

Inflammatory Neuropathies

Mechanisms, morphology, and clinicopathologic patterns

Guillain–Barré syndrome • CIDP • Autoimmune nodopathy • Vasculitis

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Learning outcomes: From injury to clinical pattern

Nerve structure



Immune mechanism



Morphologic lesion



Clinicopathologic pattern

- Distinguish segmental demyelination from axonal degeneration.
- Explain immune mechanisms and pathologic findings in GBS and CIDP.
- Recognize autoimmune and vasculitic patterns of nerve injury.
- Integrate distribution, time course, pathology, and supportive tests.

The immune-mediated neuropathy spectrum

Acute demyelinating

Guillain–Barré syndrome

Chronic demyelinating

CIDP

Nodal/paranodal

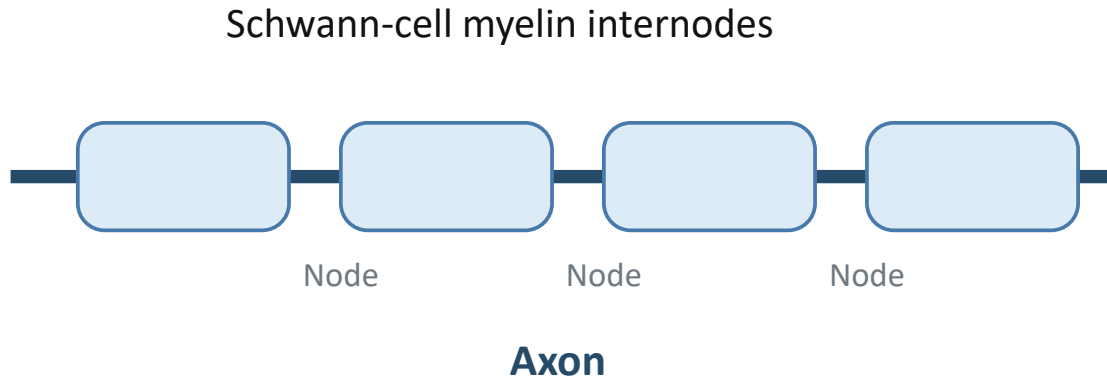
Autoimmune nodopathy

Axonal / vascular

Systemic disease; Vasculitis

- Guillain–Barré syndrome: Typically acute demyelinating radiculoneuropathy.
- CIDP: Acquired chronic inflammatory demyelinating neuropathy.
- Autoimmune nodopathies: Antibodies target nodal/paranodal proteins.
- Systemic autoimmunity and vasculitis: Often axonal patterns.

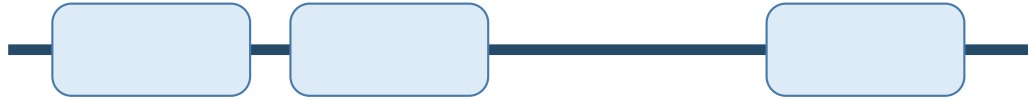
Anatomy: Axon, Schwann cell, and myelin internode



- Peripheral axons transmit impulses from neuronal cell bodies.
- Schwann cells form discrete myelin segments around individual axons.
- Nodes of Ranvier separate internodes and support saltatory conduction.

Primary demyelination differs from axonal injury

Demyelination: Axon remains



Axonal loss: Conducting fiber disrupted



- Demyelination removes myelin segments while initially sparing the axon.
- Axonal injury directly disrupts the conducting process.
- Both processes may coexist as immune-mediated disease becomes severe.

Electrophysiology mirrors the site of injury

Demyelinating

Impulse conduction slows

Axonal

Signal amplitude falls



Velocity

Amplitude

- Myelin loss slows impulse propagation and therefore conduction velocity.
- Loss of functioning axons chiefly decreases recorded signal amplitude.
- A mixed lesion can produce more than one type of abnormality.

Distribution identifies the involved compartment

Symmetric

Polyneuropathy

Roots + nerves

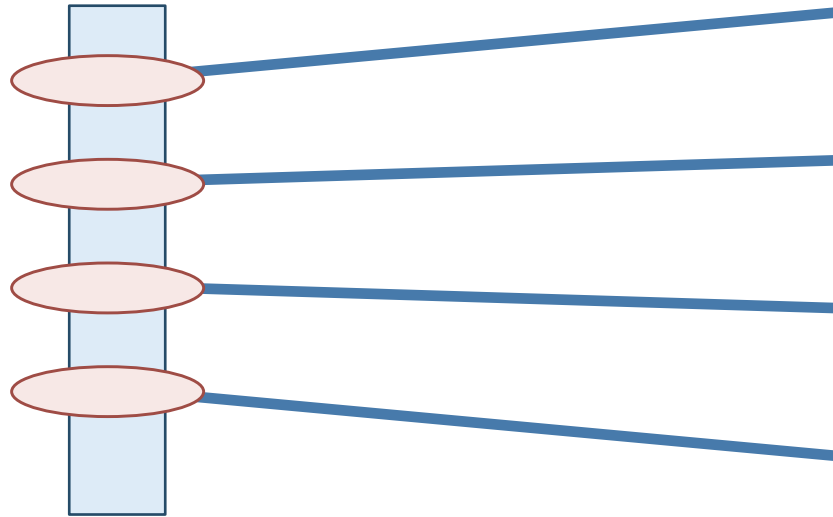
Polyradiculoneuropathy

Patchy, named nerves

Mononeuritis multiplex

- Polyneuropathy affects numerous nerves, commonly symmetrically.
- Polyradiculoneuropathy includes roots and peripheral nerves.
- Mononeuritis multiplex injures distinct named nerves asymmetrically.

Why root involvement changes the interpretation

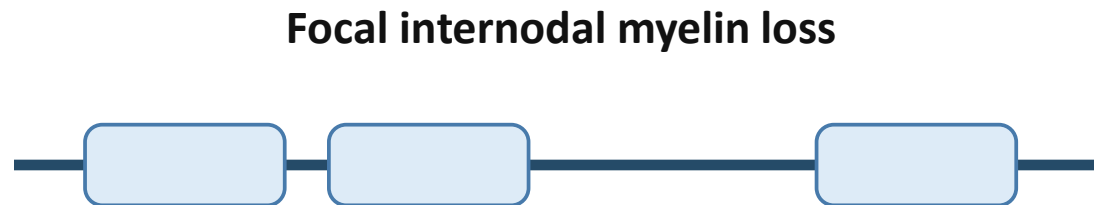
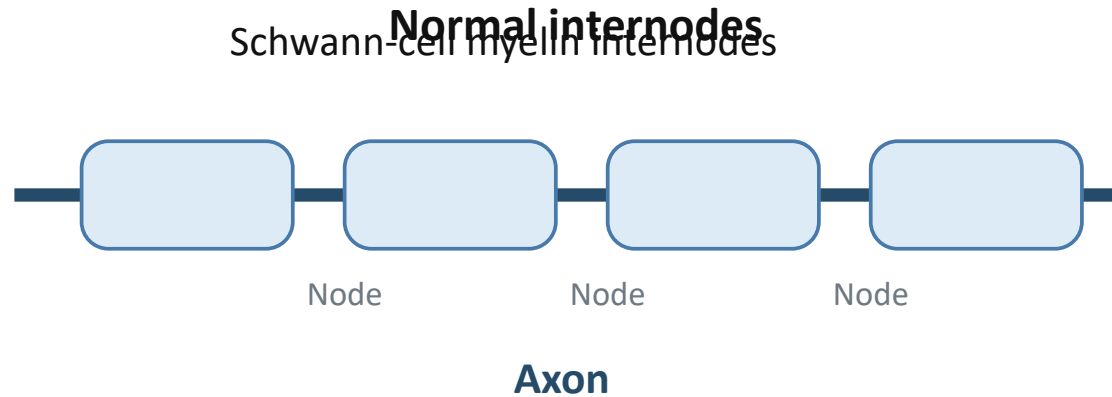


Spinal nerve roots

Peripheral nerve trunks

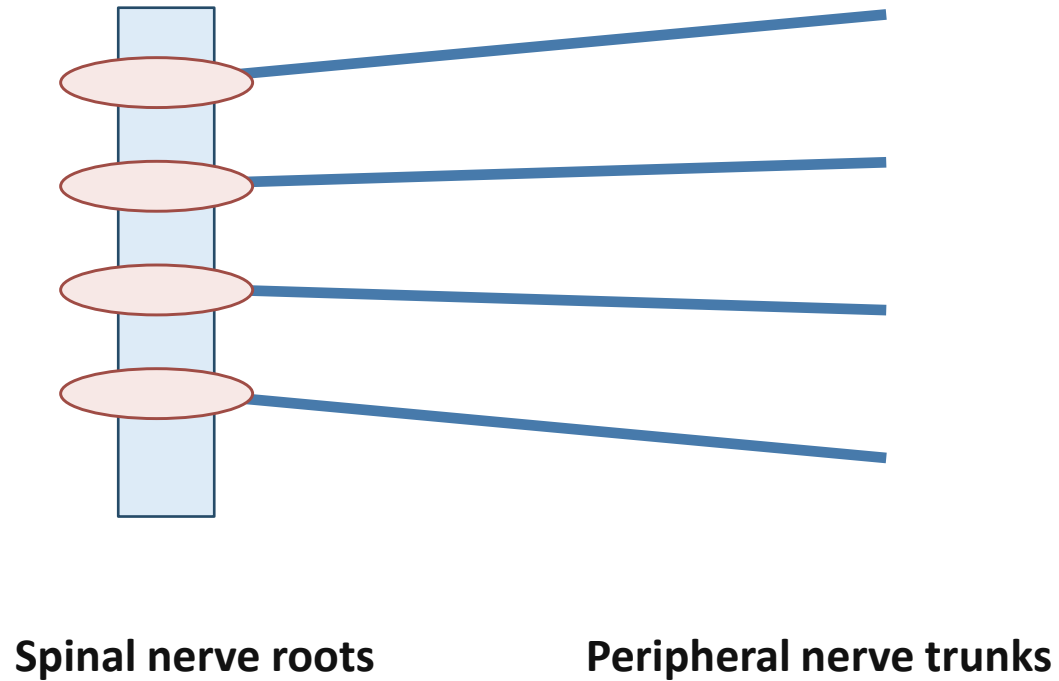
- Nerve-root plus peripheral nerve injury produces proximal and distal deficits.
- GBS and CIDP belong to this radiculoneuropathic pattern.
- Pathologic involvement cannot be inferred from a distal-nerve symptom alone.

Morphologic vocabulary used throughout the lecture



- Segmental demyelination: Loss of an internode or its myelin lamellae.
- Remyelination: A repaired segment is often shorter and thinner.
- Axonal degeneration/regeneration: Direct loss and attempted restoration of axons.
- Inflammatory cells and abnormal vessels identify the injury context.

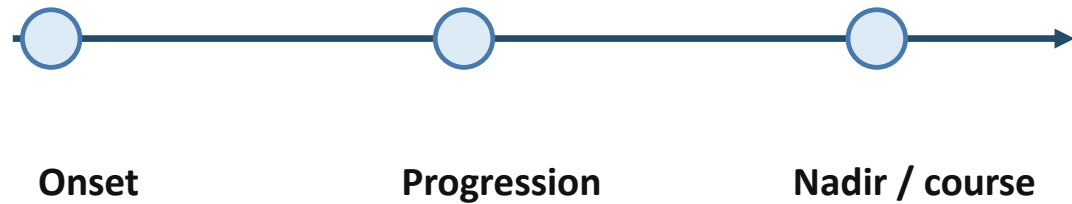
Guillain–Barré syndrome: Acute immune neuropathy



- GBS commonly manifests as acute inflammatory demyelinating polyradiculoneuropathy (AIDP).
- Inflammatory injury involves nerve roots and peripheral nerves.
- Progressive weakness can culminate in respiratory paralysis.

