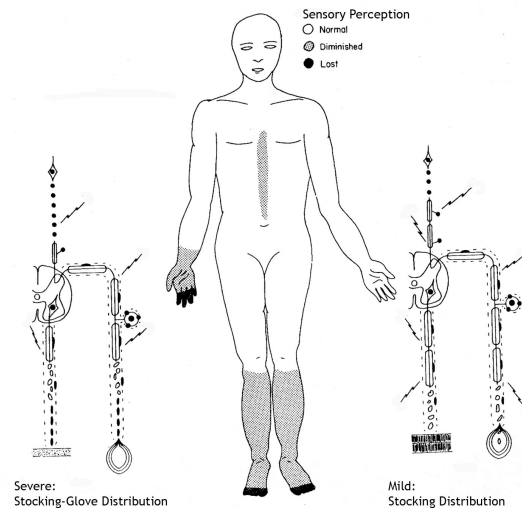


Primer of Length-Dependent Neuropathies

General: The term peripheral neuropathy refers to disorders of sensory or motor nerves (or a combination). The term is most commonly applied to the prototypic form that affects longest nerves first (length-dependent pattern), with initial symptoms and signs in the feet and lower legs. There are different types and causes of peripheral neuropathy. The first distinction is between hereditary neuropathies (due to a genetic disorder in a constituent nerve protein or functional factor) or acquired neuropathies (due to external factor affects the nerve or it's function) forms. Most acquired neuropathies most follow a length-dependent pattern but some affect nerves at multiple foci along the nerve, including nerve roots, and do not follow such a pattern, and these include acute and chronic inflammatory demyelinating polyradiculoneuropathies (AIDP, CIDP).

Clinical features: The prototypic length-dependent peripheral neuropathy follows a stocking-glove distribution of symptoms and signs (when symptoms reach the level of the knee the length of nerve involved reaches the fingers and symptoms begin in the hand). Symptoms may start in one leg, but with time become symmetric. Acquired neuropathies most commonly begin in mid to late adulthood.

There are three types of peripheral nerves: 1) Sensory nerves, bring information to the brain subserving touch, vibration, pain and proprioception, 2) Motor nerves, bring information to muscles to carry out intended or postural movements, and 3) Autonomic nerves, controlling blood pressure and other involuntary functions. While many peripheral neuropathies involve all three types of nerves forms involve predominantly sensory and motor nerves while symptoms due to autonomic nerves involvement are least common.



Prototypic length-dependent (stocking-glove) pattern primarily affecting nerve axons.

The clinical manifestations generally include a combination of negative and positive symptoms and signs.

<p>NEGATIVE SENSORY SYMPTOMS & SIGNS</p> <ul style="list-style-type: none"> • Reduced or absent touch perception • Reduced or absent pain perception • Postural instability
<p>POSITIVE SENSORY SYMPTOMS & SIGNS</p> <ul style="list-style-type: none"> • Burning, stabbing, squeezing sensations • Hypersensitivity to touch
<p>NEGATIVE MOTOR SYMPTOMS & SIGNS</p> <ul style="list-style-type: none"> • Muscle weakness
<p>POSITIVE MOTOR SYMPTOMS & SIGNS</p> <ul style="list-style-type: none"> • Muscle cramps • Fasciculations

- Negative sensory symptoms reduce the ability to feel (rough, smooth, cold, warm), and at times may be severe enough to prevent the feeling of pain. Another negative symptom is lack of proprioceptive information. Proprioception refers to the ability to know what muscles are doing (contracting or relaxing) and what joints are doing (bending one way or the other). This information normally reaches lower (subconscious) parts of the brain and one is not aware that this information is used to maintain balance. When proprioceptive information is lacking vision substitutes, but when sight is temporarily lost (eyes closed in the shower) or reduced (walking in the dark) there can be a marked feeling of unsteadiness (postural instability).
- Positive sensory symptoms are caused by spontaneous discharges of nerves leading one to “feel” things that are not truly occurring. There may be discomfort and lingering pain (allodynia and hyperpathia) following light touch. Painful sensations are frequently

worse at night and after walking longer distances.

- Negative motor symptoms are distal weakness that may not be appreciated by the patient for two reasons: 1) mild weakness of intrinsic foot muscles is rarely noticed, and 2) with loss of motor nerves there is compensatory collateral reinnervation that preserves strength until nerve loss is severe.

- Positive motor symptoms are an ease of cramping and fasciculations (spontaneous twitches of the muscle).

There are several clinical patterns of length-dependent peripheral neuropathy. 1) Sensorimotor neuropathies include distal sensory loss, but weakness may not be evident to the patient but is demonstrable upon examination and by electrodiagnostic testing. This type of neuropathy may or may not include positive sensory symptoms. 2) Primary painful sensory neuropathies may include only pain with no sensory or motor signs or pain with mild sensory signs.

Genetics: By definition these neuropathies are acquired and not genetic. However, most hereditary neuropathies also follow a length-dependent pattern and without a clear family history the likelihood of a hereditary neuropathy is low. Genetic predispositions may be a factor in acquired neuropathies but none have been found.

