

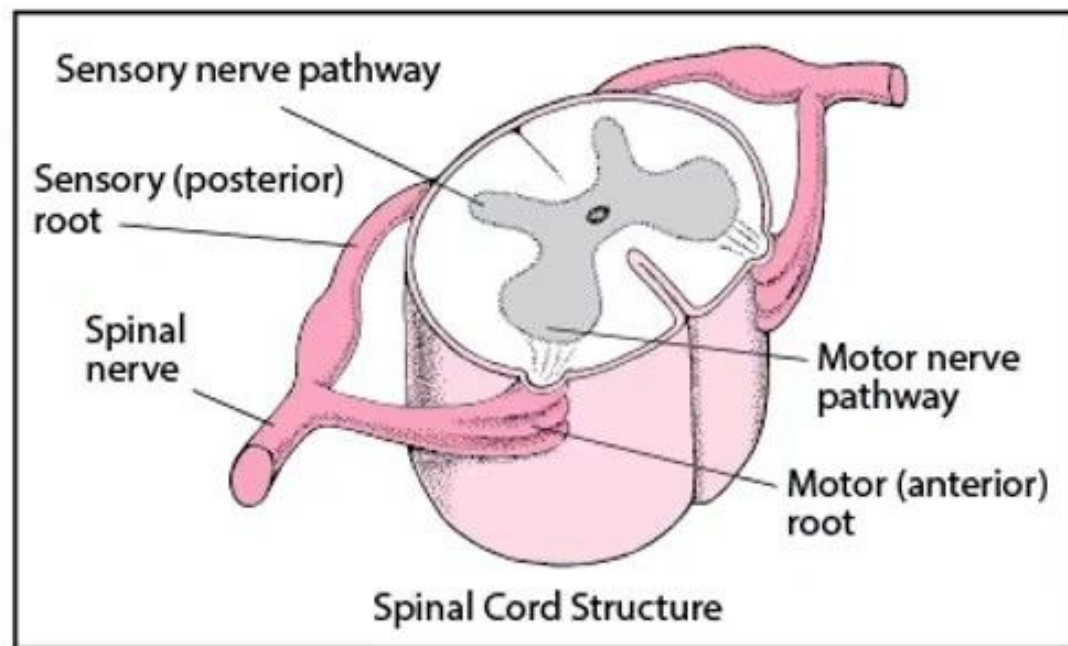
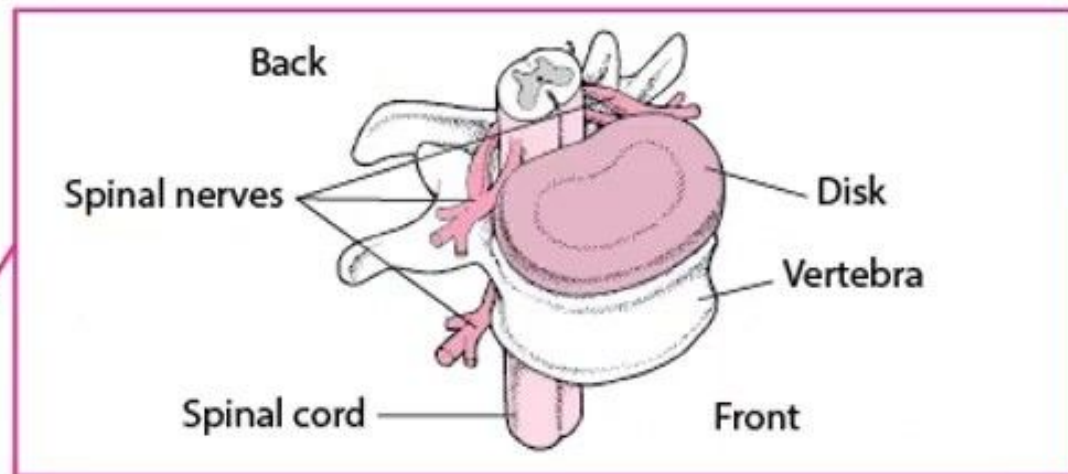
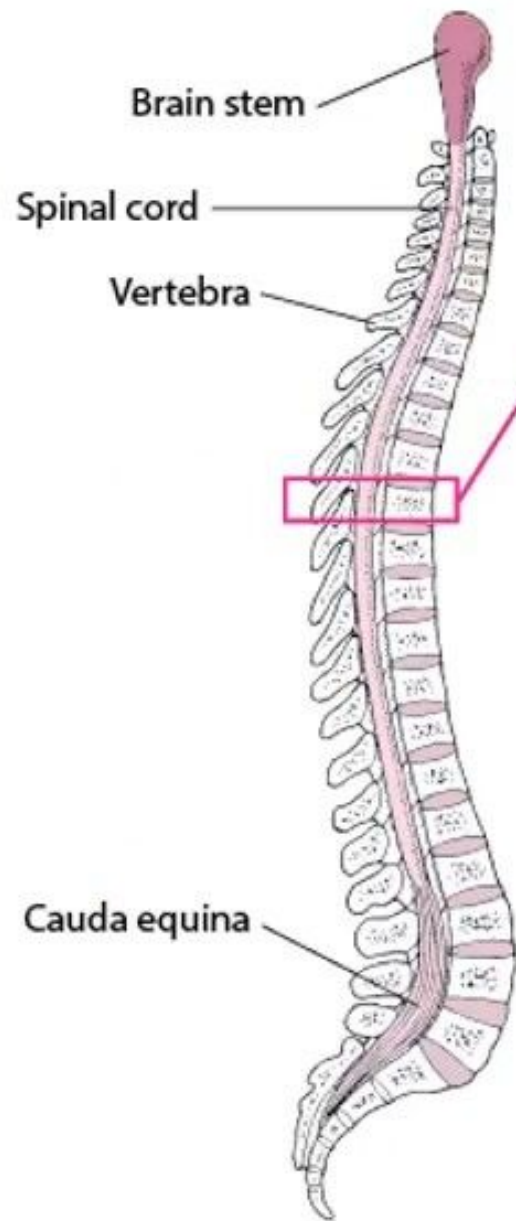
Anatomic Patterns of Peripheral Neuropathies

