CNS pathology
Third year medical students

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Lecture 2: neuropathies

ILOS

- 1. To understand patterns of peripheral nerves' response to injury.
- 2. to list types of axonal degeneration and know their differences
- 3. to know the clinical features of peripheral neuropathies.
- 4. to understand the diverse causes of axonal neuropathy and have an idea of types of neuropathies in DM
- 5. to have an idea about Guillian Barre syndrome as a prototype of demyelinating neuropathies.

Peripheral nervous system

- As you know, the CNS is composed of the brain and the spinal cord.

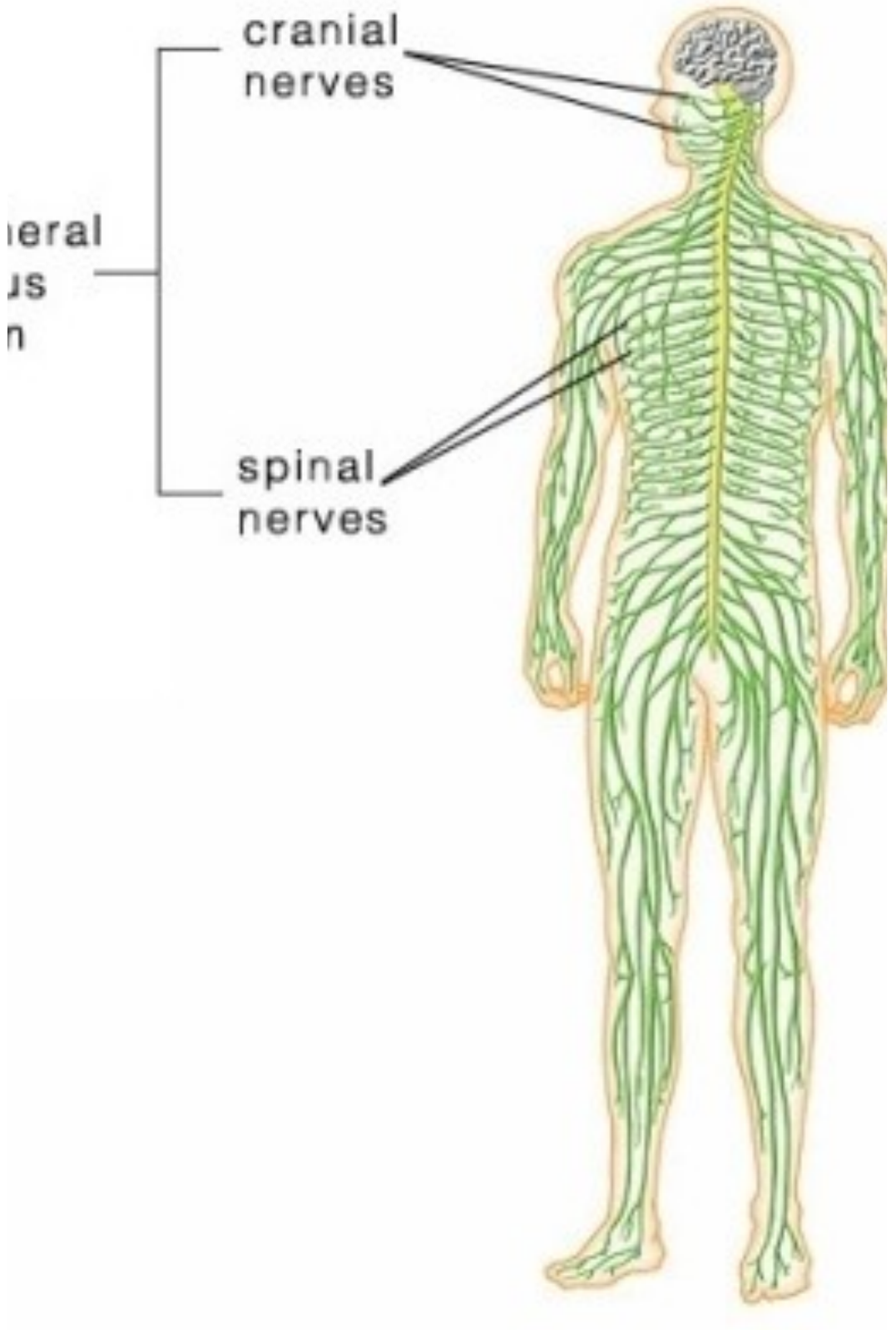
- Any neural tissue present outside the brain and the spinal cord is called peripheral nervous system (PNS).

