PERIPHERAL NERVOUS SYSTEM

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Peripheral nerve

- The two main components of peripheral nerves are axons and myelin sheaths made by Schwann cells.
- Injuries to either of these components may result in a peripheral neuropathy.
- Autonomic nerve fibers outnumber somatic fibers in the peripheral nervous system, but signs and symptoms related to their involvement are generally not prominent features of peripheral neuropathies.

Somatic motor function

- Carried out by the motor unit
- Consists of:
- (1) a lower motor neuron located in the anterior horn of the spinal cord or in the brainstem
- (2) an axon that travels to a target muscle as part of a nerve
- (3) the neuromuscular junctions
- (4) multiple innervated myofibers (muscle fibers).

Somatic sensory function

- Depends on:
- (1) the distal nerve endings, which may contain specialized structures that serve to register specific sensory modalities
- (2) an axon that travels as part of a peripheral nerve to the dorsal root ganglia
- (3) a proximal axon segment that synapses on neurons in the spinal cord or the brainstem.

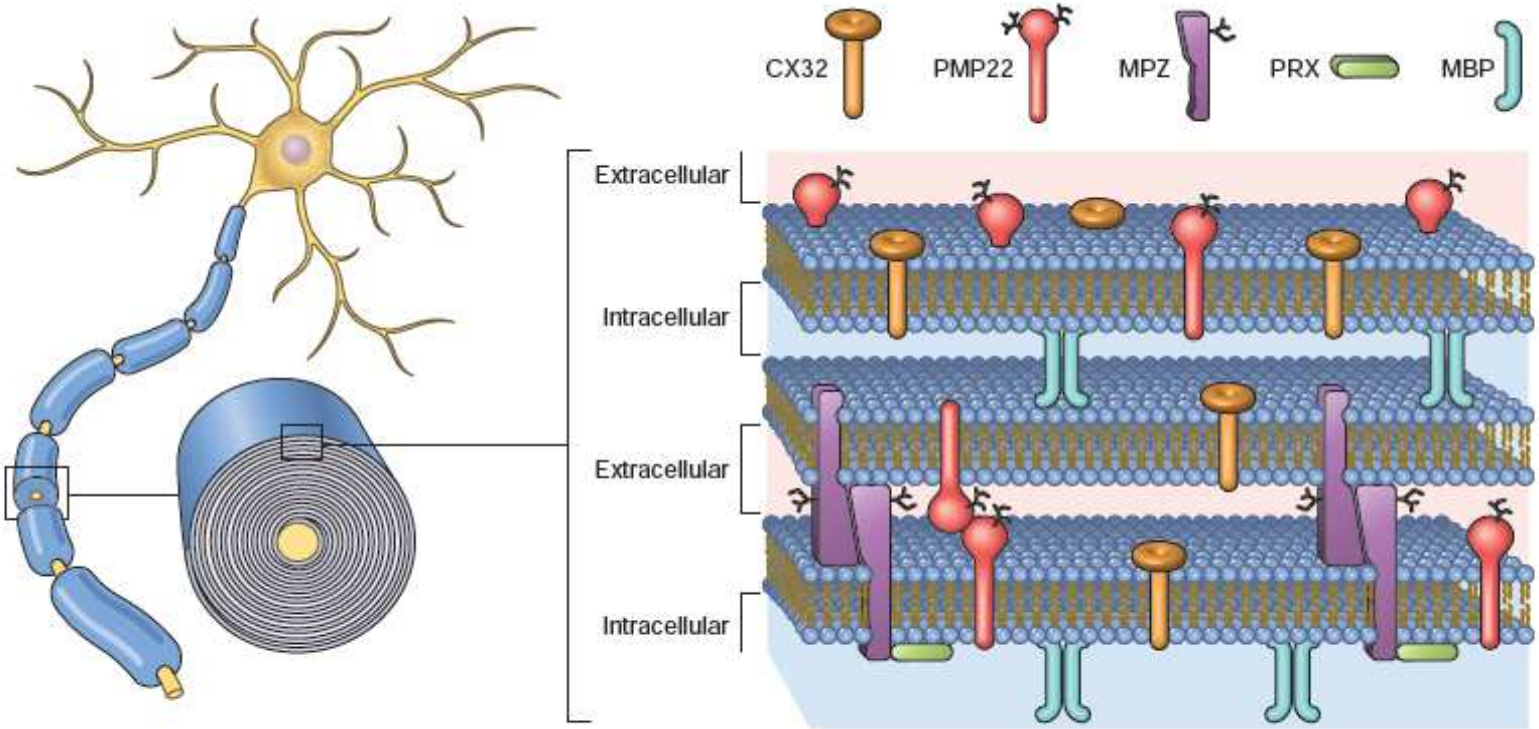

Figure 27-1 Relationship between lipid bilayers and associated proteins in myelin within internodes. Myelin basic protein (MBP) is an intracellular protein that has a role in myelin compaction. Mutant forms of myelin protein zero (MPZ), peripheral myelin protein 22 (PMP22), and periaxin (PRX) cause some forms of Charcot-Marie-Tooth disease, a hereditary demyelinating neuropathy.

Axons

- Thin unmyelinated fibers mediate autonomic functions as well as pain and temperature sensation and have the slowest conduction speeds.
- Large diameter axons with thick myelin sheaths transmit light touch and motor signals and have fast conduction speeds.
- In the case of myelinated axons, individual Schwann cells make exactly one myelin sheath that wraps around a single axon to create a myelinated segment called an internode.

Axons

- Internodes are separated by unmyelinated gaps referred to as nodes of Ranvier, which are uniformly spaced along the length of the axon.
- Unmyelinated axons are also intimately associated with Schwann cells but in a different arrangement in which one cell surrounds segments of multiple axons.
- Most peripheral nerves carry out both motor and sensory functions and thus contain axons of varying diameter and myelin thickness.

Axons

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

Axonal neuropathies

- Wallerian degeneration.
- Portions of axons that are distal to the point of transection are disconnected from the central neuron and degenerate.
- Within a day of injury, the distal axons begin to fragment and the associated myelin sheaths unravel and disintegrate into spherical structures (myelin ovoids).
- Macrophages participate in the removal of axonal and myelin debris.
- Regeneration starts at the site of trans-section with the formation of a growth cone and the outgrowth of new branches from the stump of the proximal axon.

Axonal neuropathies

- Schwann cells and their associated basement membranes guide the sprouting axons toward their distal target.
- Continuous pruning of the sprouting axons removes misguided branches.
- The Schwann cells create new myelin sheaths around the regenerating axons, but these myelin internodes tend to be thinner and shorter than in the original ones.
- The repair process is successful only if the two transected ends remain closely approximated.

Axonal neuropathies

- A failure of the outgrowing axons to find their distal target can produce a non-neoplastic haphazard whorled proliferation of axonal processes and associated Schwann cells that results in a painful nodule (traumatic neuroma)
- Reduction in signal strength
- Peripheral axonopathies preferentially affect the distal extremities

