
Axonal Neuropathies

Peripheral nerve degeneration, regeneration, and clinical patterns

Pathology lecture

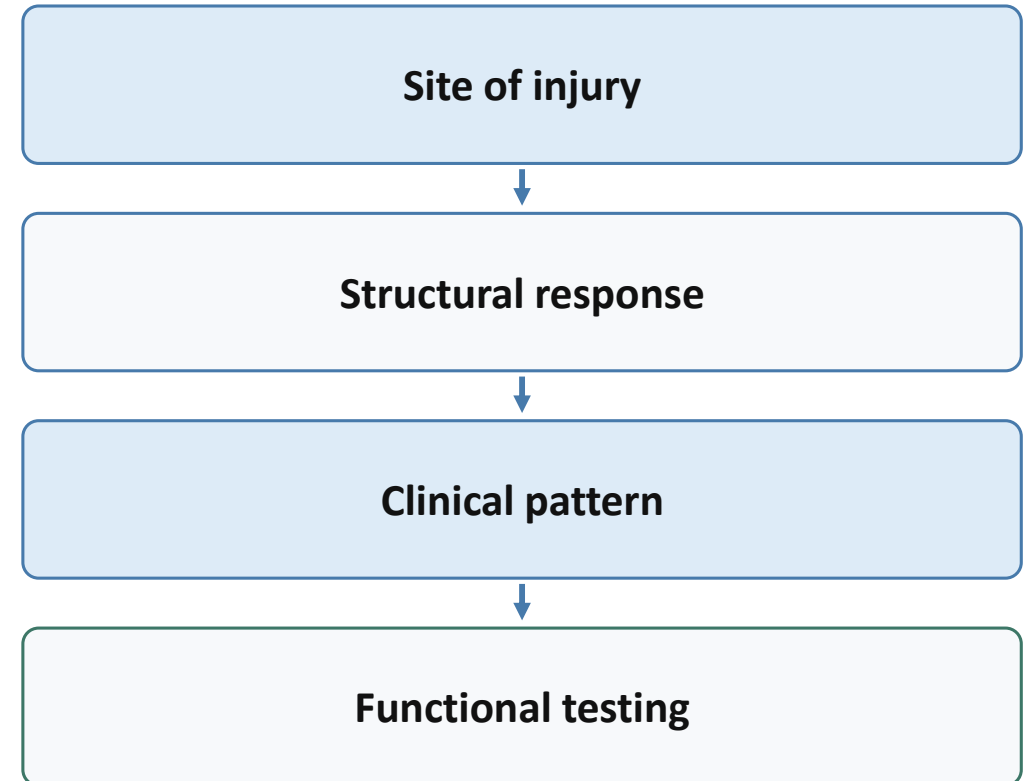
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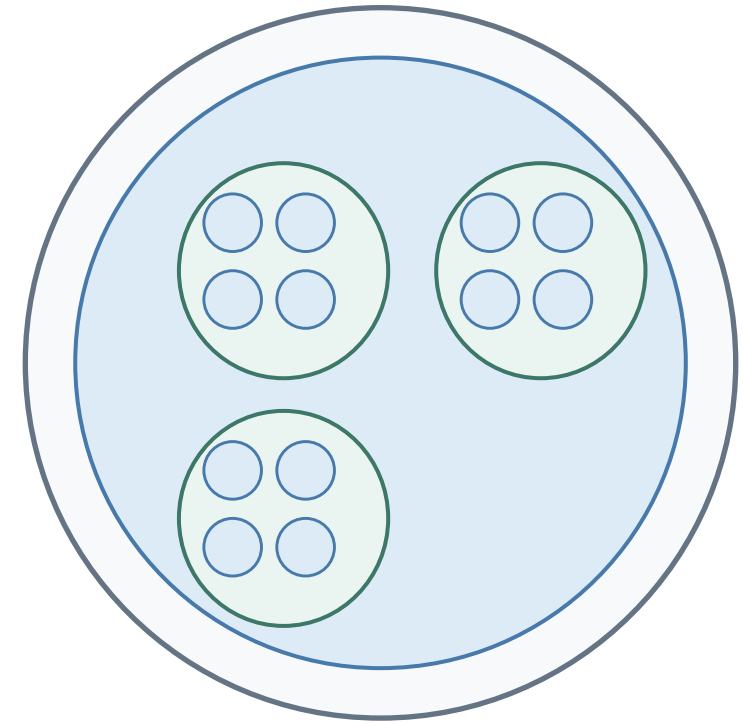
Learning outcomes

- Identify primary axonal damage and distinguish it from segmental demyelination and neuronal cell-body injury.
- Explain Wallerian degeneration, debris clearance, axonal sprouting, and the limitations of regeneration.
- Interpret length-dependent clinical patterns and the characteristic nerve-conduction profile of axon loss.
- Connect selected metabolic, toxic, vascular, physical, and inherited disorders with axonal injury.



A peripheral nerve carries several fiber classes

- Axons arise from neuronal cell bodies and transmit signals to or from peripheral targets.
- Schwann cells support both myelinated and unmyelinated axons in peripheral nerves.
- Most nerves mix motor, sensory, and autonomic fibers within connective-tissue fascicles.



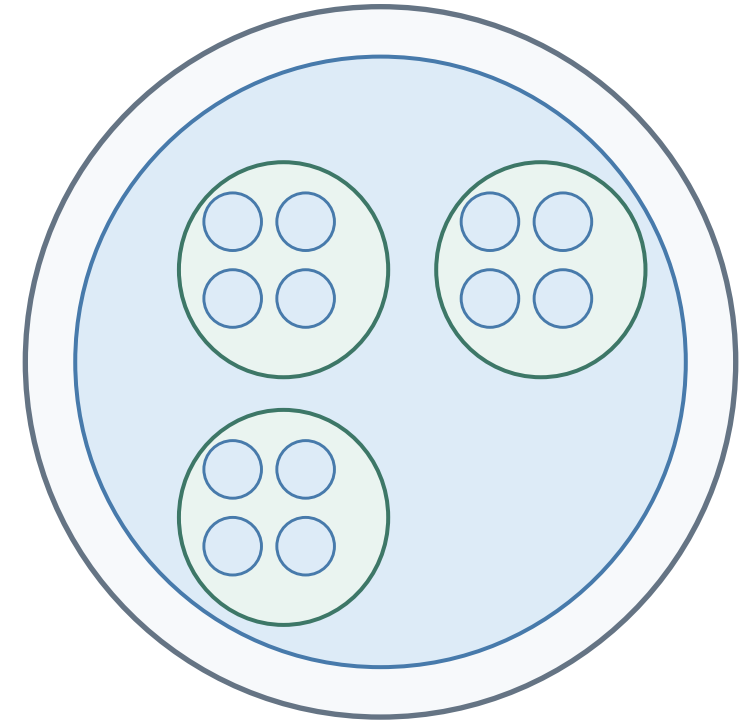
Epineurium

Perineurium

Endoneurium

Connective tissue preserves nerve architecture

- Epineurium encloses the entire peripheral nerve within fibrovascular tissue.
- Perineurium surrounds groups of nerve fibers to define fascicles.
- Endoneurium invests individual nerve fibers within a fascicle.



Epineurium

Perineurium

Endoneurium

Axon caliber and myelin determine conduction

- Large myelinated axons conduct proprioceptive, light-touch, and motor signals rapidly.
- Thin unmyelinated fibers carry autonomic functions and some pain and temperature signals.
- Fiber-class selectivity helps explain the symptoms of different axonal neuropathies.

Large myelinated fiber



Faster saltatory conduction

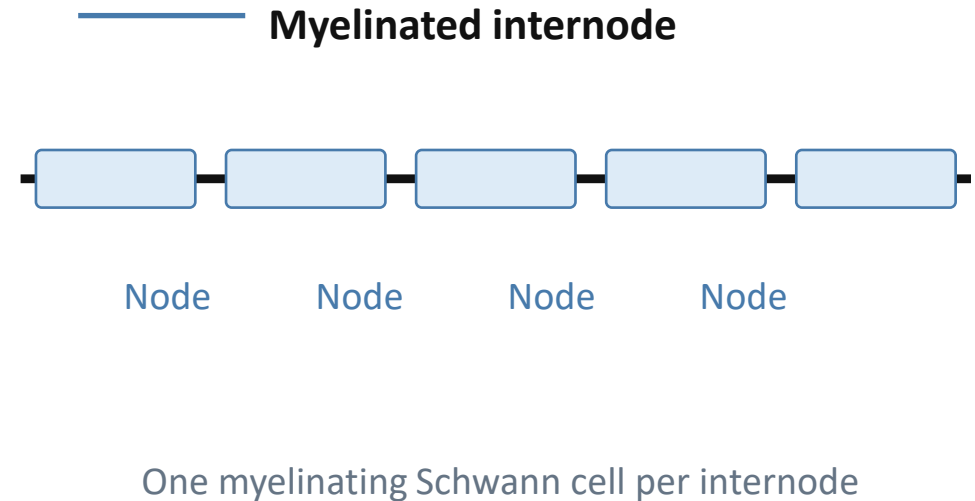
Thin unmyelinated fiber



Slower continuous conduction

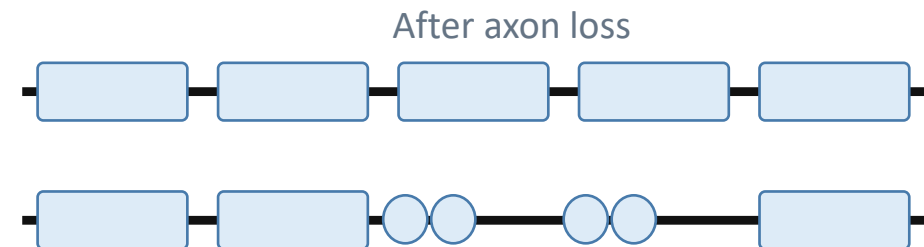
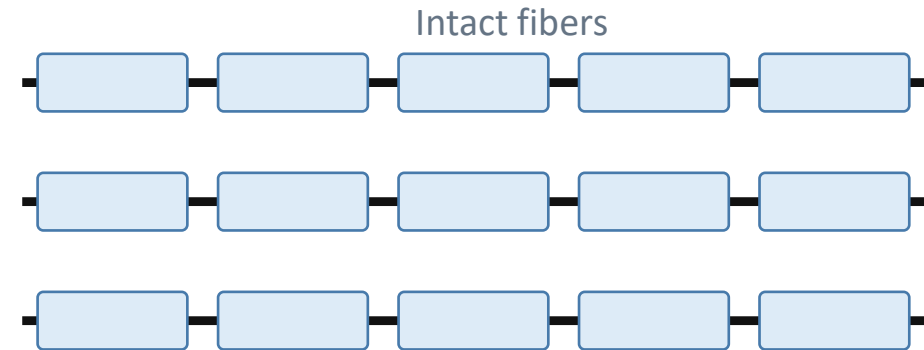
Internodes and nodes organize saltatory conduction

- Each myelinating Schwann cell forms one sheath around one axonal segment: The internode.
- Nodes of Ranvier interrupt the myelin at regular intervals.
- The distinction between axonal damage and myelin damage underlies electrodiagnostic interpretation.



