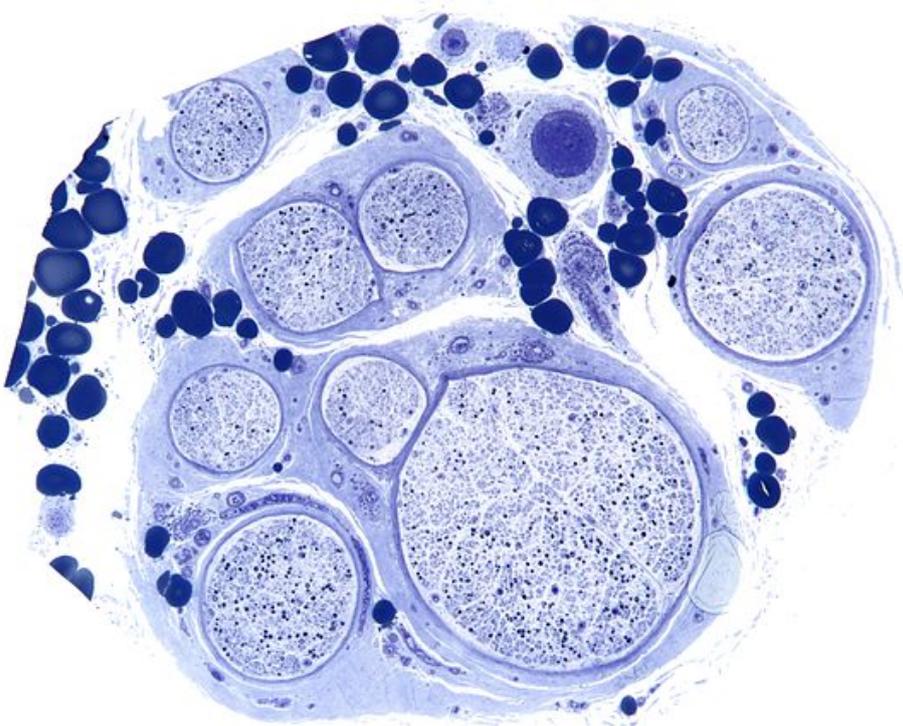


Neurology: Hereditary and Acquired Polyneuropathies

[See online here](#)

The term **diabetic polyneuropathy** is probably the one you will encounter most frequently during your medical studies. What are the most common causes of polyneuropathy? Which are hereditary, and which are acquired? How are they diagnosed and what types of therapy are available? The following article will provide you with answers to all of these questions. It has been prepared with the medical exam in mind and will not leave unanswered any questions regarding polyneuropathies.



Definition

The term **polyneuropathy** summarizes different systemic **diseases of the peripheral nervous system**, including dorsal and ventral root ganglions. The nomenclature corresponds with the number of nerves involved:

- **Mononeuropathy:** a single nerve is affected
- **Mononeuropathy multiplex:** several nerves are affected
- **Polyneuropathy:** a number of nerves are affected making it no longer possible to determine which ones are involved

Epidemiology

The **overall prevalence** of polyneuropathies is 2.5%; in individuals over the age of 55, this number increases to 8%. The number of causes of polyneuropathies is estimated at approx. 100. In approximately 20% of patients, the cause is undetermined.

Classification

Polyneuropathies can be classified based on:

- Anatomy
- Pathology—axonopathies, demyelinating diseases, and mixed lesions
- Aetiopathology
- Clinical features—acute, subacute, chronic polyneuropathies, and relapsing types

Polyneuropathies can also be classified as follows:

Classification according to	Subforms
Type of disturbance	Sensory, motor, sensorimotor, autonomic
Type of damage	Axonal, demyelinating, mixed axonal-demyelinating
Progression	Acute (up to 4 weeks after onset of symptoms), subacute (between 4 and 8 weeks), chronic (progression more than 8 weeks)
Cause	Hereditary, acquired

This article provides information about hereditary and acquired polyneuropathies. The **Guillain-Barré syndrome** and **Miller-Fisher syndrome** are discussed in the [article regarding inflammatory and immune-mediated polyneuropathies](#).