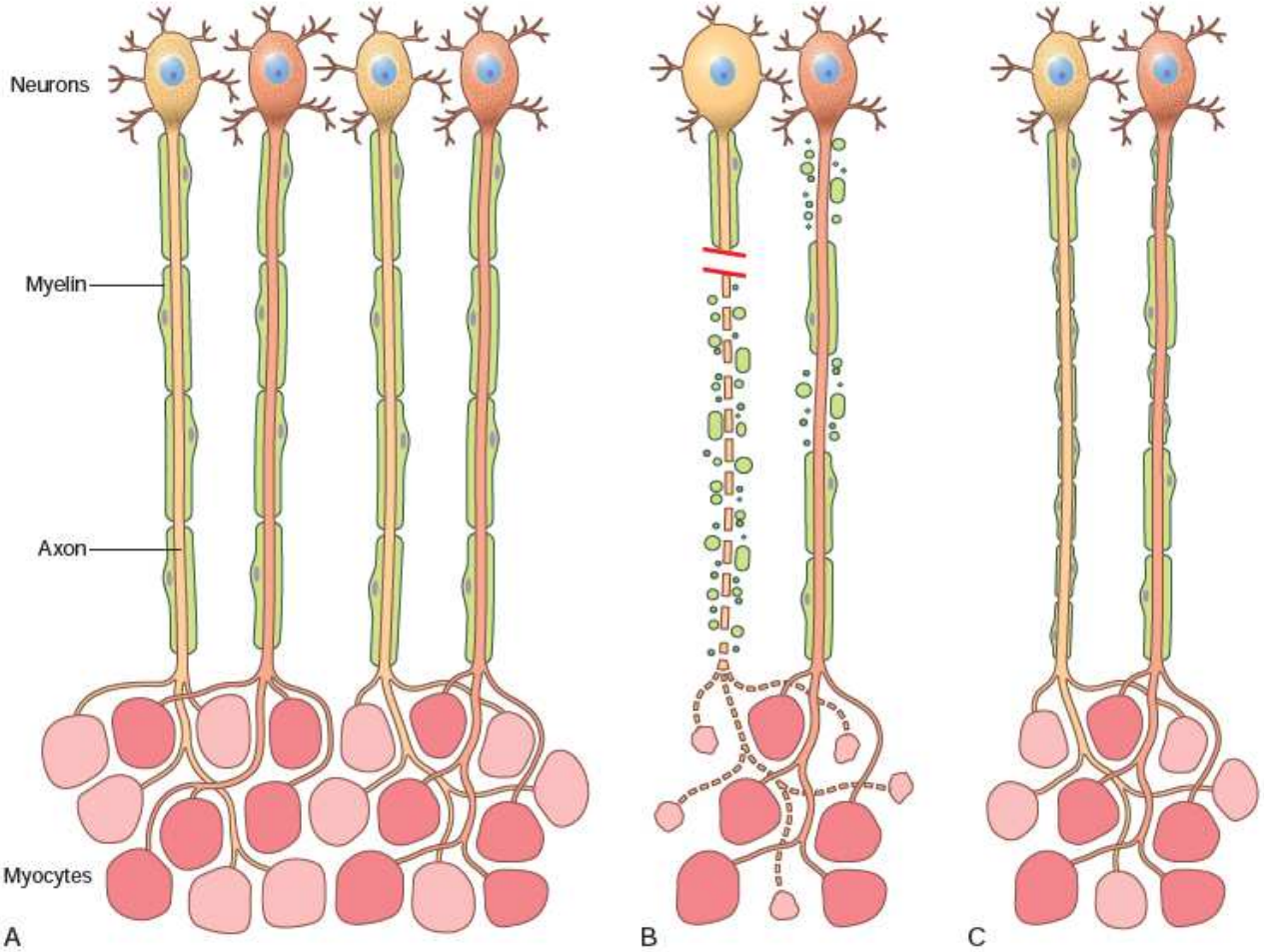

Figure 27-2 Patterns of peripheral nerve damage. **A,** In normal motor units, type I and type II myofibers are arranged in a "checkerboard" distribution, and the internodes along the motor axons are uniform in thickness and length. **B,** Acute axonal injury (*left axon*) results in degeneration of the distal axon and its associated myelin sheath, with atrophy of denervated myofibers. In contrast, acute demyelinating disease (*right axon*) produces random segmental degeneration of individual myelin internodes, while sparing the axons. **C,** Regeneration of axons after injury (*left axon*) allows reinnervation of myofibers. The regenerated axon is myelinated by proliferating Schwann cells, but the new internodes are shorter and the myelin sheaths are thinner than the original ones. Remission of demyelinating disease (*right axon*) allows remyelination to take place, but the new internodes also are shorter and have thinner myelin sheaths than flanking normal undamaged internodes. See Table 27-1 and Fig. 27-7 for comparison.

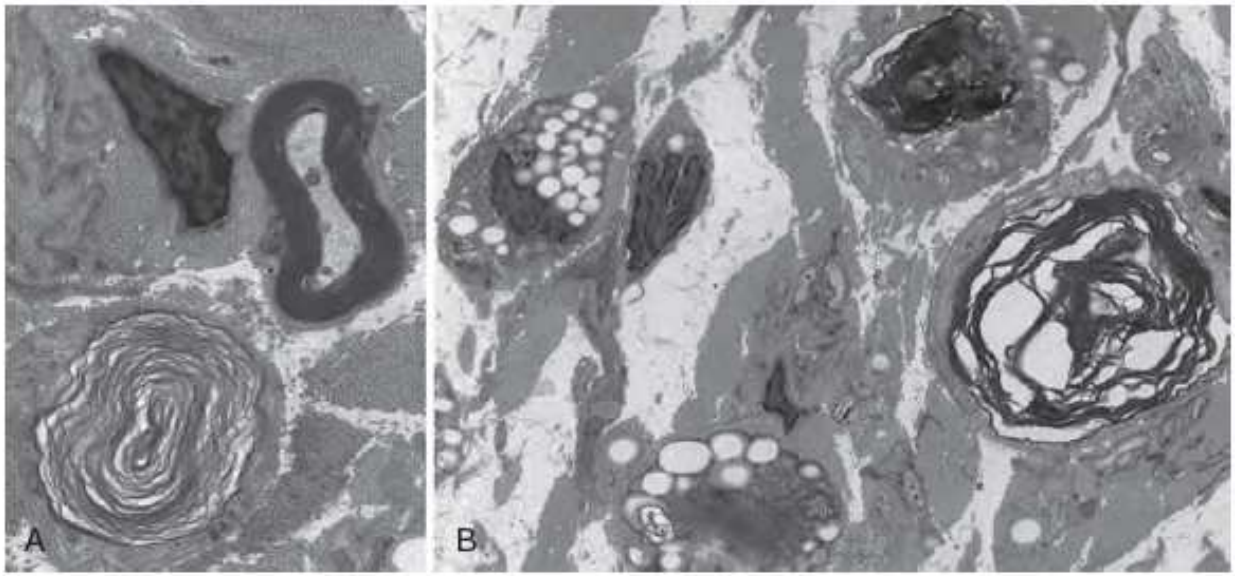

Figure 27-3 Electron micrographs illustrating features of axonal degeneration. **A,** Degenerating myelin with loosened myelin layers is seen in the degenerating axon in the lower left corner, to be contrasted with a normal myelin sheath with tightly packed myelin and intact axon in the upper right corner. **B,** In addition to an unraveling myelin sheath, several cells contain lipid droplets (seen as vacuoles) derived from degenerating myelin.

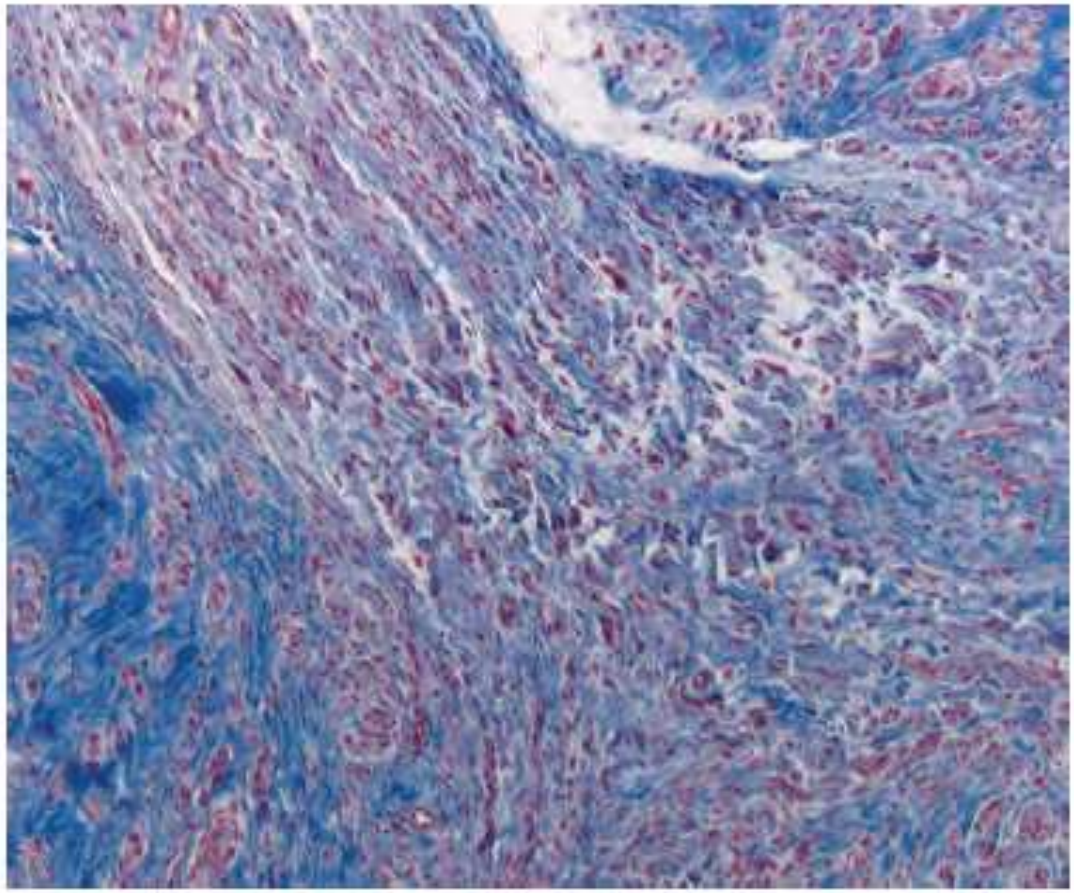

Figure 27-4 Trichrome-stained section of a traumatic neuroma showing the transition from normal nerve containing a parallel arrangement of axons (*upper left corner*) to a haphazard swirl of red stained axons associated with admixture of Schwann cells and blue-staining connective tissue.