The principal lesion is loss or degeneration of axons

- In axonal neuropathies, the axon—not the Schwann-cell myelin sheath—is the primary target.
- Affected fibers can lose their distal processes and their associated myelin.
- The ultimate effect depends on the number and type of axons lost.



Fewer conducting axons

Three primary sites of peripheral nerve injury

- Axonopathy: Primary injury to axonal processes, often affecting the longest axons first.
- Myelinopathy: Primary injury to Schwann cells or myelin internodes, with axons relatively preserved.
- Neuronopathy: Injury to neuronal cell bodies, causing subsequent degeneration of their processes.

Axonopathy

Primary axon loss

Myelinopathy

Segmental internode injury

Neuronopathy

Primary neuronal soma loss

Axon loss and myelin loss have different consequences

- Loss of an axon removes a functional signaling channel from the nerve.
- Loss of myelin disrupts impulse propagation along a structurally retained axon.
- These are idealized dominant patterns; Real neuropathies can contain both changes.

Axonopathy

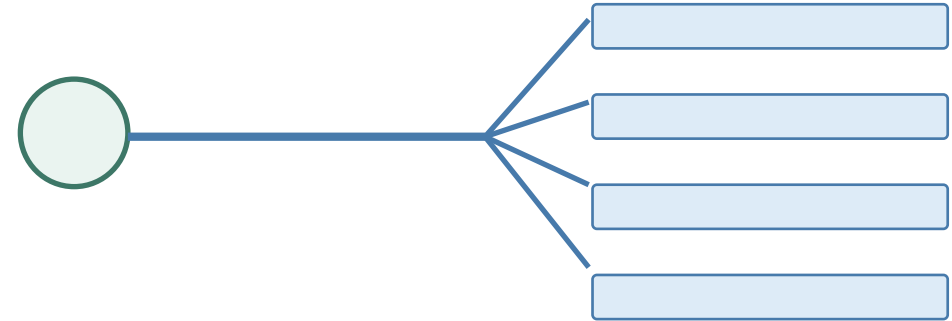
Primary axon loss

Myelinopathy

Segmental internode injury

Denervation translates axonal damage into muscle change

- Motor axon loss deprives its innervated muscle fibers of neural input.
- Acute axonal injury can produce angular atrophy of denervated myofibers.
- Regenerating motor axons may reinnervate surviving muscle fibers.

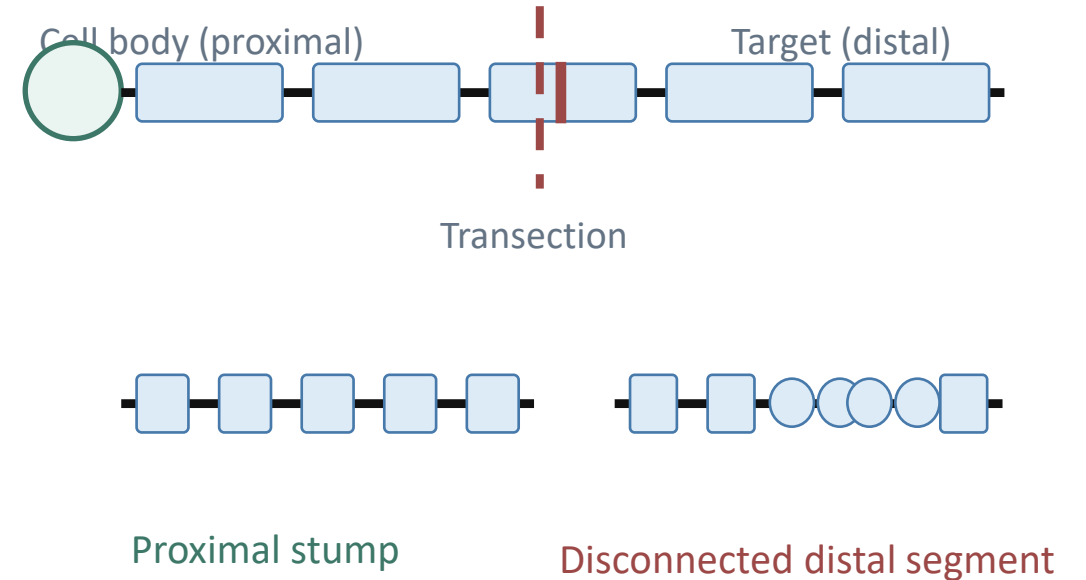


Motor neuron → axon → muscle fibers

After denervation: Affected myofibers may become angular and atrophic

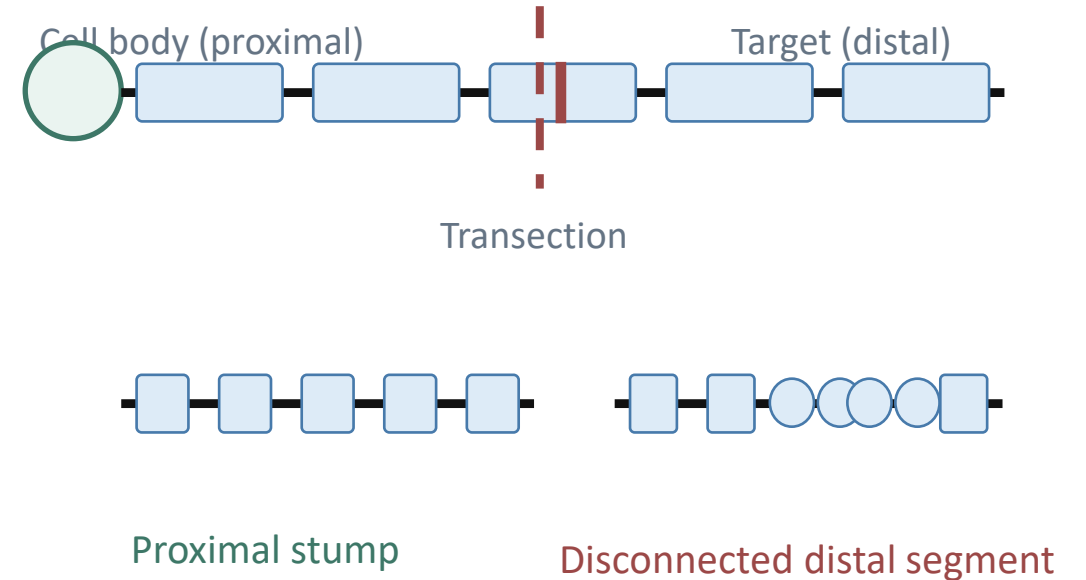
Wallerian degeneration: The experimental prototype

- Transection separates the distal axon from its neuronal cell body.
- The disconnected distal segment undergoes stereotyped axonal and myelin breakdown.
- This acute model explains the morphologic vocabulary used for axonal neuropathies.



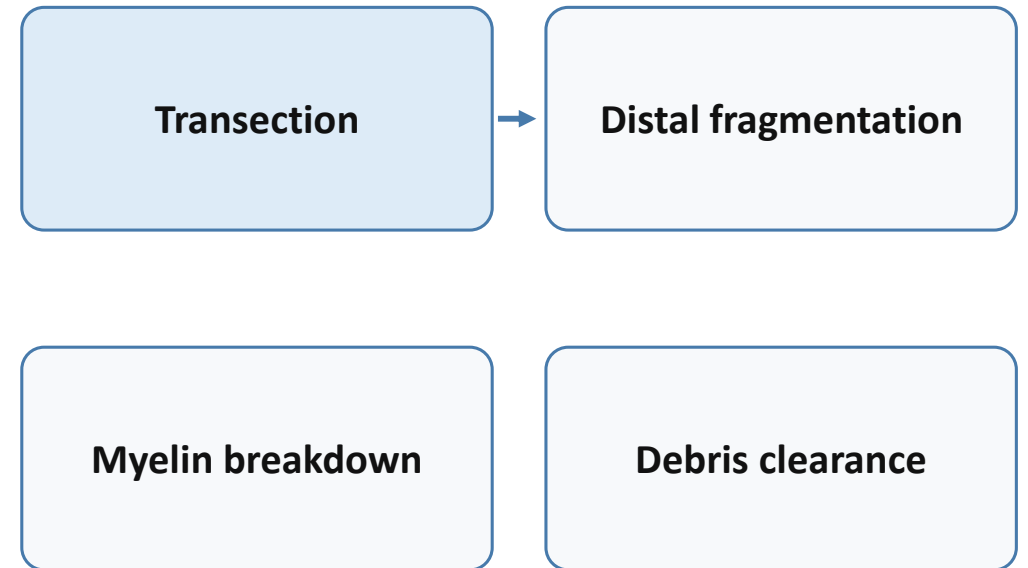
The lesion is distal to the transection site

- The proximal segment remains continuous with the perikaryon.
- The separated distal axon cannot be maintained and degenerates.
- The associated myelin sheath also breaks down after the axonal injury.



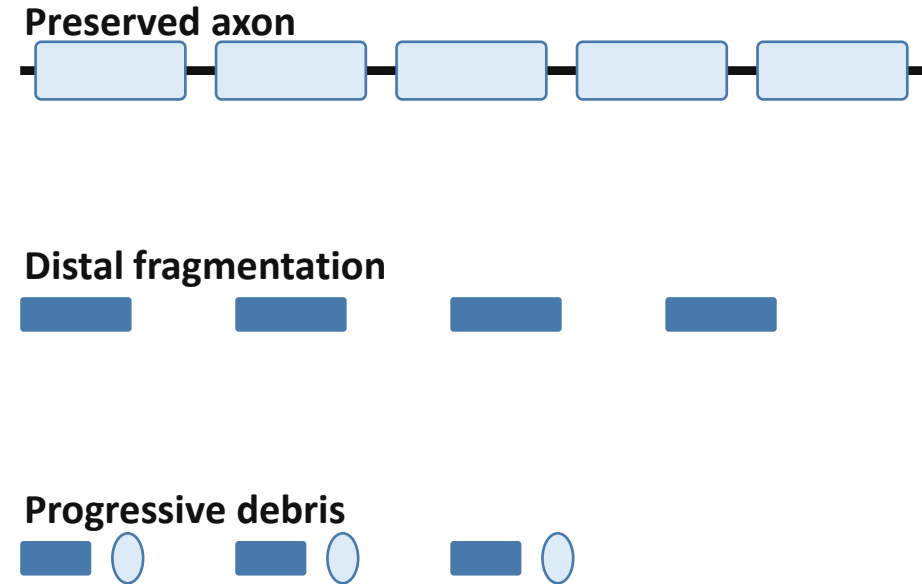
The sequence begins rapidly after injury

- Within a day, distal axons begin to fragment.
- Myelin lamellae loosen and unravel as axonal integrity is lost.
- Debris removal creates a substrate for eventual regenerative growth.



