Peripheral Nervous system Pathology

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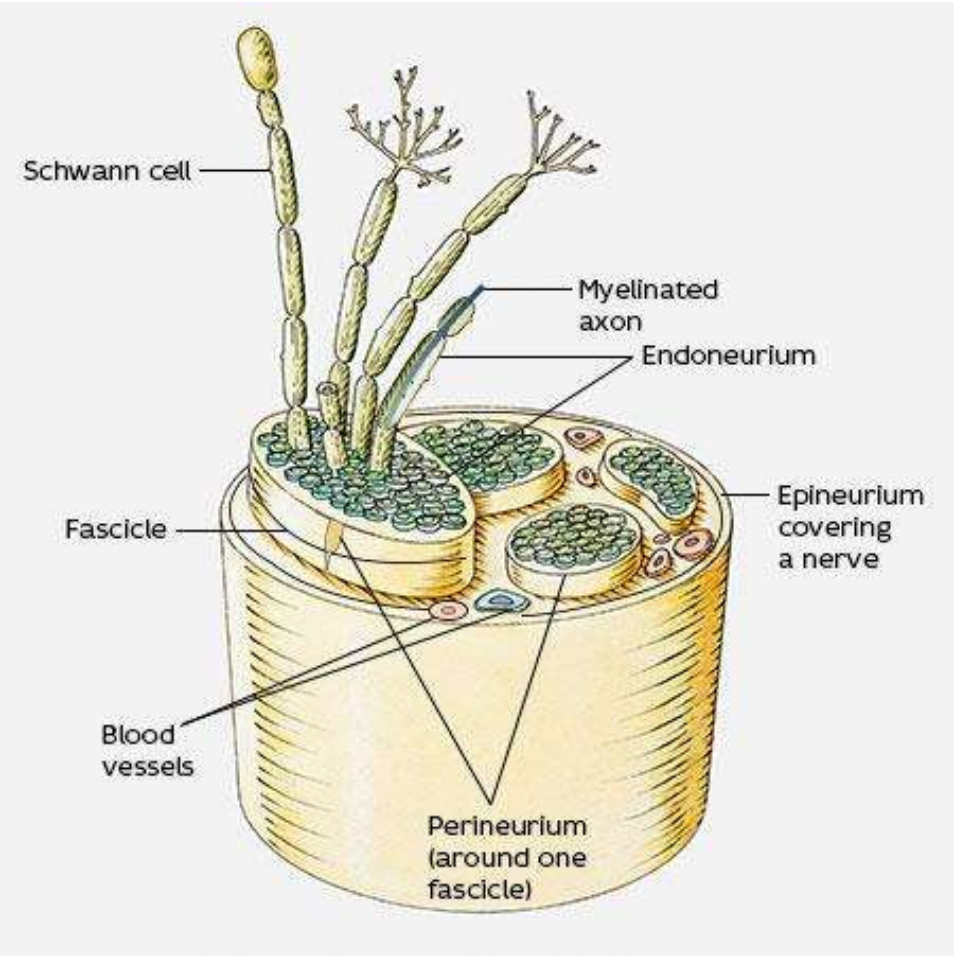


Axons are bundled
together by three major connective tissue components: + the *epineurium*: encloses the entire **nerve**.
+ the *perineurium*:
a multilayered concentric
connective tissue sheath
that groups subsets of axons into **fascicles**.
+*endoneurium*: surrounds
individual nerve **fibers**

Peripheral neuropathies are subclassified as:

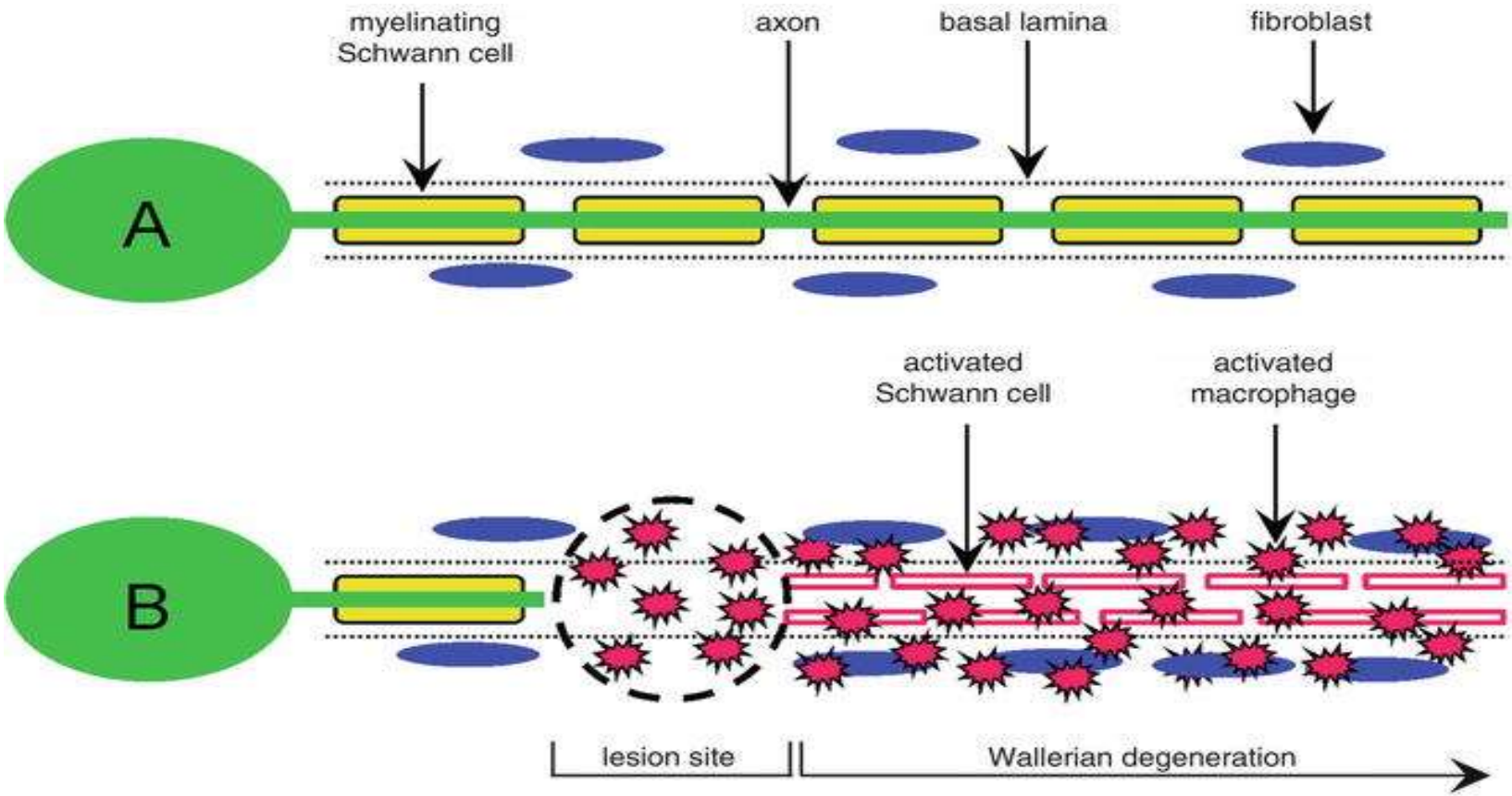
Axonal neuropathies:

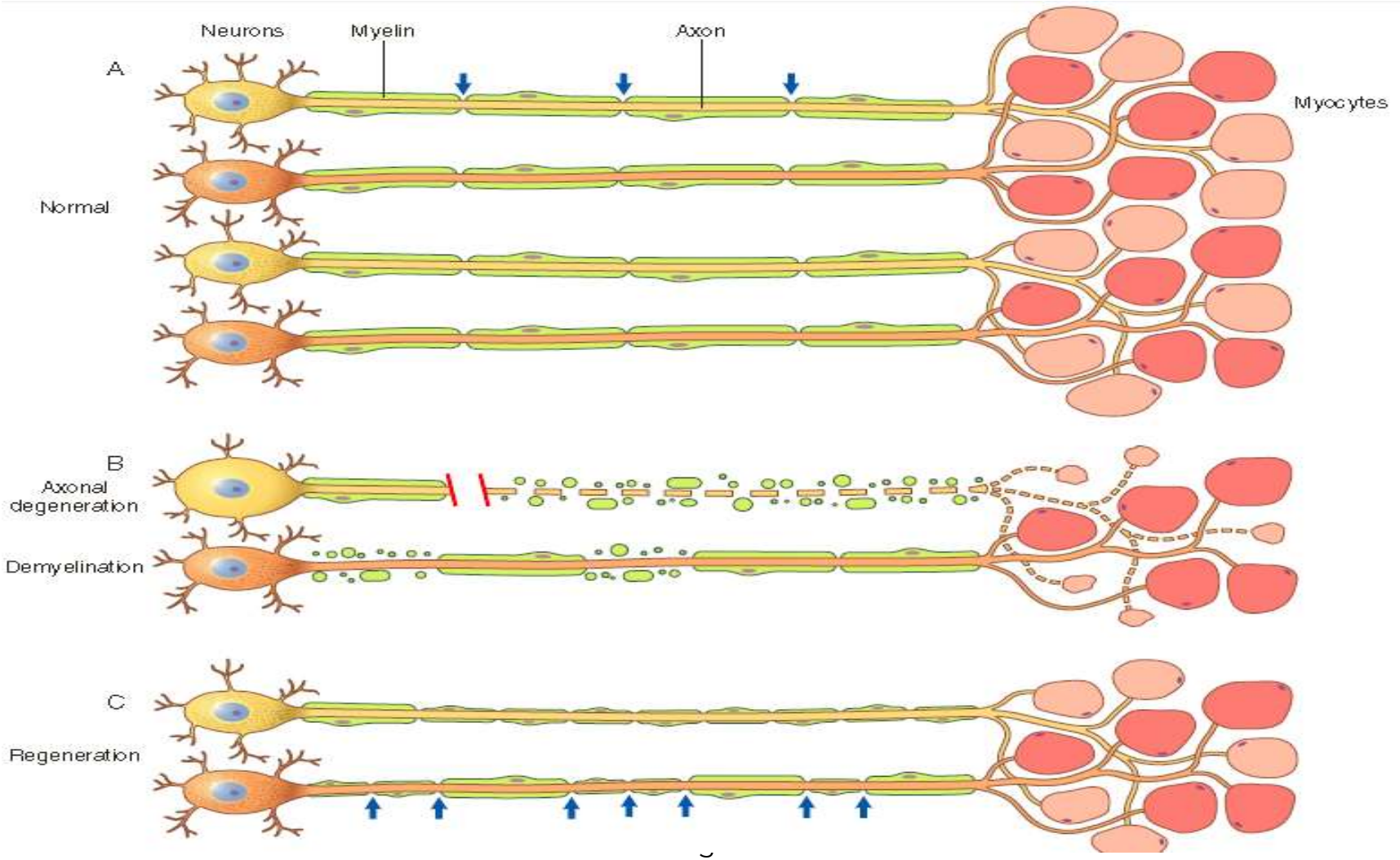
Caused by insults that directly injure the axon. The entire **distal** portion of an affected axon degenerates. Secondary myelin loss can happen . **(Wallerian degeneration**)

Demyelinating neuropathies

Damage to Schwann cells or myelin with relative axonal sparing.