Demyelinating neuropathies

- Individual myelin sheaths degenerate in a seemingly random pattern, resulting in discontinuous damage of myelin segments.
- In response to this damage, Schwann cells or Schwann cell precursors proliferate and initiate repair through the formation of new myelin sheaths, but these again tend to be shorter and thinner than the original ones.
- Slowed nerve conduction velocity.

Neuronopathies

- Result from destruction of neurons, leading to secondary degeneration of axonal processes.
- Damage is at the level of the neuronal cell body.
- Peripheral nerve dysfunction caused by neuronopathies is equally likely to affect proximal and distal parts of the body

Patterns of injury

- Mononeuropathies affect a single nerve and result in deficits in a restricted distribution dictated by normal anatomy.
- Trauma, entrapment, and infections are common causes of mononeuropathy.
- Polyradiculoneuropathies affect nerve roots as well as peripheral nerves, leading to diffuse symmetric symptoms in proximal and distal parts of the body.

Patterns of injury

- Polyneuropathies are characterized by involvement of multiple nerves, usually in a symmetric fashion.
- In most cases axons are affected in a length dependent fashion leading to deficits that start in the feet and ascend with disease progression.
- The hands often start to show involvement by the time deficits extend to the level of the knee, resulting in a characteristic “stocking and glove” distribution of sensory deficits.

Inflammatory neuropathies

- Guillain-Barré Syndrome (Acute Inflammatory Demyelinating Polyneuropathy)
- An acute onset T cell mediated demyelinating peripheral neuropathy.
- Characterized clinically by weakness beginning in the distal limbs that rapidly advances to affect proximal muscle function ("ascending paralysis").
- May follow Campylobacter jejuni, cytomegalovirus, Epstein-Barr virus, and Mycoplasma pneumonia infection, or prior vaccination,
- 5% die of respiratory paralysis
- 20% have long term sequelae

Inflammatory neuropathies

- The dominant histopathologic finding is inflammation of peripheral nerves
- Perivenular and endoneurial infiltration by lymphocytes, macrophages, and a few plasma cells
- Segmental demyelination affecting peripheral nerves is the most prominent lesion, but damage to axons is also seen.
- The cytoplasmic processes of macrophages penetrate the basement membrane of Schwann cells, particularly in the vicinity of the nodes of Ranvier, and extend between the myelin lamellae, stripping the myelin sheath from the axon

Inflammatory neuropathies

- Chronic inflammatory demyelinating poly(radiculo)neuropathy
- Most common chronic acquired inflammatory peripheral neuropathy
- Symmetrical mixed sensorimotor polyneuropathy that persists for 2 months or more
- Complement-fixing IgG and IgM can be found on the myelin sheath
- The deposition of these opsonins leads to recruitment of macrophages that strip myelin from axons.

Inflammatory neuropathies

- Sural nerve biopsies show evidence of recurrent demyelination and remyelination associated with proliferation of Schwann cells.
- Leads to the formation of "onion-bulbs"
- Structures in which multiple layers of Schwann cells wrap around an axon

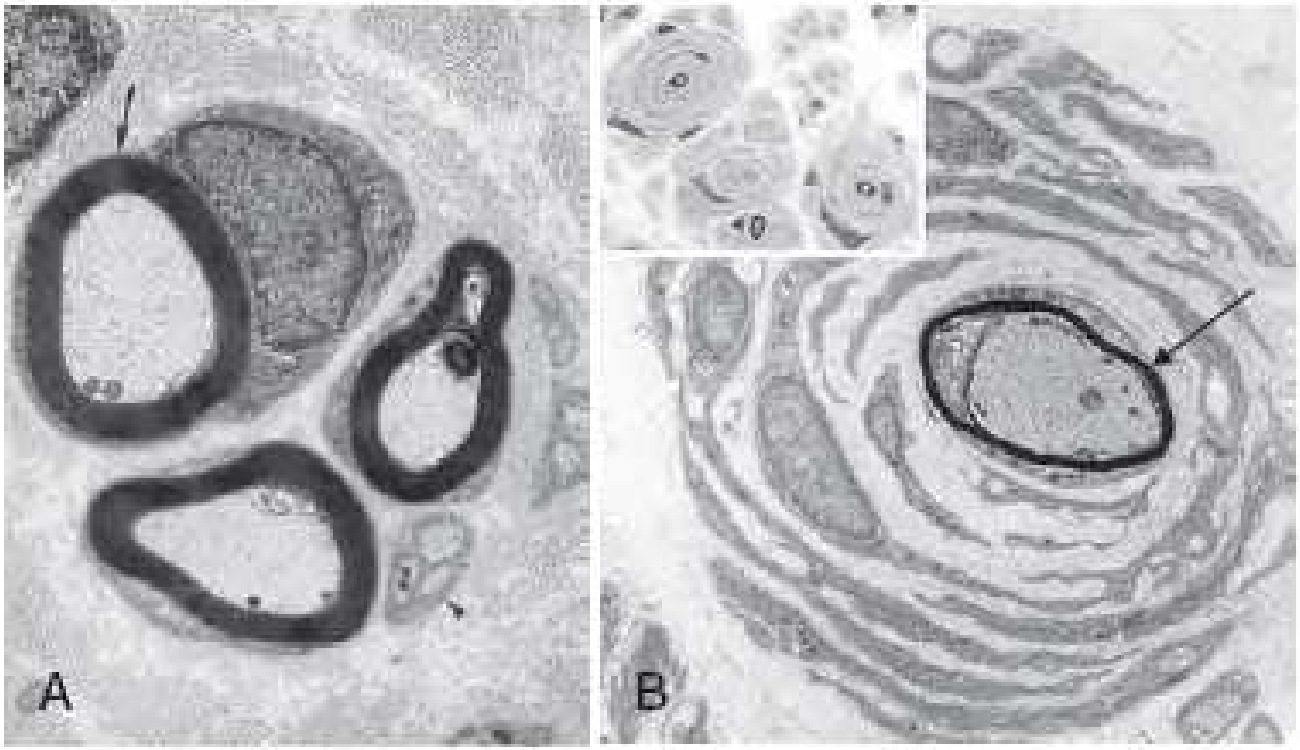

Figure 27-5 Onion bulb neuropathy. Compared with the normal ultrastructure of axons in a nerve **(A)**, an "onion bulb" **(B)** is composed of a thinly myelinated axon (*arrow*) surrounded by multiple concentrically arranged Schwann cells. *Inset*, Light-microscopic appearance of an onion bulb neuropathy, characterized by "onion bulbs" surrounding axons. (**B**, Courtesy G. Richard Dickersin, MD, from Diagnostic Electron Microscopy: A Text Atlas. New York, Igaku-Shoin Medical Publishers, 2000, p 984.)

Inflammatory neuropathies

- Systemic autoimmune diseases can be associated with peripheral neuropathies that often take the form of distal sensory or sensorimotor polyneuropathies.
- Vasculitis is a noninfectious inflammation of blood vessels that can involve and damage peripheral nerves.
- About one third of patients with vasculitis have peripheral nerve involvement, and neuropathy may be the presenting feature.
- Vasculitis often presents as mononeuritis multiplex,
- Patchy axonal loss and perivascular inflammation

Infectious neuropathies

- Leprosy (Hansen's disease)
- Symmetric polyneuropathy that is most severe in the relatively cool distal extremities and in the face because lower temperatures favor mycobacterial growth.
- The infection prominently involves pain fibers.

