontine myelinolysis, tumor, or encephalitis.

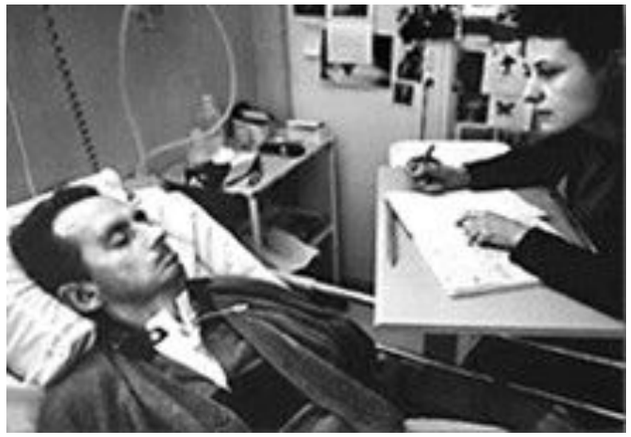
locked in syndrome

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.

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 publication.

Dysmylinating diseases

- = leukodystrophies
- Inherited diseases
- Most are autosomal recessive, some are X linked
- Caused by mutations in myelin proteins or the enzymes responsible for myelin turnover (balance between destruction and synthesis)
- They are a heterogenous group of disorders.

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

- The main pattern of myelin injury in the PNS is known as segmental demyelination.

- In these diseases myelin sheath breaks but the underlying axons remains viable.

- The demyelinating neuropathies are caused mainly by **hereditary causes or immune** destruction of myelin.

Segmental demyelination

- Occurs due to Schwann cell dysfunction which could be **primary** if the injury is related to Schwann cells or the myelin sheath or **secondary** if demyelination is due to underlying axonal abnormality.