Typically occurs discontinuously → **segmental demyelination**


myelinating
Schwann cell
axon
basal lamina
fibroblast
A
activated
Schwann cell
activated
macrophage
B
lesion site
Wallerian degeneration


Neurons
Myelin
Axon
A
Normal
Myocytes
B
Axonal degeneration
Demyelination
C
Regeneration

Axonal neuropathies

Regeneration takes place through axonal regrowth and subsequent remyelination of the distal axon, where the proximal stump of the axon sprouts and elongate.

The morphologic hallmark of axonal neuropathies is a decrease in the density of axons, which in electrophysiologic studies correlates with a decrease in the signal strength or amplitude of nerve impulses.

Demyelinating neuropathies

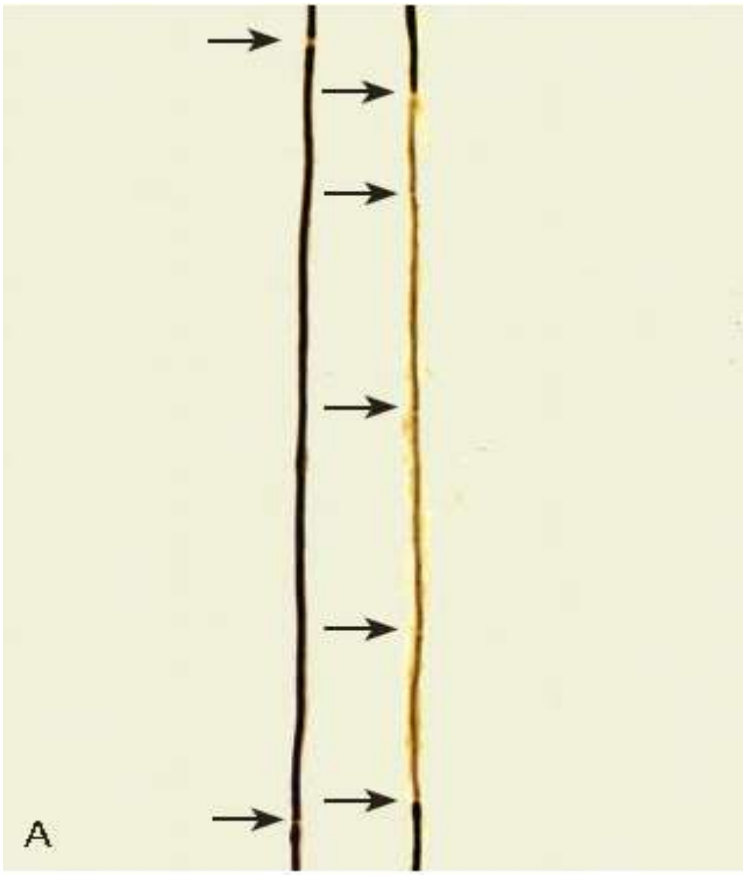
Segmental demyelination: affecting individual internodes along the length of an axon (while saving others) in a random pattern.

Resulting in slow nerve conduction velocities but preserved amplitude, with relatively normal density of axons.

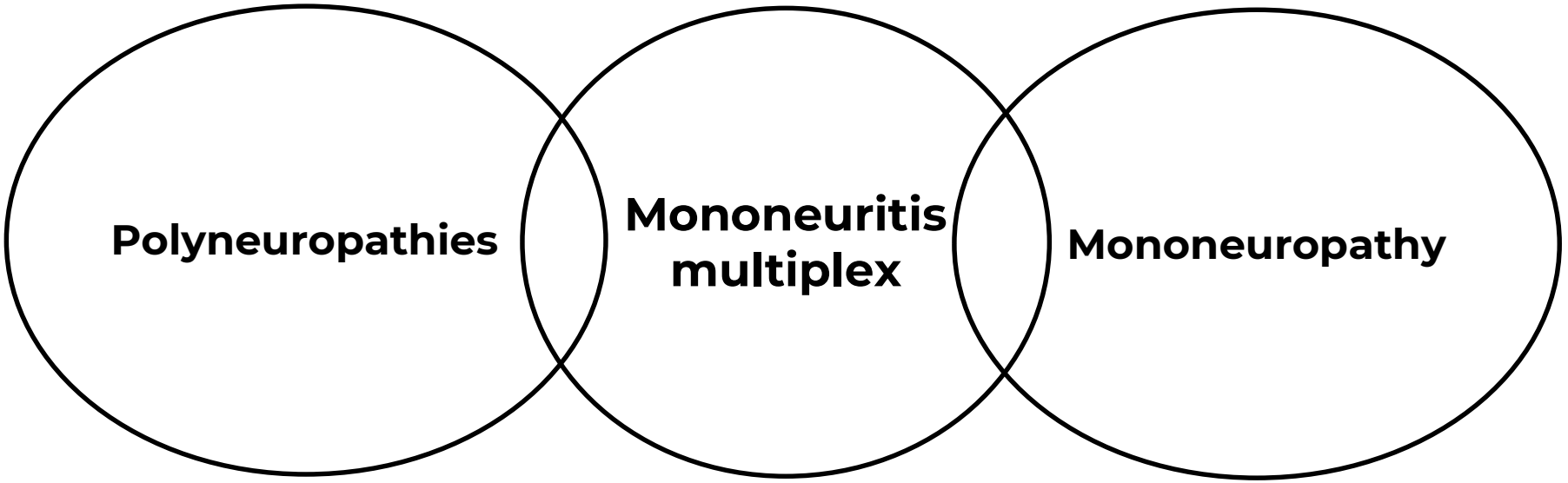
Demyelinating neuropathies

Denuded axon provides a stimulus for remyelination & cells within the endoneurium differentiating to replace injured Schwann cells.

Regeneration gives thinly myelinated internodes of uneven length (shorter).



Peripheral neuropathies anatomic patterns.