Infectious neuropathies

- In lepromatous leprosy, Schwann cells are invaded by Mycobacterium leprae, which proliferate and eventually infect other cells.
- There is evidence of segmental demyelination and remyelination and loss of both myelinated and unmyelinated axons.
- Endoneurial fibrosis and multilayered thickening of the perineural sheaths occur.
- Weak T_{H1} and T_{H2} responses

Infectious neuropathies

- Tuberculoid leprosy

- T_{H1} response to Mycobacterium leprae associated with production of IL-2 and IFN-γ.
  - Usually manifest as dermal nodules containing granulomatous inflammation.
  - The inflammation injures cutaneous nerves in the vicinity
  - Axons, Schwann cells, and myelin are lost, and there is fibrosis of the perineurium and endoneurium.
  - Localized nerve involvement.

Infectious neuropathies

- Lyme disease
- Borellia burgdorferi
- In second or third phase, may manifest polyradiculoneuropathy as well as unilateral or bilateral facial palsies.
- HIV
- Early, mononeuritis multiplex and polyradiculoneuropathy that may resemble Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy.
- Late, painful distal sensory neuropathy

Infectious neuropathy

- Corynebacterium diphtheriae
- Gram positive rod with clubbed ends
- Peripheral nerve dysfunction results from the effects of the diphtheria exotoxin.
- Produces an acute peripheral neuropathy associated with prominent bulbar and respiratory muscle dysfunction
- Toxin A inhibits protein synthesis by ADP-ribosylating the ribosomal protein EF-2, leading to the death of host cells.

Infectious neuropathy

- Varicella-zoster
- Latent in nerve ganglia.
- If the virus is reactivated, sometimes many years later, it may be transported along the sensory nerves to the skin. Infects keratinocytes.
- Vesicular skin eruption (shingles) in a distribution that follows sensory dermatomes.
- Most common is the involvement of thoracic or trigeminal nerve dermatomes

Infectious neuropathy

- Affected ganglia show neuronal death, usually accompanied by abundant mononuclear inflammatory cell infiltrates
- Focal necrosis and hemorrhage may also be found.
- Peripheral nerves show degeneration of the axons that belong to the dead sensory neurons.
- Focal destruction of the large motor neurons of the anterior horns or cranial nerve motor nuclei may be seen at the corresponding levels.
- Intranuclear inclusions generally are not found in the peripheral nervous system.

Neuropathies

Disease	Signs and symptoms	Treatment
Guillan-Barré (acute inflammatory demyelination)	**Ascending level of weakness. Often associated with antecedent viral illness, immunization, Mycoplasma pneumoniae or Campylobacter infection. Elevated CSF protein.**	**Intravenous immunoglobulin beneficial early. Plasmapheresis if circulating antibody (to myelin).**
Chronic inflammatory demyelinating polyneuropathy	**>40 years old with both weakness and painless sensory deficits. Slow conduction on EMG (axonal degeneration).**	**Corticosteroids. Possibly intravenous immunoglobulins or plasmapheresis.**
Multifocal motor neuropathy	**Progressive, symmetric weakness of distal muscles with areflexia. Sensation spared. Conduction block of motor nerves on EMG.**	**Intravenous immunoglobulins; later, cyclophosphamide**
Paraprotein	**Usually monoclonal gammopathy. May see IgM autoantibodies that bind myelin-associated glycoprotein.**	**Plasmapheresis**

Neuropathy syndromes

- Predominantly symmetrical motor deficits
- Amyotrophic lateral sclerosis
- Guillan-Barré
- Chronic inflammatory demyelinating polyneuropathy
- Acute porphyria

Neuropathy syndromes

- Predominantly asymmetrical or focal motor deficits
- Neuropathy such as ALS, poliomyelitis, spinal muscular atrophy
- Radiculopathy or plexus lesion
- Mononeuropathy such as compartment syndrome or lead poisoning
- Multiple mononeuropathy such as vasculitis, diabetes mellitus, leprosy, sarcoid, cryoglobulinemia

Neuropathy syndromes

- Predominantly autonomic disturbances
- Diabetes mellitus
- Amyloidosis
- Guillan-Barré
- Porphyria
- Vincristine
- Botulism
- Paraneoplastic syndrome

Neuropathy syndromes

- Predominantly painful
- Diabetes mellitus
- Amyloidosis
- Guillan-Barré
- Uremia
- Arsenic poisoning
- Stocking and glove pattern polyneuropathy
- Circulating toxic factors.

Neuropathy syndromes

- Predominantly sensory disturbances
- Diabetes mellitus
- Alcohol
- Vitamin B_{12} deficiency or folic acid deficiency
- Excessive vitamin B_6 intake
- Amyloidosis
- Syphilis
- Paraprotein
- Vinca alakaloids, taxanes, cisplatin,
- Friedrich's ataxia

Neuropathy syndromes

- Asymmetrical proprioceptive loss (without paralysis)
- Paraneoplastic
- Excessive vitamin B_6 intake
- Cisplatin
- Sjögren's

Diabetic neuropathy

- The most common cause of peripheral neuropathy.
- Up to 50% of patients with diabetes
- Up to 80% of those who have had the disease for more than 15 years
- Axonal neuropathy.
- Numbness, loss of pain sensation, difficulty with balance, and paresthesias or dysesthesias
- Late, may manifest brachial or lumbar plexus radiculopathy
- 20-40% will also have autonomic neuropathy
- Postural hypotension, incomplete bladder emptying, sexual dysfunction

Diabetic neuropathy

- The most common cause of peripheral neuropathy.
- Up to 50% of patients with diabetes
- Up to 80% of those who have had the disease for more than 15 years
- Axonal neuropathy.
- Reduced numbers of axons with varying degrees of ongoing axonal damage, marked by degenerating myelin sheaths and regenerative axonal clusters
- Endoneurial arterioles show thickening, hyalinization and intense periodic acid–Schiff positivity of their walls and extensive reduplication of basement membranes

Diabetic neuropathy

- Hyperglycemia causes the non-enzymatic glycosylation of proteins, lipids, and nucleic acids.
- The resulting advanced glycosylation end products (AGEs) may interfere with normal protein function and activate inflammatory signaling through the receptor for AGE.
- Excess glucose within cells is reduced to sorbitol, a process that depletes NADPH and increases intracellular osmolality
- The vascular injuries that occur in chronic diabetes due to hyperlipidemia and other metabolic alterations may cause ischemic damage of the nerves.

Metabolic neuropathy

- Uremia
- Distal, symmetric neuropathy
- May be associated with muscle cramps, distal dysesthesias, and diminished deep tendon reflexes.
- Axonal degeneration.
- Demyelination is secondary.
- Regress with dialysis.

Hormonal and metabolic neuropathy

- Thyroid
- Hypothyroidism associated with compression neuropathy (e.g., carpal tunnel syndrome) or distal symmetric neuropathy
- Hyperthyroidism may mimic Guillan-Barré
- Deficiencies of vitamin B1 (thiamine), folate, vitamin E, copper, and zinc
- Excess of vitamin B6 (pyridoxine)

Metabolic neuropathy

- Vitamin B12 deficiency
- Subacute combined degeneration with damage to long tracts in the spinal cords as well as to peripheral nerves
- Neurologic symptoms may precede megaloblastic changes
- Diminished myelinotrophic cytokines in CSF
- MRI show T2 hyper-intense signal involving posterior columns
- Pattern also seen in Copper deficiency
- Subacute combined degeneration may also be precipitated by nitrous oxide (oxidizes cobalt core)

Metabolic neuropathy

- Methyl-vitamin B12 (Met B12) and 5′-deoxy-5′-adenosylcobalamin (Ado B12) are two physiologically active forms of vitamin B12 in the human body.
- Met B12 is needed as a cofactor by the methyltetrahydrofolate-homocysteine methyltransferase (MTR) enzyme to generate methionine from homocysteine and tetrahydrofolate from methyltetrahydrofolate.
- Methionine is the precursor of S-adenosylmethionine, a universal methyl donor which is important in the methylation of myelin basic protein and myelin lipids.