Peripheral neuropathies can be separated into several groups according to the anatomic distribution of involvement and the associated neurologic deficits. This approach can be helpful clinically, since each pattern has a different set of potential underlying causes. These anatomic patterns of injury are as follows:

- **Mononeuropathies** affect a single nerve and result in deficits in a restricted distribution dictated by nerve anatomy Trauma, entrapment, and infections are common causes of mononeuropathy

- **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.
- **Mononeuritis multiplex** describes a disease process that damages individual nerves in a haphazard fashion. An affected patient might have a right wrist drop from involvement of the right radial nerve and a left foot drop from peroneal nerve damage. Vasculitis is a common cause of this injury.
- **Poly(radiculo)neuropathies** affect nerve roots as well as peripheral nerves, leading to diffuse symmetric symptoms in proximal and distal parts of the body.





Specific Peripheral Neuropathies

Patients with peripheral neuropathy often complain of numbness, painful “pins and needles” sensations, and weakness, most often in the distal portions of the extremities.

PRINCIPAL CAUSES OF PERIPHERAL NEUROPATHY

1. Autoimmunity (inflammatory demyelinating polyradiculoneuropathies).
2. Vasculitis (connective tissue diseases).
3. Systemic illness (diabetes, uremia, sarcoidosis, myxedema, acromegaly).
4. Cancer (paraneoplastic neuropathy).
5. Infections (diphtheria, leprosy, Lyme disease, AIDS, herpes zoster).
6. Dysproteinemia (myeloma, cryoglobulinemia).
7. Nutritional deficiencies and alcoholism.
8. Compression and trauma.
9. Toxic industrial agents and drugs.
10. Inherited neuropathies.