Polyneuropathies

A symmetrical multiple nerves involvement, length-dependent fashion;

Axonal loss is more pronounced in the distal segments of the longest nerves;

Patients present with loss of sensation and paresthesias that start in the toes and spread upward. “**stocking-and-glove**” distribution.

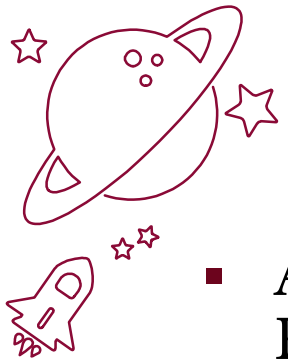
This pattern is often encountered with toxic and metabolic damage. (Diabetes mellitus)

Simple & multiplex Mononeuritis

Mononeuritis multiplex: the damage randomly affects individual nerves, resulting (eg. A right radial nerve palsy & wrist drop, & at a separate point in time, a left foot drop.) Often caused by vasculitis.

A simple mononeuropathy: only involves a single nerve & is most commonly the result of traumatic injury, entrapment (e.g., carpal tunnel syndrome), or certain infections such as Lyme disease.

Etiologic Category	Causative Disorders/Agents
Nutritional and metabolic	Diabetes mellitus Uremia Vitamin deficiencies—thiamine, vitamin B6, vitamin B12
Toxic	Drugs, including vinblastine, vincristine, paclitaxel, colchicine, and isoniazid Toxins—alcohol, lead, aluminum, arsenic, mercury, acrylamide
Vasculopathic	Vasculitis Amyloidosis
Inflammatory	Autoimmune diseases Guillain-Barré syndrome Chronic inflammatory demyelinating polyneuropathy (CIDP)
Infections	Herpes zoster Leprosy HIV infection Lyme disease
Inherited	Charcot-Marie-Tooth neuropathy, type I, type II, and X-linked Hereditary neuropathy with liability to pressure palsy
Others	Paraneoplastic, some leukodystrophies

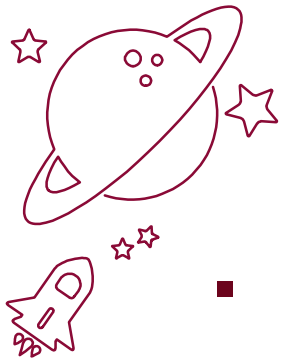


Guillain-Barré Syndrome

- A rare Acute Inflammatory Demyelinating Polyneuropathy.
- A rapidly progressive acute demyelinating disorder characterized clinically by weakness beginning in the distal limb→ rapidly advances to proximal muscle function → “ascending paralysis”
- One of the most common life-threatening diseases of PNS, may lead to death from failure of respiratory muscles in days.

GBS – pathogenesis & morphology

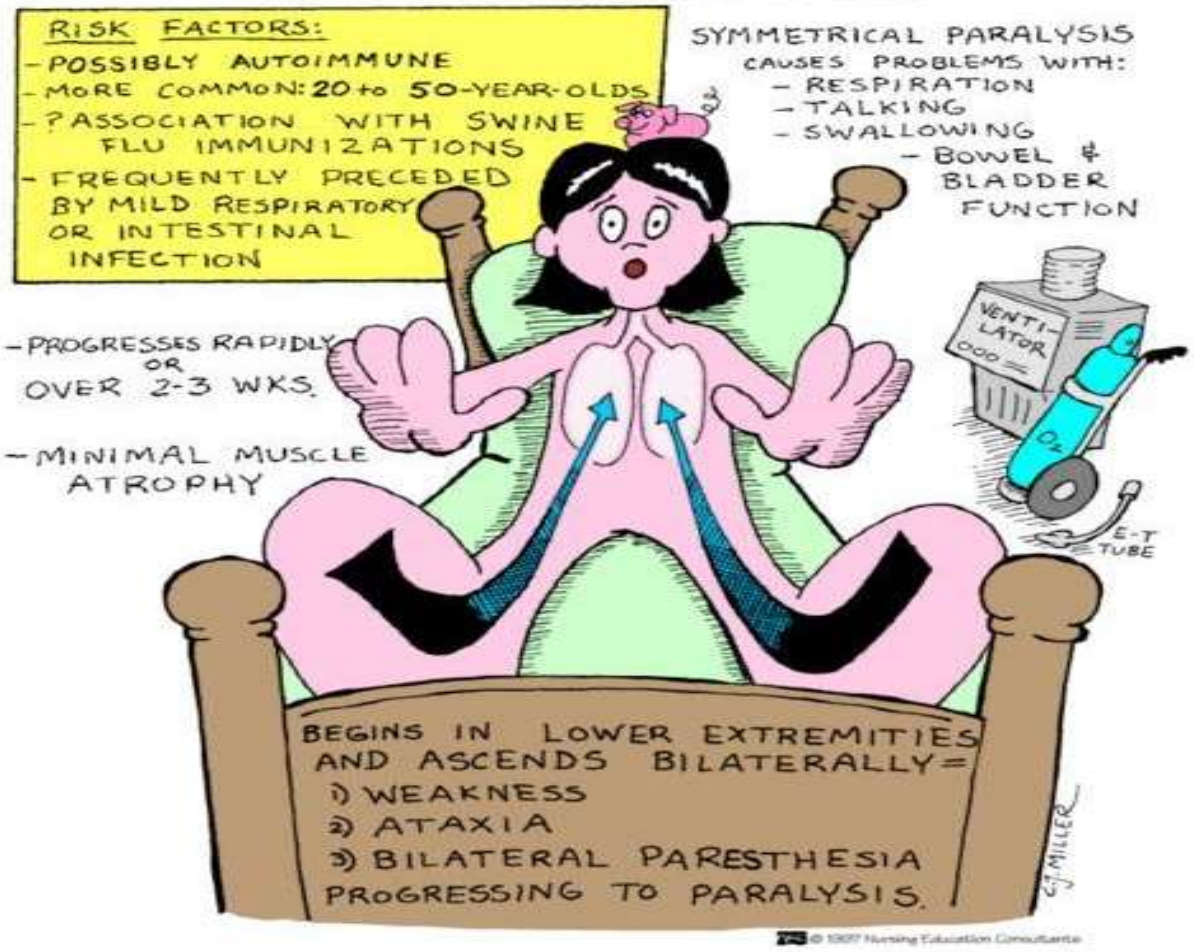
- Triggered by an infection or vaccination → breaks down self-tolerance → an autoimmune response.
- Usually acute, influenza-like illness from which the affected individual has recovered by the time the neuropathy becomes symptomatic.
- Infections with Campylobacter jejuni, CMV, Epstein-Barr virus, & Mycoplasma pneumoniae are ass./w GBS
- Histological findings include Segmental demyelination & inflammation of peripheral nerves, (perivenular and endoneurial mononuclear cell infiltrates rich in macrophages).