Metabolic neuropathy

- Decreased methionine and S-adenosylmethionine lead to instability of the myelin sheath.
- Tetrahydrofolate is necessary for de novo DNA synthesis
- Ado B12 is required as a cofactor by the methylmalonyl-CoA mutase (MMCoAM) for the conversion of methylmalonyl-coenzyme A to succinyl coenzyme A.
- Intracellular accumulation of both propionyl-CoA and methylmalonyl-CoA leading to the formation of abnormal fatty acids.

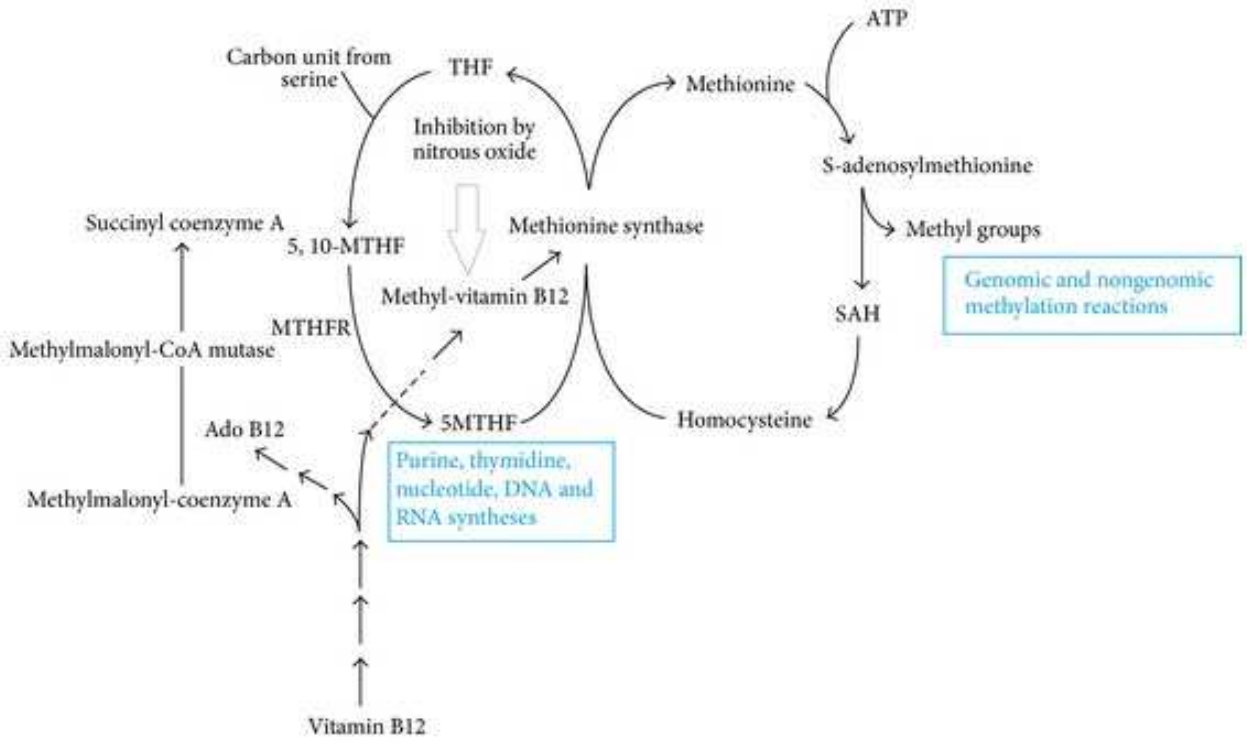

Figure 4

Pathways of intracellular vitamin B12 metabolism. MTHFR: methylenetetrahydrofolate reductase; 5,10-MTHF: 5,10-methylenetetrahydrofolate; 5-MTHF: 5-methylenetetrahydrofolate; THF: tetrahydrofolate; SAH: S-adenosyl homocysteine.

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Toxic neuropathy

- Alcohol (independent of associated nutritional deficiencies)
- Heavy metals (lead, mercury, arsenic, and thallium)
- Organic solvents.
- Vinca alkaloids, taxanes, cisplatin
- Radiation

Neuropathy with malignancy

- Direct infiltration or compression of peripheral nerves
- A common cause of mononeuropathy and may be a presenting symptom of cancer.
- Brachial plexopathy from neoplasms of the apex of the lung
- Obturator palsy from pelvic malignant neoplasms
- Cranial nerve palsies from intracranial tumors or tumors of the base of the skull.
- Polyradiculopathy involving the lower extremity may develop when the cauda equina is involved by meningeal carcinomatosis.

Paraneoplastic neuropathy

- Sensorimotor neuronopathy is the most common paraneoplastic form
- Usually associated with small cell lung cancer
- CD8+ T-cell mediated attack on dorsal root ganglion cells.
- Lambert-Eaton (anti-Hu antibodies)
- Mixed axonal degeneration and demyelination
- anti-CV2 autoantibodies (which recognize CRMP5, an intracellular signaling protein)

Paraprotein neuropathy

- IgM paraprotein is thought to bind directly to myelin-associated antigens such as myelin associated glycoprotein (MAG).
- IgM is deposited between the membrane layers of the myelin sheath.
- IgG or IgA paraproteins may also be associated with peripheral neuropathy.
- AL amyloid

POEMS

- Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
- Sensorimotor polyneuropathy
- Lymphoproliferative disorder
- Visceromegaly
- Hypogogonadism
- Hyperpigmentation
- Demyelinating
- Paraprotein is deposited between non-compacted myelin lamellae

Mechanical causes

- Compression neuropathy (entrapment neuropathy) occurs when a peripheral nerve is chronically subjected to increased pressure, often within an anatomic compartment.
- Carpal tunnel syndrome, the most common entrapment neuropathy, results from compression of the median nerve at the level of the wrist within the compartment delimited by the transverse carpal ligament.
- Women are more commonly affected than men, and the problem is frequently bilateral.

Mechanical causes

- Other nerves prone to compression neuropathies include:
- The ulnar nerve at the level of the elbow
- The peroneal nerve at the level of the knee
- The radial nerve in the upper arm
- The interdigital nerve at inter-metatarsal sites
- May lead to perineural fibrosis (Morton neuroma)
- More common in women

Inherited peripheral neuropathies

- The major types include:
- (1) hereditary motor and sensory neuropathies, also known as Charcot-Marie-Tooth (CMT) disease
- (2) hereditary motor neuropathies
- (3) hereditary sensory neuropathies, with or without autonomic neuropathy
- (4) other inherited conditions such as
- familial amyloidosis and inherited metabolic diseases.

Charcot-Marie-Tooth (HMSN IA)

- Hereditary motor and sensory neuropathy with ataxia
- One of the most common inherited neurologic disorders
- Autosomal dominant
- Presents in early adolescence or adulthood
- Slowly progressive
- Weakness and atrophy of the muscles of the lower legs beginning in childhood
- Loss of fine motor skills (first, in toes)
- Later, hand weakness, distal sensory loss, and muscle atrophy.

Charcot-Marie-Tooth (HMSN IA)

- Foot drop and high stepped gait, claw toes
- “Inverted champagne bottle” appearance to lower legs as muscle bulk lost
- Duplication of PMP22 gene at 17p11.2 in 55% of cases
- Regulate Schwann cell growth and maturation

Charcot-Marie-Tooth (HMSN IA)

- Hereditary neuropathy with predisposition to pressure palsy (HNPP) is caused by a deletion of one of the PMP22 genes.
- Abnormally low levels of the PMP22 gene result in episodic, recurrent demyelinating neuropathy

HMSN IB

- CMT1B
- Myelin protein zero (MPZ) gene at 1p36.22 produces an identical clinical phenotype
- Adhesion molecule for myelin
- 9% of cases

Charcot-Marie-Tooth (HSN 1E)

- Progressive weakness of the feet and/or ankles; foot drop; atrophy of muscles below the knee; absent tendon reflexes of upper and lower extremities; and a decreased sensitivity to touch, heat, and cold in the feet and/or lower legs
- Cochlear earing loss associated with alanine to proline change at position 67 in PMP22 gene
- Autosomal dominant .