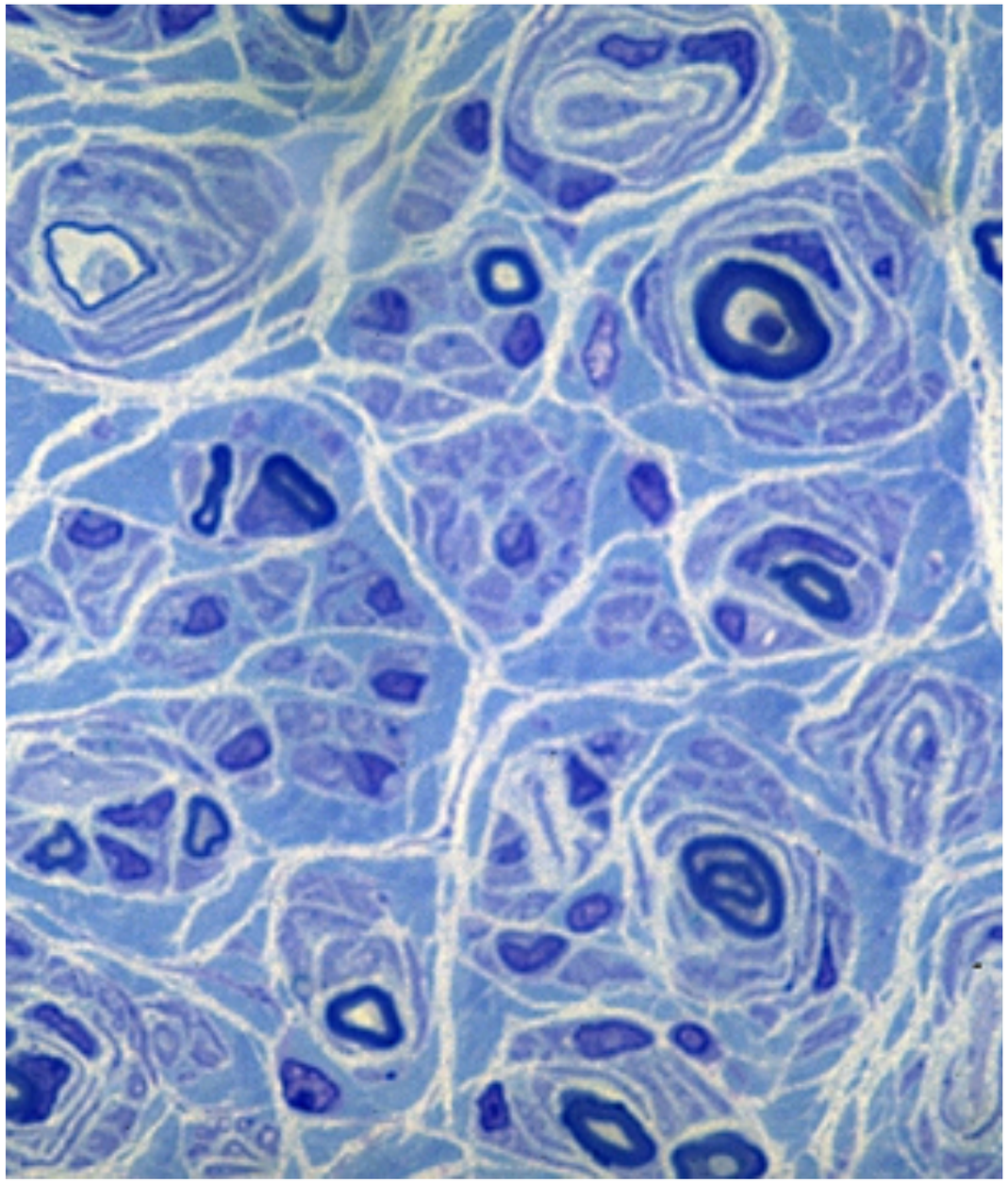
Segmental demyelination

- In these diseases **re-myelination occurs via proliferation of Schwann cells and function can be restored (depending on the extent of damage)**

- If there are repeated demyelination- re-myelination cycles, this will cause increased number of Schwann cells that encircle the axon causing enlarged nerves (**hypertrophic neuropathy**) and these are seen as **onion bulb** appearance under the microscope.

Onion bulb appearance

- This pic shows the thickened nerve fibres due to increased number of schwan cells after several cycles of de and re-myelination
- The appearance is termed: onion bulb
- It manifests clinically as hypertrophic neuropathy.



Guillian Barre syndrome

- Is an ***autoimmune neuropathy.***
- Often follows bacterial, viral or mycoplasma infection
- Can follow immunization or surgery
- Most commonly after Campylobacter jejuni, CMV, EBV
- CSF: increased proteins and few WBC
- **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**

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.