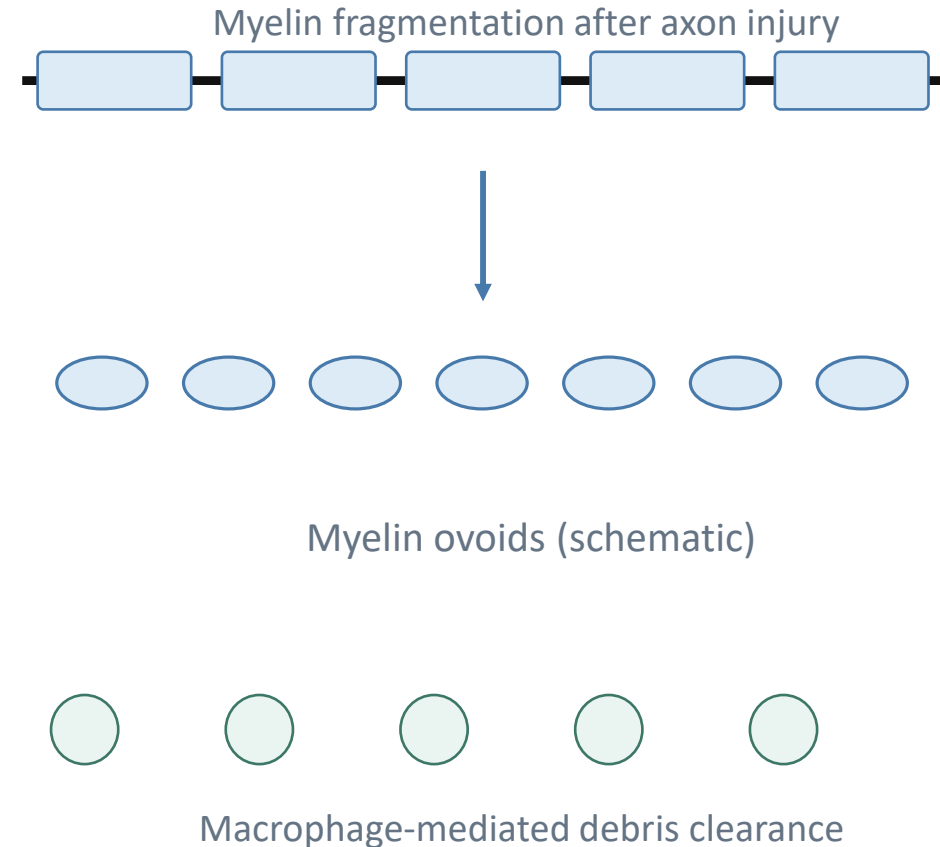
Axonal fragmentation is a structural hallmark

- The distal segment breaks into discontinuous axonal fragments.
- Loss of axonal continuity prevents effective signal transmission along the injured fiber.
- Adjacent intact fibers can coexist with degenerating axons in a mixed nerve.



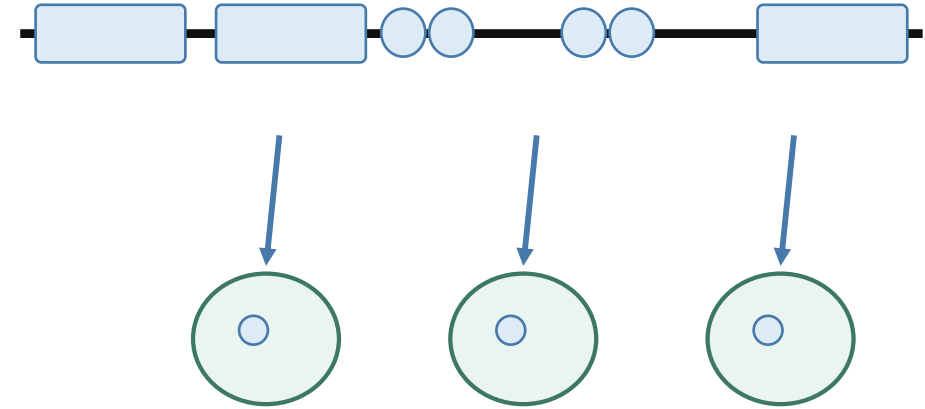
Myelin disintegrates into ovoids

- The myelin sheath unravels after distal axonal degeneration.
- Fragments form rounded myelin ovoids rather than a continuous internode.
- Myelin breakdown therefore does not by itself establish primary demyelinating disease.



Macrophages clear axonal and myelin debris

- Macrophages are recruited to the affected nerve after fragmentation.
- They participate in removal of both axonal and myelin remnants.
- Debris clearance and Schwann-cell support set the stage for regeneration.

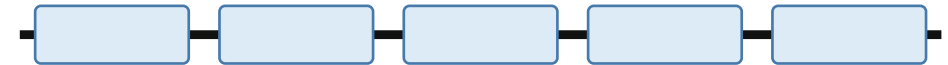


Phagocytes remove fragmented myelin and axon

Morphologic recognition requires lesion context

- A degenerating myelin sheath can accompany primary axonal injury.
- Interpret loss of axons, fragments, myelin ovoids, and regenerative clusters together.
- Compare injured fascicles with preserved fibers before assigning the primary process.

Intact fiber



Degenerating fiber

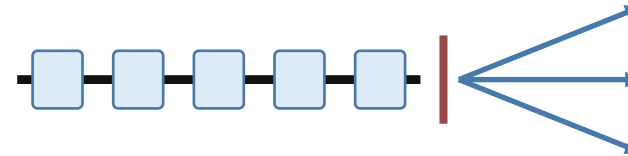


Regenerating fiber



Regeneration begins at the proximal stump

- A growth cone forms at the axonal stump on the cell-body side of the injury.
- New axonal branches emerge from this proximal stump.
- Growth proceeds toward a distal target rather than restoring the original axon instantaneously.

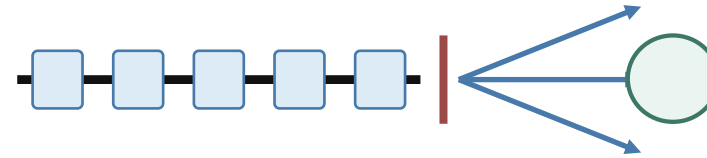


New branches from proximal axon

Repair depends on target-directed extension

Growth cones and branch formation

- An axonal growth cone leads the advancing regenerative process.
- Several new branches may sprout from a single proximal stump.
- The branches must find suitable distal pathways to re-establish function.

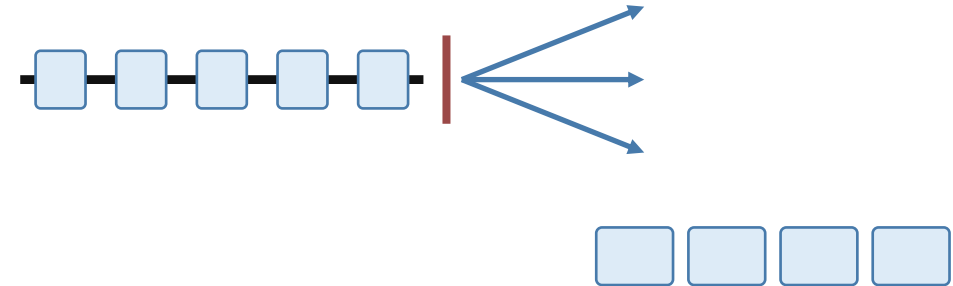


Advancing growth cone

Repair depends on target-directed extension

Schwann cells provide a regeneration pathway

- Schwann cells and their basement membranes guide axonal sprouts.
- Preserved supporting structures help direct sprouts toward distal targets.
- Disruption of these tracks contributes to unsuccessful nerve repair.



Schwann-cell basal-lamina guide

Repair depends on target-directed extension

Axonal regrowth is slow and distance-limited

- Peripheral axonal growth at approximately 1–2 mm per day.
- The longer the distance to the target, the more prolonged the regeneration pathway.
- Successful regrowth still requires anatomically aligned proximal and distal ends.

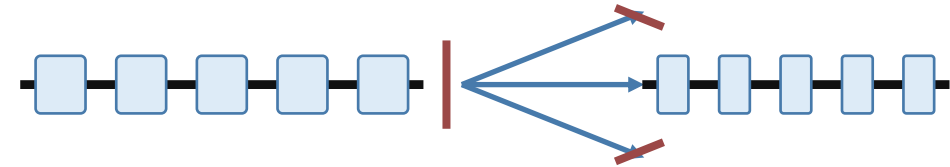
Regrowth $\approx$ 1–2 mm/day



Approximate textbook rate, not a patient-specific prognosis

Regenerating branches undergo pruning

- Early regrowth produces multiple competing or misdirected axonal branches.
- Continuous pruning removes branches that do not follow productive routes.
- Mature reinnervation depends on effective selection and target contact.

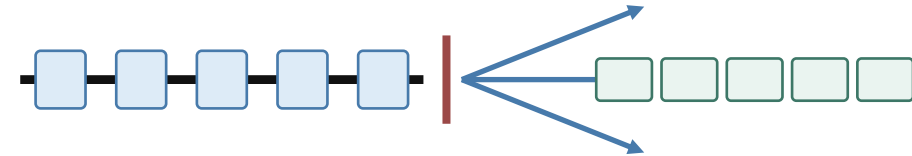


Selected branch reaches target

Repair depends on target-directed extension

Regenerated axons are remyelinated

- Schwann cells form new myelin sheaths around successful regenerating axons.
- New internodes are typically shorter and myelin thinner than before injury.
- Histologic evidence of remyelination must be interpreted with axonal regeneration.