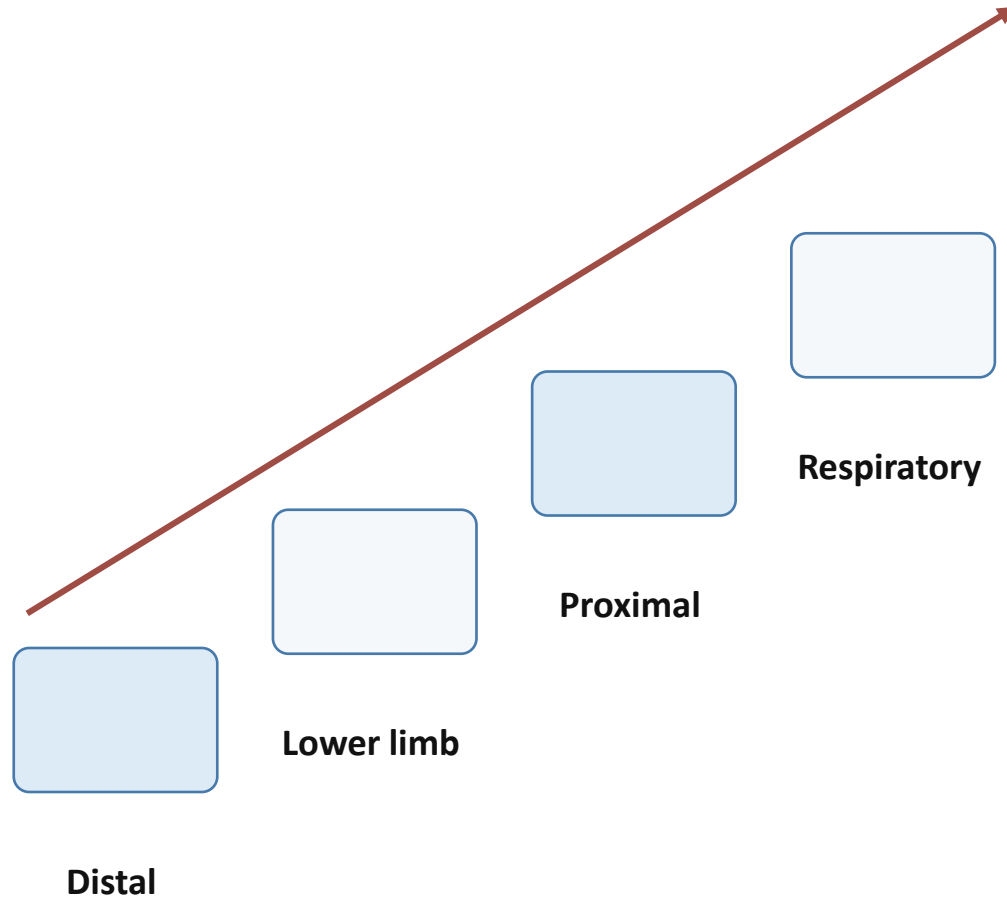
GBS: Epidemiology and overall phenotype

Clinical change over time



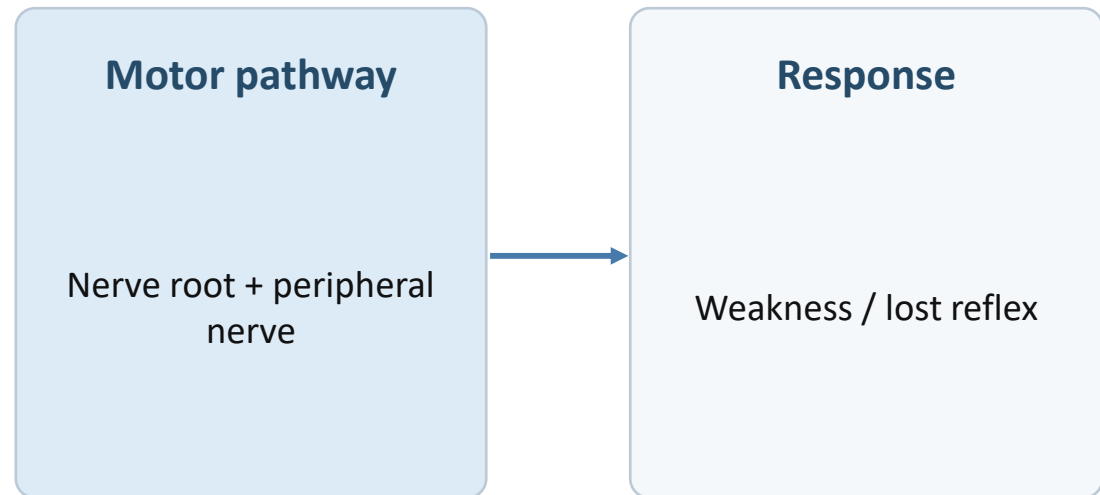
- The textbook estimates approximately one new case per 100,000 persons annually.
- Weakness often begins distally and advances toward proximal muscle groups.
- This rapid ascending paralysis is a defining clinical pattern.

GBS: The ascending weakness pattern



- Distal limb weakness develops first in the classic presentation.
- Weakness extends to larger proximal muscle groups as disease progresses.
- This clinical pattern directs attention toward an acute diffuse peripheral process.

GBS: Loss of tendon reflexes



- Deep tendon reflexes are lost early in the illness.
- Areflexia accompanies the progressive limb weakness.
- Combined weakness and reduced reflexes support peripheral nerve/root dysfunction.

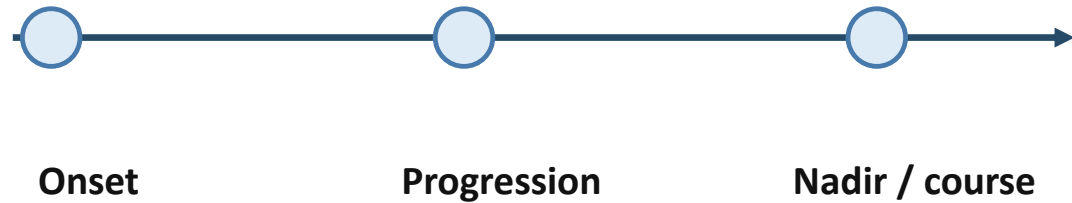
GBS: Sensory findings are usually less prominent

- Sensory disturbance may accompany weakness, including impaired pain sensation.
- The motor syndrome generally dominates the clinical presentation.
- Absence of a striking sensory deficit does not exclude the classic pattern.

GBS: The characteristic acute time course

GBS: Nadir ≤ 4 weeks

CIDP: ≥ 8 weeks



- Weakness reaches its nadir within 4 weeks of onset.
- The early course may be rapidly progressive rather than steadily chronic.
- Time to maximal weakness distinguishes it from the typical CIDP course.

Illustrative case: Acute areflexic weakness

Clinical observation

Localize the nerve dysfunction



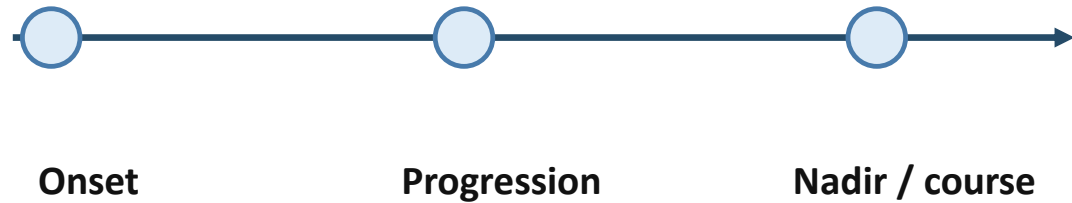
Pathologic interpretation

Identify the injury pattern

- An adult develops distal weakness after an upper respiratory illness.
- Weakness rapidly extends proximally; Tendon reflexes disappear.
- Question: Which clinical features favor GBS over a chronic neuropathy?

The antecedent illness is a major etiologic clue

Clinical change over time



- Approximately two-thirds of patients have a preceding acute upper respiratory illness.
- Neuropathy often begins after apparent recovery from that illness.
- The temporal interval supports an immune response rather than direct nerve infection.

Microbial exposures associated with GBS

C. Jejuni

CMV

EBV

M. Pneumoniae

Zika

SARS-CoV-2

- Campylobacter jejuni and cytomegalovirus have epidemiologic associations.
- Epstein–Barr virus and Mycoplasma pneumoniae are also associated.
- The textbook also lists Zika virus and SARS-CoV-2.

Vaccination: Interpret temporal reports cautiously

- Rare GBS cases have been reported following certain vaccinations.
- The textbook mentions influenza, varicella-zoster, and non-mRNA SARS-CoV-2 vaccines.
- A report of temporal association should not be equated with proof of causality.