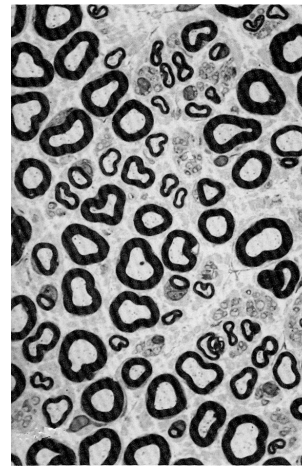
Diagnosis: The diagnosis is initially based on the prototypic pattern of

symmetric length-dependent positive and negative symptoms. Neurologic examination shows some degree of negative sensory signs with reduced perception of light touch to the foot or reduced ability to sense the vibration of a tuning fork applied to the toe. There can be reduced ability to sense the sharpness of a safety pin applied to the foot. However, in a painful sensory neuropathy there are no sensory abnormalities. Motor signs include weakness of toe flexion or extension and reduced ability to stand on heels (reduced elevation of the toes) and tendon reflexes may be reduced or absent at the ankles. Electrodiagnostic studies are important to define which nerves are affected as there may be no weakness despite involvement of motor nerves. Nerve conduction studies may show reduced or absent sensory nerve responses (but in some cases of painful sensory neuropathies these are normal). Motor nerve conduction studies may show low or absent responses. Conduction velocities are generally normal or mildly slowed. Needle EMG studies are the most sensitive to document mild degrees of motor nerve involvement and can show the distal predilection of nerve involvement.

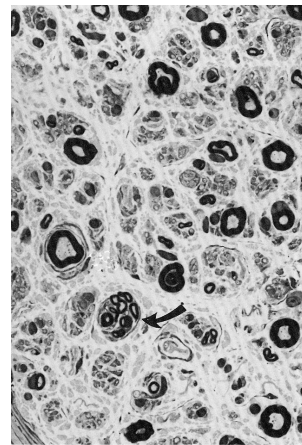
Pathogenesis: The most common cause of prototypic neuropathies is diabetes mellitus, including very mild forms of glucose dysregulation (impaired glucose tolerance). Aside from drug-induced neuropathies (most commonly neurotoxicity of

chemotherapeutic drugs) and a few other conditions the pathogenesis is rarely known. When the cause is not obvious from routine laboratory tests it is rare to find a cause even after more detailed tests are run and the neuropathy is called “idiopathic” or “cryptogenic”.

Peripheral neuropathy indicates damage to nerves and nerve endings. This accounts for negative symptoms. Sometimes only the smallest nerve endings in the skin are affected. The nerve endings die back and the neuropathy progresses over time with shorter lengths of nerves affected.



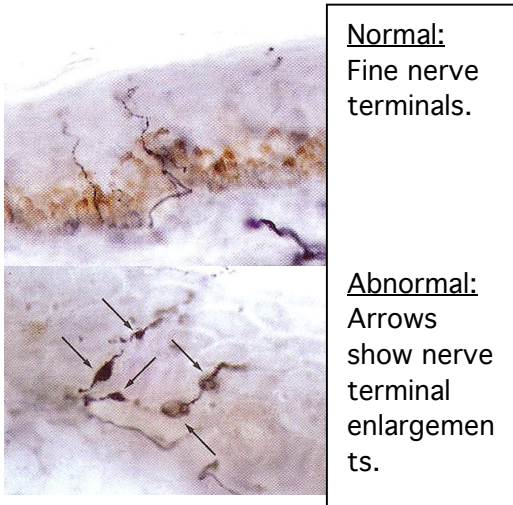
Normal:
Many myelinated fibers.



Neuropathy:
Few fibers. Arrow shows regenerating fibers.

In painful sensory neuropathies with no nerve conduction abnormalities

skin biopsies frequently show abnormalities, reduced numbers, or absence of Intraepidermal nerve terminals.



Treatment: Few types of peripheral neuropathy can be stopped with treatment. Unfortunately, painful sensory neuropathies are rarely treatable. Thus, most medications are to reduce positive symptoms. Since the cause of positive symptoms is felt to be spontaneous nerve discharges due to open channels, many drugs are designed to reduce or block these channels. Medications include gabapentin (Neurontin®) and pregabalin (Lyrica®). Other medications were initially designed as antidepressants but have been found to be effective at lower doses for positive symptoms. These medications include amitriptyline (Elavil®), imipramine (Tofranil®) and duloxetine (Cymbalta®). These drugs are quite effective when used optimally.

Management: Choosing comfortable shoes can help reduced

pain while walking. When there are negative symptoms it is important not to walk barefoot or wear open-toe shoes to prevent injury. Perhaps the most important issue is foot inspection on a daily basis to identify cuts, blister and sores. It is wise to have a podiatrist cut toenails to prevent inadvertent nicks to the skin.

Clinical Course: Most prototypic neuropathies progress up the leg but rarely beyond the knee. The exceptions are those caused by diabetes where the hands and forearms can be affected. Most progress slowly and do not markedly affect function although pain may limit activities. Painful sensations generally reach a maximum and do not increase further over time. Increased pain after walking a long way does not mean that the neuropathy is getting worse nor does walking further damage nerves. In the setting of diabetes there may also be decreased blood flow to the feet and lower legs and undetected lesions may not heal easily and become infected and could lead to loss of a toe or limb.

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