HMSN 1X

- CMT1X
- X-linked dominant form
- Secoond most common type
- 15% of cases
- GJB1 gene at Xq13.1 (gap junction or connexin-32 protein)
- Delayed transmission as gap covered by radial diffusion
- Demyelination

HMSN II

- CMT2A
- Autosomal dominant.
- Clinical presentation is as with classic Charcot-Marie-Tooth.
- Onset 5-25 years of age
- Loss of myelinated axons is prominent.
- Internodal demyelination is infrequent.
- Nerve conduction velocity impaired.
- Mutation involves the mitofusion protein 2, MFN2, at 1p36.22
- Prevents the mitochondrion from moving down the axon; synapse is inoperative.
- 4% of cases

HMSN II

- Some cases involve mutations in the KIF1B gene at 1p36.22, encoding the microtubular transport motor, kinesin, that transports synaptic vesicles (neurons) and mitochondria (other cells)
- GARS1 gene (glycyl tRNA synthetase) at 7p14.3
- Blocks glycine translation and attachment to cognate RNA
- Mutant protein product binds with neurolipin 1, leading to VEGF overexpression
- Associated with disease in hands.

HMSN II

- The constant cycle of demyelination and remyelination, which occurs in CMT, can lead to the formation of layers of myelin around some nerves, termed an "onion bulb".
- Muscles show fiber type grouping, a finding that indicates a cycle of denervation/reinnervation
- Generally milder than CMT I
- Some types of CMT2 may have vocal cord or phrenic nerve involvement, causing speech or breathing problems

Charcot-Marie-Tooth (HSN II)

- Another severe form of CMT2B is also associated with the formation of ulcers in the hands and feet.
- Onset in late childhood
- Four missense mutations in RAB7A gene at 3q21.3
- Alters autophagy

Charcot-Marie-Tooth (HSN II)

- CMT2F
- HSPBI gene at 7q11.23
- Chaperone function of heat shock protein altered by N-terminal change
- Autosomal dominant
- Onset in adolescence
- normal nerve conduction velocities
- upper limb amyotrophy, talipes equinovarus, steppage gait,

Charcot-Marie-Tooth (HSN II)

- MFN2-HMSN
- MFNP at 1p36.22
- Onset before 10 years of age
- Autosomal dominant (90%)
- Optic atrophy in 20% of those with autosomal recessive inheritance (7%, if autosomal dominant)
- Severe loss of sensation in the feet, lower legs, hands, and forearms; reduced tendon reflexes in the ankles; weakness in the lower limbs; muscle atrophy.

HMSN III, now HMSN IVF

- Dejerine-Sottas disease
- Can be inherited either dominantly or recessively
- Severe demyelinating neuropathy that begins in infancy.
- Involves both trunk and limb muscles
- Severe muscle atrophy and weakness, delayed motor skills development, sensory problems
- Progress to severe disability, loss of sensation, and curvature of the spine.

HMSN III, now HMSN IVF

- Caused by mutations in multiple genes
- PMP22, MPZ, and GJB1
- Protein degradation pathways (LITAF at 16p13.13)
- Mediate TNF-a
- Also in Type 1C
- Myelination induction (early growth response or EGR2 at 18q21.3)
- Transcription factor with three tandem C2H2 zinc fingers
- Also in Type 1D and 4E

Charcot-Marie-Tooth (HSN-IV)

- Rare in the U.S.
- Autosomal recessive.
- CMT4B2 SBF1 gene at 22q13.33
- Converts GDP to GTP
- Myoblast differentiation
- Pseudogenes found on chromosomes 1 and 8 as well
- Onset in childhood

  Poor fine motor control, leg weakness and distal upper limb weakness
- Myelin outfoldings in peripheral nerve sheath

Familial amyloid polyneuropathy

- Sensory neuropathy
- Loss of temperature sensation in the feet
- Orthostatic hypotension
- Incontinence.
- Autosomal dominant.
- TTR (Transthyretin) gene at 18q11.2-q12.1
- Amyloid deposits in vessel walls and endoneurium with axonal degeneration.

Refsum disease

- Mixed motor and sensory neuropathy
- Autosomal recessive
- Onset before 20 years of age.
- Night blindness and retinitis pigmentosa
- Loss of smell
- Ataxia as later development
- Icthyosis as later development
- PEX7 gene at 6q23.3 with PHYH gene at 10p13
- Perioxisomal enzyme phaytanoyl CoA deficiency.
- Phytanic acid accumulates

Leukodystrophy

- Adrenal leukodystrophy
- Cerebral form
- Presents between 4-10 years (males)
- Learning and behavioral disability
- Adrenal insufficiency

Leukodystrophy

- Adrenomyeloneuropathy form
- Presents between early adulthood and middle age
- 4% of females are symptomatic
- Paraparesis
- Bladder and bowel dysfunction
- Adrenal insufficiency
- Addison disease only form
- Presents any time between childhood and adulthood
- Adrenal insufficiency
- Paraparesis, bladder and bowel dysfunction appear later

Molecular change

- ABCD1 gene at Xq28 (ATP Binding Cassette Transporter)
- Adrenaleukodystrophy protein production impaired
- Elevated levels of long chain fatty acids in serum and tissues as a result of deficiency in enzyme that degrades very long chain fatty acids.
- Segmental demyelination with onion bulbs as well as myelinated and unmyelinated axonal degeneration noted.
- More severe in parietal and occipital regions
- Linear inclusions are present in Schwann cells.

HSAN I

- Hereditary sensory and autonomic neuropathy
- Loss of pain and temperature sensation early
- Lancinating pain
- Orthostatic hypotension
- Without muscle weakness.
- Autosomal dominant
- Presents in young adults
- SPTLC1 gene at 9q22.31
- Cys133Trp common mutation
- Serine palmitoyl transferase, long chain base unit.
- Produces deoxysphingoid bases (abnormal), diminishing production of sphingolipid

HSAN I

- HSAN IB
- Sensory neuropathy with cough
- GERD
- 3p22-24
- HSAN IC
- Presents as HSAN IA
- SPTLC2 missense mutation

HSAN I

- HSAN ID
- Distal sensory loss and amyotrophy of lower limbs
- ALT1 gene encodes atlastin-1
- Reduced GTPase activity
- Also associated with hereditary spastic paraplegia
- HSAN IE
- Somatosensory loss
- Sensorineural hearing loss
- Dementia
- DNMT1 gene at (DNA methyltransferase)

Inherited neuropathies

- HSAN II
- Presents in childhood
- Sensory neuropathy
- GERD
- Autosomal recessive
- WNK/HSAN2 gene at 12q13.3. (HSAN IIA)
- Regulate Na^+ and K^+ channel transport
- RETREG1 gene at 5p15.1 (HSAN IIB)
- Autophagy
- Axonal degeneration of myelinated fibers prominent in HSAN I and HSAN II.

Inherited neuropathies

- HSAN III (Riley-Day syndrome).
- Presents in infancy
- Autonomic neuropathy
- Autosomal recessive
- ELP1 (IKPKAP) gene at 9q31.3 (histone acetyltransferase)
- Affects transcription of proteins that deal with cytoskeleton and with cell motility
- Described in Ashkenazi cohorts.
- Axonal degeneration of unmyelinated fibers with atrophy and loss of sensory and autonomic ganglion cells

Inherited neuropathies

- HSAN IV
- Presents in infancy
- Congenital insensitivity to pain
- Anhidrosis
- Autosomal recessive
- NTRK1 gene at 1q23.1-22
- Neurotrophic tyrosine kinase receptor type I affects phosphorylation
- Nearly complete loss of small unmyelinated and myelinated fibers prominent

Inherited neuropathies

- HSAN V
- Presents in infancy
- Insensitivity to pain and temperature
- Nearly complete loss of small myelinated fibers
- autosomal recessive
- NGFB gene at 1p31.1
- Nerve growth factor β-subunit affects phosphorylation
- HSAN V shows loss of myelinated fibers

Hereditary spastic paraplegia

- Pure form (Troyer syndrome)
- Presents in second and fourth decades
- Progressive upper motor neuron disease with spasticity in legs and urinary urgency
- Gait disturbance
- Impaired pain sensation
- 75-80% of affected individuals
- Autosomal dominant
- SPART gene at 13q13.3
- Spartin regulates endocytosis (here, nonfunctional)

Hereditary spastic paraplegia

- Complex form
- Ataxia in 30%
- Seizures
- Cognitive impairment
- Possible upper limb involvement

