

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.



- Vitamin B12 (cyanocobalamin) deficiency classically results in subacute combined degeneration with damage to long tracts in the spinal cord and also peripheral nerves.
- Deficiencies of vitamin B1 (thiamine), vitamin B6 (pyridoxine), folate, copper, and zinc all have been associated with peripheral neuropathy

Toxic Neuropathies

Peripheral neuropathies may appear after exposure to industrial or environmental chemicals, biologic toxins, or therapeutic drugs. Important causes of toxic peripheral nerve damage include alcohol (independent of associated nutritional deficiencies), heavy metals (lead, mercury, arsenic, and thallium), and organic solvents. Various medications can cause toxic nerve damage, but the most notorious are chemotherapeutic agents. These include vinca alkaloids and taxanes, microtubule inhibitors that interfere with axonal transport, and cisplatin, which may cause a neuronopathy.



Neuropathies Associated With Malignancy

Neuropathies associated with cancers may stem from local effects, complications of therapy, paraneoplastic effects, or (in the case of B-cell tumors) tumor-derived immunoglobulins.

- **Direct infiltration or compression** of peripheral nerves by tumors is a common cause of mononeuropathy and may be a presenting symptom of cancer. These neuropathies include brachial plexopathy from neoplasms of the apex of the lung, obturator palsy from pelvic malignant neoplasms, and cranial nerve palsies from intracranial tumors or tumors of the base of the skull. A polyradiculopathy involving the lower extremity may develop when the cauda equina is involved by meningeal carcinomatosis.

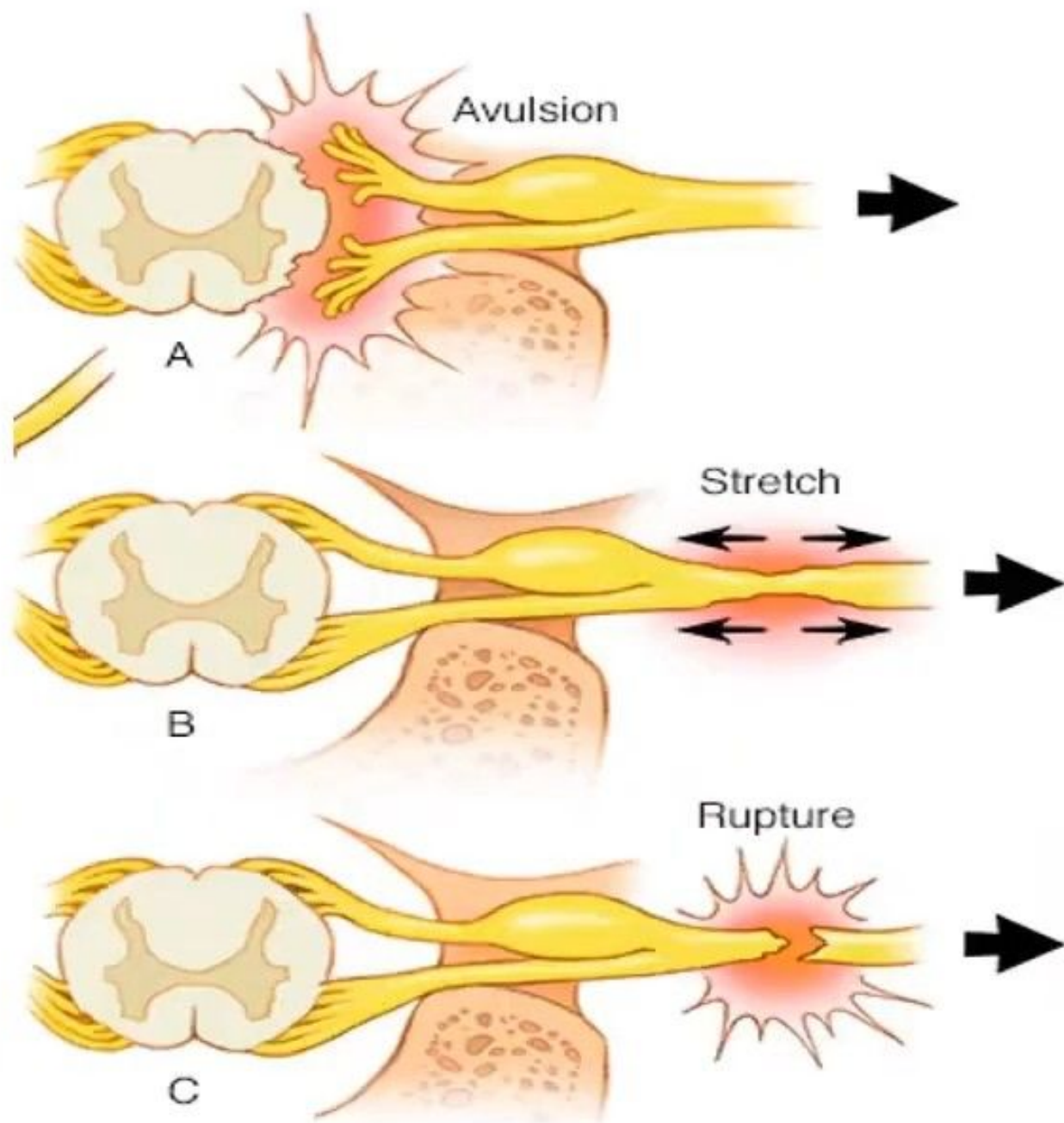
- **Paraneoplastic neuropathies.** These can occur at any time during the patient's course, but often precede the diagnosis of the underlying tumor. Sensorimotor neuropathy is the most common paraneoplastic form, but a pure sensory neuronopathy, chronic inflammatory demyelinating polyneuropathy, plexopathy, and autonomic neuropathy may also be seen. Paraneoplastic sensory neuronopathy is most commonly associated with small cell lung cancer.