- PNS includes: spinal roots, spinal nerves and their branches, ganglia, and the cranial nerves III to XII

- The cranial nerves will be covered in the anatomy and physiology lectures, so we will not discuss them here.

PNS

the picture shows the network of nerves that constitute the majority of the PNS



Peripheral nerves' response to injury

- peripheral nerves have limited patterns of response to injurious stimuli, the main patterns are :

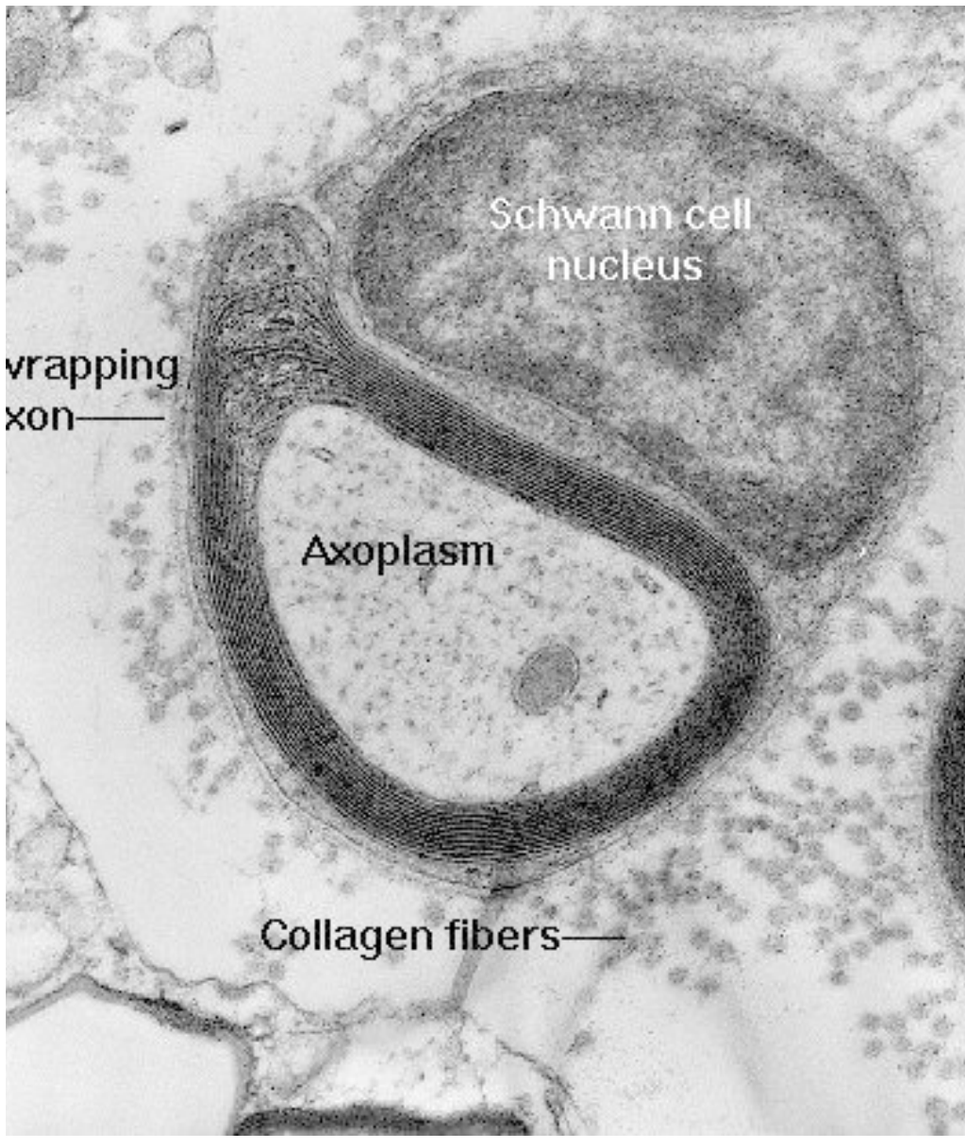
- **Axonal degeneration**: here the axon of the nerve becomes necrotic.