Hereditary spastic paraplegia

- Autosomal dominant
- HSP IIIA
- Presents at age 4
- 15% of cases
- Lower limb disease with hyperactive bladder
- ATL-1 gene at 14q21.3
- Atlastin
- HSP IV
- Also describes hyperreflexia
- SPAST gene at 2p23
- Spastin regulates microtubule transport
- 40% of cases

Hereditary spastic paraplegia

- Autosomal dominant
- HSP Type 31
- Ages 20-30
- Spasticity and amyotrophy
- REEP1 gene at 2p11.2
- Impaired activation of G-coupled receptors
- Function in mitochondria unknown
- 5% of cases

Hereditary spastic paraplegia

- Autosomal recessive
- HSP Type 5A
- Presents from infancy to adulthood
- CYP7B1 gene at 8q12.3 (P450 system)
- Oxysterol-7-α-hydroxylase
- Impaired hydroxylation of nuclear DHEA leads to cholesterol accumulation
- 7% of cases

Hereditary spastic paraplegia

- Autosomal recessive
- HSP Type 7
- Adult onset
- Pure: spastic paraplegia
- Complex: with cerebellar dysfunction
- 5% of cases
- CYP7B1 gene at 8q12.3 (P450 system)
- Oxysterol-7-α-hydroxylase
- Impaired hydroxylation of nuclear DHEA leads to cholesterol accumulation

Hereditary spastic paraplegia

- Autosomal recessive
- HSP Type 11
- SPG11 gene at 15q21.1
- Thin or absent corpus callosum (radiographic evidence) prominent finding
- Spatacsin involved in axon maintenance
- 5% of cases
- X-linked recessive
- Cognitive impairment common
- L1CAM gene at Xq28
- Adhesion molecule

Antibody-Mediated Diseases of the Neuromuscular Junction

- Myasthenia gravis
- 85% have autoantibodies against postsynaptic acetylcholine receptors
- Lead to the aggregation and degradation of the receptors, and also to damage of the postsynaptic membrane through complement fixation
- 15% have antibodies against the sarcolemmal protein muscle-specific receptor tyrosine kinase.
- Interfere with the trafficking and clustering of acetylcholine receptor within the sarcolemmal membrane.

Antibody-Mediated Diseases of the Neuromuscular Junction

- 10% associated with thymoma
- 30% associated with thymic hyperplasia
- B-cell follicles appear in the thymus
- Fluctuating weakness that worsens with exertion and often over the course of the day.
- Diplopia and ptosis due to involvement of extraocular muscles are common
- Cases with antibodies against muscle-specific receptor tyrosine kinase differ from typical cases by exhibiting more focal muscle involvement (neck, shoulder, facial, respiratory, and bulbar muscles)

Antibody-Mediated Diseases of the Neuromuscular Junction

- Lambert-Eaton myasthenic syndrome is an autoimmune disorder caused by antibodies that block acetylcholine release by inhibiting a voltage gated presynaptic calcium channel.
- In contrast to myasthenia gravis, rapid repetitive stimulation increases muscle response.
- Patients typically present with weakness of their extremities
- Diplopia and ptosis are late findings, mild, and improve during the day
- 60% associated with small cell carcinoma of the lung

Antibody-Mediated Diseases of the Neuromuscular Junction

- Congenital myasthenia
- Most common are loss-of-function mutations in the gene encoding the ε-subunit of the acetylcholine receptor.
- Another group of mutations affect proteins that are important in normal clustering of acetylcholine receptors on postsynaptic membranes.
- Usually present in perinatal period with poor muscle tone, external eye muscle weakness, and breathing difficulties.

Toxin mediated diseases of the neuromuscular junction

- Botulism
- Clostridium botulinum toxin blocks release of acetycholine from presynaptic neurons.
- Weakness of muscles of the eye and throat
- May spread to trunk, limbs, and respiratory muscles (symmetric descending flaccid paralysis)
- Usually foodborne illness
- May present in infant as floppy baby
- Colonization of gut by Clostridum botulinum
- May be confused with Guillan-Barré (adults) or congenital myopathy or dystrophy (infants)

Schwann cell tumors

- Schwannomas present at the cerebello-pontine angle. (CN VIII)
- Well-circumscribed, encapsulated masses that abut the associated nerve without invading it
- Schwann cells are characterized by the presence of a spindled elongated nucleus with a wavy or buckled shape.
- Replaces nerve of origin as it grows.
- Electron microscopy shows basement membrane deposits encasing single cells and collagen fibers.
- Clinical symptoms related to compression syndrome.

Schwann cell tumors

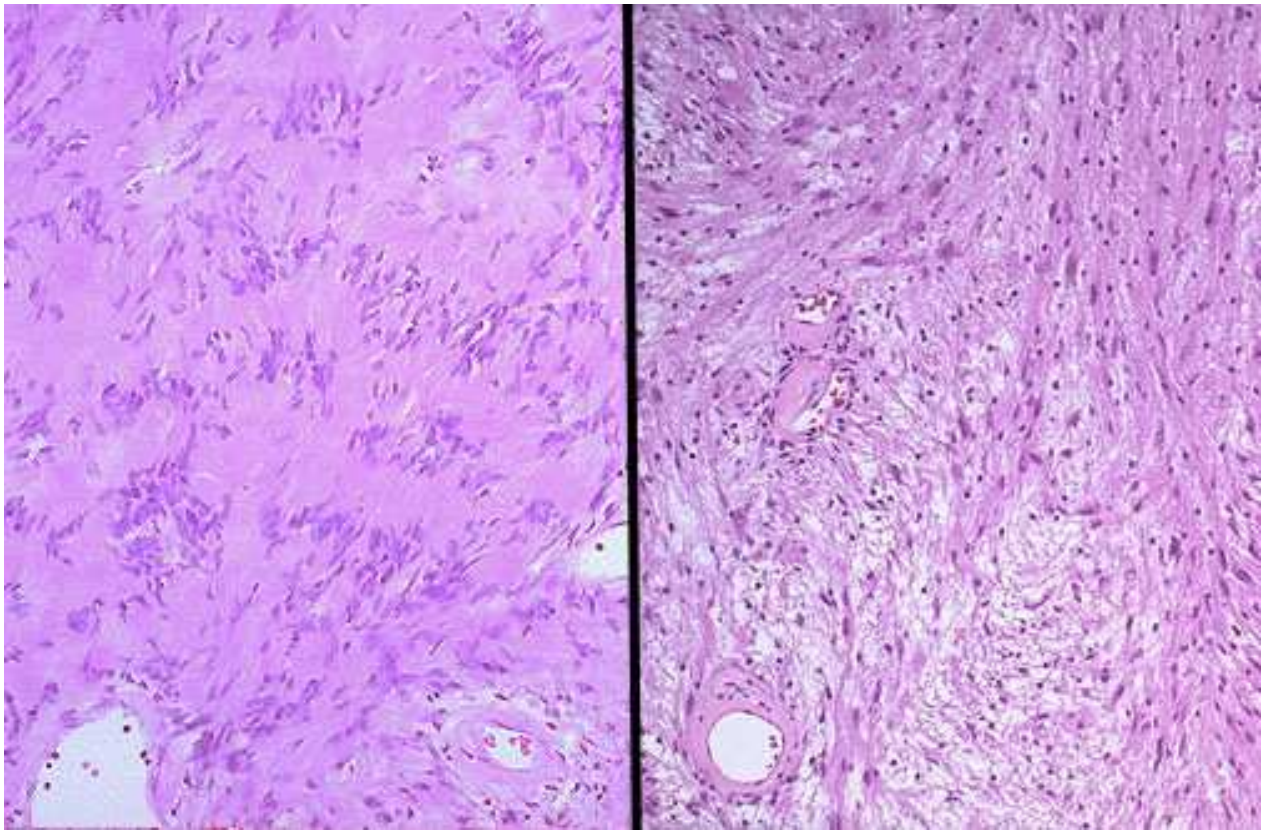
- The dense eosinophilic Antoni A areas often contain spindle cells arranged into cellular intersecting fascicles.
- Palisading of nuclei is common and “nuclear-free zones” that lie between the regions of nuclear palisading are termed Verocay bodies.
- Rare mitoses
- In the loose, hypocellular Antoni B areas the spindle cells are spread apart by a prominent myxoid extracellular matrix that may be associated with microcyst formation.