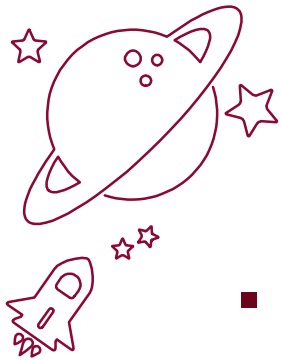


GBS- Clinical

- CSF protein levels are elevated due to inflammation and altered permeability of the microcirculation within the spinal roots.
- Treatments include plasmapheresis (to remove offending antibodies), intravenous immunoglobulin, and supportive care, such as ventilatory support.
- Patients who survive the initial acute phase of the disease usually recover with time.

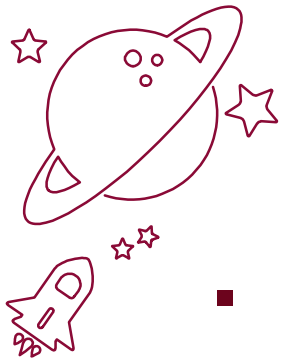
GUILLAIN-BARRE' SYNDROME





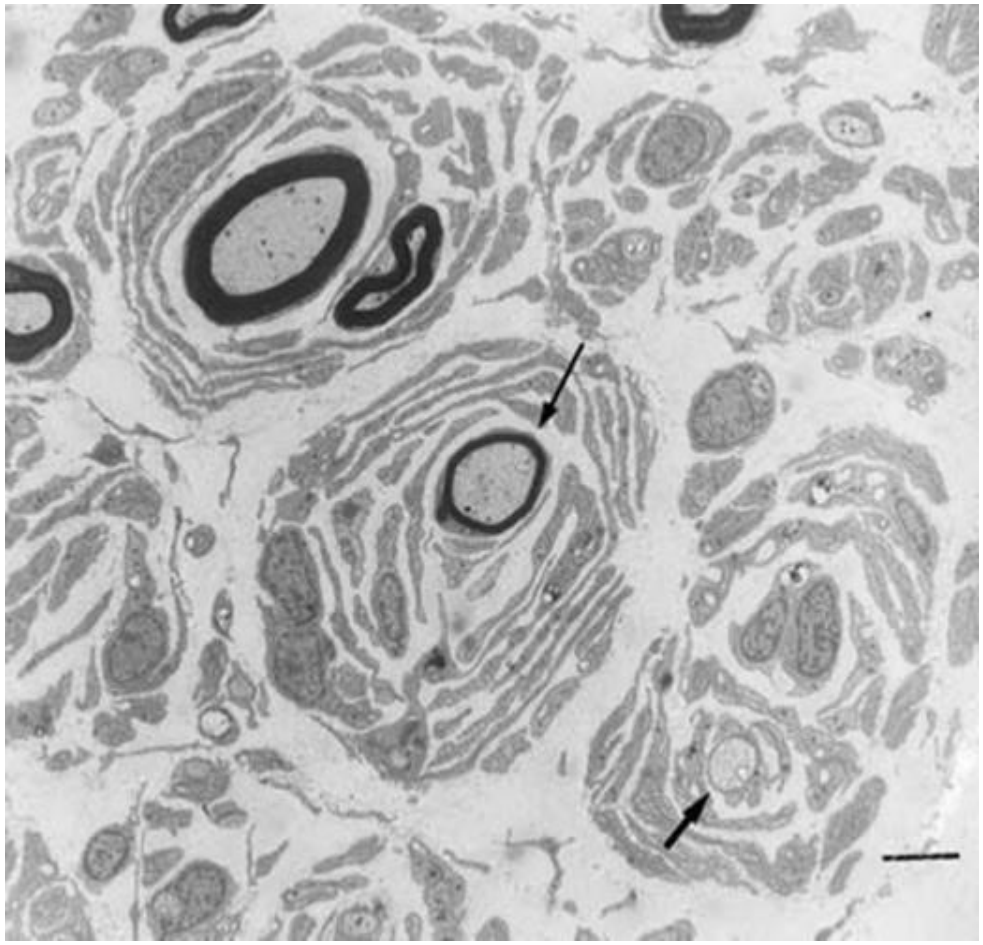
Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (CIDP)

- The most common chronic acquired inflammatory peripheral neuropathy.
- Characterized by symmetrical mixed sensorimotor polyneuropathy that persists for 2 months (at least) or more.
- Abnormalities include weakness, difficulty in walking, numbness, and pain or tingling sensations.
- CIDP is immune mediated also, but in contrast to GBS, CIDP follows a chronic relapsing-remitting, or progressive course.