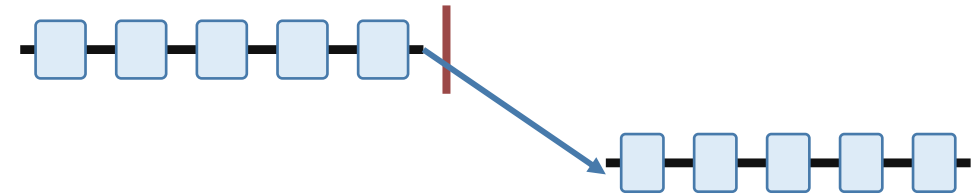


Short, thin replacement internodes

Repair depends on target-directed extension

Anatomic alignment determines repair success

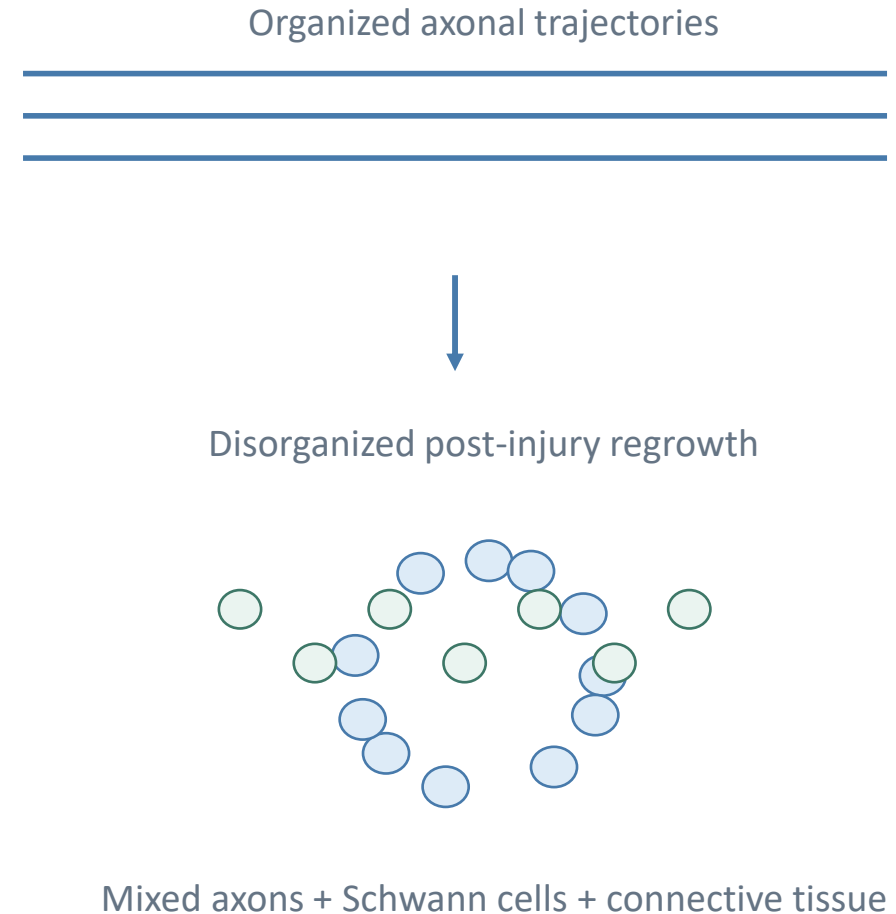
- Regeneration is most successful when transected nerve ends remain closely approximated.
- Misdirected sprouts may fail to establish their intended distal connections.
- Anatomic separation can convert useful sprouting into a disorganized mass.



Distal pathway misaligned

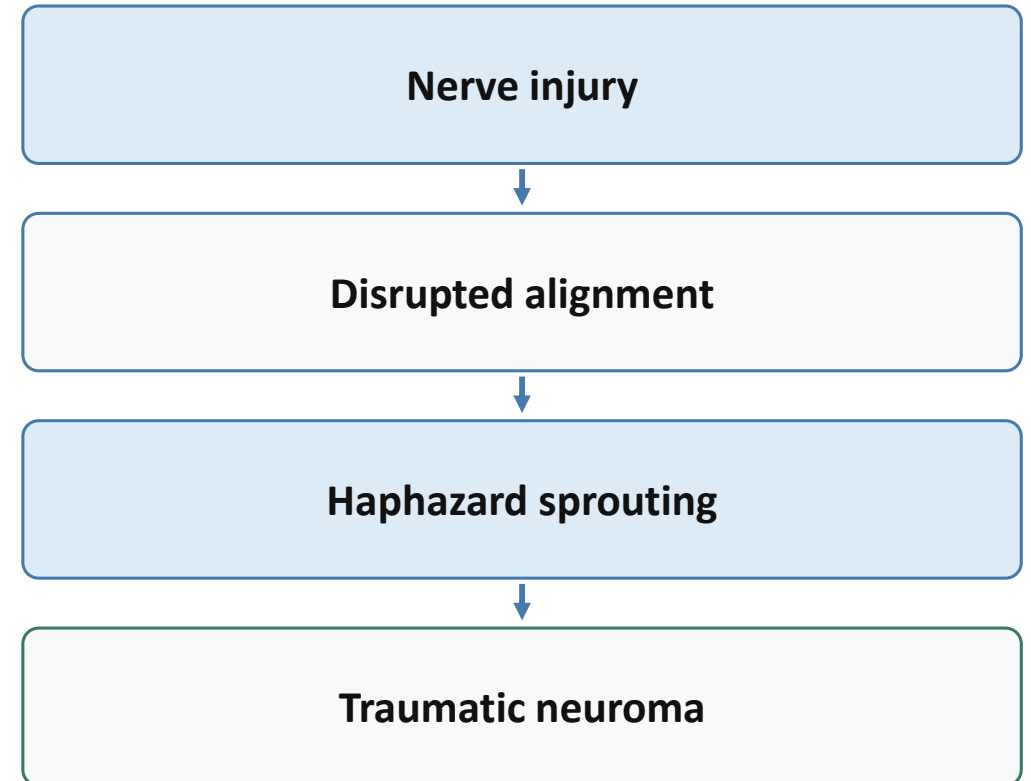
Traumatic neuroma is not a true neoplasm

- A traumatic neuroma consists of disorganized axonal processes with accompanying Schwann cells.
- It may form when regenerating axons cannot reach appropriate distal targets.
- The resulting nonneoplastic proliferation can present as a painful nodule.



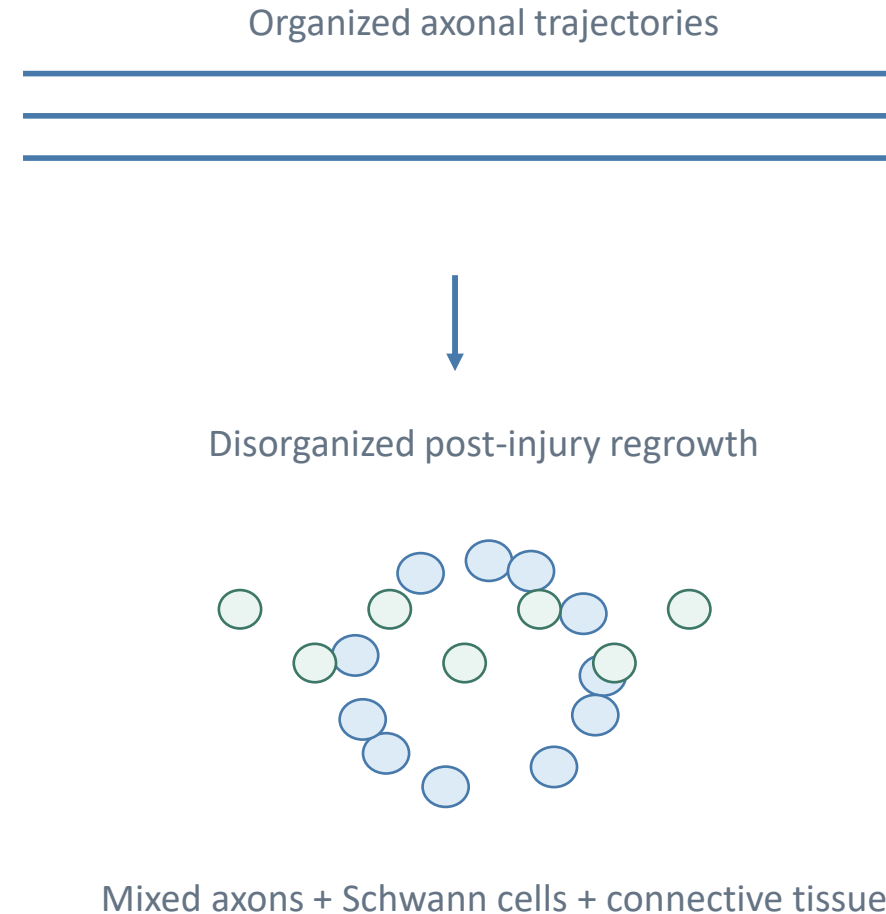
Traumatic neuroma: Causal sequence

- A nerve is transected and the proximal segment initiates sprouting.
- Loss of a navigable distal pathway produces misdirected regrowth.
- Intermingled axons, Schwann cells, and connective tissue form a painful mass.



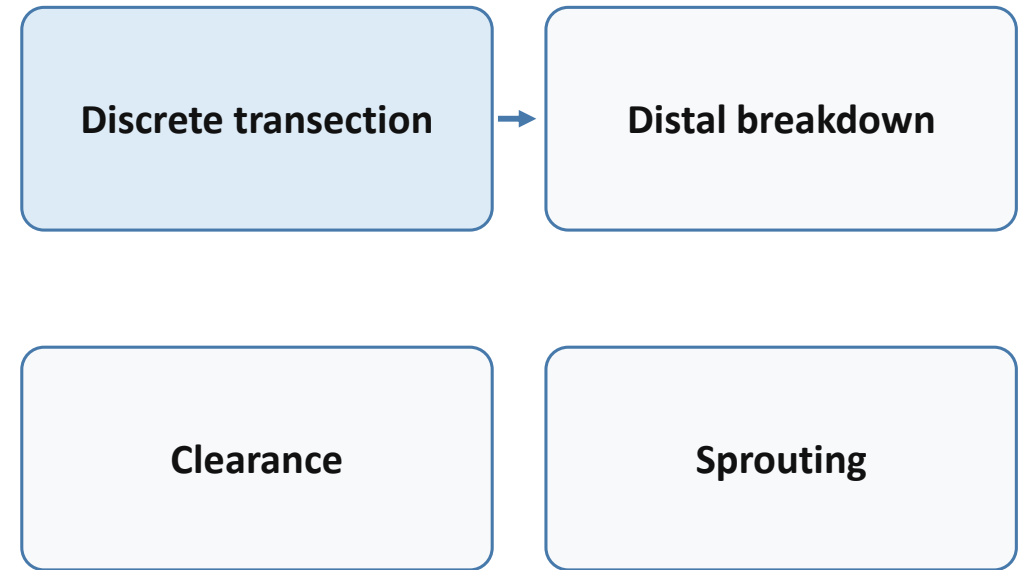
Microscopic organization in traumatic neuroma

- Normal nerves contain parallel, organized axons.
- Traumatic neuroma has haphazard, swirling axons admixed with Schwann cells and connective tissue.
- The disordered architecture reflects attempted regeneration, not autonomous neoplastic growth.



Acute transection differs from chronic neuropathy

- Transection is an abrupt, spatially defined experimental injury.
- In chronic axonal neuropathies, damaging events persist over time.
- The biopsy can therefore show ongoing degeneration alongside axonal regeneration.