- Neuropathies associated with monoclonal gammopathies. Neoplastic B cells may secrete monoclonal immunoglobulins or immunoglobulin fragments (so-called paraproteins) that damage nerves. For example, tumors that secrete IgM immunoglobulin may be associated with a demyelinating peripheral neuropathy. In most cases, the pathogenic IgM paraprotein is thought to bind directly to myelin-associated antigens such as myelin-associated glycoprotein. Deposition of IgM can be seen ultrastructurally between the membrane layers of the myelin sheath.

Neuropathies Caused by Physical Forces

Peripheral nerves are commonly injured by trauma or entrapment.

- Lacerations result from cutting injuries and from sharp fragments of fractured bone, both of which may sever a nerve.
- Avulsion of a nerve may occur when tension is applied, often to one of the limbs.
- 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.



The disorder may be observed in association with many conditions including tissue edema, pregnancy, inflammatory arthritis, hypothyroidism, amyloidosis (especially related to $\beta 2$ -microglobulin deposition in individuals on renal dialysis), acromegaly, diabetes mellitus, and excessive repetitive motions of the wrist. Symptoms are limited to dysfunction of the median nerve and typically include numbness and paresthesias of the tips of the thumb and first two digits. 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, and the radial nerve in the upper arm; the latter occurs from sleeping with the arm in an awkward position ("Saturday night palsy"). Another form of compression neuropathy is found in the foot, affecting the interdigital nerve at intermetatarsal sites. This problem, which occurs more often in women than in men, leads to foot pain (metatarsalgia) and is associated with a histologic lesion called a Morton neuroma, which is marked by perineural fibrosis.



Inherited Peripheral Neuropathies

are a group of genetically diverse disorders with overlapping clinical phenotypes that often present in adults. Because of the delayed onset, the possibility of an inherited neuropathy has to be considered in the differential diagnosis for any patient who presents with a peripheral neuropathy. The major types of inherited peripheral neuropathies include (1) hereditary motor and sensory neuropathies, sometimes known as Charcot-Marie-Tooth (CMT) disease which is a genetically heterogeneous disorder caused by mutations in genes that encode proteins involved in the structure and function of either the peripheral nerve axon or the myelin sheath; (2) hereditary motor neuropathies; (3) hereditary sensory neuropathies, with or without autonomic neuropathy; and (4) other inherited conditions causing neuropathy, including familial amyloidosis and inherited metabolic diseases.