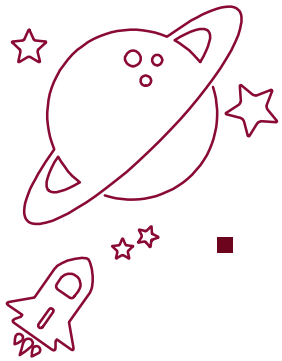


Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy (CIDP)

- The peripheral nerves show segments of demyelination and remyelination.
- Tx : Plasmapheresis and administration of immunosuppressive agents. Some patients recover completely, but more often recurrent bouts of symptomatic disease lead to permanent loss of nerve function.
- The time course and the response to steroids distinguish chronic inflammatory demyelinating polyradiculoneuropathy from Guillain-Barré syndrome.



In long-standing cases, repeated activation and proliferation of Schwann cells result in the concentric arrangement of multiple Schwann cells around individual axons to produce multilayered structures → **onion bulbs**.



Diabetic Peripheral Neuropathy

- **Diabetes is the most common cause of peripheral neuropathy → developing with long-standing disease.**
- Includes several forms (can occur singly or together)

1. ***Autonomic neuropathy*** is characterized by changes in bowel, bladder, cardiac, or sexual function.

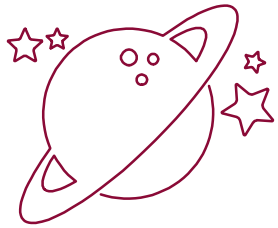
2. ***Lumbosacral radiculopathy*** manifests with asymmetric pain that can progress to lower extremity weakness & muscle atrophy.

3. ***Distal symmetric sensorimotor polyneuropathy*** <u>is the most common form of diabetic neuropathy.</u>

Diabetic Peripheral Neuropathy

- Sensory axons are more severely affected than motor axons → a presentation dominated by paresthesias & numbness.
- This form results from the length-dependent degeneration of peripheral nerves & often exhibits features of both axonal & myelin injuries.
- Pathogenesis is complex; hyperglycemia → accumulation of advanced glycosylation end products(AGEs), increased levels of reactive oxygen species, microvascular injuries, & changes in axonal metabolism.
- The best therapy: Strict glycemic control.

PERIPHERAL NERVE SHEATH TUMORS

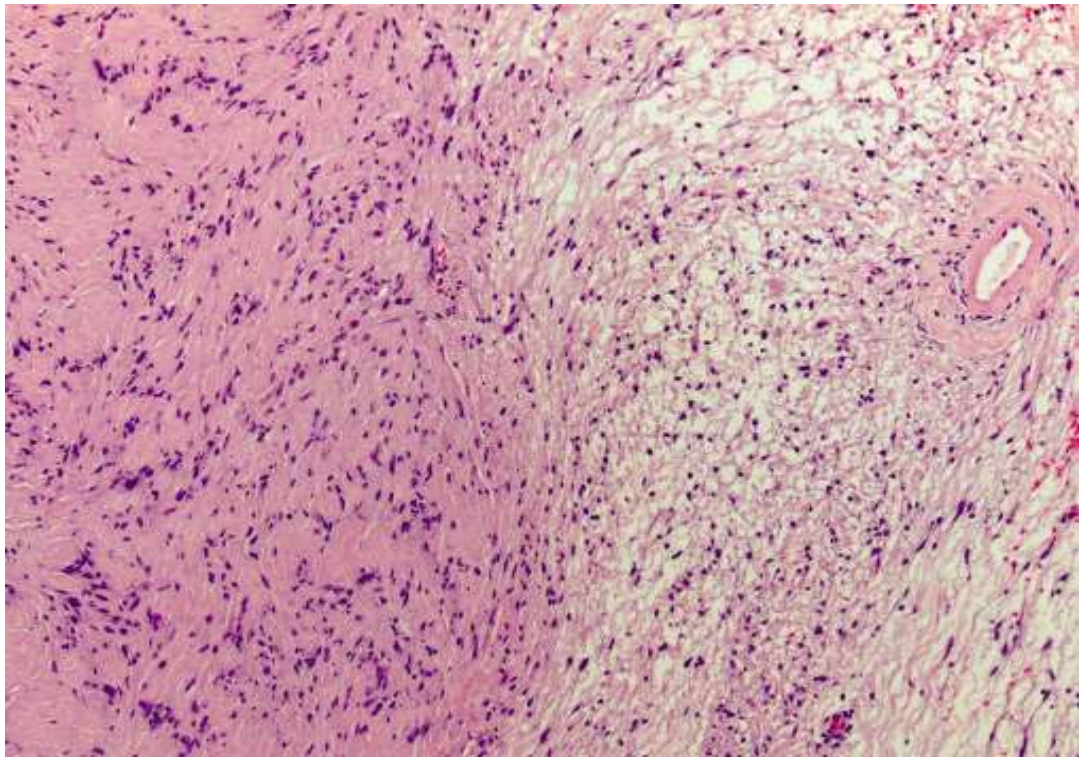


Schwannomas

- Benign encapsulated tumors that may occur in soft tissues, internal organs, or spinal nerve roots.
- The most commonly affected CN is the vestibular portion of the eighth nerve, symptoms related to nerve root compression, which includes hearing loss here.
- Most are sporadic, ~10% are ass with familial neurofibromatosis type 2 (NF2)