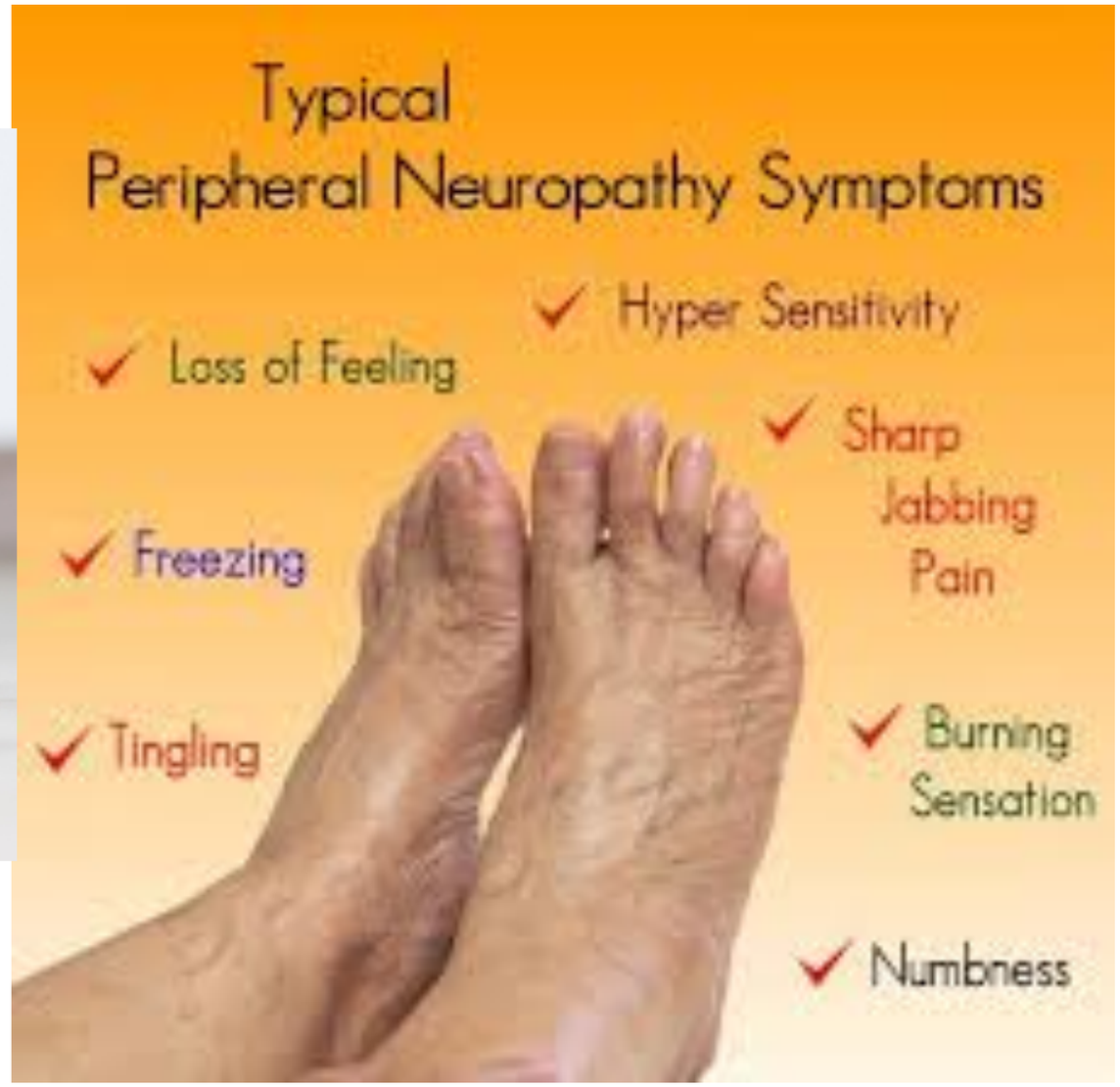
Peripheral neuropathies

- This is a process that affects the function of one or more of the peripheral nerves.
- Neuropathies can be due to **axonal degeneration or segmental demyelination.**
- As such they are divided to : axonal neuropathy or demyelinating neuropathy
- 80-90% of neuropathies are axonal

Clinical features

- The symptoms are related to impaired function of the damaged nerve, these include:
- Muscle weakness and atrophy
- Sensory loss
- Pain
- Parasthesia = any abnormal sensation including numbness, tingling, pricking, or burning sensation with NO physical explanation of the sensation
- autonomic dysfunction which might include loss of bowel and bladder control.

Clinical features of neuropathy



Causes of peripheral neuropathies

- The demyelinating neuropathies are caused mainly by hereditary causes or immune destruction of myelin.
- Axonal neuropathies have a very diverse list of causes. Any disease process that affects the nerves or their blood supply can cause axonal neuropathy.
- **The most common cause of generalised peripheral neuropathy is diabetic neuropathy**
- Other causes include: hereditary, alcoholism, chronic renal failure, neurotoxic drugs, autoimmune diseases, nutritional deficiencies, vasculitis, infections, tumours , trauma and amyloidosis. So : any toxins , infections, or infiltrative disease process or vascular disease can affect the nerve and cause neuropathy.

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.
- 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:
- 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
- 3. **Lumbosacral** neuropathy causing pain in lower legs.

Symptoms of peripheral diabetic neuropathy

- Numbness or reduced ability to feel pain or temperature changes
- Tingling or burning sensation
- Sharp pains or cramps
- Increased sensitivity to touch — for some people, even the weight of a bedsheet can be painful
- Muscle weakness
- Loss of reflexes, especially in the ankle
- Loss of balance and coordination
- Serious foot problems, such as ulcers, infections, and bone and joint pain

Pathogenesis of diabetic peripheral neuropathy

- Increased glucose in diabetics damages the nerves by two ways:
- 1. formation of advanced glycated end products that damage small blood vessels supplying the nerves. This results in ischemic damage to the nerves.
- 2. changes in polyol pathway resulting in increased sorbitol and decreased NADPH and reduced glutathione, this results in direct nerve damage.

1. Advanced glycation end products (AGE)

- AGE: formed by nonenzymatic interaction between glucose derived precursors and the amino groups on the proteins.

- So: glycated proteins are formed.

- These glycated proteins have receptors (RAGE) which are present on macrophages, T lymphocytes, endothelial cells and vascular smooth muscle cells.

- Interaction between AGE and RAGE causes several effects..

