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Peripheral Neuropathy

Peripheral neuropathy is the term for damage to nerves of the peripheral nervous system, [1] which may be caused either by diseases of the nerve or from the side-effects of systemic illness.

The four cardinal patterns of peripheral neuropathy are polyneuropathy, mononeuropathy, mononeuritis multiplex and autonomic neuropathy. The most common form is (symmetrical) peripheral polyneuropathy, which mainly affects the feet and legs. The form of neuropathy may be further broken down by cause, or the size of predominant fiber involvement, i.e., large fiber or small fiber peripheral neuropathy. Frequently the cause of a neuropathy cannot be identified and it is designated idiopathic.

Neuropathy may be associated with varying combinations of weakness, autonomic changes and sensory changes. Loss of muscle bulk or fasciculations, a particular fine twitching of muscle may be seen. Sensory symptoms encompass loss of sensation and "positive" phenomena including pain. Symptoms depend on the type of nerves affected; motor, sensory, autonomic, and where the nerves are located in the body. One or more types of nerves may be affected. Common symptoms associated with damage to the motor nerve are muscle weakness, cramps, and spasms. Loss of balance and coordination may also occur. Damage to the sensory nerve can produce tingling, numbness, and pain. Pain associated with this nerve is described in various ways such as the following: sensation of wearing an invisible "glove" or "sock", burning, freezing, or electric-like, extreme sensitivity to touch. The autonomic nerve damage causes problems with involuntary functions leading to symptoms such as abnormal blood pressure and heart rate, reduced ability to perspire, constipation, bladder dysfunction (e.g., incontinence), and sexual dysfunction. [2]

Causes

The causes are broadly grouped as follows:

Genetic diseases: Friedreich's ataxia, Charcot-Marie-Tooth syndrome [3]

Metabolic/Endocrine: diabetes mellitus [4], chronic renal failure, porphyria, amyloidosis, liver failure, hypothyroidism

Toxic causes: Drugs (vincristine, phenytoin, nitrofurantoin, isoniazid, ethyl alcohol), organic metals, heavy metals, excess intake of vitamin B_6 (pyridoxine)

Fluoroquinolone toxicity: Irreversible neuropathy is a serious adverse reaction of fluoroquinolone drugs [5]

Inflammatory diseases: Guillain-Barré syndrome, systemic lupus erythematosis, leprosy, Sjögren's syndrome

Vitamin deficiency states: Vitamin B_{12} (cyanocobalamin), vitamin A, vitamin E, vitamin B_1 (thiamin)

Physical trauma: compression, pinching, cutting, projectile injuries (i.e. gunshot wound), strokes including prolonged occlusion of blood flow

Others: shingles, malignant disease, HIV [6], radiation, chemotherapy [7]

Many of the diseases of the peripheral nervous system may present similarly to muscle problems (myopathies), and so it is important to develop approaches for assessing sensory and motor disturbances in patients so that a physician may make an accurate diagnosis.

Types by pattern of nerve involvement

Mononeuropathy

See also: Compression neuropathy

Mononeuropathy is a type of neuropathy that only affects a single nerve.[8] It is diagnostically useful to distinguish them from polyneuropathies, because the limitation in scope makes it more likely that the cause is a localized trauma or infection.

The most common cause of mononeuropathy is by physical compression of the nerve, known as compression neuropathy. Carpal tunnel syndrome is one example of this. The "pins-and-needles" sensation of one's "foot falling asleep" (paresthesia) is caused by a compression mononeuropathy, albeit a temporary one which can be resolved merely by moving around and adjusting to a more appropriate position. Direct injury to a nerve, interruption of its blood supply (ischemia), or inflammation can also cause mononeuropathy.

Mononeuritis multiplex

Mononeuritis multiplex, or **mononeuropathy multiplex**, is the clinical result of damage to several different nerves, either serially or concurrently.

Mononeuritis multiplex typically presents with acute or subacute loss of sensory and motor function of individual peripheral nerves. The pattern of involvement is asymmetric.

Mononeuritis multiplex may also cause pain, which is characterized as deep, aching pain that is worse at night, is frequently in the lower back, hip, or leg. In people with diabetes mellitus, mononeuritis multiplex is typically encountered as acute, unilateral, severe thigh pain followed by anterior muscle weakness and loss of knee reflex.

Electrodiagnostic studies will show multifocal sensory motor axonal neuropathy.