The major distinction: Postinfectious versus infectious nerve injury

Microbial exposure



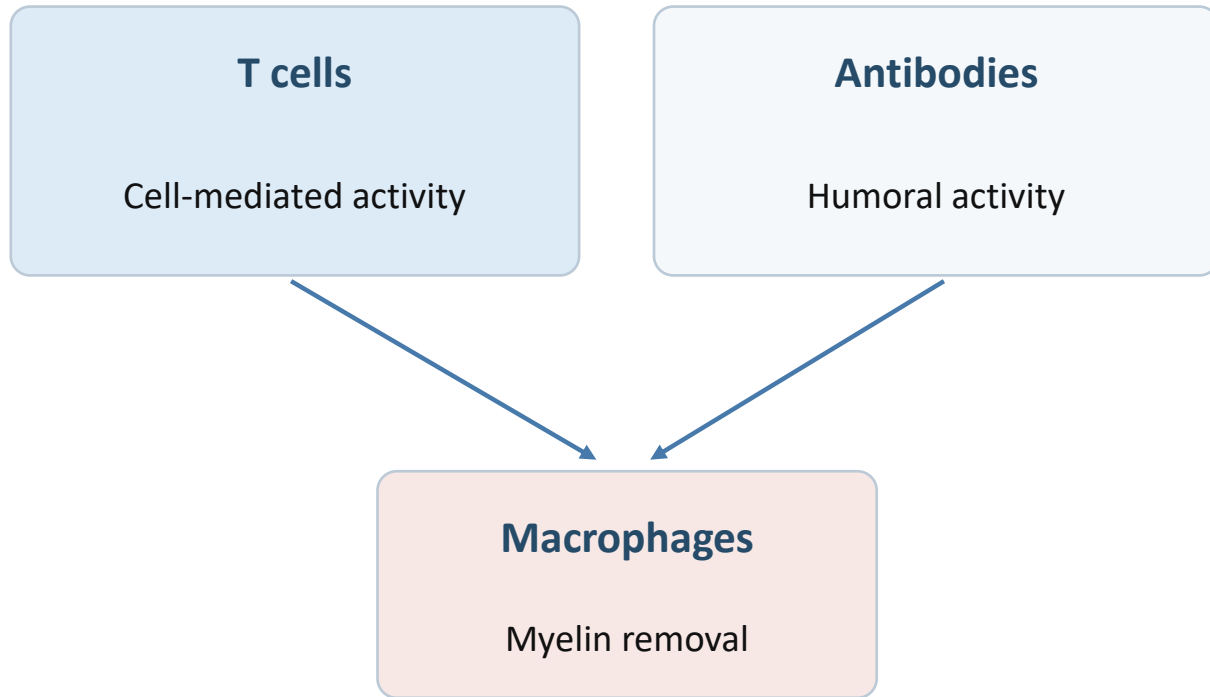
Host immune response



Peripheral nerve injury

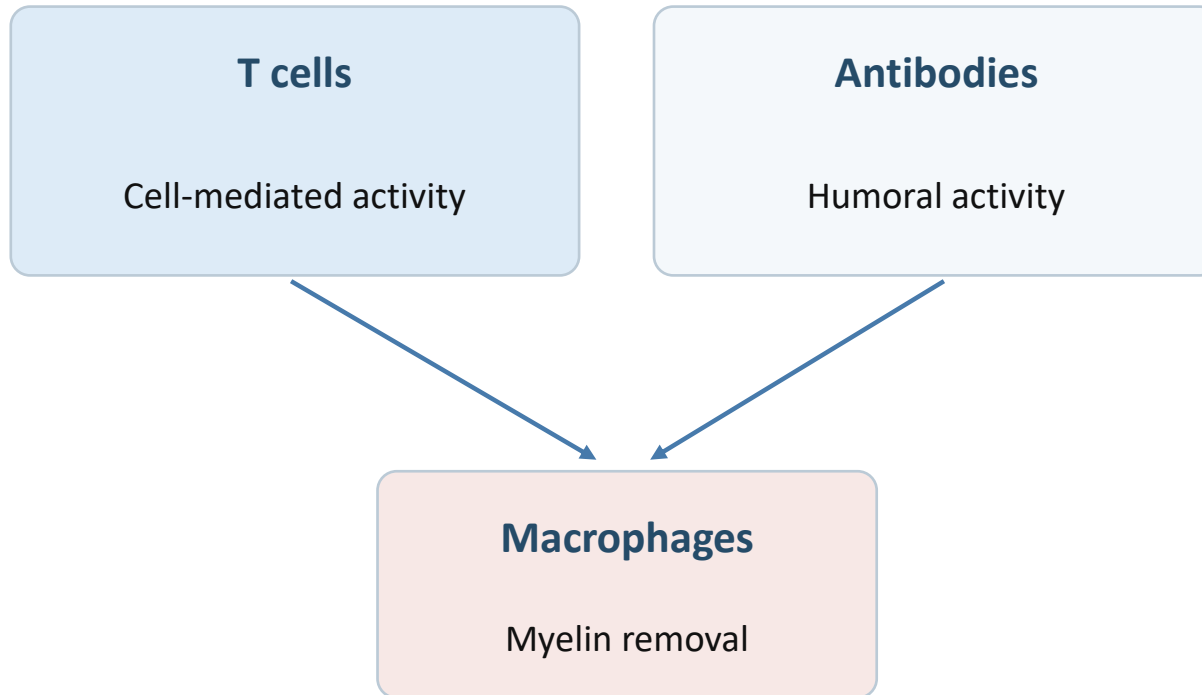
- No infectious organism has been demonstrated in affected GBS nerves.
- The favored mechanism is an immune reaction following exposure to microbial antigens.
- This contrasts with neuropathies resulting from direct infectious damage.

Experimental models support cell-mediated demyelination



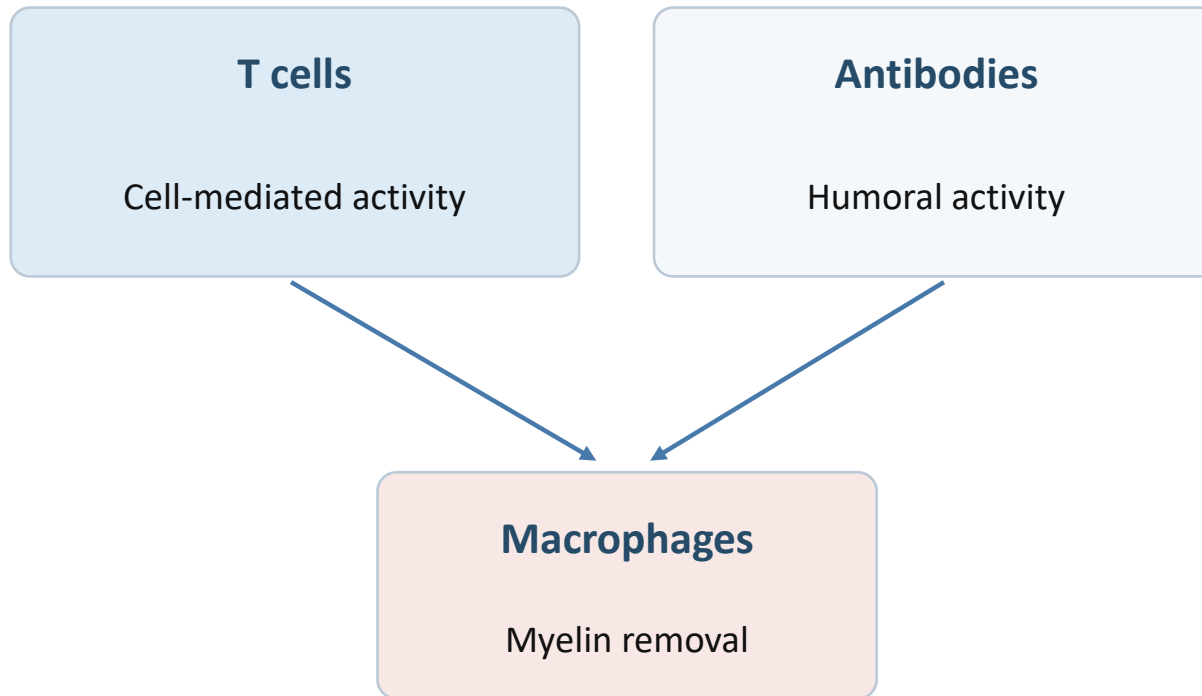
- Immunization with a peripheral-nerve myelin protein can reproduce inflammatory lesions.
- T-cell responses accompany macrophage-induced segmental myelin loss.
- Transfer of sensitized T cells can reproduce comparable lesions.

Patient lymphocytes can damage myelinated fibers



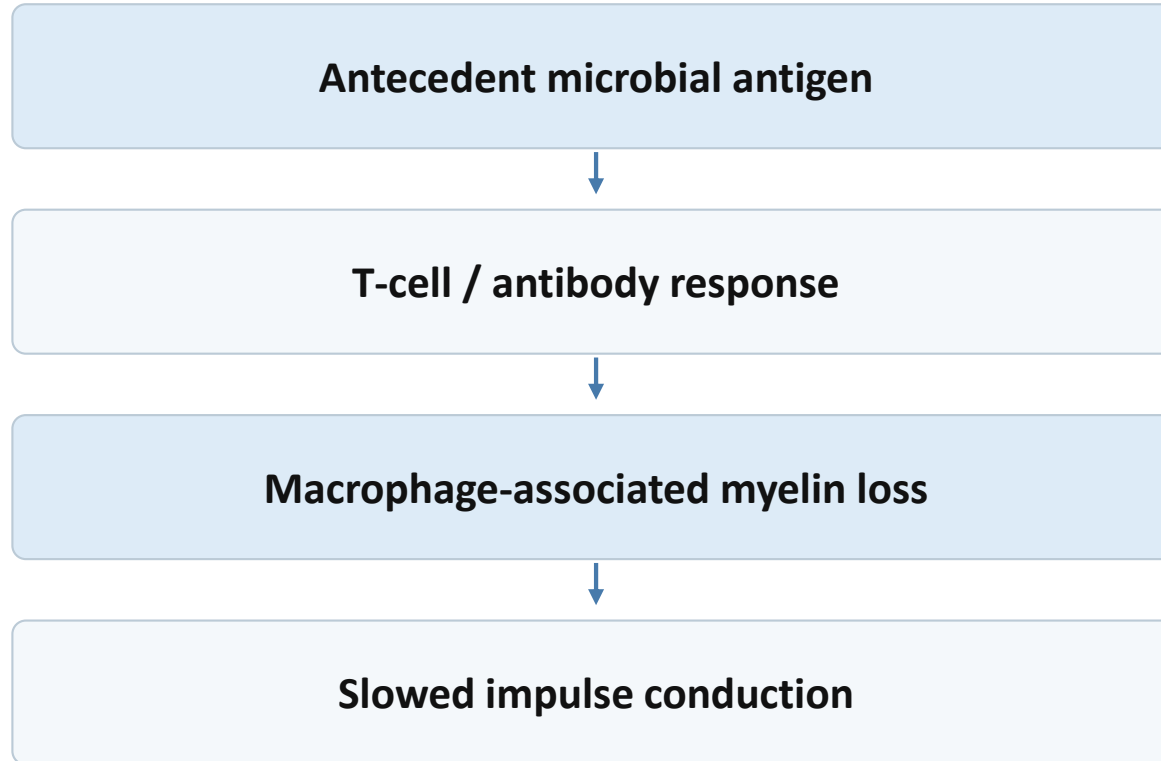
- In experimental co-culture, lymphocytes from individuals with GBS cause demyelination.
- This supports a role for cellular immune mechanisms.
- Cell-based evidence complements, rather than excludes, antibody effects.

Humoral immunity may also contribute



- Circulating antibodies may cross-react with peripheral nerve components.
- Antibody-mediated injury is one proposed part of the autoimmune response.
- The GBS phenotype is not attributed to a single uniform mechanism.

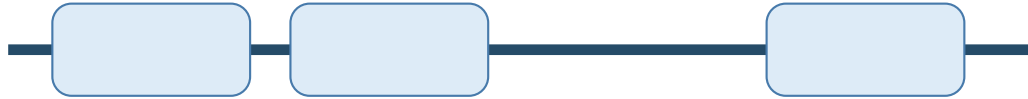
GBS pathogenesis: From trigger to myelin injury



- An antecedent microbial exposure is followed by immune activation.
- T lymphocytes and macrophages participate in demyelinating injury.
- Cross-reacting antibodies may contribute in at least some cases.

AMAN: An axonal variant within the GBS spectrum

Demyelination: Axon remains



Axonal loss: Conducting fiber disrupted



- Acute motor axonal neuropathy (AMAN) is an uncommon axonal form of GBS.
- Its morphology features axonal degeneration and attempted regeneration.
- It shows a stronger association with antecedent *Campylobacter jejuni*.

AIDP and AMAN have different primary targets

AIDP

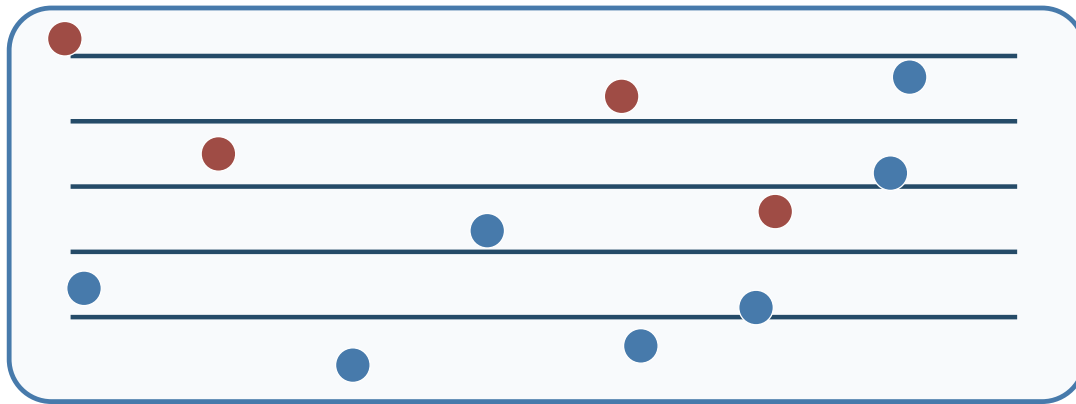
Segmental myelin injury

AMAN

Predominantly motor axon injury

- AIDP: Segmental myelin loss and remyelination dominate the lesion.
- AMAN: Motor axonal injury and regeneration dominate.
- This distinction prevents all GBS cases from being mislabeled as demyelinating.

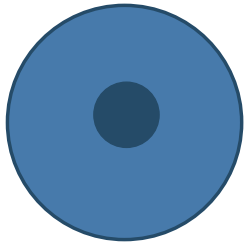
GBS pathology: Inflammation accompanies demyelination



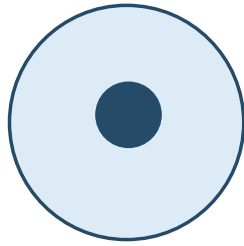
Perivenular / endoneurial inflammatory infiltrates

- H&E sections show inflammation within peripheral nerves.
- Inflammatory cells accumulate around venules and in the endoneurium.
- Both the inflammatory pattern and the myelin lesion matter.