Schwannomas - Morphology

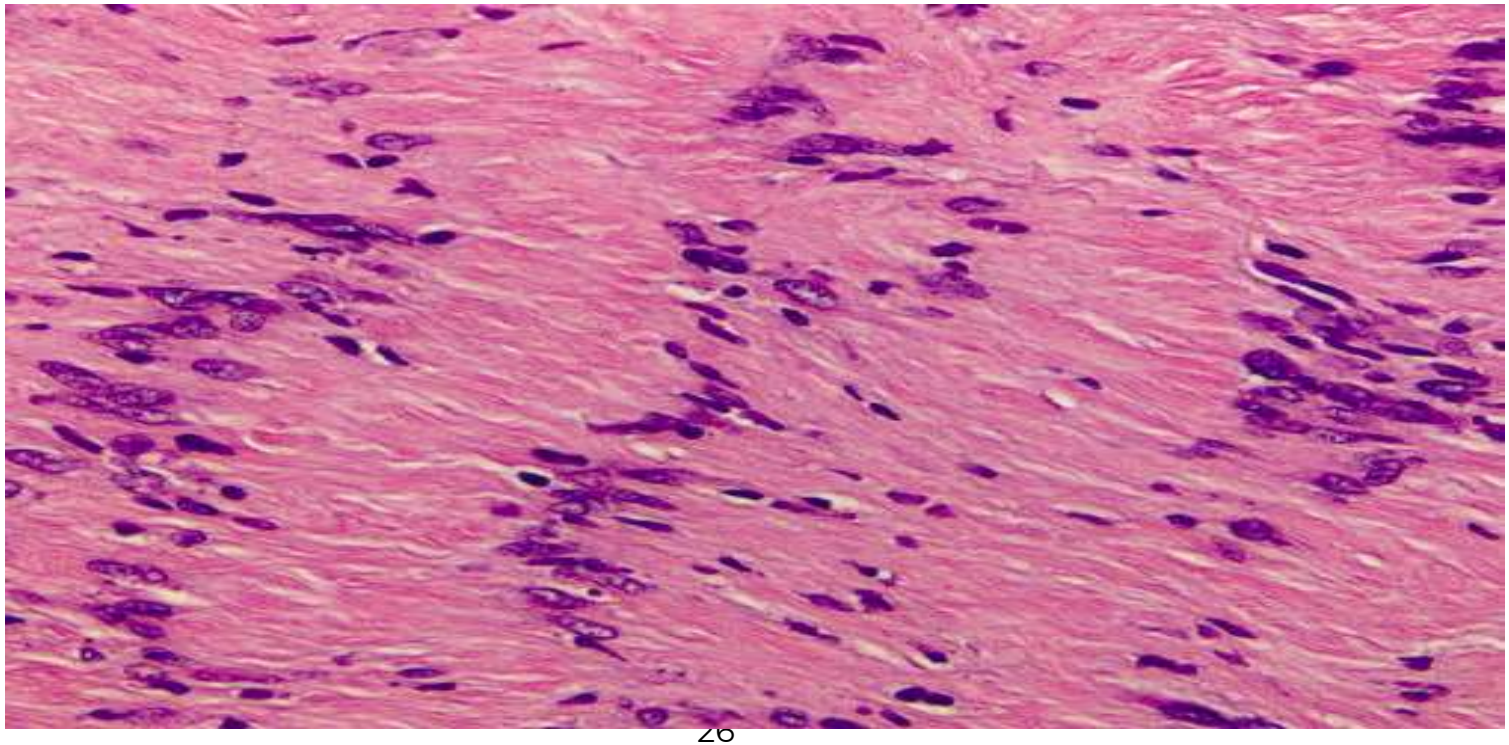
- Grossly: Circumscribed masses abutting an adjacent nerve.
- Microscopically: an admixture of dense & loose areas referred to as Antoni A and B, respectively.



Schwannomas - Morphology

- Antoni A: dense areas, bland spindle cells arranged into intersecting fascicles, often align to produce nuclear palisading →
- Verocay bodies: alternating bands of nuclear & anuclear areas.
- Antoni B: loose areas, the spindle cells are spread apart by a prominent myxoid extracellular matrix. Thick-walled hyalinized vessels often are present
- Axons are largely excluded from the tumor.
- Hemorrhage or cystic changes.

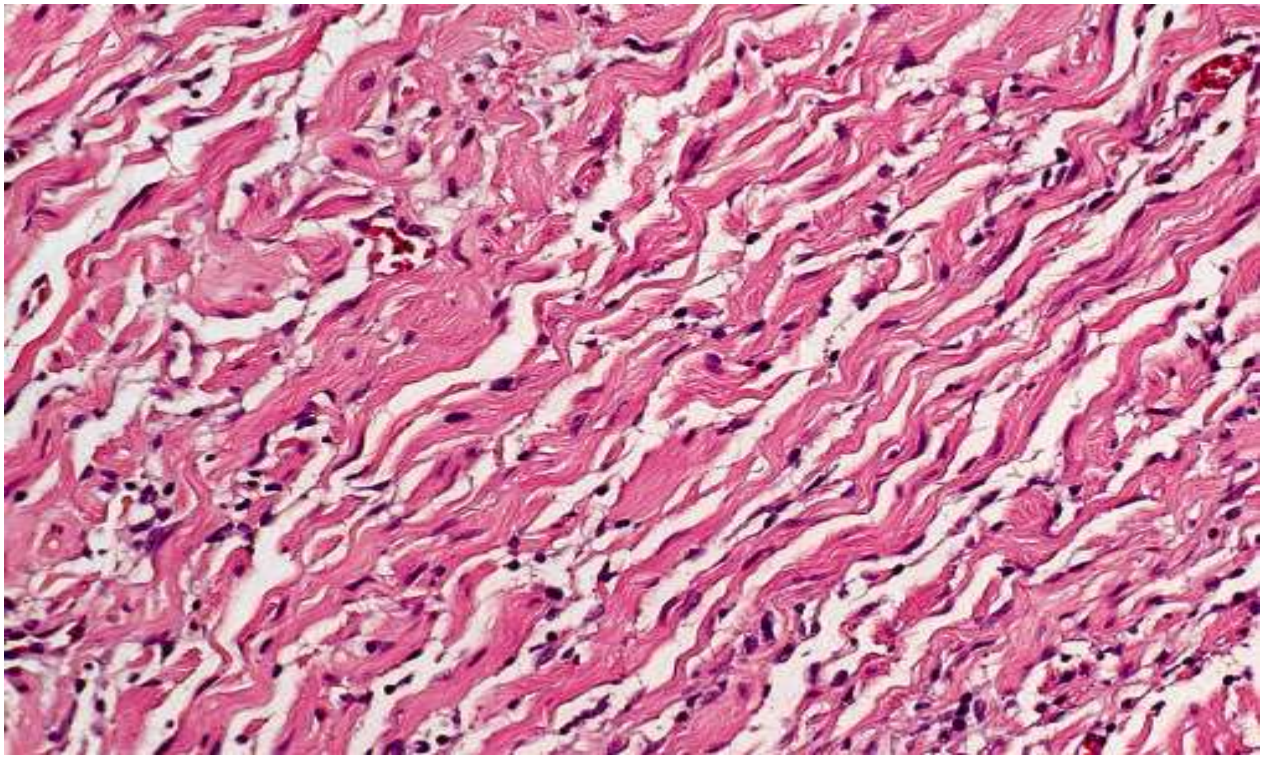
Tumor cells aligned in palisading rows → Verocay bodies:



Neurofibromas

- Neurofibromas are not encapsulated benign PNS tumor.
- Can be localized cutaneous tumors, Diffuse or Plexiform,
- In contrast to schwannomas, the neoplastic Schwann cells in neurofibroma are admixed with other cell types, mast cells, fibroblast like cells, & perineurial-like cells.
- The background stroma often contains loose wavy collagen bundles.
- Malignant Peripheral Nerve Sheath Tumors can arise from them or de novo (50% of MPNST have NF1)

Neurofibromas



Familial Neurofibromatosis

Type 1 (1:3000)

AD, Chr. 17

Neurofibromas, malignant peripheral nerve sheath tumors, optic gliomas.

pigmented nodules in iris *(Lisch nodules)*.

pigmented skin lesions (freckling & café-au-lait spots)

Type 2(1:40,000)

AD, Chr. 22

risk of developing multiple schwannomas, meningiomas, & ependymomas.

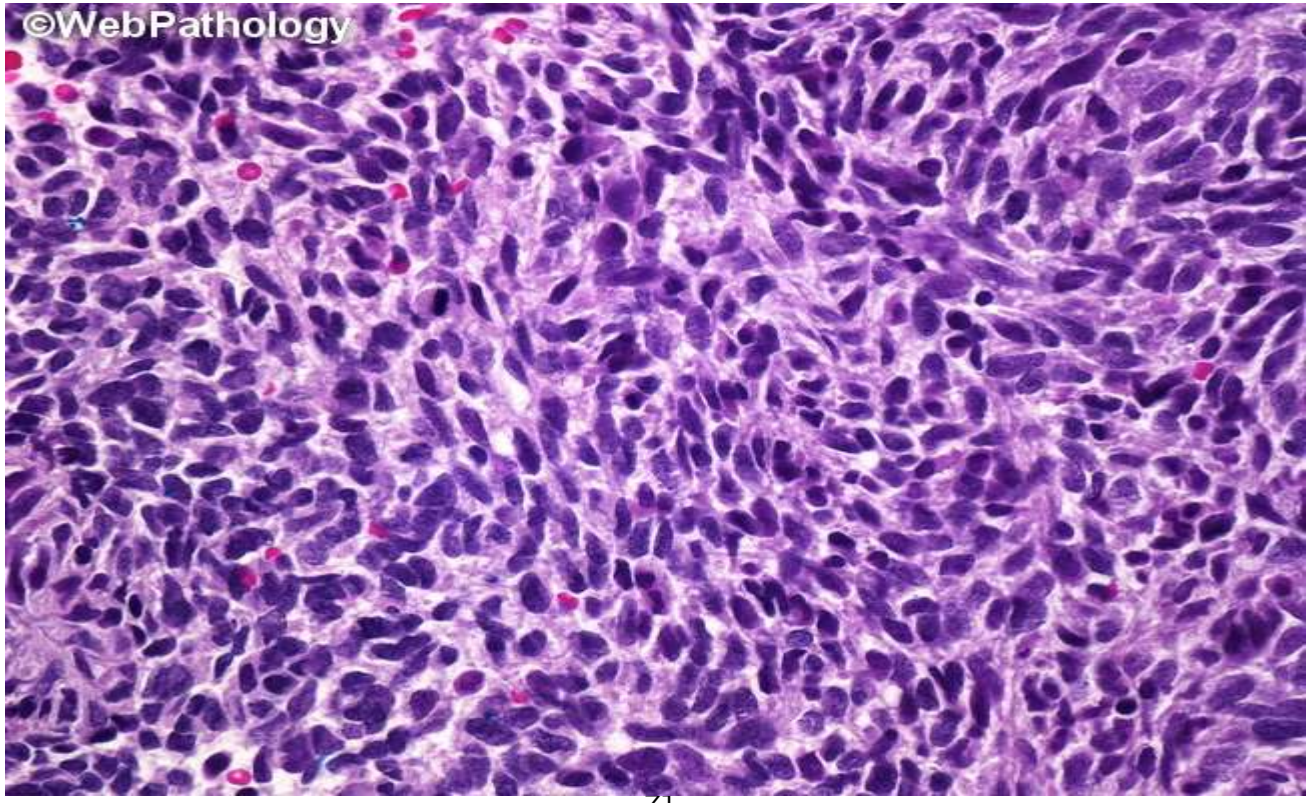
Hearing loss, vertigo

Multiple CN neuropathies.

Malignant Peripheral Nerve Sheath Tumors

- Neoplasms seen in adults.
- They may arise from transformation of a neurofibroma, (usually of the plexiform type).
- About one-half of such tumors arise in patients with NF1, (3-10%) of all patients with NF1 develop MPNST.
- Histologically, highly cellular and exhibit features of overt malignancy; anaplasia, necrosis, infiltrative growth pattern, pleomorphism, and high proliferative activity (mitoses).

MPNST



Thank You ..&
Good Luck! ☺