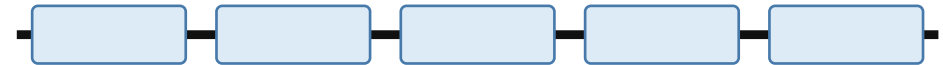


Chronic axonopathy: Several phases may coexist

Degeneration and regeneration can coexist

- One fascicle may contain degenerating fibers, surviving axons, and regenerative sprouts.
- Regenerative activity should not be mistaken for complete functional recovery.
- Sustained injury can continue while repair is underway.

Intact fiber



Degenerating fiber



Regenerating fiber



Progressive dropout reflects an injury–repair imbalance

- With continuing injury, cumulative damage can exceed regenerative capacity.
- The result is a gradual reduction in the number of functioning axons.
- Fewer intact axons underlie reduced electrophysiologic response amplitudes.

Continuing injury



Regenerative repair



When damage outpaces repair

Progressive decline in surviving axons

Length dependence produces a “dying-back” pattern

- Toxic and metabolic insults commonly affect the longest axons most severely.
- Degeneration is prominent distally, producing a dying-back distribution.
- As disease advances, successively more proximal segments may become involved.

Longest axon



Intermediate axon



Shorter axon



Distal end is affected earliest in length-dependent damage

Why distal feet tend to be affected first

- Distal lower-limb axons are among the longest peripheral projections.
- Length-dependent injury produces symptoms first in the toes and feet.
- Upper limbs become involved later as the affected distal territory expands.

Longest axon



Intermediate axon



Shorter axon



Distal end is affected earliest in length-dependent damage

Stocking-and-glove involvement reflects axonal length

- Distal symmetric polyneuropathy generally begins in the feet and ascends.
- Hand deficits often appear when lower-limb symptoms have progressed toward the knees.
- This distribution suggests a length-dependent process; It does not identify a unique cause.

Longest axon



Intermediate axon



Shorter axon



Distal end is affected earliest in length-dependent damage

Axonopathy and neuronopathy differ anatomically

- Peripheral axonopathies preferentially affect distal extremities when length-dependent.
- Neuronopathies begin with neuronal-cell-body destruction and secondary axonal degeneration.
- Cell-body injury can affect proximal and distal peripheral territories without the same distal gradient.

Longest axon



Intermediate axon



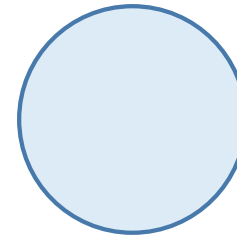
Shorter axon



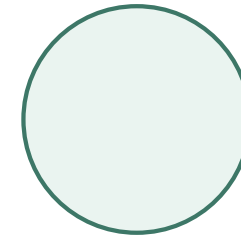
Distal end is affected earliest in length-dependent damage

Sensory manifestations reflect fiber loss

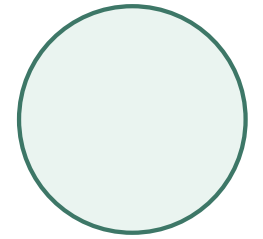
- Numbness and diminished pain sensation represent loss of normal sensory signaling.
- Paresthesia and dysesthesia can arise from abnormal discharges in damaged nerve fibers.
- Affected modalities vary with the sensory fiber populations involved.



Large sensory



Small sensory

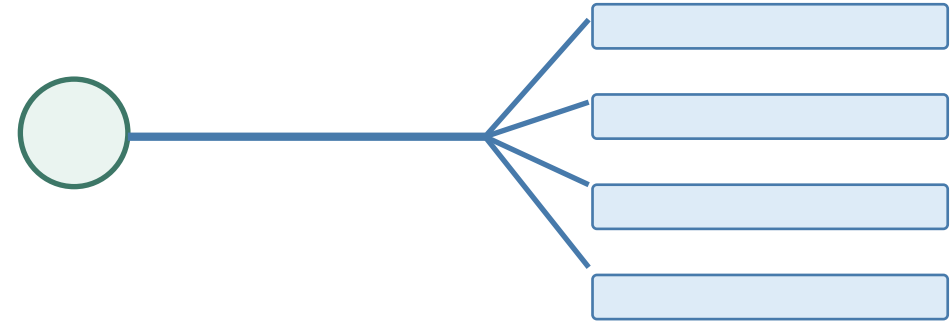


Autonomic

Loss of function + abnormal positive sensations

Motor axon loss can produce weakness and atrophy

- Loss of functional motor axons reduces activation of the associated muscle fibers.
- Denervated muscle fibers may show angular atrophy.
- Reinnervation by regenerative axons can partially restore the motor unit.

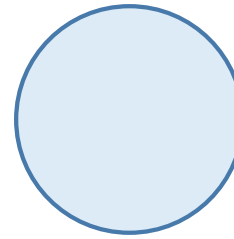


Motor neuron → axon → muscle fibers

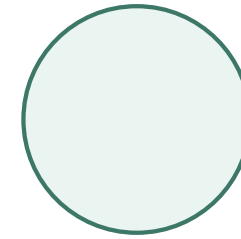
After denervation: Affected myofibers may become angular and atrophic

Autonomic fibers may be involved

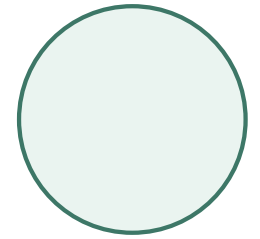
- Autonomic signals travel in thin unmyelinated peripheral fibers.
- Diabetes can produce autonomic neuropathy along with distal sensorimotor deficits.
- Examples include postural hypotension, bladder-emptying dysfunction, and sexual dysfunction.



Large sensory



Small sensory



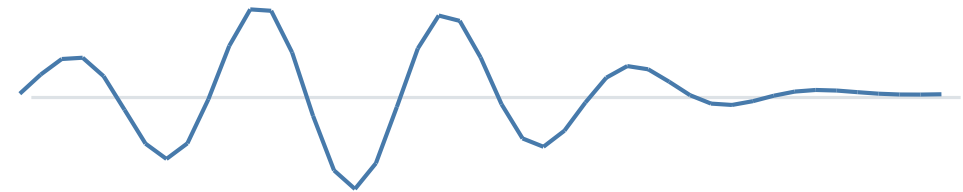
Autonomic

Visceral function may be disturbed

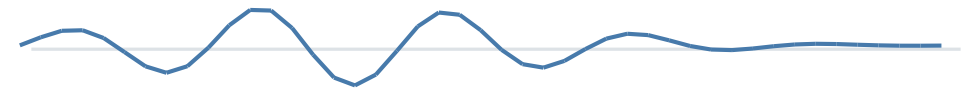
Electrodiagnostic hallmark: Low signal amplitude

- Nerve-conduction response amplitude falls as contributing axons are lost.
- Conduction velocity is relatively preserved among remaining conducting fibers.
- The interpretation is a dominant pattern, not an absolute rule for every affected nerve.

Relatively preserved



Axonal pattern: Lower amplitude

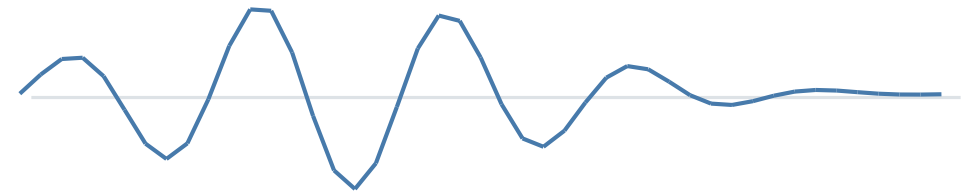


Qualitative schematic — not patient data

Demyelination primarily slows conduction

- Primary myelin injury disrupts saltatory propagation across individual internodes.
- Nerve-conduction velocity is reduced demyelinating pattern.
- Unlike axon loss, amplitude may remain preserved when sufficient axons remain functional.

Normal propagation



Myelin injury: Slower conduction

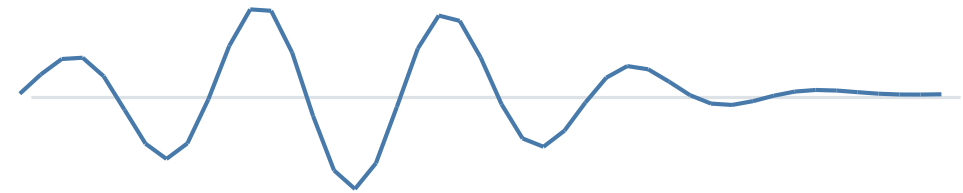


Qualitative schematic — not patient data

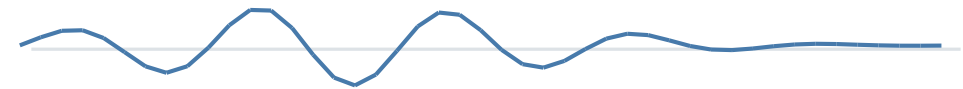
Amplitude and velocity answer different questions

- Reduced amplitude chiefly suggests fewer functioning axons in an axonal process.
- Slow velocity chiefly reflects a myelin-conduction problem comparison.
- Mixed or advanced diseases can affect both electrophysiologic domains.

Relatively preserved



Axonal pattern: Lower amplitude



Qualitative schematic — not patient data

Anatomic pattern helps narrow the cause

- Mononeuropathy involves one nerve; Trauma, compression, and infiltration are considerations.
- Symmetric polyneuropathy often suggests a diffuse metabolic or toxic mechanism.
- Asymmetric multifocal deficits suggest a patchy process such as vasculitic neuropathy.

Single named nerve

Symmetric distal

Patchy multifocal

Localization pattern constrains the differential

Etiologies cannot be classified by mechanism alone

- Metabolic, toxic, vascular, physical, hereditary, and neoplastic disorders can damage axons.
- Some named diseases produce axonal and demyelinating changes together.
- The neuropathy pattern must be interpreted alongside history, distribution, and morphology.