Inflammatory Neuropathies

Guillain-Barré Syndrome (Acute Inflammatory Demyelinating Polyneuropathy)

Guillain-Barré syndrome is an immunologically mediated demyelinating peripheral neuropathy that may lead to life-threatening respiratory paralysis. The overall annual incidence is approximately 1 case per 100,000 persons. The disease is characterized clinically by weakness beginning in the distal limbs that rapidly advances to affect proximal muscle function (“ascending paralysis”). Histologic features are inflammation and demyelination of spinal nerve roots and peripheral nerves (radiculoneuropathy).



Pathogenesis

In most cases, Guillain-Barré syndrome is thought to be an acute-onset immune-mediated demyelinating neuropathy. Approximately two-thirds of cases are preceded by an acute, influenza-like illness from which the affected individual has recovered by the time the neuropathy becomes symptomatic. Infections with *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, and *Mycoplasma pneumoniae* as well as prior vaccination have significant epidemiologic associations with Guillain-Barré syndrome. No infectious agent has been demonstrated in affected nerves, and an immunologic reaction is favored as the underlying cause.

MORPHOLOGY

The dominant finding in sections stained with hematoxylin and eosin is inflammation of peripheral nerves, manifested as 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, particularly when the disease is severe.

Clinical Features The clinical picture is dominated by ascending paralysis and areflexia

Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy

This is the most common chronic acquired inflammatory peripheral neuropathy, characterized by symmetric mixed sensorimotor polyneuropathy that persists for 2 months or more. By definition, signs and symptoms must be present for at least 2 months, but often the disease evolves over years, usually with relapses and remissions. Typically there is a symmetric, mixed sensorimotor polyneuropathy, but some patients may present with predominantly sensory or motor impairment. Clinical remissions can often be achieved with intravenous immunoglobulin, or with other immunosuppressive therapies, such as plasmapheresis, glucocorticoids, and cytotoxic agents directed against T cells or B cells. The time course and the response to steroids distinguish chronic inflammatory demyelinating polyradiculoneuropathy from Guillain-Barré syndrome.



Neuropathy Associated With Systemic Autoimmune Diseases

Systemic autoimmune diseases like rheumatoid arthritis, Sjögren syndrome, or systemic lupus erythematosus may be associated with peripheral neuropathies that often take the form of distal sensory or sensorimotor polyneuropathies. These neuropathies are distinct from vasculitic peripheral neuropathies, which can arise as secondary manifestations of these same diseases.

Neuropathy Associated With Vasculitis

Vasculitis is a noninfectious inflammation of blood vessels that can involve and damage peripheral nerves. About one-third of patients with vasculitis, depending on the type of vasculitis, have peripheral nerve involvement, and neuropathy may be the presenting feature. Vasculitis often presents as mononeuritis multiplex, but mononeuritis and polyneuropathy are also encountered. When peripheral neuropathy occurs in systemic vasculitis, it is most common in the MPO-ANCA–associated vasculitides (microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis/Churg-Strauss syndrome) and polyarteritis nodosa and much less common in PR3-ANCA–associated granulomatosis with polyangiitis.



The most common form of vasculitis associated with peripheral neuropathy is a localized form referred to as nonsystemic vasculitic neuropathy, which is not associated with any anti-neutrophil cytoplasmic antibodies (ANCA). Regardless of the type of vasculitis, peripheral nerves involved by vasculitis typically show patchy axonal degeneration and loss, with some fascicles being more severely affected than others. Perivascular inflammatory infiltrates are often present. Identification of blood vessels with characteristic forms of acute or chronic damage helps establish the diagnosis

Infectious Neuropathies

Many infectious processes affect peripheral nerves. Among these, leprosy, diphtheria, and varicella-zoster cause relatively specific pathologic changes in nerves that are the focus here.

Leprosy (Hansen Disease)

Peripheral nerves are involved in both lepromatous and tuberculoid leprosy.

- In lepromatous leprosy, Schwann cells are invaded by *Mycobacterium leprae*
- Tuberculoid leprosy is characterized by an active cell mediated immune response to *M. leprae* that usually manifests as dermal nodules containing granulomatous inflammation.