Schwann cell tumors

- NF2 (22q12) mutation with loss of gene product, merlin, related to red cell cytoskeletal protein 4.1 (ERM family)

  Does not establish stable cell-cell junctions
- S100+

Schwann cell tumor



Left: Antoni A pattern

Right: Antoni B pattern

https://webpath.med.utah.edu/CNSHTML/CNS187.html
Accessed 04/27/2010

Neurofibroma

- Neurofibromas are benign nerve sheath tumors that are more heterogeneous in composition than schwannomas.
- The neoplastic Schwann cells are admixed with perineural-like cells, fibroblasts, mast cells, and CD34+ spindle cells.
- Neurofibromas may be either sporadic or NF1-associated.
- NF1 (17q22) loss leads to constitutive activation of RAS as inhibitory GTPase (neurofibromin) is lost.

Superficial cutaneous neurofibroma

- These are small, well delineated but unencapsulated nodular lesions that arise in the dermis and subcutaneous fat.
- They have relatively low cellularity
- Contain bland Schwann cells admixed with stromal cells such as mast cells, perineurial cells, CD34+ spindle cells, and fibroblasts.
- Adnexal structures are sometimes entrapped at the edges of the lesion.
- The stroma of these tumors contains loose collagen.

Diffuse neurofibroma

- Present as a large plaque-like elevation of skin
- The tumor diffusely infiltrates the dermis and subcutaneous connective tissue, entrapping fat and appendage structures and producing a plaque-like appearance
- Focal collections of cells mimicking the appearance of Meissner corpuscles (tactile-like bodies) are found.
- Else, microscopically similar to superficial cutaneous neurofibroma
- NF1 associated

Plexiform neurofibroma

- Found in deep or superficial locations in association with nerve roots or large nerves
- Grow within and expand nerve fascicles, entrapping associated axons
- The external perineurial layer of the nerve is preserved, giving individual nodules an encapsulated appearance.
- The expanded, ropy thickening of multiple nerve fascicles results in what is sometimes referred to as a “bag of worms” appearance.
- The tumor has cellular composition similar to that of other neurofibromas.

Plexiform neurofibroma

- The extracellular matrix varies from loose and myxoid to more collagenous and fibrous.
- Often the collagen is seen in bundles likened to “shredded carrot”
- Uniformly NF1-associated.
- Only the Schwann cells in neurofibromas have complete loss of NF1.
- Transformation to malignant peripheral nerve sheath tumor (MPNST) is only seen in plexiform neurofibromas.
- The overall incidence of MPNST in NF1 patients is about 5% to 10%.

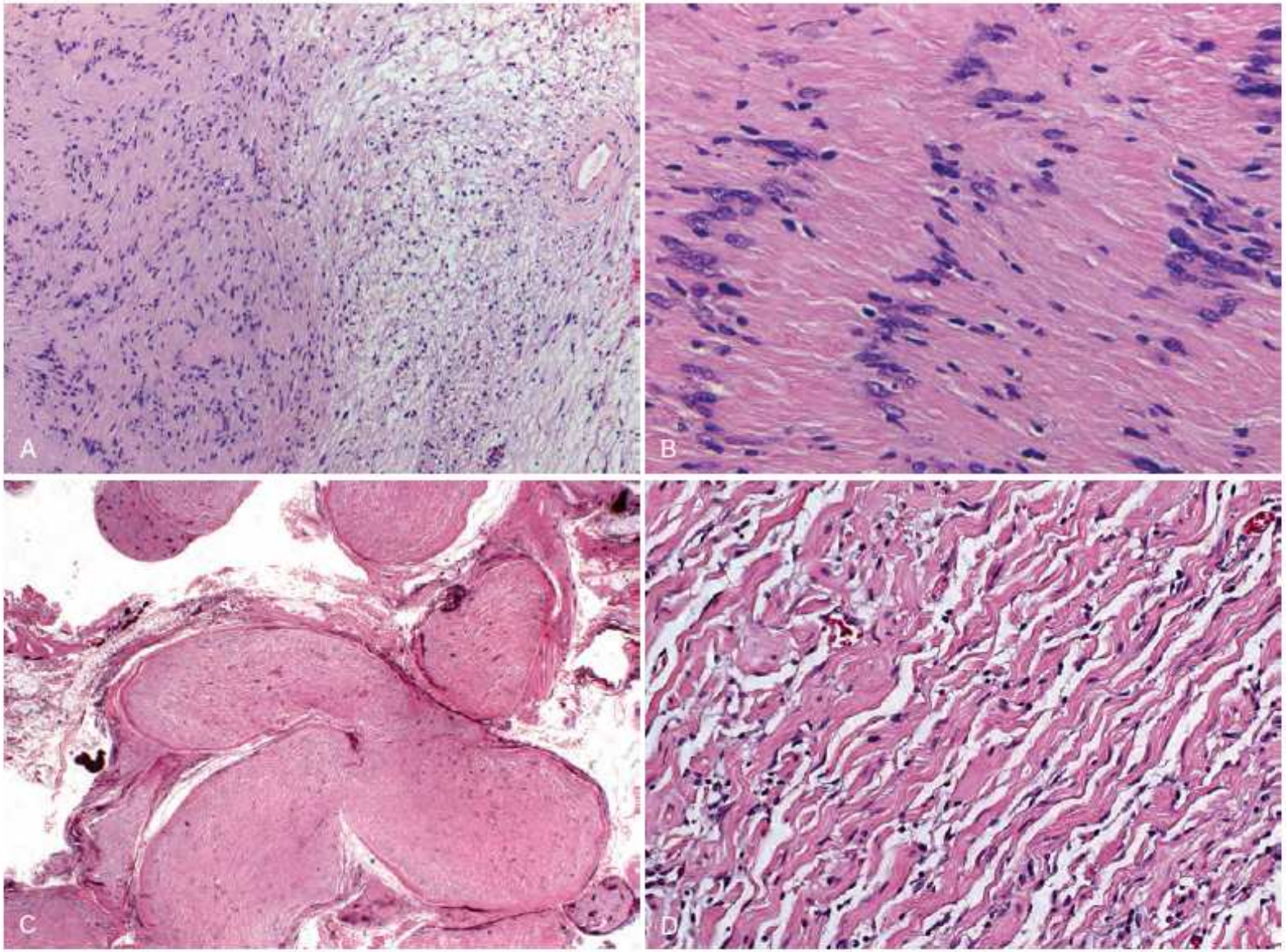


Figure 27-14 Schwannoma and plexiform neurofibroma. **A** and **B,** Schwannoma. As seen in **A,** schwannomas often contain dense eosinophilic Antoni A areas (*left*) and loose, pale Antoni B areas (*right*), as well as hyalinized blood vessels (*right*). **B,** Antoni A area with the tumor cell nuclei aligned in palisading rows leaving anuclear zones and resulting in the formation of structures termed *Verocay bodies*. **C** and **D,** Plexiform neurofibroma. **C,** Multiple nerve fascicles are expanded by infiltrating tumor cells. **D,** At high power bland spindle cells are admixed with wavy collagen bundles resembling carrot shavings.

Malignant peripheral nerve sheath tumor

- Generally high-grade
- Arise from NF1 lesions
- The lesions are poorly defined tumor masses that frequently infiltrate along the axis of the parent nerve and invade adjacent soft tissues.
- Typical cases show a fasciculated arrangement of spindle cells. At low power the tumor often appears “marbleized” due to variations in cellularity.
- Mitoses, necrosis, and nuclear anaplasia are common.

Malignant peripheral nerve sheath tumor

- “Divergent differentiation” refers to foci that exhibit other lines of differentiation (mesenchymal, endodermal, ectodermal)
- A tumor exhibiting the latter is referred to as Triton tumor.

Neurofibromatosis 1

- More common
- Characterized by:
- Neurofibromas of peripheral nerve
- Gliomas of the optic nerve
- Pigmented nodules of the iris (Lisch nodules)
- Cutaneous hyperpigmented macules (café au lait spots).
- NF1 (17q22) loss leads to constitutive activation of RAS as inhibitory GTPase (neurofibromin) is lost.

Neurofibromatosis 2

- Schwann cell tumor
- Present at the cerebello-pontine angle. (CN VIII)
- NF2 (22q12) mutation with loss of gene product, merlin, related to red cell cytoskeletal protein 4.1 (ERM family)

  Does not establish stable cell-cell junctions