It is caused by, or associated with, several medical conditions:

- diabetes mellitus
- vasculitides: polyarteritis nodosa, Wegener granulomatosis, and Churg-Strauss syndrome
- immune-mediated diseases like rheumatoid arthritis, lupus erythematosus (SLE), and sarcoidosis
- infections: leprosy, Lyme disease, HIV
- amyloidosis
- cryoglobulinemia
- chemical agents, including trichloroethylene and dapsone

Polyneuropathy

Main article: Polyneuropathy

Polyneuropathy is a pattern of nerve damage which is quite different from mononeuropathy. The term "peripheral neuropathy" is sometimes used loosely to refer to polyneuropathy. In a polyneuropathy, many nerve cells in different parts of the body are affected, without regard to the nerve through which they pass. Not all nerve cells are affected in any particular case. In one common pattern (distal axonopathy), the cell bodies of neurons remain intact, but the axons are affected in proportion to their length. Diabetic neuropathy is the most common cause of this pattern. In *demyelinating* polyneuropathies, the myelin sheath around axons is damaged, which affects the ability of the axons to conduct electrical impulses. The third and least common pattern affects the cell

bodies of neurones directly. This usually picks out either the motor neurones (known as motor neurone disease), or the sensory neurones (known as *sensory neuronopathy* or *dorsal root ganglionopathy*).

The effect of this is to cause symptoms in more than one part of the body, often on left and right sides symmetrically. As for any neuropathy, the chief symptoms include weakness or clumsiness of movement (motor); unusual or unpleasant sensations such as tingling or burning, reduction in the ability to feel texture, temperature etc., and impaired balance when standing or walking (sensory). In many polyneuropathies, these symptoms occur first and most severely in the feet. Autonomic symptoms may also occur, such as dizziness on standing up, erectile dysfunction and difficulty controlling urination.

Polyneuropathies are usually caused by processes that affect the body as a whole. Diabetes (or impaired glucose tolerance) is the most common cause. Other causes relate to the particular type of polyneuropathy, and there are many different causes of each type, including inflammatory diseases, vitamin deficiencies, blood disorders, and toxins (including alcohol and certain prescribed drugs). Most types of polyneuropathy progress fairly slowly, over months or years, but rapidly progressive polyneuropathy also occurs. Sometimes this has an identifiable cause; when it does not it is often referred to as Guillain–Barré syndrome. It is important to recognize that glucose levels in the blood can spike to nerve-damaging levels after eating even though fasting blood sugar levels and average blood glucose levels can still remain below normal levels (currently typically considered below 100 for FBP, Fasting Blood Plasma, and 6.0 for HGBA1c, hemoglobin A1C the test commonly used to measure average blood glucose levels over an extended period). Studies have shown that many of the cases of peripheral small fiber neuropathy with typical symptoms of tingling, pain and loss of sensation in the feet and hands are due to glucose intolerance prior to a diagnosis of diabetes or pre-diabetes. Such damage is often reversible, particularly in the early stages, with diet, exercise and weight loss. [17]

The treatment of polyneuropathies is aimed firstly at eliminating or controlling the cause, secondly at maintaining muscle strength and physical function, and thirdly at controlling symptoms such as neuropathic pain.

Other classifications

Peripheral neuropathy may also be classified according to the type of nerve cell affected (motor, sensory, autonomic), or the process affecting the nerves (e.g. inflammation in neuritis).

Autonomic neuropathy

Autonomic neuropathy is a form of polyneuropathy which affects the non-voluntary, non-sensory nervous system (i.e. the autonomic nervous system) affecting mostly the internal organs such as the bladder muscles, the cardiovascular system, the digestive tract, and the genital organs. These nerves are not under a person's conscious control and function automatically. Autonomic nerve fibers form large collections in the thorax, abdomen and pelvis outside spinal cord, however they have connections with the spinal cord and ultimately the brain. Most commonly autonomic neuropathy is seen in persons with long-standing diabetes mellitus type 1 and 2. In most but not all cases, autonomic neuropathy occurs alongside other forms of neuropathy, such as sensory neuropathy.

Autonomic neuropathy is one cause of malfunction of the autonomic nervous system, but not the only one; some conditions affecting the brain or spinal cord can also cause autonomic dysfunction, such as multiple system atrophy, and therefore cause similar symptoms to autonomic neuropathy.

The signs and symptoms of autonomic neuropathy include the following:

- urinary bladder conditions: bladder incontinence or urine retention

gastrointestinal tract: dysphagia, abdominal pain, nausea, vomiting, malabsorption, fecal incontinence, gastroparesis, diarrhea, constipation

cardiovascular system: disturbances of heart rate (tachycardia, bradycardia), orthostatic hypotension, inadequate increase of heart rate on exertion

other: hypoglycemia unawareness; genitalimpotence; sweat disturbances

Neuritis

Neuritis is a general term for inflammation of a nerve [9] or the general inflammation of the peripheral nervous system. Symptoms depend on the nerves involved, but may include pain, paresthesia, paresis, hypoesthesia (numbness), anesthesia, paralysis, wasting, and disappearance of the reflexes. Causes include:

Infection:

- Herpes simplex
- Shingles
- Leprosy
- Guillain-Barre syndrome

Chemical injury

Physical injury

Radiation

Underlying conditions causing localized neuritis (affecting a single nerve):

- Diphtheria
- Localized injury
- Diabetes

Underlying conditions causing polyneuritis (affecting multiple nerves):

- Beriberi
- Vitamin B12 deficiency
- Metabolic diseases
- Diabetes
- Hypothyroidism
- Porphyria
- Infections, bacterial and/or viral
- Autoimmune disease, especially Multiple Sclerosis
- Cancer
- Alcoholism
- Wartenbergs migratory sensory neuropathy

Types of neuritis include:

- Polyneuritis or Multiple neuritis (not to be confused with multiple sclerosis)
- Brachial neuritis
- Optic neuritis
- Vestibular neuritis
- Cranial neuritis, often representing as Bell's Palsy
- Arsenic neuritis

Signs and symptoms

Those with diseases or dysfunctions of their peripheral nerves can present with problems in any of the normal peripheral nerve functions.

In terms of sensory function, there are commonly *loss of function* (*negative*) symptoms, which include numbness, tremor, and gait imbalance.

Gain of function (*positive*) symptoms include tingling, pain, itching, crawling, and pins and needles. Pain can become intense enough to require use of opioid (narcotic) drugs (i.e., morphine, oxycodone).

Skin can become so hypersensitive that patients are prohibited from having anything touch certain parts of their body, especially the feet. People with this degree of sensitivity cannot have a bedsheet touch their feet or wear socks or shoes, and eventually become housebound.

Motor symptoms include *loss of function* (*negative*) symptoms of weakness, tiredness, heaviness, and gait abnormalities; and *gain of function* (*positive*) symptoms of cramps, tremor, and fasciculations.

There is also pain in the muscles (*myalgia*), cramps, *etc*., and there may also be autonomic dysfunction.

During physical examination, those with generalized peripheral neuropathies most commonly have distal sensory or motor and sensory loss, though those with a pathology (problem) of the peripheral nerves may be perfectly normal; may show proximal weakness, as in some inflammatory neuropathies like Guillain–Barré syndrome); or may show focal sensory disturbance or weakness, such as in mononeuropathies. Ankle jerk reflex is classically absent in peripheral neuropathy.

Treatment

Many treatment strategies for peripheral neuropathy are symptomatic. Some current research in animal models has shown that neurotrophin-3 can oppose the demyelination present in some peripheral neuropathies.[10]

A range of drugs that act on the central nervous system such as drugs originally intended as antidepressants and antiepileptic drugs have been found to be useful in managing neuropathic pain. Commonly used treatments include using a Tricyclic antidepressant (such as amitriptyline) and antiepileptic therapies such as gabapentin or sodium valproate. These have the advantage that besides being effective in many cases they are relatively low cost.

A great deal of research has been done between 2005 and 2010 which indicates that synthetic cannabinoids and inhaled cannabis are effective treatments fo a range of neuropathic disorders.[11] Research has demonstrated that the synthetic oral cannabinoid Nabilone is an effective adjunct treatment option for neuropathic conditions, especially for people who are resistant, tolerant, or

allergic to common medications.[12] Orally, opiate derivatives were found to be more effective than cannabis for most people.[13] Smoked cannabis has been found to provide relief from HIV-associated sensory neuropathy.[14] Smoked cannabis was also found to relieve neuropathy associated with CRPS type I, spinal chord injury, peripheral neuropathy, and nerve injury.[15]

Pregabalin (INN) (pronounced /prɪ□gæbəlɪn/) is an anticonvulsant drug used for neuropathic pain. It has also been found effective for generalized anxiety disorder. It was designed as a more potent successor to gabapentin but is significantly more expensive, especially now the patent on gabapentin has expired and gabapentin is available as a generic drug. Pregabalin is marketed by Pfizer under the trade name Lyrica.

As noted above in the section on Polyneuropathies and their causes, symmetric small fiber neuropathy, commonly called peripheral neuropathy, can often be reversed, particularly in the early stages before a diagnosis of diabetes or pre-diabetes with diet, exercise and weight loss. It is also suggested that, because alcohol is a neurotoxin, even individuals with neuropathies from causes other than alcoholism may benefit from limiting or eliminating their alcohol intake.

TENS (Transcutaneous Electrical Nerve Stimulation) can be an effective in some cases as a non-pharmacological treatment and is free from adverse effects. It is believed to work via stimulating large afferent fibers, which in turn leads to an inhibition of small pain afferent fibers.[16]

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External links

The Foundation for Peripheral Neuropathy

The Canadian Neuropathy Association

National Diabetes Information Clearinghouse at National Institute of Diabetes and Digestive and Kidney Diseases

The Neuropathy Association

Reference centre for rare neuropathies