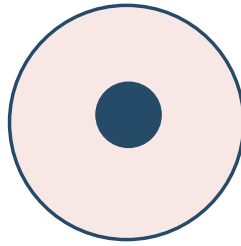
The cellular infiltrate is macrophage-rich



Macrophage



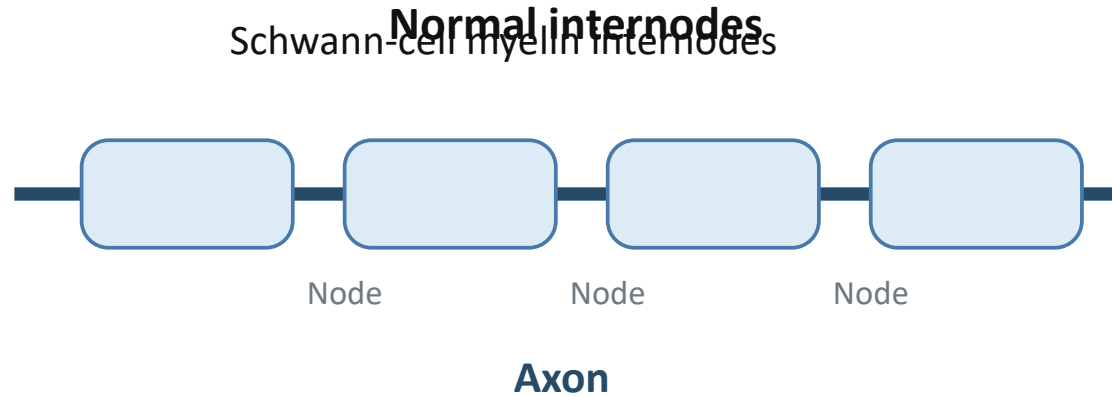
Lymphocyte



Plasma cell

- Macrophages are prominent in the affected nerves.
- Lymphocyte numbers vary; Plasma cells are comparatively few.
- Macrophages also participate directly in removal of damaged myelin.

Segmental demyelination is the dominant AIDP lesion

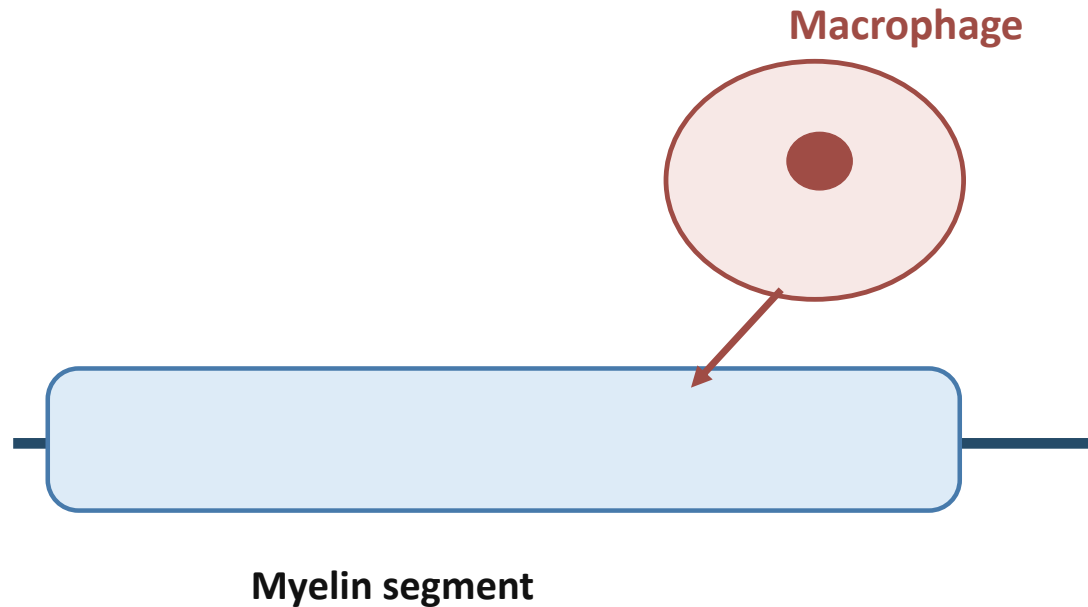


Focal internodal myelin loss



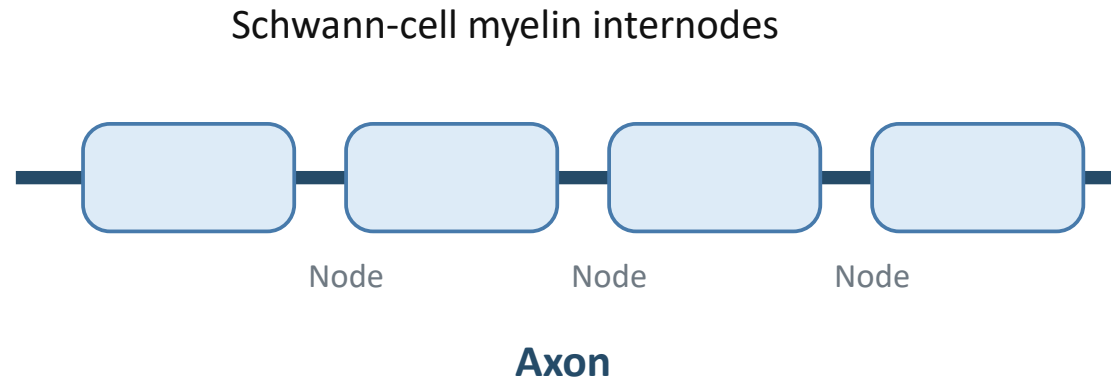
- Inflammatory attack removes portions of myelin along affected axons.
- Other internodes can remain relatively preserved.
- Widespread multifocal loss disrupts efficient nerve impulse conduction.

Macrophages can physically strip myelin



- Macrophage processes penetrate the Schwann-cell basement membrane.
- They extend between myelin lamellae and separate the sheath from the axon.
- Myelin fragments are subsequently engulfed and cleared.

Nodes of Ranvier are important sites of early injury



Node–paranode interface

- Ultrastructural observations place macrophage attack near nodal regions.
- Macrophages enter between lamellae rather than requiring initial axonal destruction.
- The microanatomic finding reinforces myelin-directed injury.

GBS may also produce axonal damage

Demyelination: Axon remains

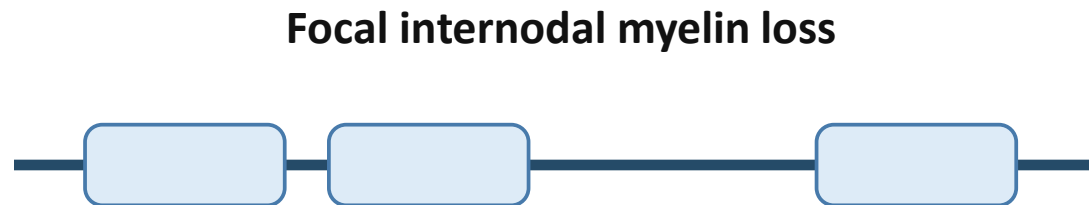
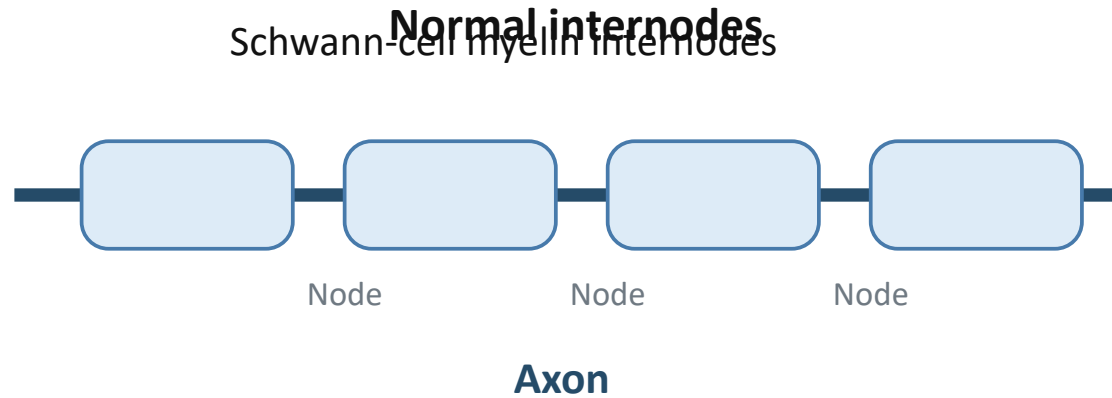


Axonal loss: Conducting fiber disrupted



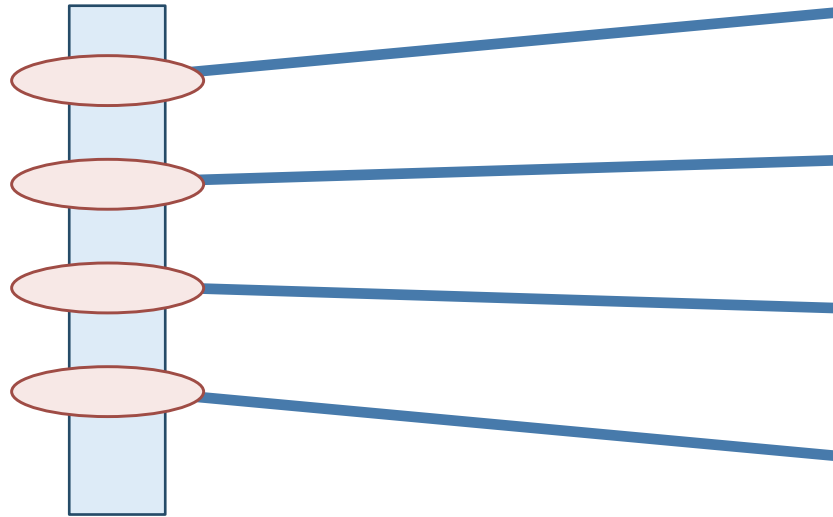
- Although myelin loss predominates in AIDP, axons can also be damaged.
- Secondary axonal injury becomes particularly relevant in severe disease.
- Mixed tissue injury helps explain residual functional impairment.

Myelin repair does not immediately restore normal architecture



- Schwann cells can form new myelin after segmental loss.
- The replacement internodes are typically shorter and thinner.
- The repaired fiber may differ structurally from the original.

Inflammation may extend across the peripheral nervous system



Spinal nerve roots

Peripheral nerve trunks

- Both roots and peripheral nerves can show inflammatory demyelination.
- The lesions tend to be more prominent proximally, near spinal roots.
- The proximal emphasis matches the designation polyradiculoneuropathy.