Metabolic

Diabetes • uremia

Toxic

Alcohol • solvents • drugs

Vascular / focal

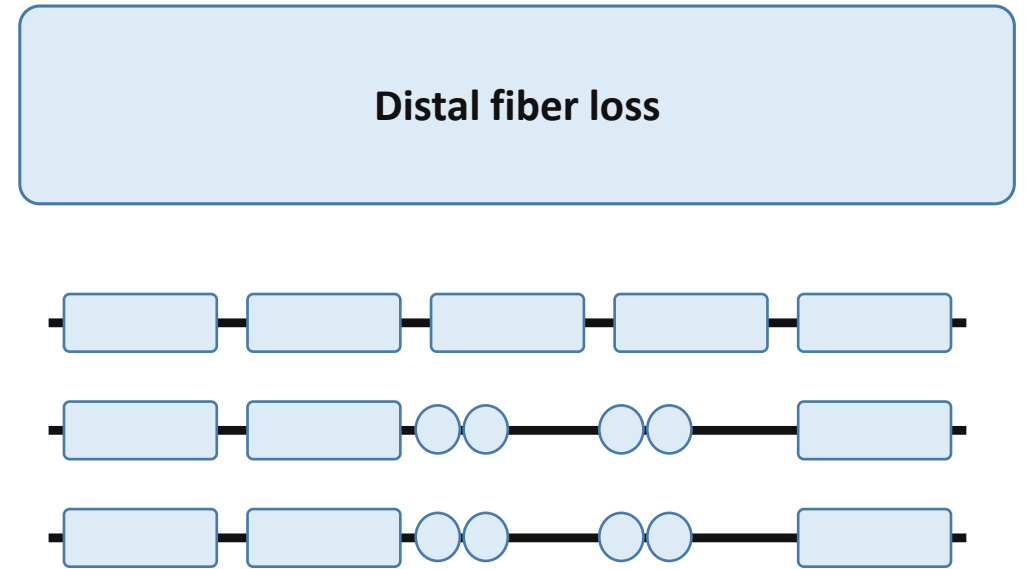
Vasculitis • compression

Hereditary

CMT2 • amyloid

Diabetes is a major cause of axonal polyneuropathy

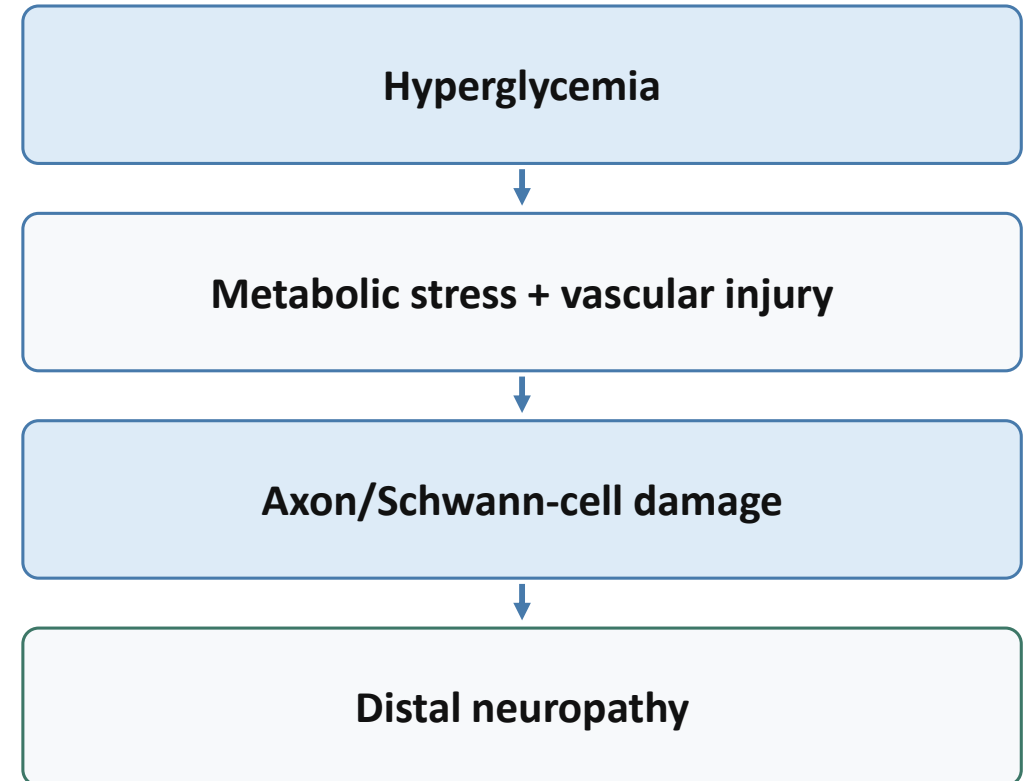
- The most common diabetic pattern is distal symmetric sensorimotor polyneuropathy.
- Predominant pathologic change is axonal loss, with variable ongoing degeneration and regeneration.
- Sensory fibers are usually most affected; Autonomic fibers can also be involved.



Educational schematic, not histology

Diabetic injury involves metabolic and vascular factors

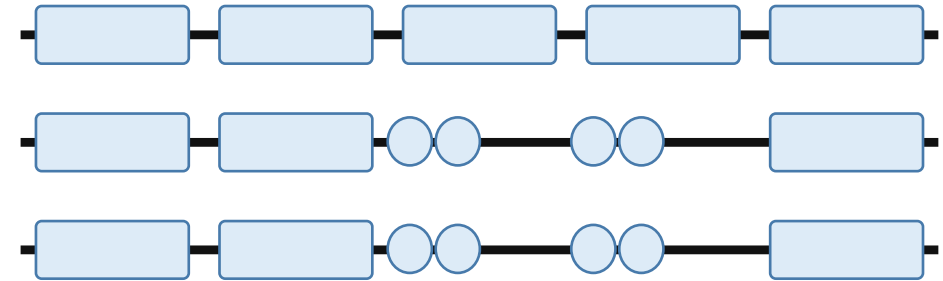
- Hyperglycemia contributes to nonenzymatic glycosylation and advanced glycosylation end products.
- Polyol-pathway flux, oxidative stress, and altered vascular supply may add to injury.
- The overall mechanism is complex and not completely defined.



Microangiopathic change accompanies diabetic axon loss

- Endoneurial arteriolar walls may be thickened and hyalinized.
- PAS-positive vascular walls and reduplicated basement membranes.
- Nerve sections show reduced axon numbers with degeneration or regenerative clusters.

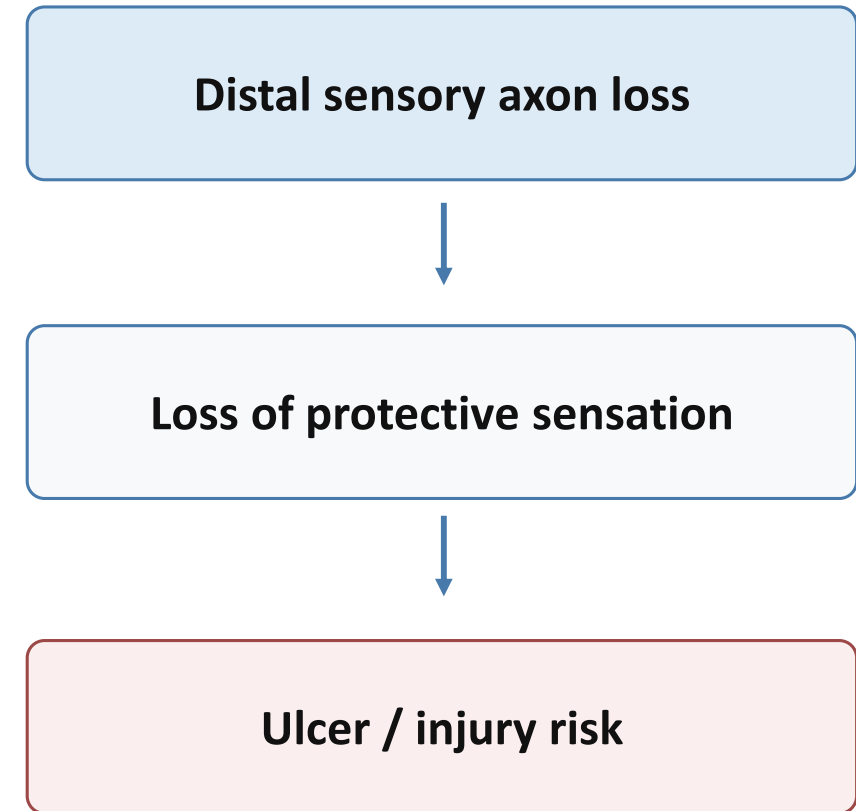
Axon loss + endoneurial vascular thickening



Educational schematic, not histology

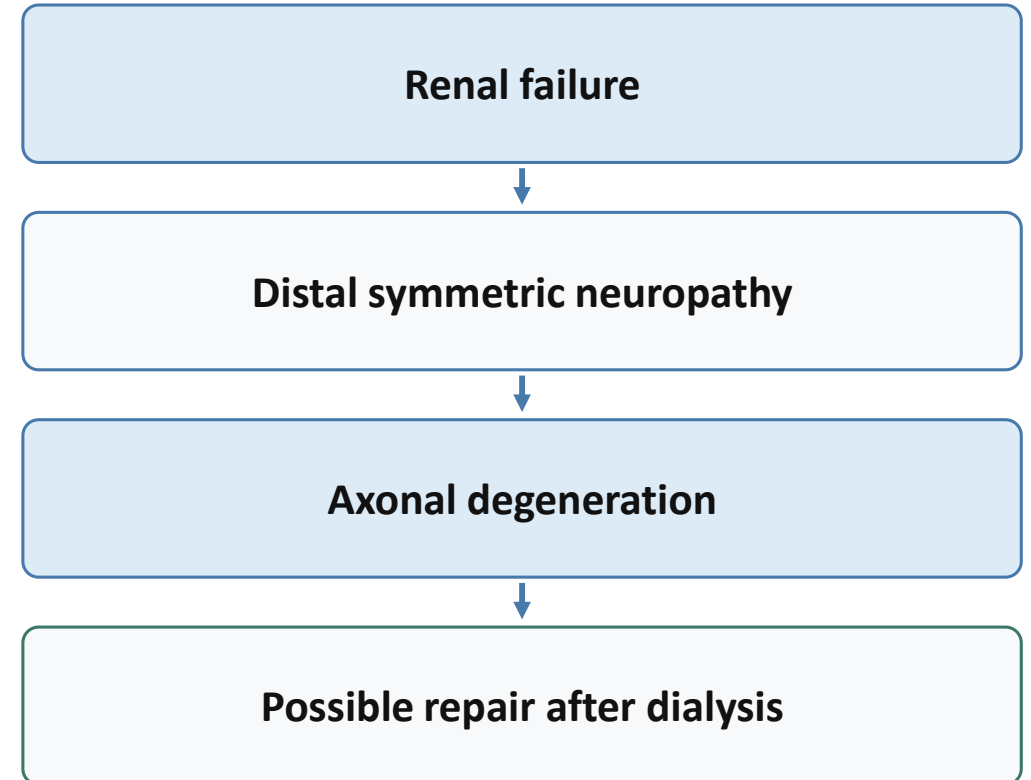
Clinical effects of diabetic distal axon loss

- Loss of protective sensation contributes to chronic skin injury and ulcers.
- Sensory impairment can make balance difficult and increase susceptibility to foot and ankle injury.
- Positive sensory symptoms include painful paresthesias and dysesthesias.



Uremia commonly causes distal axonal degeneration

- Uremic neuropathy is usually a distal symmetric neuropathy.
- Manifestations can include distal dysesthesias, cramps, and reduced deep tendon reflexes.
- Axonal degeneration is primary; Secondary demyelination may occur.



Endocrine and nutritional disorders add alternatives

- Hypothyroidism may cause an axonal sensory polyneuropathy or focal entrapment neuropathy.
- Deficiencies of thiamine, pyridoxine, vitamin E, folate, copper, and zinc are associated with neuropathy.
- Vitamin B12 deficiency produces additional long-tract spinal-cord disease and mixed peripheral changes.