- **Segmental demyelination**: here the myelin sheath is degraded while the underlying axon is normal.

- Sometimes both patterns coexist, but one might predominate.

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

- Peripheral Neuropathy can result from damage to the axon or to the myelin.



Axonal degeneration

- Reflects injury to axons or involves both the axons and neuronal cell bodies.
- if only distal axons affected (i: e cell bodies are not affected) , regeneration is possible and starts a week after injury.
- **Types of axonal degeneration**:

- 1. Distal axonal degeneration= distal neuropathy. the neuronal cell body is spared (not affected) so if the underlying cause is removed regeneration and restoration of nerve function occurs.
- 2. ***Neuronopthies***: the neuronal ***cell body*** is damaged. Recovery is impossible because cell bodies do not regenerate.
- 3. Wallerian degeneration.. this occurs after trauma to a nerve. this process is very important for repair after trauma and we will discuss this in the next lecture.

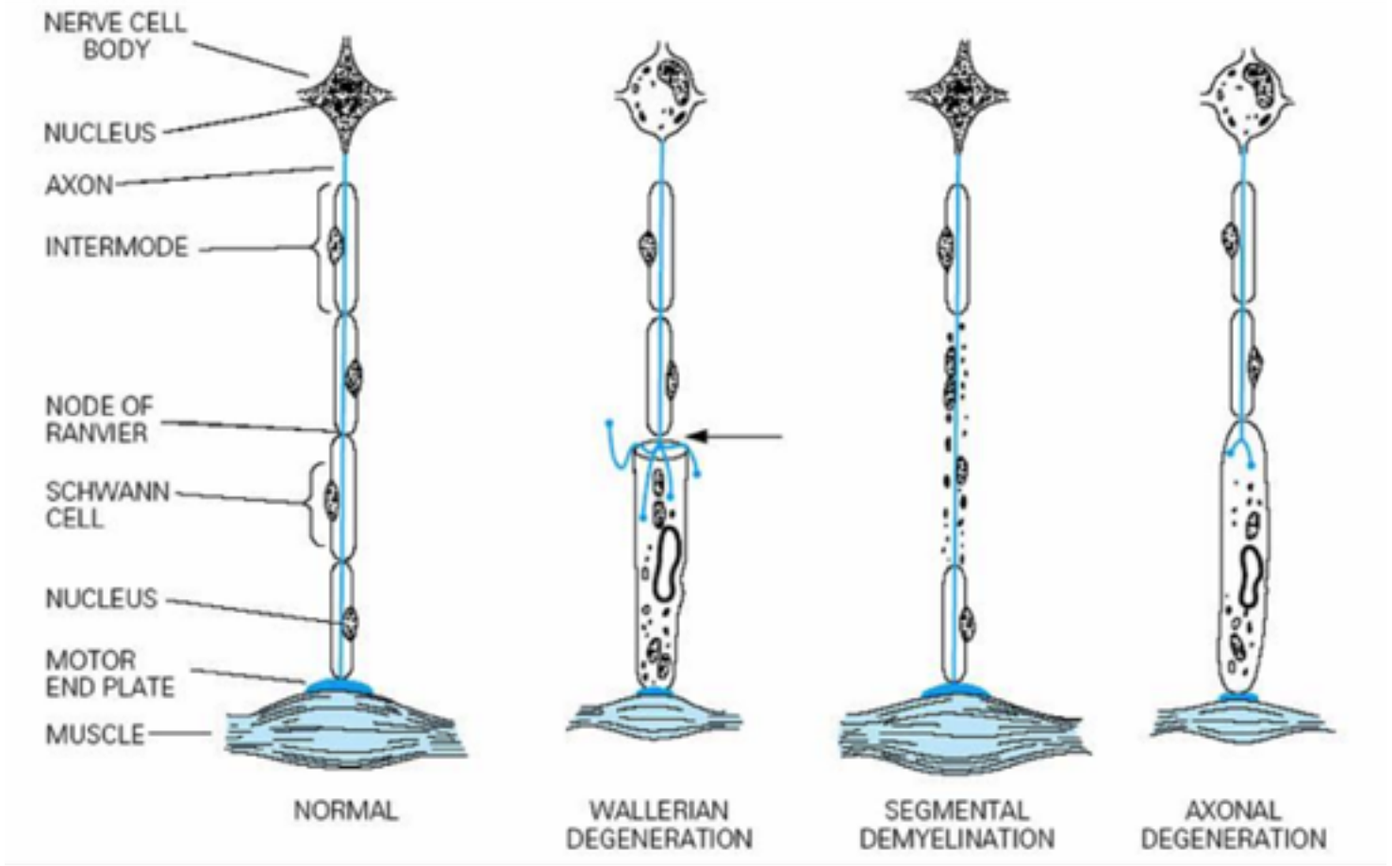
Don’t be confused!