GBS electrophysiology: Why conduction is slowed

Demyelinating

Impulse conduction slows

Axonal

Signal amplitude falls

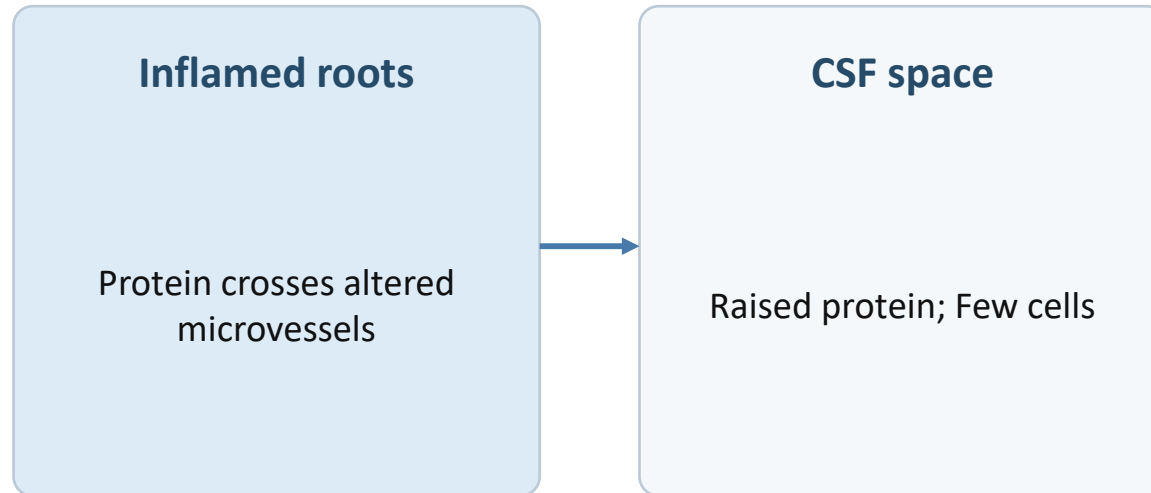


Velocity

Amplitude

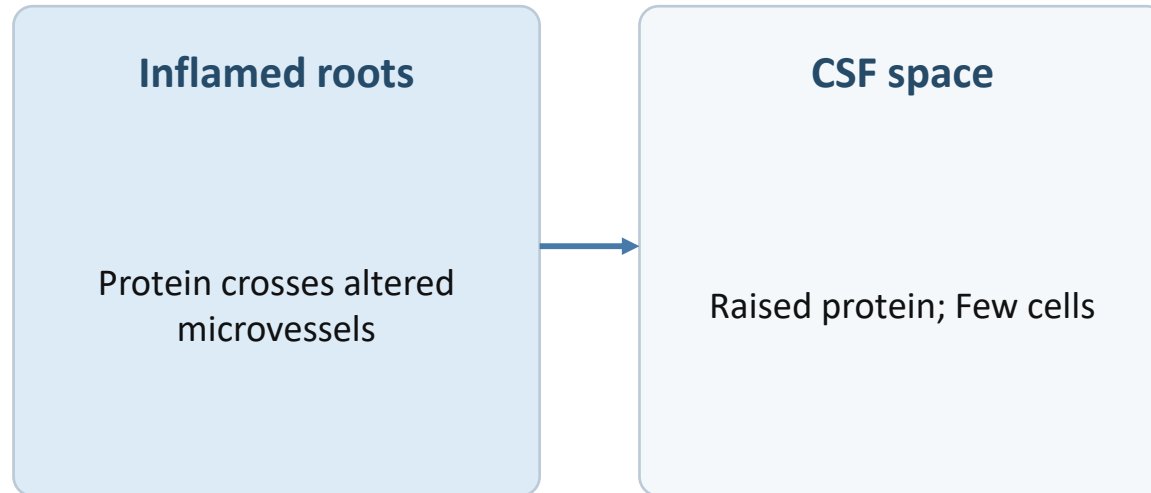
- Loss of multiple myelin segments disrupts saltatory impulse transmission.
- Consequently, nerve conduction velocities decrease.
- This finding supports a demyelinating pattern when integrated clinically.

GBS cerebrospinal fluid: Increased protein



- Inflammation alters the permeability of root microvessels.
- Root-associated proteins can enter cerebrospinal fluid (CSF).
- This accounts for raised CSF protein in the classic presentation.

GBS cerebrospinal fluid: Few inflammatory cells



- Inflammatory leukocytes generally remain localized within affected roots.
- Consequently, CSF has little or no pleocytosis despite raised protein.
- The mechanism explains the characteristic protein–cell dissociation.

GBS recognition integrates three evidence streams

Clinical distribution

- Clinical: Rapidly progressive ascending weakness with areflexia.

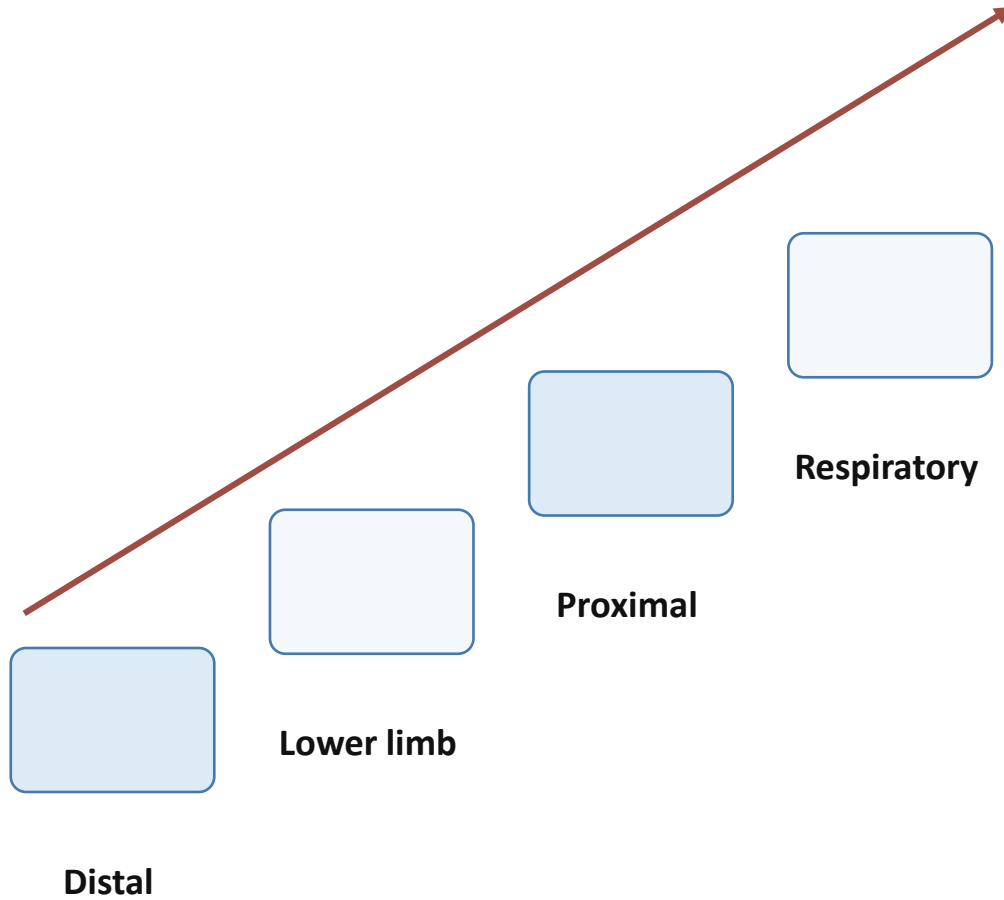
Nerve injury pattern

- Electrophysiology: Conduction slowing in the demyelinating form.

Corroborating pathology

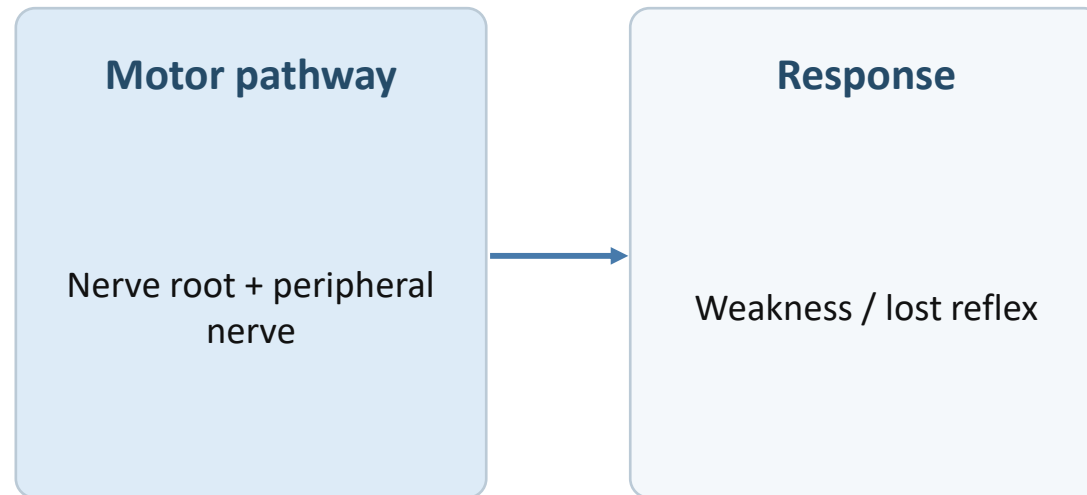
- CSF: High protein with few or no inflammatory cells.

Respiratory failure makes GBS time-critical



- Ascending weakness can impair the muscles required for ventilation.
- Severely affected individuals may require prolonged intensive care.
- Respiratory function requires close supportive monitoring.

Autonomic and cardiovascular complications



- Autonomic instability contributes to life-threatening complications.
- Cardiac arrest is a recognized cause of death in severe disease.
- Cardiovascular monitoring is an essential supportive measure.

Supportive measures reduce preventable complications

Ventilation

- Improved respiratory care has contributed to lower mortality.

Cardiovascular monitoring

- Cardiovascular surveillance addresses instability.

DVT prevention

- Deep venous thrombosis prophylaxis is part of supportive inpatient care.

GBS immunotherapy aims to accelerate recovery

Immune-mediated nerve injury



Immunomodulatory intervention



Improved clinical function

- Plasmapheresis and intravenous immunoglobulin (IVIg) hasten recovery.
- Plasma exchange removes circulating pathogenic mediators, including antibodies.
- IVIg is used for its immunomodulatory effects.

GBS outcomes: Substantial recovery, persisting risk

2%–5%

Reported mortality

Up to 20%

Disability among
hospitalized survivors

- 2%–5% mortality among affected individuals.
- Deaths may involve respiratory paralysis, autonomic instability, or cardiac arrest.
- Up to 20% of hospitalized survivors have long-term disability.

Case resolution: Localizing the lesion

Clinical observation

Localize the nerve dysfunction



Pathologic interpretation

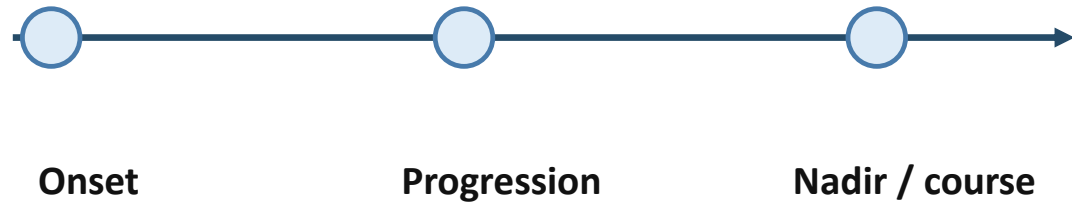
Identify the injury pattern

- The combination of rapid ascent and areflexia favors an acute neuropathic process.
- Root plus nerve involvement makes radiculoneuropathy appropriate.
- Electrophysiologic and CSF features can support the clinical interpretation.

CIDP: The principal chronic inflammatory neuropathy

GBS: Nadir ≤ 4 weeks

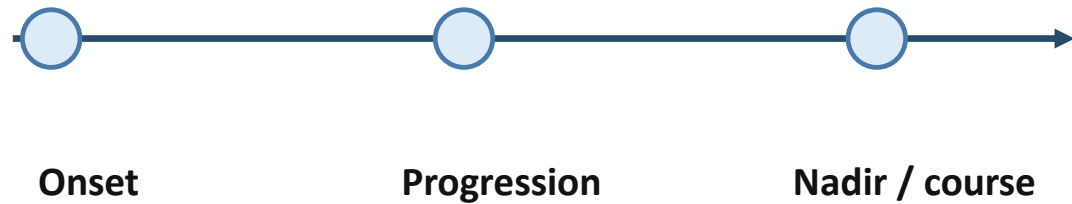
CIDP: ≥ 8 weeks



- CIDP is a chronic, acquired, inflammatory peripheral neuropathy.
- The common pattern is symmetric, mixed motor and sensory impairment.
- Its required duration is at least 8 weeks (about 2 months).