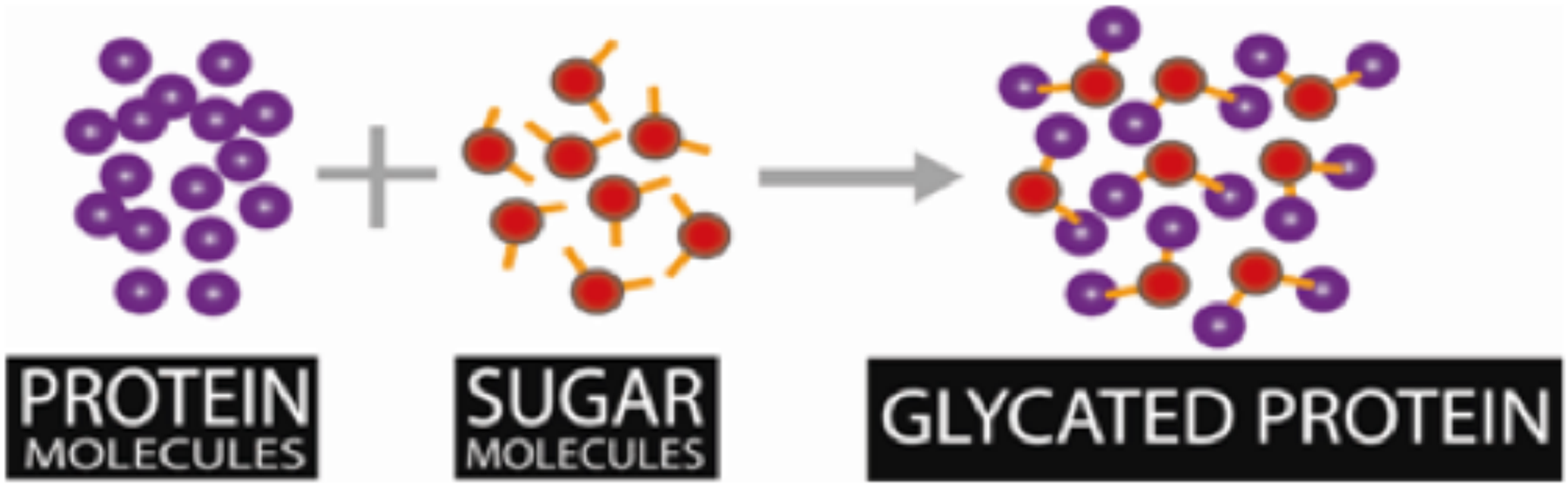
AGE- RAGE interaction effects

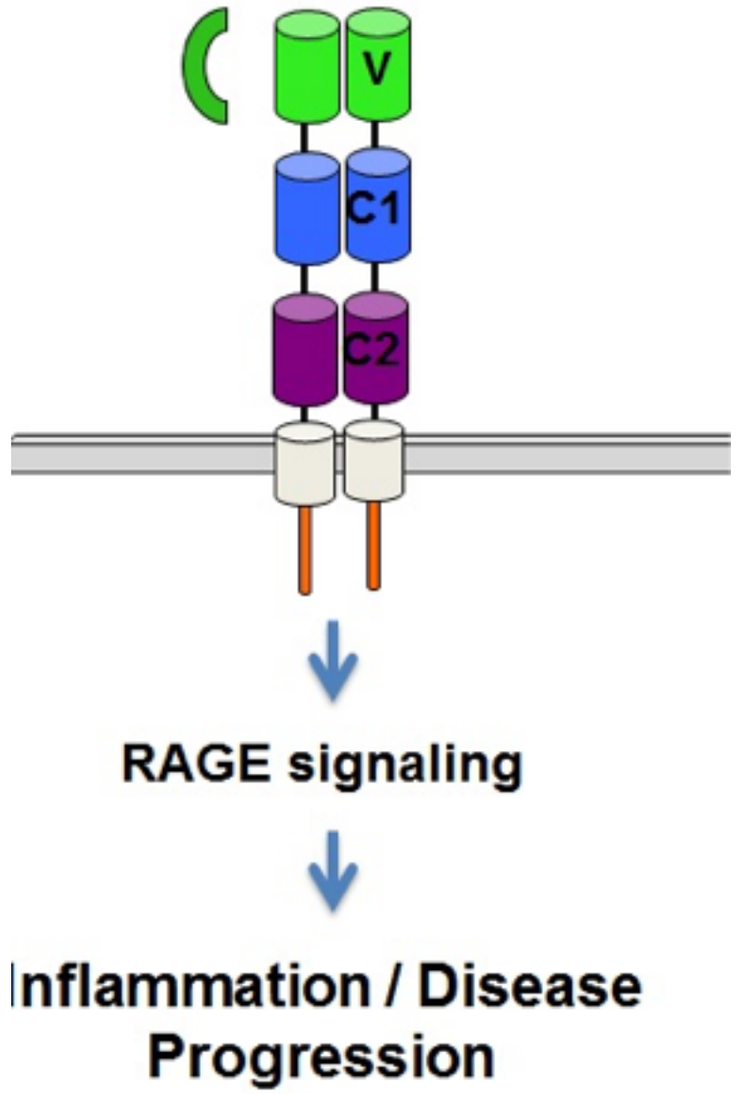
1. Formation of reactive oxygen species (ROS).. Causing tissue damage
2. Cytokines and growth factors formation
3. Procoagulant activity
4. Proliferation of smooth muscle cells and Increased extracellular matrix.