- Please make sure you differentiate between neuropathy (a pathy in a nerve) and neuronopathy (the cell body of the neurone is affected) !!

- Neuropathy can be distal neuropathy: affecting the axon or myelin, or Proximal neuropathy: affecting the cell body= neuronopathy.

- Distal neuropathy is more commonly called peripheral neuropathy

types of neural response to injury



Segmental demyelination

- Myelin sheath breaks but the underlying axon remains viable.

- 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.

- *please note: axonal injury can secondarily affect the myelin sheath and cause myelin damage, whereas loss of myelin sheath doesn't cause degeneration of the underlying axon*.

Segmental demyelination

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

- we will discuss regeneration in more detail in the next lecture, don't worry

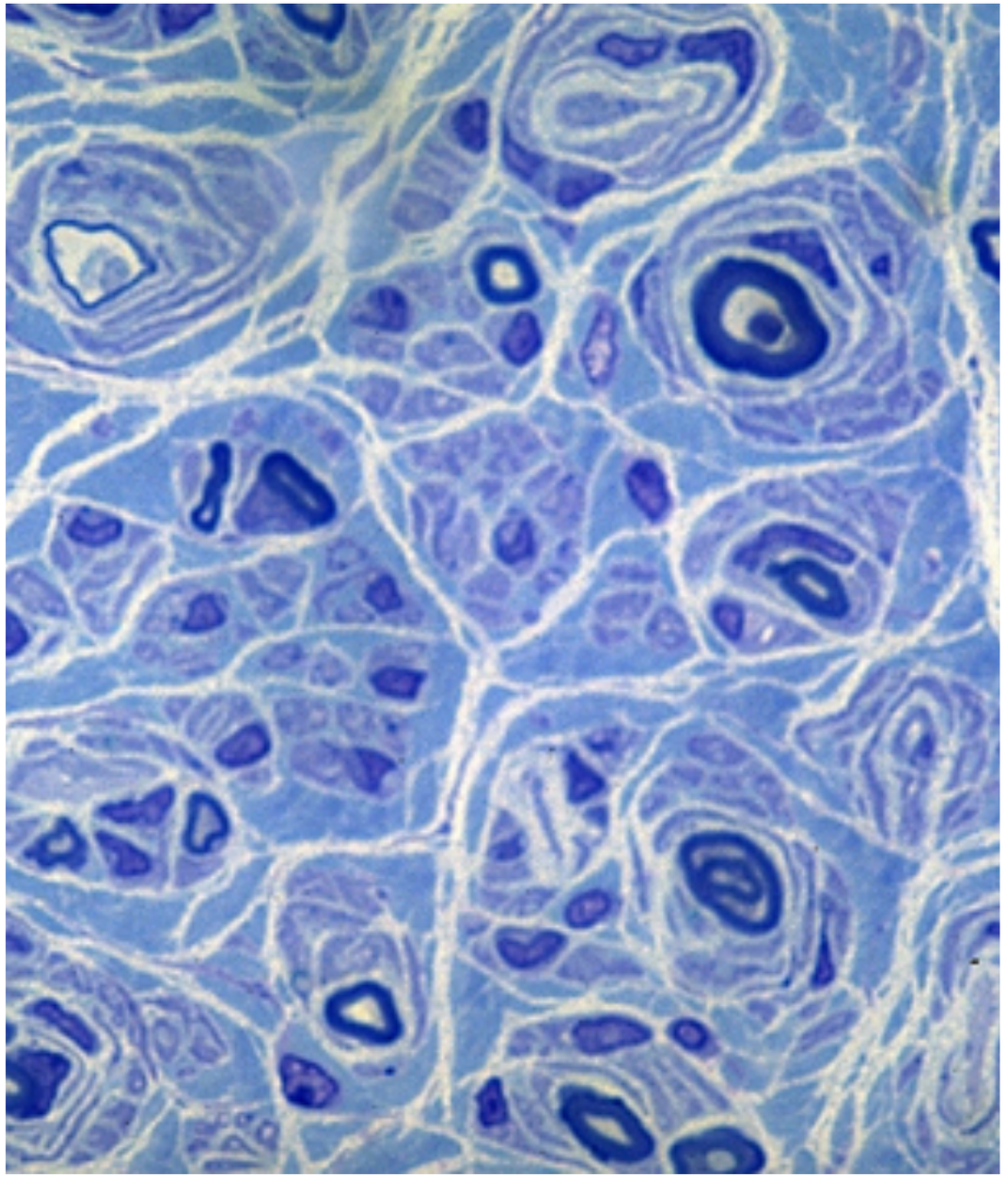
- if there are repeated demyelination- re-myelination cycles, this will cause increased number of Schwann cells that encircle the axon causing enlarged nerves (**hypertrophic neuropathy**) and these are seen as **onion bulb** appearance under the microscope.