CIDP evolves over a longer time horizon

Clinical change over time



- Symptoms can evolve over years rather than days to weeks.
- Relapses and remissions are a common course.
- Prolonged activity allows repeated cycles of injury and repair.

CIDP commonly affects motor and sensory function

Symmetric

Polyneuropathy

Roots + nerves

Polyradiculoneuropathy

Patchy, named nerves

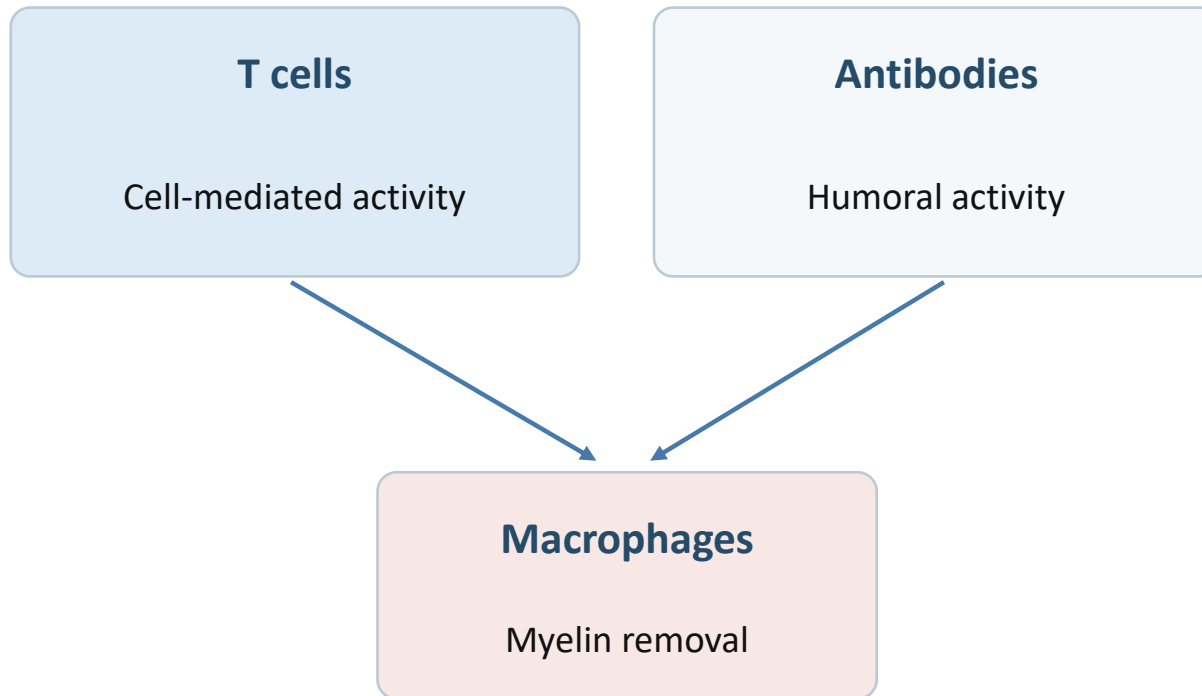
Mononeuritis multiplex

- Weakness and difficulty walking reflect motor involvement.
- Numbness and pain reflect sensory involvement.
- The usual phenotype is a symmetric sensorimotor polyneuropathy.

CIDP phenotype can be motor- or sensory-predominant

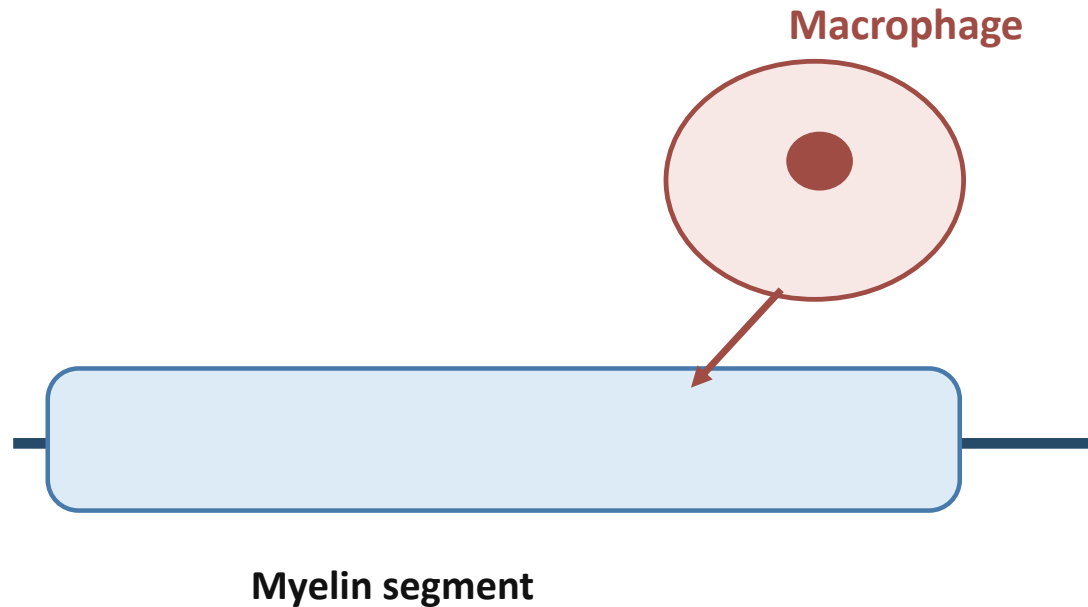
- Although mixed deficits are common, isolated motor impairment may occur.
- Some patients present with predominantly sensory symptoms.
- Phenotypic diversity does not negate the chronic inflammatory framework.

CIDP pathogenesis involves cellular and humoral immunity



- T-cell-mediated and antibody-mediated mechanisms are implicated.
- Immune targets include the Schwann-cell-axon junction and compact myelin.
- Inflammatory injury results in cycles of demyelination and remyelination.

Complement-fixing antibodies can decorate myelin



- Immunoglobulin G and immunoglobulin M may localize to myelin sheaths.
- Their deposition promotes macrophage recruitment.
- Macrophages contribute to removal of myelin from underlying axons.

Recurrent demyelination drives repeated repair

Segmental myelin loss



Schwann-cell proliferation



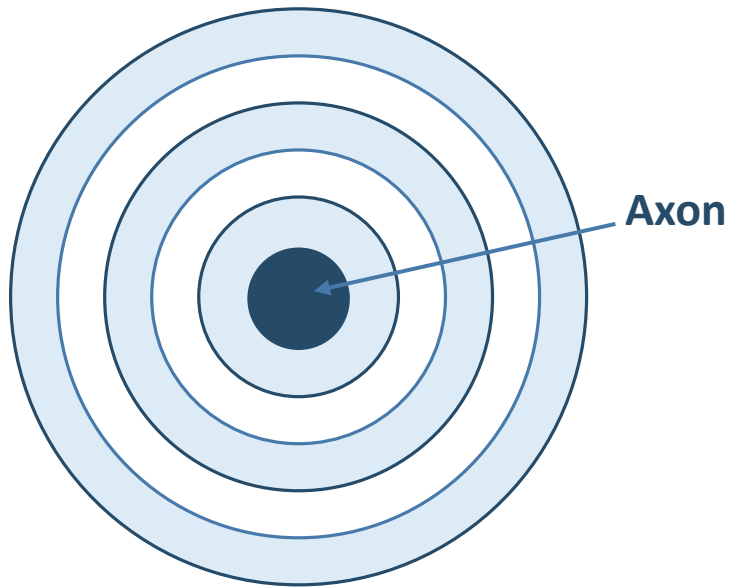
Thin / short remyelinated internodes



Repetitive repair

- Myelin is lost in discrete segments rather than uniformly from every axon.
- Schwann cells re-form myelin around surviving axons.
- Repetitive injury and repair change the architecture over time.

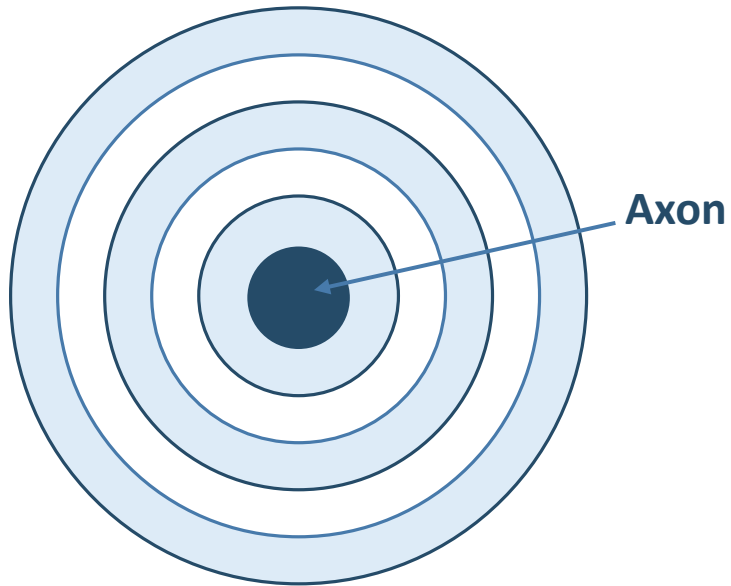
Onion bulbs: A structural memory of repeated myelin repair



Concentric Schwann-cell layers

- Repeated Schwann-cell proliferation can encircle the same axon.
- Concentric cellular layers create an onion-bulb configuration.
- An axon with a relatively thin myelin sheath may occupy the center.

Onion bulbs are not specific for CIDP



Concentric Schwann-cell layers

- They indicate repeated demyelination and remyelination.
- Other chronic demyelinating neuropathies can also produce them.
- This morphological finding must be interpreted within the complete context.

CIDP inflammation may resemble GBS pathology

GBS

Acute root/nerve inflammation

CIDP

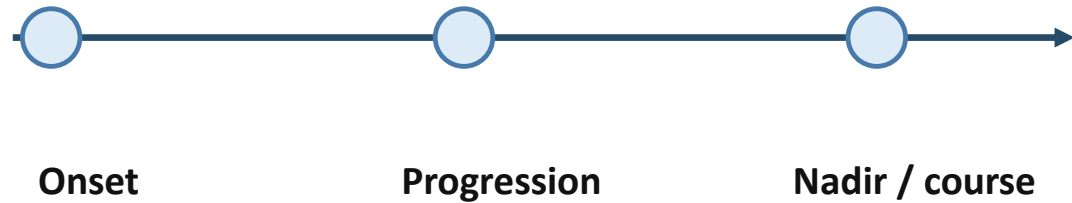
Chronic repeated
demyelination

- Macrophage infiltration accompanies myelin injury in both disorders.
- The chronicity of CIDP may add conspicuous onion-bulb formation.
- The principal distinction is not a uniquely identifying inflammatory cell.

Time course and steroid response help separate GBS/CIDP

GBS: Nadir ≤ 4 weeks

CIDP: ≥ 8 weeks



- GBS: Reaches maximal weakness within 4 weeks.
- CIDP: Signs and symptoms persist for at least 8 weeks.
- A positive steroid response as a CIDP discriminator.