Endocrine

Hypothyroidism

Nutritional

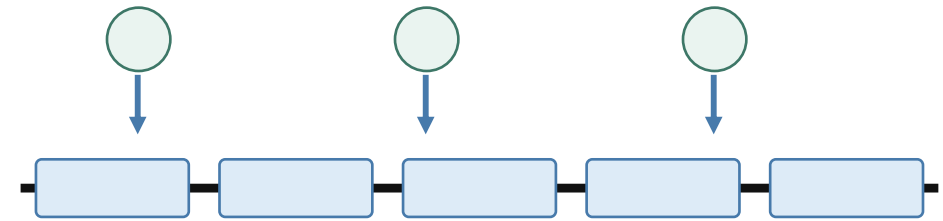
B1, B6, E, folate, copper, zinc

B12

Mixed peripheral + spinal disease

Toxic insults can target peripheral axons

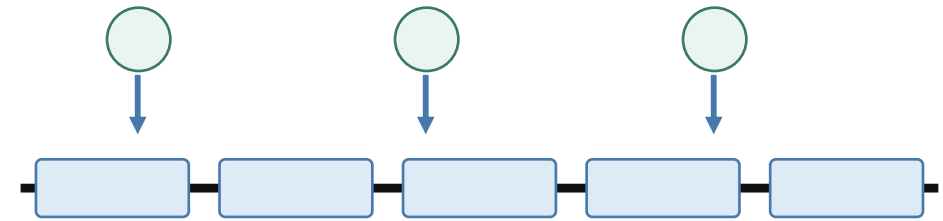
- Potential exposures include alcohol, heavy metals, organic solvents, and therapeutic drugs.
- Industrial exposures and neurotoxic chemotherapy merit specific history-taking.
- Toxic neuropathy may be axonal, demyelinating, or mixed depending on the agent.



Axonal transport can be disrupted by microtubule inhibitors

Microtubule inhibitors disrupt axonal transport

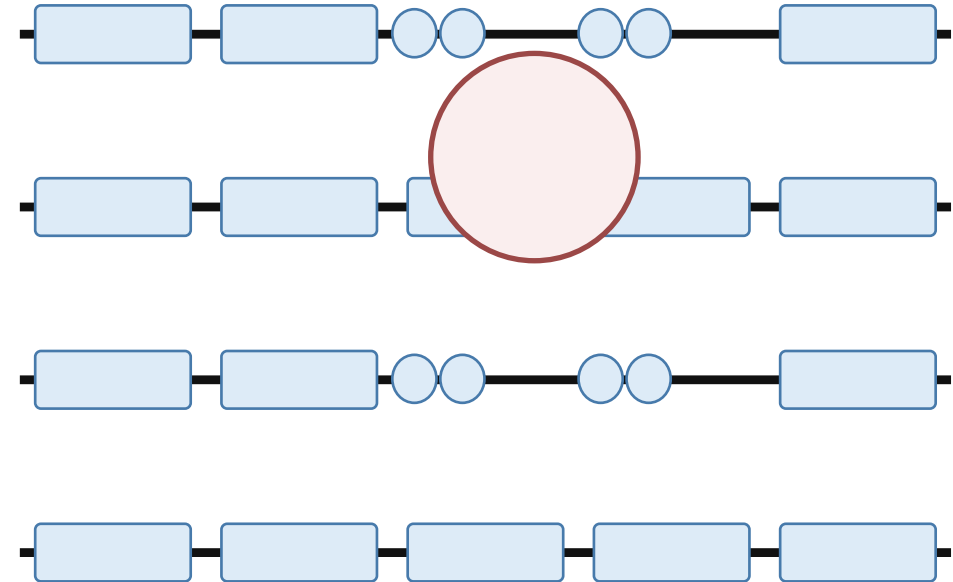
- Vinca alkaloids and taxanes are cited as microtubule inhibitors that interfere with axonal transport.
- Peripheral axons rely on structural integrity along extensive distances.
- The specific exposure and clinical pattern should guide attribution; Not all chemotherapy neuropathies are identical.



Axonal transport can be disrupted by microtubule inhibitors

Vasculitis produces patchy axonal loss

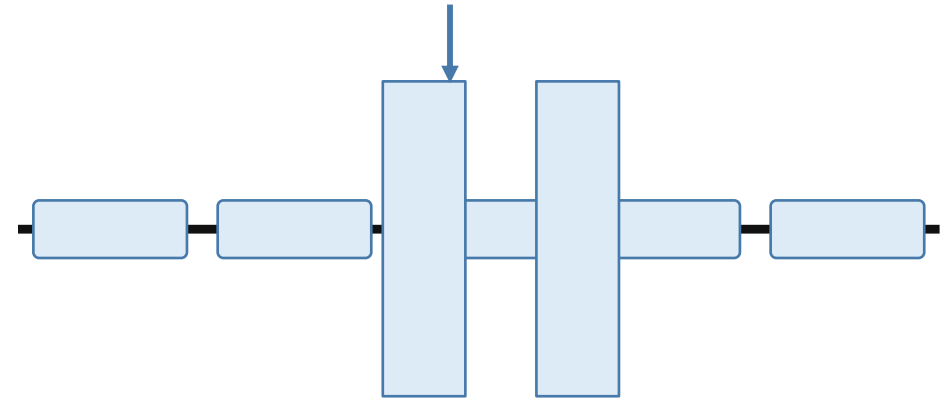
- Destructive inflammation of supplying vessels can damage peripheral nerve fascicles.
- The loss is commonly asymmetric, with some fascicles affected more severely than others.
- Mononeuritis multiplex is a typical presentation; Vessel injury supports the histologic diagnosis.



Focal vascular injury

Physical forces generate axonal injury

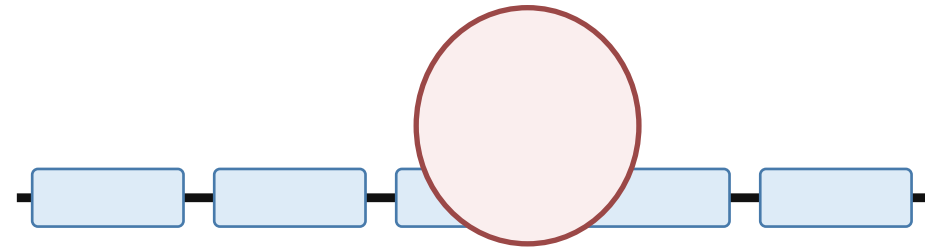
- Laceration and avulsion can sever peripheral nerve axons.
- Prolonged compression within anatomic compartments can damage nerve fibers.
- A focal neurologic deficit follows the distribution of the injured nerve.



Mechanical constriction or transection

Cancer-associated nerve lesions have several routes

- Direct infiltration or compression by a tumor can cause an axonal mononeuropathy.
- Paraneoplastic disease and treatment-related toxicity are additional pathways.
- Protein deposition, including amyloid, can contribute in selected hematologic disorders.



Mass effect near peripheral nerve

Inherited neuropathy may have an axonal phenotype

- Charcot–Marie–Tooth disease comprises genetically heterogeneous motor and sensory neuropathies.
- CMT2 is predominantly axonal; CMT1 is generally demyelinating.
- The overlap means neither the clinical phenotype nor the family history alone establishes the molecular cause.

CMT1

Predominantly demyelinating

CMT2

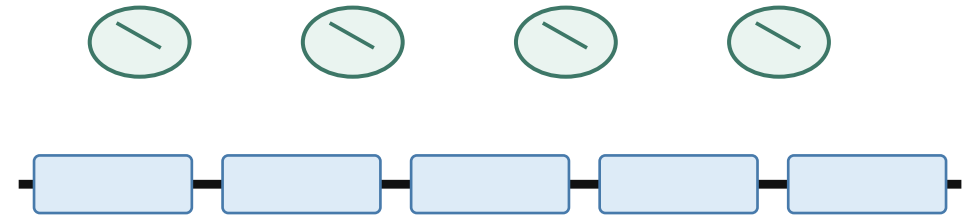
Predominantly axonal

Clinical

Distal weakness, sensory change

MFN2-related CMT2A links mitochondria to axons

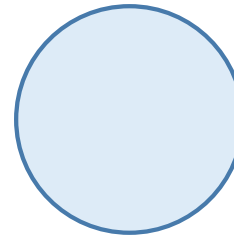
- CMT2A is described as an axonal Charcot–Marie–Tooth subtype.
- Pathogenic MFN2 variants affect mitofusin 2, required for normal mitochondrial fusion.
- The hereditary mechanism provides an example of how axonal maintenance can fail.



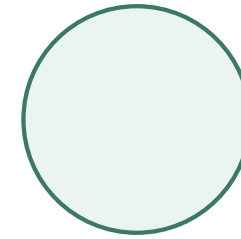
MFN2: Mitochondrial fusion pathway

Hereditary sensory and autonomic axonopathies

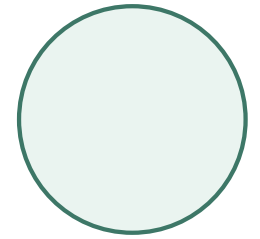
- Hereditary sensory neuropathies commonly produce loss of pain and temperature sensation.
- Motor strength may be preserved despite extensive sensory dysfunction.
- Impaired nociception predisposes to unrecognized injuries of hands and feet.