Onion bulb appearance

- this pic shows the thickened nerve fibres due to increased number of scan cells after several cycles of de and re-myelination

- the appearance is termed: onion bulb

- it manifests clinically as hypertrophic neuropathy.



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

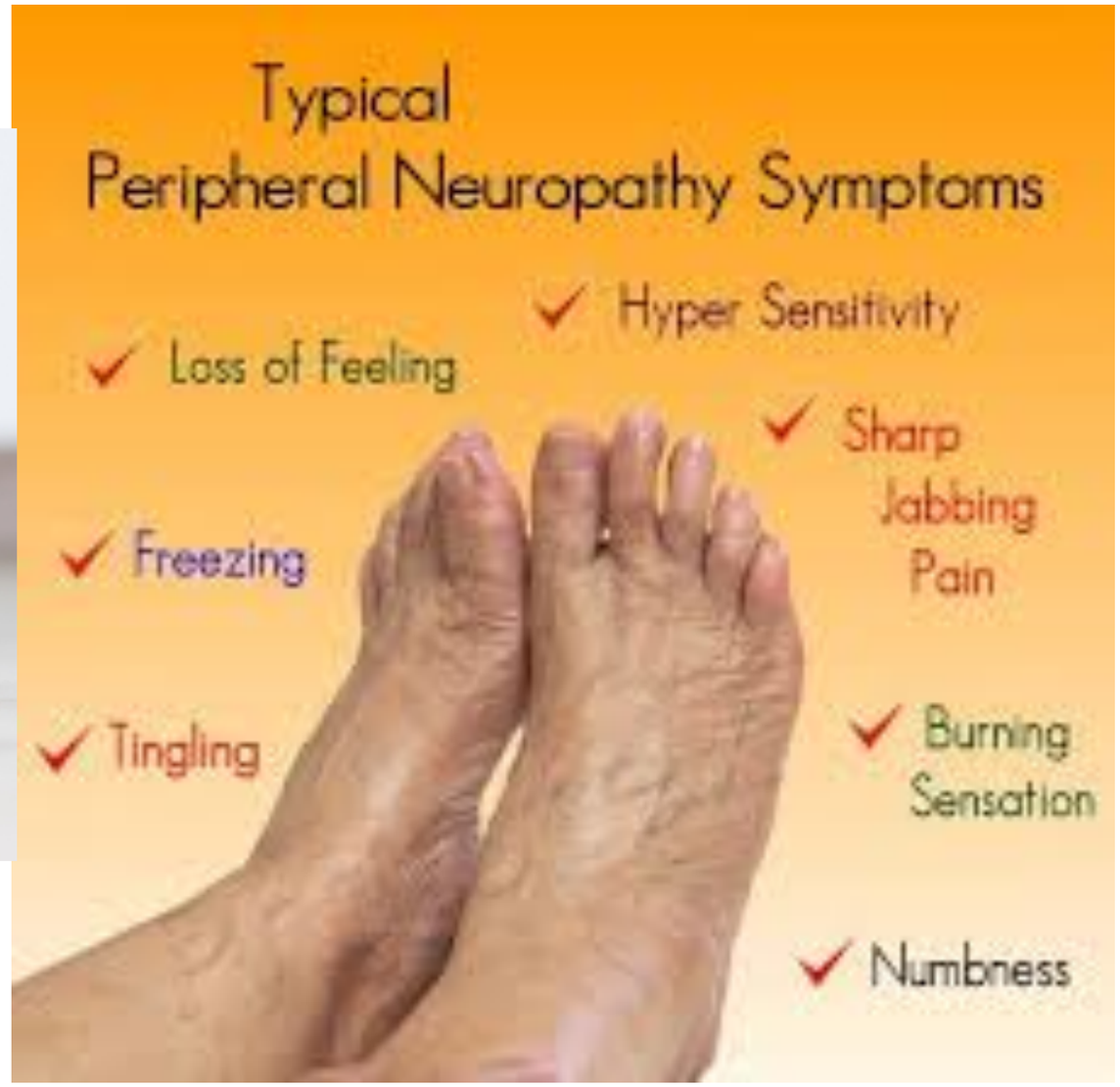
- Sensory loss

- 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.

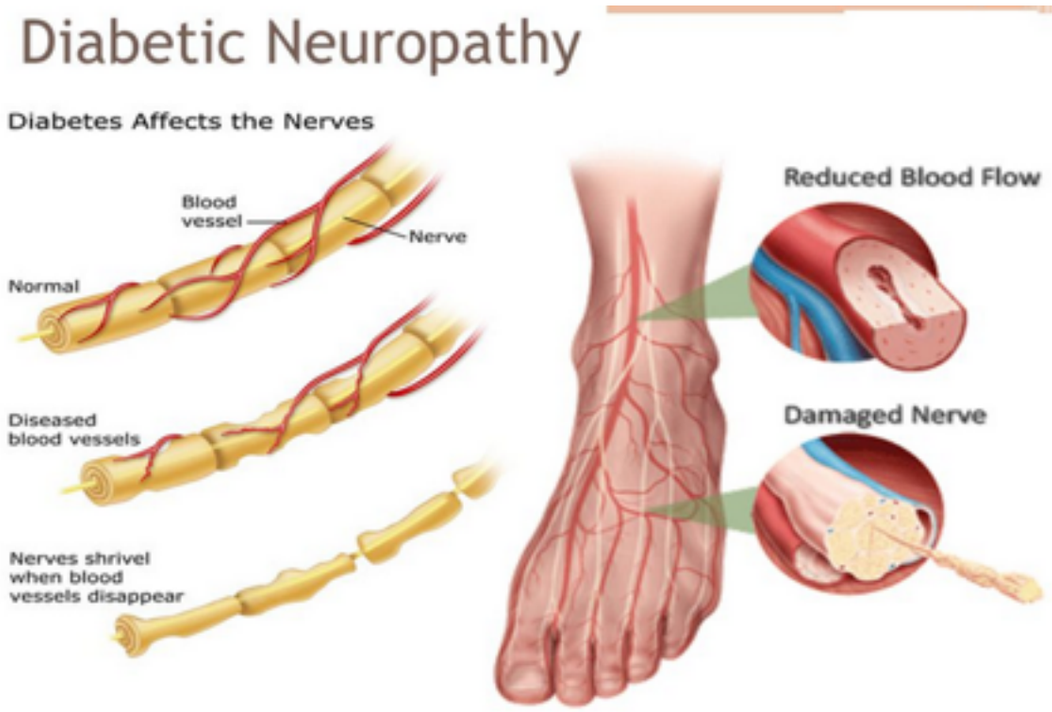
- **The most common cause of generalised peripheral neuropathy is diabetic neuropathy**