CIDP treatment can yield clinical remission

Immune-mediated nerve injury



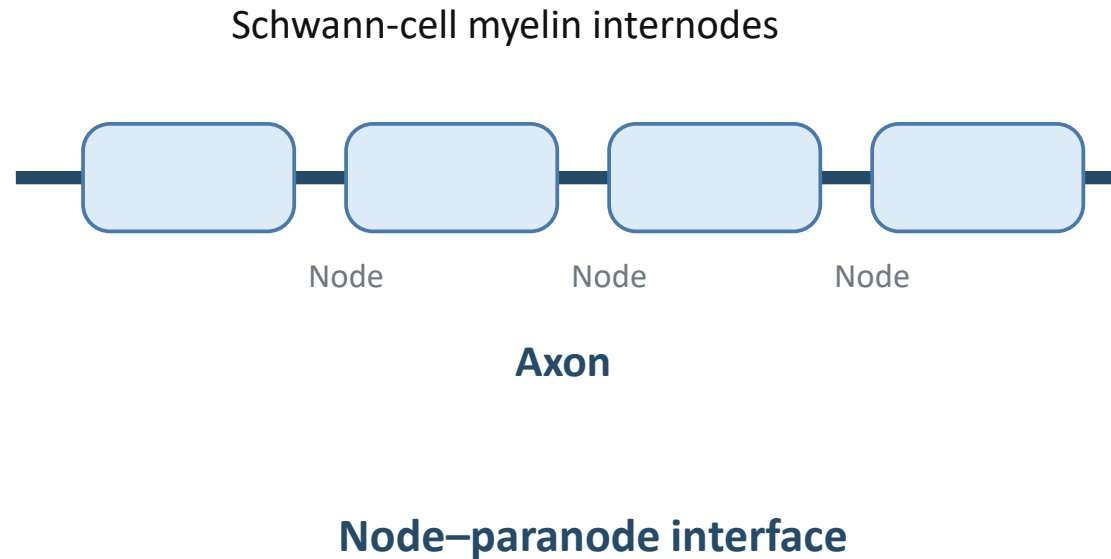
Immunomodulatory intervention



Improved clinical function

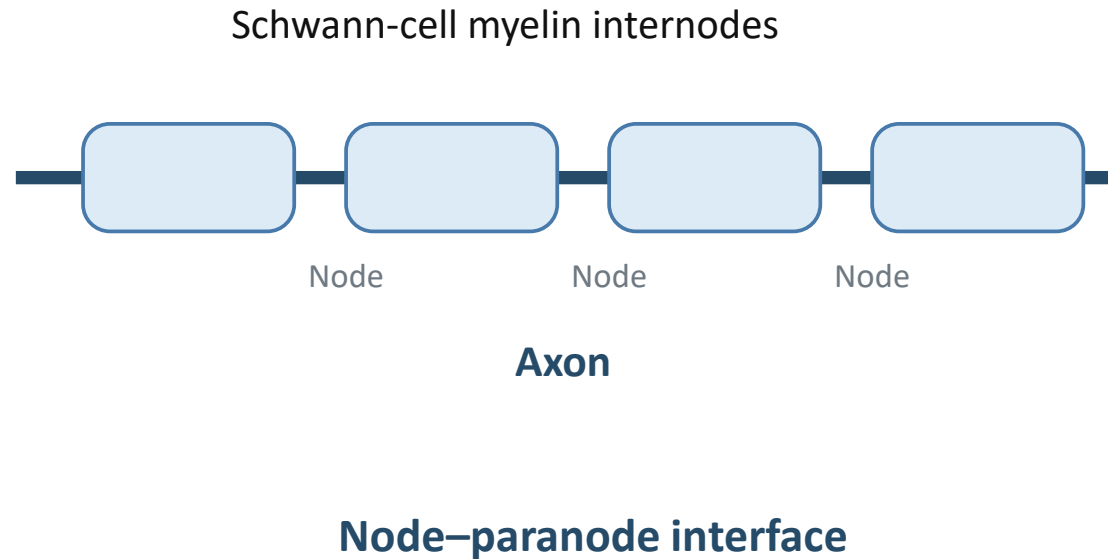
- Intravenous immunoglobulin often produces improvement or remission.
- Plasmapheresis and glucocorticoids are additional immunomodulatory options.
- T-cell– or B-cell–directed cytotoxic agents are also described.

Autoimmune nodopathy is conceptually distinct from CIDP



- Antibodies directed against nodal and paranodal proteins define this emerging group.
- These proteins are associated with noncompact myelin regions.
- Because of overlap, such cases were previously grouped with CIDP.

Why nodopathy should not be presented as ordinary CIDP



- The identified antibody target lies at specialized nodal/paranodal structures.
- The textbook favors a separate autoimmune nodopathy category.
- Clinical/pathologic overlap alone does not establish identical mechanisms.

Illustrative chronic case: Relapsing weakness and numbness

Clinical observation

Localize the nerve dysfunction



Pathologic interpretation

Identify the injury pattern

- A patient reports months of gait difficulty, limb weakness, and numbness.
- The presentation is symmetric with an intermittent course.
- Question: Which temporal and structural clues favor CIDP over GBS?

Systemic autoimmunity can also damage peripheral nerves

Acute demyelinating

Guillain–Barré syndrome

Chronic demyelinating

CIDP

Nodal/paranodal

Autoimmune nodopathy

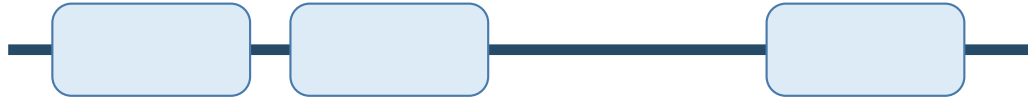
Axonal / vascular

Systemic disease; Vasculitis

- Rheumatoid arthritis, Sjögren syndrome, and systemic lupus erythematosus are examples.
- Associated peripheral neuropathy often involves distal sensory or sensorimotor deficits.
- Both primary axonal and demyelinating injury may be found.

Connective-tissue-associated neuropathy often is axonal

Demyelination: Axon remains



Axonal loss: Conducting fiber disrupted



- Classical descriptions emphasize axonal polyneuropathy.
- Demyelination can nevertheless occur in some cases.
- This mixed potential prevents equating all autoimmune neuropathies with AIDP.

Autoimmune neuropathy is not synonymous with vasculitis

Nonvasculitic

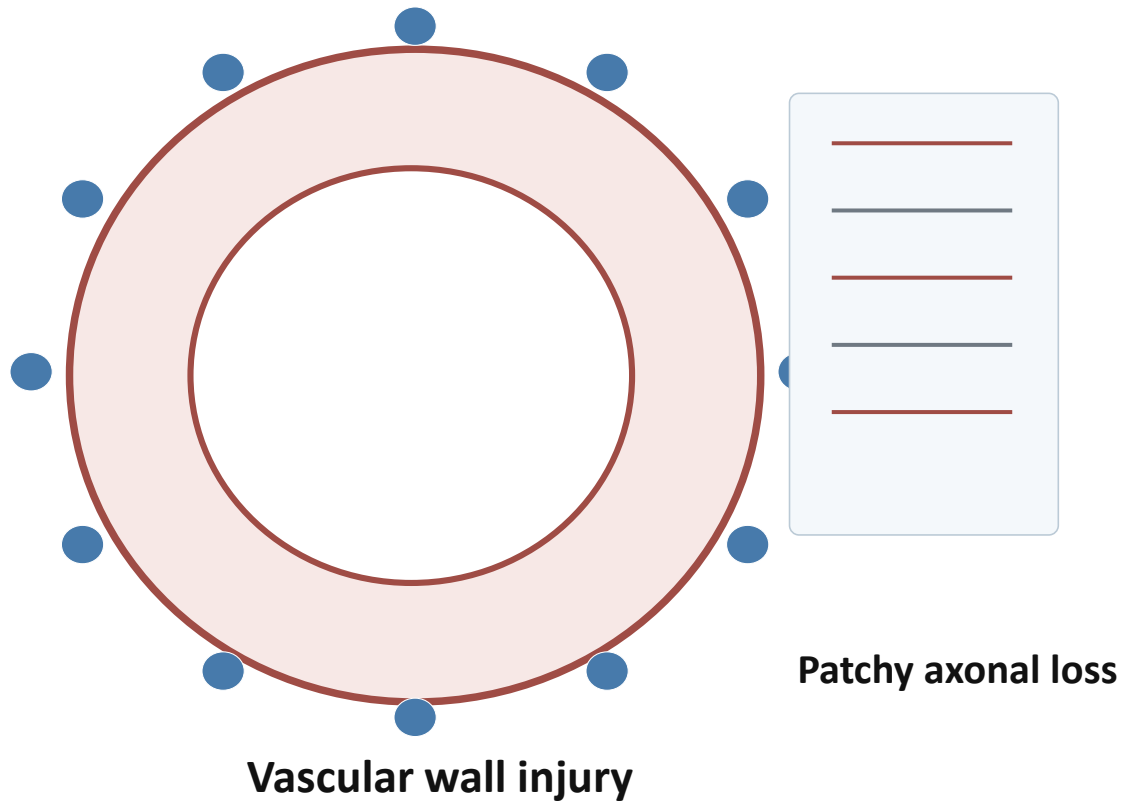
Immune-associated
axon/myelin injury

Vasculitic

Destructive blood-vessel injury

- Connective-tissue disease may produce neuropathy without demonstrable vasculitis.
- The same systemic disorders can also cause secondary vasculitic neuropathy.
- Tissue evidence of vascular injury supports the distinct vasculitic mechanism.

Vasculitic neuropathy targets the vascular supply



- Vasculitis is destructive, noninfectious inflammation of blood vessels.
- Vessel injury can damage the peripheral nerve and produce axonal degeneration.
- Its often uneven distribution differs from symmetric demyelinating disease.

Vasculitic nerve involvement is clinically important

Symmetric

Polyneuropathy

Roots + nerves

Polyradiculoneuropathy

Patchy, named nerves

Mononeuritis multiplex

- The textbook estimates peripheral nerve involvement in about one-third of vasculitis cases.
- Neuropathy can be the first manifestation of the vascular disorder.
- Mononeuritis multiplex is especially characteristic, though not exclusive.

Mononeuritis multiplex creates patchy neurologic deficits

Symmetric

Polyneuropathy

Roots + nerves

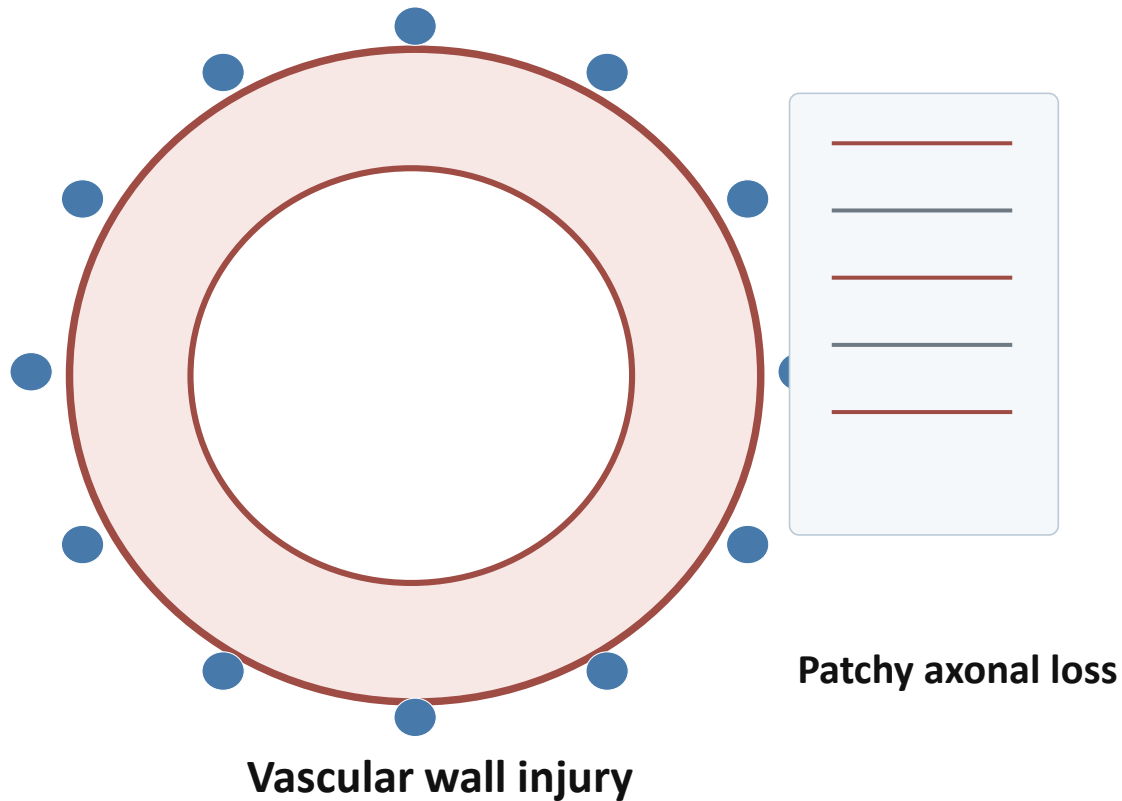
Polyradiculoneuropathy

Patchy, named nerves

Mononeuritis multiplex

- Different named nerves are damaged in an asymmetric, irregular sequence.
- Illustrative pattern: Right radial-nerve dysfunction and left peroneal-nerve dysfunction.
- The combination localizes to multiple discrete peripheral nerves.