Lyme Disease Lyme disease causes various neurologic manifestations in the second and third stages of the disease. These include polyradiculoneuropathy and unilateral or bilateral facial nerve palsies.



HIV/AIDS

Patients infected with human immunodeficiency virus (HIV) develop several patterns of peripheral neuropathy that are poorly understood, but all appear to be related in some way to immune dysregulation. Early-stage HIV infection can be associated with mononeuritis multiplex and demyelinating disorders that may resemble Guillain Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy. More commonly, later stages of HIV infection are associated with a distal sensory neuropathy that is often painful.

Diphtheria

Peripheral nerve dysfunction results from the effects of the diphtheria exotoxin. It produces an acute peripheral neuropathy associated with prominent bulbar and respiratory muscle dysfunction, which can lead to death or long-term disability. Diphtheria is most commonly found in low income countries and is a continuing medical problem because of incomplete immunization or waning immunity in adults.

Varicella-Zoster Virus

Varicella-zoster is one of the most common viral infections of the peripheral nervous system. Following chickenpox, a latent infection persists within neurons of sensory ganglia. If the virus is reactivated, sometimes many years later, it may be transported along the sensory nerves to the skin. Here it infects keratinocytes, leading to a painful, vesicular skin eruption in a distribution that follows sensory dermatomes (shingles). Most common is the involvement of thoracic or trigeminal nerve dermatomes. The factors underlying reactivation of the virus are not fully understood, but decreased cell-mediated immunity is suspected to play a role.



Metabolic, Hormonal, and Nutritional Neuropathies

Diabetes

Diabetes is the most common cause of peripheral neuropathy. The prevalence of this complication depends on the duration of the disease; up to 50% of patients with diabetes overall and up to 80% of those who have had the disease for more than 15 years have clinical evidence of peripheral neuropathy. Patients with both type 1 and type 2 diabetes are affected. Several distinct clinicopathologic patterns of diabetes-related peripheral neuropathy are recognized, but the most common by far is an ascending distal symmetric sensorimotor polyneuropathy.

Pathogenesis

The mechanism of diabetic neuropathy is complex and not completely resolved; both metabolic and secondary vascular changes are believed to contribute to the damage of axons and Schwann cells. Hyperglycemia causes the nonenzymatic glycosylation of proteins, lipids, and nucleic acids.

MORPHOLOGY In individuals with a distal symmetric sensorimotor neuropathy, the predominant pathologic finding is an axonal neuropathy. Nerve biopsies show reduced numbers of axons. Variable degrees of ongoing axonal damage, marked by degenerating myelin sheaths and regenerative axonal clusters, may be present. Endoneurial arterioles show thickening, hyalinization, and intense periodic acid–Schiff positivity of their walls and extensive reduplication of basement membranes .

Clinical Features

Distal symmetric diabetic polyneuropathy typically presents with sensory symptoms like numbness, loss of pain sensation, difficulty with balance, and paresthesias or dysesthesias.

another manifestation is dysfunction of the autonomic nervous system; this affects 20% to 40% of individuals with diabetes mellitus, nearly always in association with a distal sensorimotor neuropathy. Diabetic autonomic neuropathy has protean manifestations, including postural hypotension, incomplete emptying of the bladder (resulting in recurrent infections), and sexual dysfunction

Other Metabolic, Hormonal, and Nutritional Neuropathies

A diverse group of metabolic, hormonal, and nutritional disorders are associated with peripheral neuropathy, including the following:

- Uremic neuropathy. Most individuals with renal failure have a peripheral neuropathy. Typically this is a distal, symmetric neuropathy that may be asymptomatic or may be associated with muscle cramps, distal dysesthesias, and diminished deep tendon reflexes. In these patients, axonal degeneration is the primary event; occasionally there is secondary demyelination. Regeneration and recovery are common after dialysis.
- Thyroid dysfunction. Hypothyroidism can lead to compression mononeuropathies such as carpal tunnel syndrome or cause a distal symmetric predominantly sensory polyneuropathy. In rare cases, hyperthyroidism is associated with a neuropathy resembling Guillain-Barré syndrome.