- 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

- can manifest as polyneuropathy or mononeuropathy
- Several forms of neuropathy can occur:
- 1. **distal symmetric sensorimotor polyneuropathy which is the most common form.**
- 2. **autonomic** neuropathy causing changes in bowel, bladder, or cardiac function
- 3. **Lumbosacral** neuropathy causing pain in lower legs.
- Mechanism of diabetic neuropathies :unknown, probably due to nerve ischemia because of small vessel disease

Diabetic neuropathy



main concepts/ a recap

- Because the causes of neuropathies are so diverse, please make sure you know the following concepts
- 1. there are two types of neuropathies, the demyelinating and the axonal neuropathies.
- 2. If the conduction velocity of the nerve is decreased then the patient has a demyelination problem.
- 3. if you decided that his problem is in the myelin then the cause is usually hereditary or immunologic.
- 4. Demyelinating neuropathies can be acute or chronic.
- 5. one of the most important immunologically mediated diseases that cause acute demyelinating neuropathy is Guillian Barre syndrome which we will discuss shortly.

main concepts/2

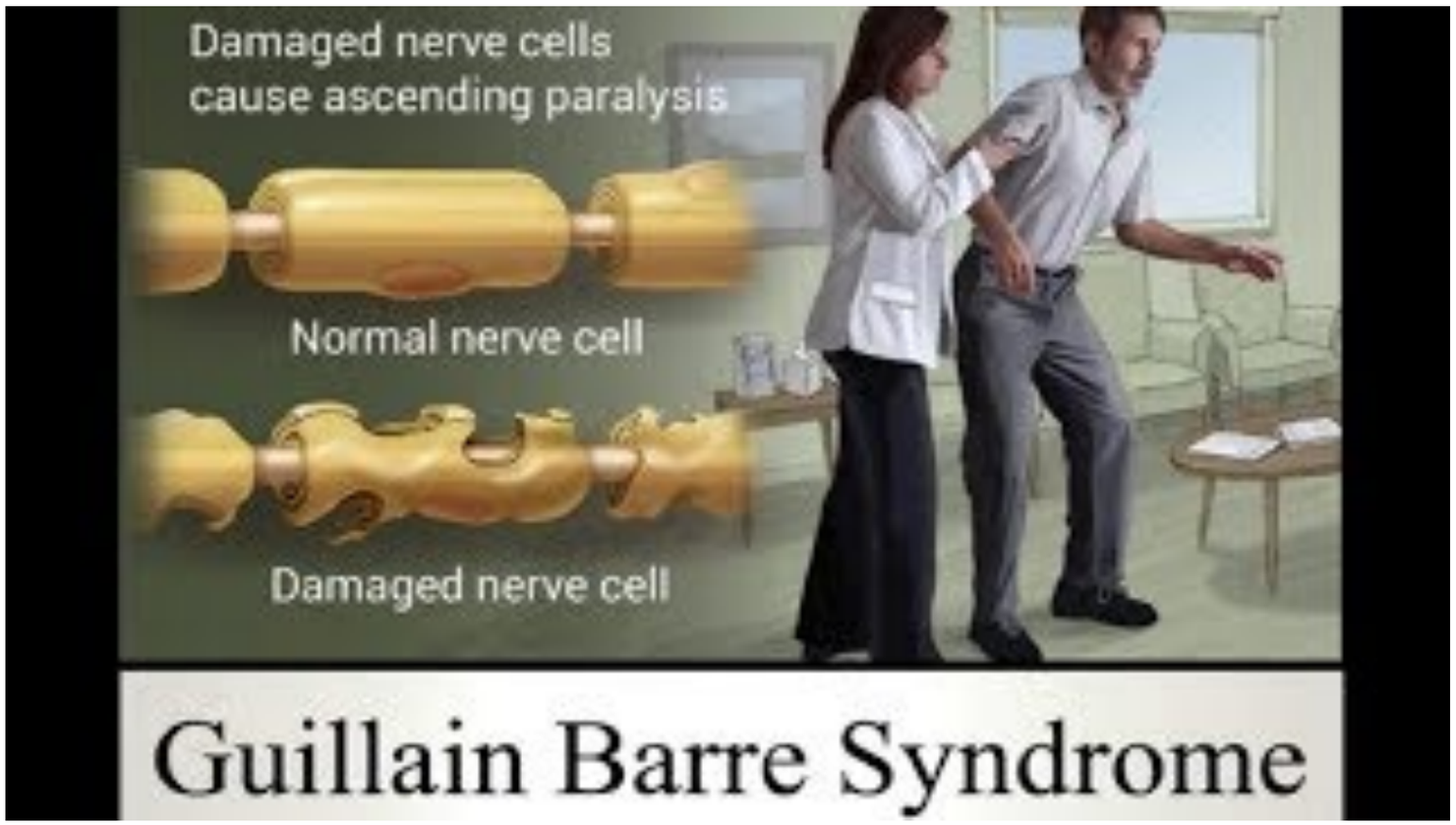
- 6. if the nerve conduction velocity is near normal, then the patient has an axonal neuropathy.
- 7. Any disease that affects the blood vessels supplying the nerve can damage the axon via ischemia. this occurs in DM and in vasculo-pathies like Wegener's granulomatosis or necrotising vasculitis or infectious vasculitis. Polyarteritis nodosa and SLE also can cause this.
- 8. Any systemic infiltrative disease which can infiltrate the nerve will also cause damage, this includes sarcoidosis and amyloidosis.
- 9.cancer can also infiltrate a nerve and damage it.
- 10. Trauma of a nerve can also be complicated by axonal damage resulting in neuropathy.
- 11. Certain toxins and nutritional deficiencies can damage the nerve and cause axonal neuropathy. Certain drugs can also do so.
- *NOTE: you don't have to memorise the list.. just understand that any disease process affecting the nerve can be complicated by neuropathy, which is usually axonal in type because neurones are more susceptible to injury than Schwann cells.*