Large sensory



Small sensory

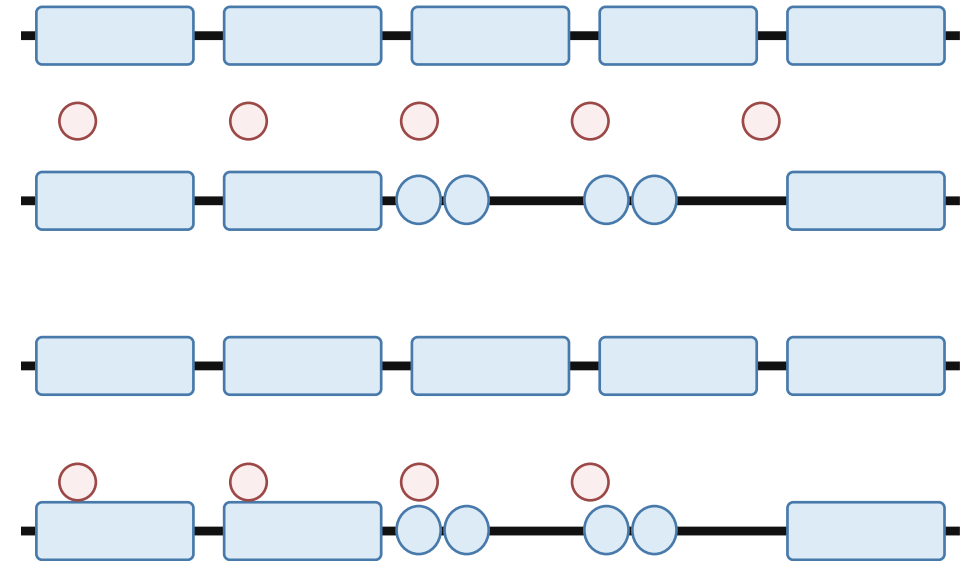


Autonomic

Loss of protective pain sensation

Amyloid deposition can damage peripheral nerves

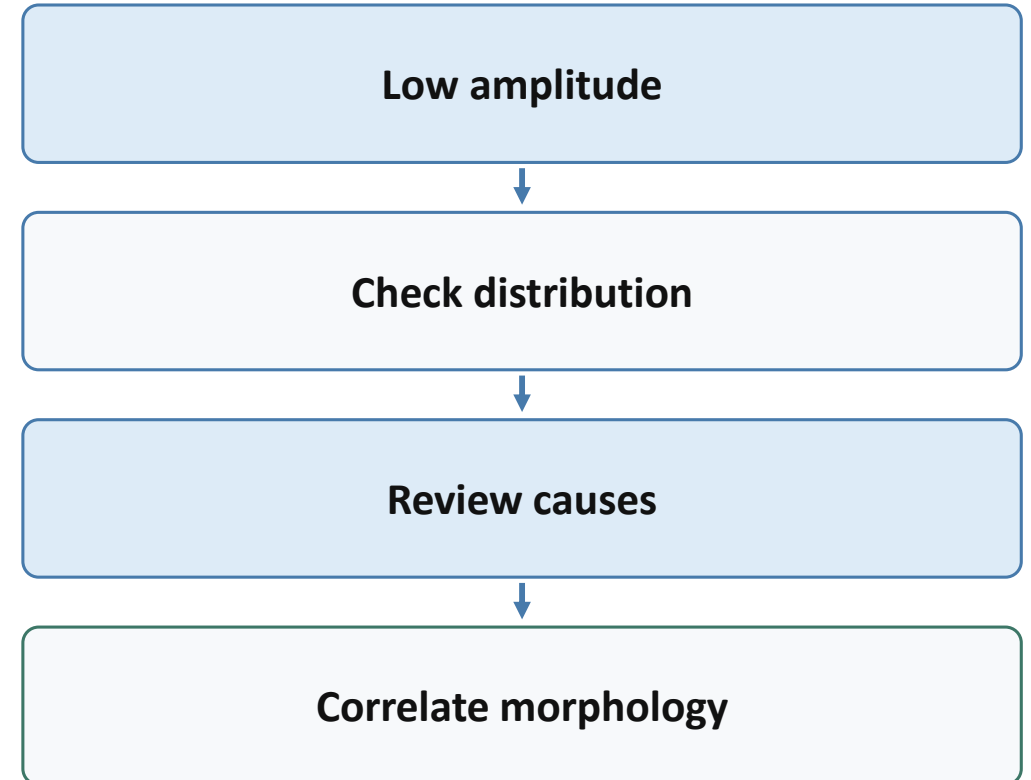
- Familial amyloid polyneuropathy is often associated with pathogenic TTR variants.
- Amyloid deposition within peripheral nerve accompanies a sensory–autonomic phenotype.
- Congo-red staining under polarized light and electron microscopy as morphologic methods.



Amyloid deposition around nerve fibers (schematic)

A low-amplitude response is not an etiologic diagnosis

- The finding supports reduced numbers of conducting axons.
- It does not specify whether injury was metabolic, toxic, vascular, inherited, or traumatic.
- Clinical distribution and history determine the next diagnostic branch.



Do not equate myelin debris with demyelinating disease

- Myelin degeneration occurs secondarily when a distal axon degenerates.
- Primary demyelinating injury predominantly targets Schwann-cell internodes.
- Consider intact axon numbers and the electrophysiologic pattern before assigning the category.

Myelin debris



Could follow primary axon injury

Classify by the primary damaged structure

Case: Length-dependent sensory symptoms

- A person with longstanding diabetes reports bilateral toe numbness that gradually spreads up the feet.
- The distribution suggests a length-dependent distal symmetric neuropathy.
- Predominantly axonal injury is consistent with the common diabetic neuropathy pattern.

Longest axon



Intermediate axon



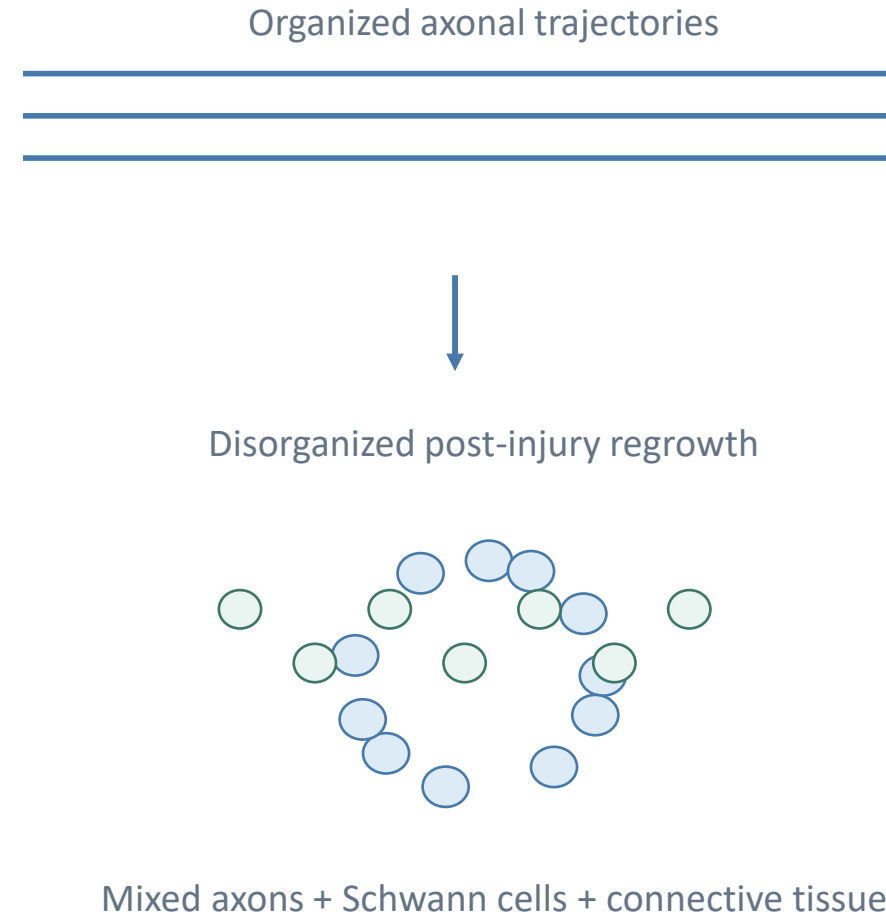
Shorter axon



Distal end is affected earliest in length-dependent damage

Case: A painful nodule after transection

- A painful nodule develops at the site of a previously severed peripheral nerve.
- Disorganized axonal sprouting with Schwann cells suggests traumatic neuroma.
- The lesion is a regenerative pseudotumor rather than a true neoplasm.



Case: Multifocal asymmetric weakness

- An individual develops deficits in two anatomically unrelated peripheral nerves.
- The asymmetry points toward a multifocal pattern rather than symmetric dying-back neuropathy.
- Vasculitis is an important cause because it produces patchy axonal degeneration.

Single named nerve

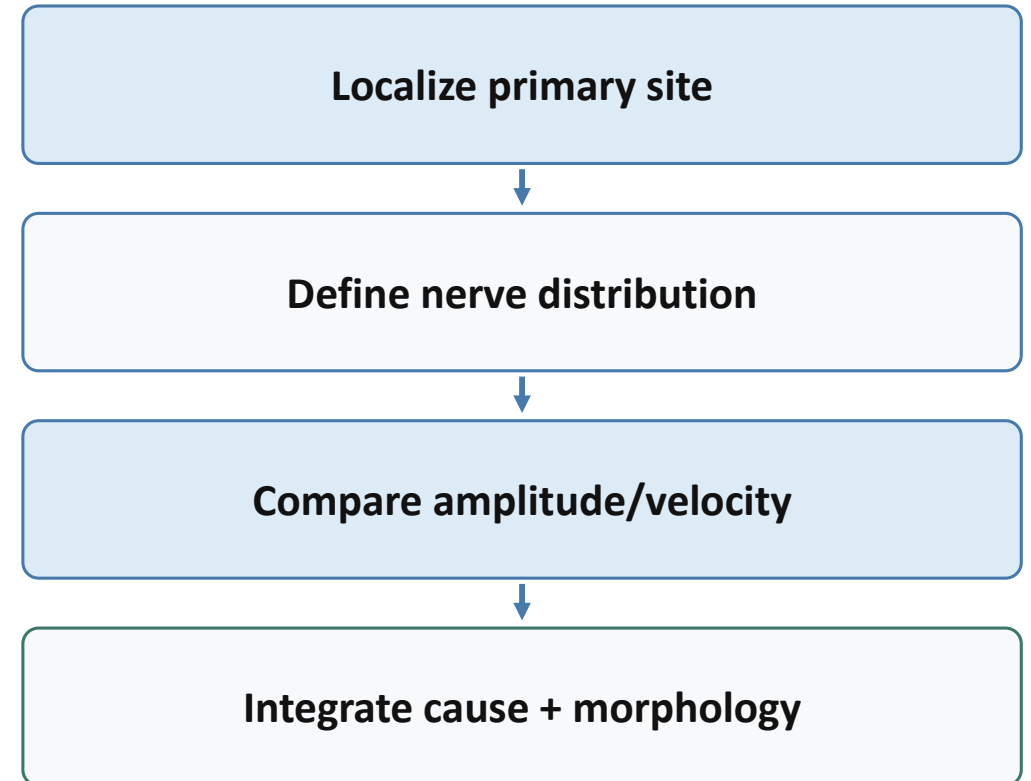
Symmetric distal

Patchy multifocal

Localization pattern constrains the differential

A practical pattern-based interpretation

- Localize the dominant process: Axon, myelin, or neuronal cell body.
- Identify the distribution: Single nerve, symmetric length-dependent, asymmetric multifocal, or root/nerve involvement.
- Correlate response amplitude, conduction velocity, history, and available morphology.
- Consider coexisting mechanisms rather than forcing a purely axonal or demyelinating label.



Synthesis: injury, repair, and outcome

- Primary axonal injury can cause distal fragmentation with myelin-ovoid formation and macrophage clearance.
- Proximal sprouts regenerate along Schwann-cell pathways; the replacement internodes are shorter and thinner.
- Continuing injury may overwhelm repair, producing distal axon loss and falling nerve-response amplitude.
- Mechanism, anatomy, and cause must be integrated rather than inferred from a single isolated finding.