2-4 above cause thickening of the vessel wall. This is called microangiopathy because it affects small vessels like those innervating nerve endings.

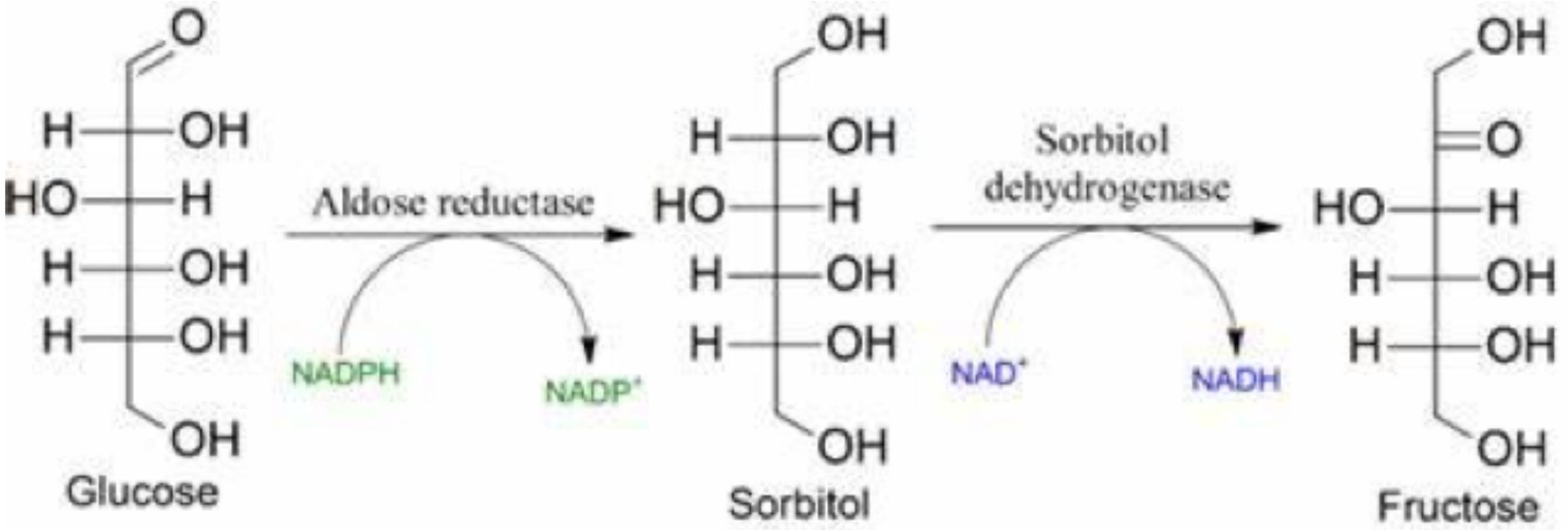
Microangiopathy causes ischemia to the nerves and ischemic damage.

AGE




V
C1
C2
RAGE signaling
Inflammation / Disease
Progression

2. Polyol pathway



- The polyol pathway is a two-step reaction that metabolises glucose to sorbitol then to fructose.

- In DM, glucose is increased and this pathway is activated.

- Sorbitol cannot cross the plasma membrane so it accumulates in cells causing increased osmotic pressure, so water enters cells resulting in edema and damage.

- Also the polyol pathway uses NADPH,, so less NADPH is available to reduce glutathione. Reduced glutathione is an important antioxidant, when it decreases oxidative stress in cells increases resulting in damage in the neurones.

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.
- Although MS is a diseases of myelin, with time and with recurrent immune and inflammatory response, axonal damage can occur.

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.

Summary 3/3

- In the PNS: Segmental demyelination can be primary or secondary to axonal damage
- Chronic, repeated de and re-myelination cause hypertrophic neuropathy due to increased Schwann cells. this is seen as onion bulb under EM.
- Axonal neuropathies occur due to any disease affecting the nerve: vessel diseases causing ischemic damage, infiltrative diseases, tumours…
- Demyelinating neuropathies 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 gliosis. Astrocytes are the main cells responsible for this.

thank you!