Guillian Barre syndrome

- is an ***autoimmune neuropathy.***
- 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
- **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**


Damaged nerve cells
cause ascending paralysis
Normal nerve cell
Damaged nerve cell
Guillain Barre Syndrome

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.

exam style question

- A 5 year old boy was given a polio vaccine as part of an immunisation program. Several days later he told his mother he felt tingling sensation in his feet. 2 weeks after the vaccination his mother noted that he fell frequently while walking and after there weeks he was unable to walk and he dropped the spoon several times while eating. Which of the following statements best describes his illness?

- A. A nerve biopsy is expected to show onion bulb appearance if examined under the EM.

- B. the disease is treatable and doesn't need hospitalisation as it is not life threatening

- C. CSF examination will show increased proteins and numerous white blood cells

- D. The tingling sensation can not be explained by the disease process because his illness affects motor nerves exclusively.

- E None of the above

Explanation of the question

- All statements are incorrect
- A. is incorrect because onion bulb reflects several episodes of de and re- myelination. this occurs in chronic demyelinating diseases and Gullian Barre is an acute illness
- B. Wrong because involvement of respiratory muscles can be fatal
- C. CSF shows increased proteins but few WBCs
- D. Although the symptoms are mainly motor, sensory or autonomic nerve fibres can be affected

Summary 1/2

- Neurones respond to injury by : axonal degeneration or segmental demyelination
- Axonal degeneration has three types: distal axonal degeneration which is the commonest, neuronopathy where the degeneration involves the cell bodies, and wallerian degeneration which occurs following trauma.
- Segmental demyelination can be primary or secondary to axonal damage
- neuropathies are a group of diseases that cause damage in the neurones. they can be acute or chronic and can be divided into axonal or demyelinating types depending on the dominant pattern of injury although both do exist in some situations
- Chronic, repeated de and re-myelination cause hypertrophic neuropathy due to increased Schwann cells. this is seen as onion bulb under EM

summary 2/2

- Axonal neuropathies occur due to any disease affecting the nerve: vessel diseases causing ischemic damage, infiltrative diseases, tumours…
- the most common cause of neuropathy is DM which can cause autonomic, lumbosacral or sensorymotor neuropathies. the latter is the most common
- 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.

GOOD LUCK