Key symptoms of polyneuropathies

Although the cause and severity of polyneuropathy can markedly differ, there are certain typical key symptoms:

- Stocking- and glove-like sensorimotor disturbances in the extremities
- Flaccid paralysis

Note: The goal of diagnosing polyneuropathies is to clarify the etiology in order to achieve successful therapy

Etiology of polyneuropathies

Note: Diabetes mellitus and alcohol abuse combined are responsible for almost 50% of all polyneuropathies.

Other common causes are Guillain-Barré syndrome, infections with [Borrelia](#), [HIV](#), and vasculitides. The spectrum of causes of polyneuropathy is large. The following shows possible causes:

- **Genetic:** hereditary motor and sensory polyneuropathy, hereditary polyneuropathy with the possibility of pressure palsy, Friedreich ataxia, amyloidosis
- **Metabolic disorders:** [diabetes mellitus](#), uremia, [hypothyroidism](#), hyperlipidemia, [acromegaly](#), gout, hepatopathies, [porphyria](#)
- **Exogenous toxic:** alcohol, medications (frequently chemotherapeutics),

heavy metals, solvents

- **Infectious:** Borreliosis, HIV, leprosy, typhoid, paratyphoid
- **Immunological:** Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculopolyneuropathy (CIDP), multifocal motor neuropathy with conduction block (MMN)
- **Deficiency/malnutrition:** vitamin resorption disturbance (vitamin B12 deficiency), malnutrition, [celiac disease](#)
- **Collagenoses:** Lupus erythematosus, scleroderma, rheumatoid arthritis, Sjögren's syndrome
- **Paraneoplastic:** especially bronchial, ovarian, stomach, colon, lymphoma
- **Dysproteinemia/paraproteinemia:** gammopathies, Waldenström's disease
- **Other:** critical illness neuropathy/myopathy, chronic inflammatory bowel diseases

Clinical signs of polyneuropathy

Case study: A 60-year-old patient has known for several years that his blood glucose levels have been in the pathological range. Over the past year, he has been experiencing slight sensory disturbances in his toes and foot soles. The [skin](#) is becoming dry. After a long walk, he notices pain-free changes in his left foot resulting in pressure points in his shoe.

The orthopedic examination, which includes X-rays of the foot, shows a fracture of the arch, the so-called Charcot foot. He receives orthopedic and podiatric treatment. With appropriate footwear and skincare, the patient will be able to walk normally again.

Now he is experiencing morning sensory disturbances in his right hand and is mostly unable to move the fingertips of the first 3 fingers. Some mornings, pain and clumsiness in the hand occur. The general practitioner suspects the sensory disturbance is the result of a polyneuropathy.

Clinical signs of damage to sensory nerve fibers

As described in the case study, **symptoms usually** begin **slowly**. In many cases, the 2 feet are simultaneously affected first (the longest nerve fibers are primarily affected). The sensory disturbances that occur are described as stocking- and glove-like by patients. These sensory disorders can have different classifications:

- **Hypoesthesia**
- **Paresthesia** (burning and unpleasant sensation)
- Poor depth perception with loss of vibratory perception and position sense

Clinical signs of damaged motor nerve fibers

- **Distal flaccid paresis** (foot flexor paresis)
- Loss of distal **reflexes** (Achilles tendon reflex)
- **Fasciculations**
- **Atrophies** during progression

Clinical signs of damage to the autonomic nervous system

If autonomic nerve fibers are impacted, vascular dysregulation with distal cyanosis can occur, resulting in **hyperhidrosis**, **anhidrosis**, as well as trophic changes in the skin and nails.