Nonsystemic vasculitic neuropathy



- Localized nerve vasculitis may occur without an accompanying systemic vasculitic syndrome.
- Nonsystemic vasculitic neuropathy as ANCA-negative.
- The localized phenotype still has destructive vascular nerve pathology.

Systemic vasculitides linked to neuropathy

Polyarteritis nodosa

- Polyarteritis nodosa is a major associated systemic vasculitis.

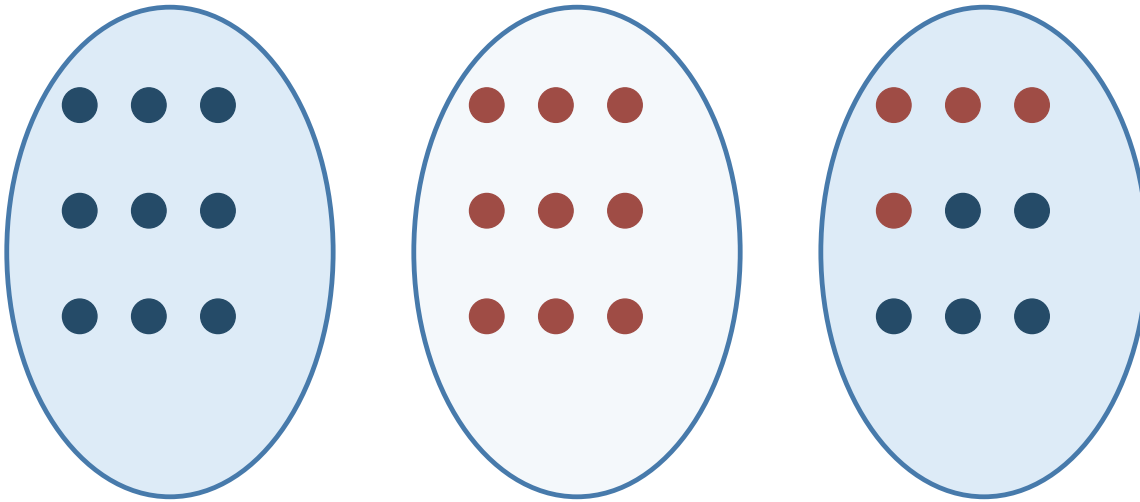
MPO-ANCA group

- MPO-ANCA diseases include microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis.

PR3-ANCA group

- PR3-ANCA granulomatosis with polyangiitis is less commonly associated.

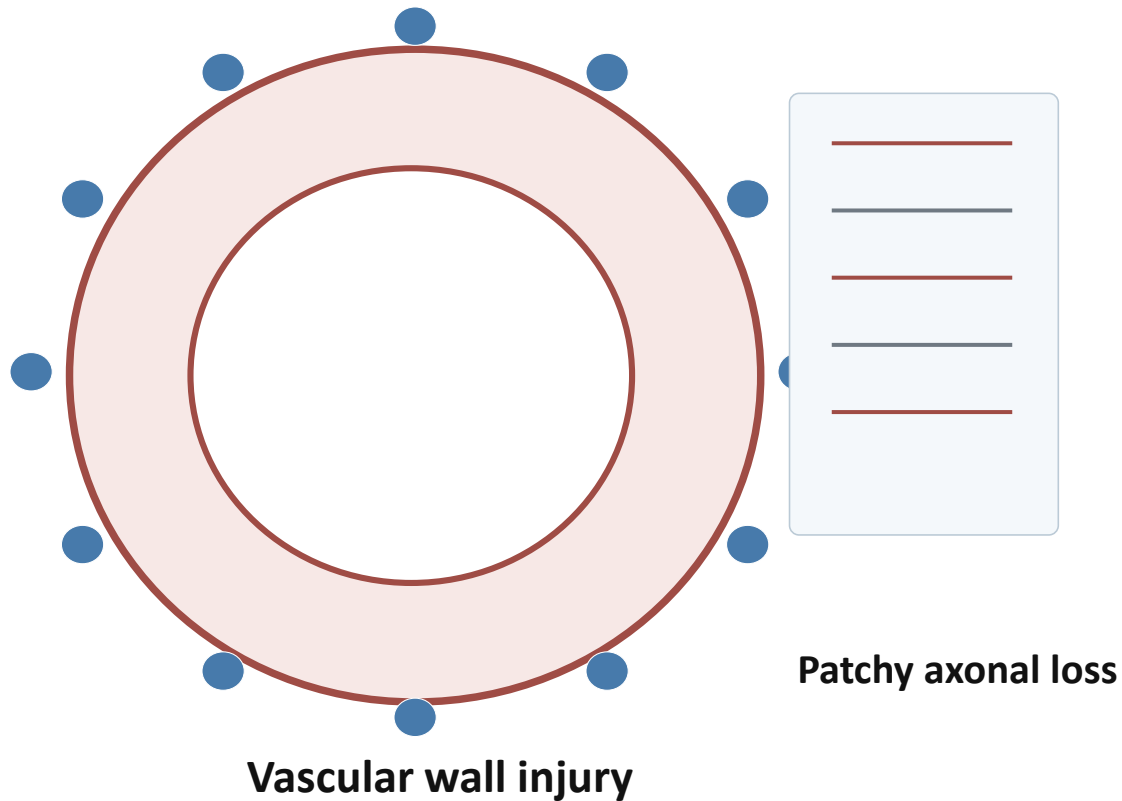
Vasculitic neuropathy: Patchy fascicular axon loss



Unequal axonal involvement across fascicles

- Degeneration and loss of axons are distributed irregularly across fascicles.
- Some fascicles are severely involved while adjacent ones are less affected.
- Asymmetry supplies a key morphologic clue to vascular injury.

Vasculitis morphology: Perivascular inflammation



- Inflammatory cells often surround affected intraneural vessels.
- Vessels may show changes indicating acute or chronic wall damage.
- The presence of vascular destruction strengthens a vasculitic diagnosis.

The decisive observation is vessel injury

Axonal loss

Perivascular infiltrate

Vessel-wall injury

- Perivascular inflammation alone requires cautious interpretation.
- Characteristic acute or chronic vessel-wall damage establishes the mechanism.
- Axonal loss and asymmetric fascicular distribution are supportive clues.

Compare the major inflammatory neuropathy patterns

Acute

GBS

Chronic

CIDP

Nodal antibody

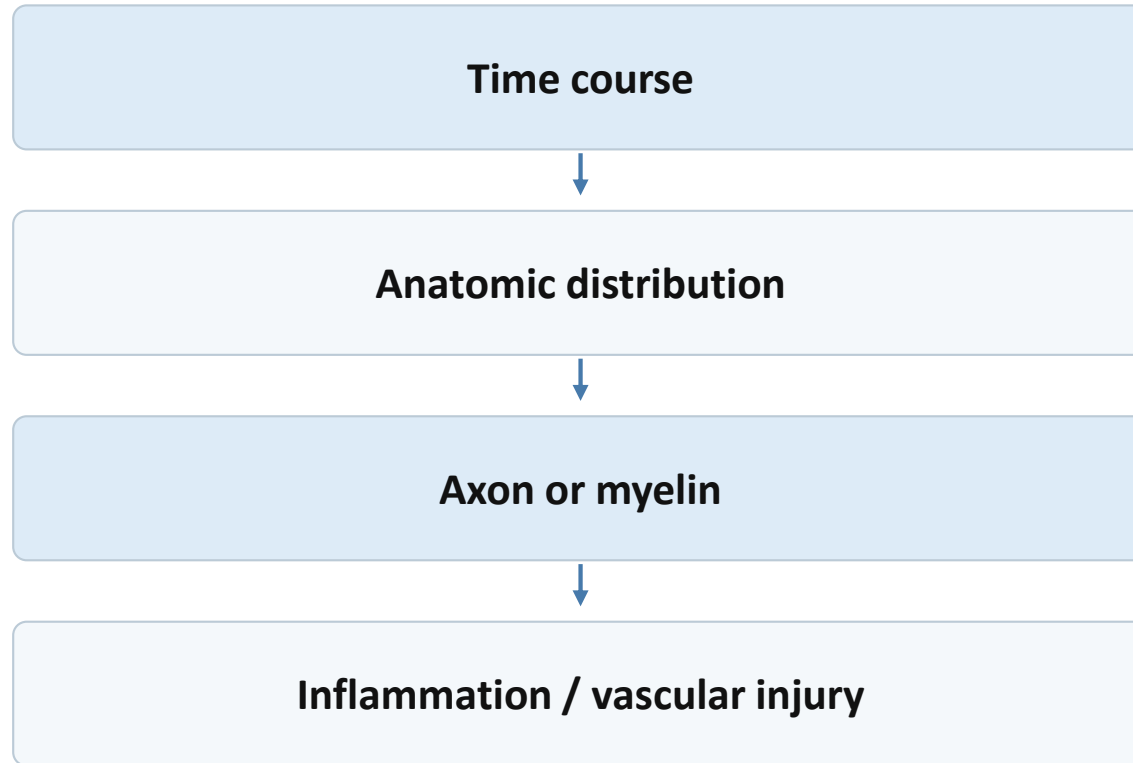
Nodopathy

Asymmetric axonal

Vasculitis

- GBS: Acute ascending weakness; Demyelinating roots and nerves (AIDP).
- CIDP: Prolonged or relapsing, symmetric sensorimotor demyelination.
- Autoimmune nodopathy: Nodal/paranodal antigen-directed disorder.
- Vasculitis: Destructive vascular inflammation with patchy axonal loss.

A pathology-first diagnostic framework



- First define time course: Acute progression versus chronic or relapsing disease.
- Next localize: Symmetric polyneuropathy, radiculoneuropathy, or multifocal nerve loss.
- Then classify lesion: Segmental myelin injury or axonal loss.
- Finally integrate inflammation, onion bulbs, or vessel-wall injury.

Final clinical-pathologic application

Clinical observation

Localize the nerve dysfunction



Pathologic interpretation

Identify the injury pattern

- A patient has abrupt, asymmetric wrist and foot weakness involving different limbs.
- Nerve tissue demonstrates uneven fascicular axonal loss and damaged inflamed vessels.
- Interpretation: Vasculitic neuropathy is favored over GBS/CIDP.

Inflammatory neuropathies: four durable distinctions

Acute

GBS

Chronic

CIDP

Nodal antibody

Nodopathy

Asymmetric axonal

Vasculitis

- Acute ascending areflexic weakness suggests GBS; assess respiratory/autonomic risk.
- Chronic, often relapsing demyelination with onion bulbs supports CIDP in context.
- Antibodies against nodal/paranodal proteins indicate autoimmune nodopathy.
- Patchy axonal loss with destructive vascular inflammation supports vasculitis.