Distribution of Peripheral Neuropathy

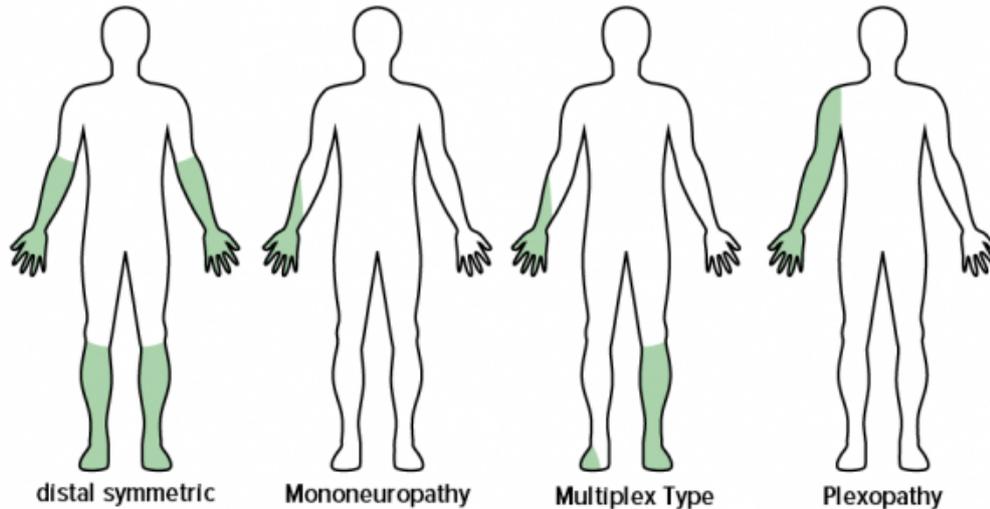


Image: Distribution of peripheral neuropathy. By Lecturio

Diagnosing Polyneuropathy

History of a **familial predisposition** is important in diagnosis.

Various laboratory parameters are indicative of possible causes. The levels of the following parameters should be examined via laboratory/chemical testing in order to determine the likely cause of polyneuropathy:

Laboratory parameter	Disease/cause
Fasting glucose, HbA1c	Diabetes mellitus
ESR, CRP	Inflammation, vasculitis
Complete blood count	Paraneoplastic, exogenous toxic
Liver and kidney tests, electrolytes, creatine kinase	Metabolic disorder
Protein and immunoelectrophoresis	Dysproteinemia/paraproteinemia
Thyroid function	
Vitamin B12 levels, methylmalonic acid in the urine	Deficiency/malnutrition
Molecular genetic tests	Genetic causes

Further tests to determine polyneuropathy

Neurography: A tool to distinguish between axonal, demyelinating, and axonal-demyelinating diseases.

In demyelinating diseases, the nerve conduction velocity is reduced. There is some temporal dispersion as some nerves conduct faster than others and thus cause a widening of the compound muscle action potential (CMAP) duration.

In axonal diseases, the overall muscle action potential is reduced. Thus, reducing CMAP and sensory nerve action potential (SNAP) amplitudes.

- **Electromyography (EMG):** determines muscle involvement
- **Somatosensory evoked potentials (SEP), transcranial magnetic stimulation:** determines CNS involvement
- **Nerve/muscle biopsy:** It is used if the cause is unknown, i.e., if inflammatory processes or storage diseases are suspected. Especially suitable for the nerve

biopsy is the sural nerve; for muscle biopsy, a moderately affected muscle is preferred

D = **d**emyelinating in cases of **d**iabetic polyneuropathy.

A = **a**xonal in cases of **a**symmetric diabetic and **a**lcoholic polyneuropathy.

General polyneuropathy therapy

If the etiology is known, treating the underlying disease is recommended. The pain that develops due to neuropathy can be treated with different types of medications as follows:

- **Antidepressants:** amitriptyline, clomipramine, venlafaxine, duloxetine
- **Antiepileptic drugs:** sodium channel blockers (carbamazepine, oxcarbazepine, lamotrigine), modulation of calcium channels (gabapentin, pregabalin)
- **Long-acting opioids:** tramadol retard, oxycodone
- **α-lipoic acid**
- In cases of cramp-like pain: contrast foot baths, baclofen, quinine sulfate products

Hereditary Polyneuropathies

HMSN = **H**ereditary **M**otor and **S**ensory **N**europathies

Hereditary motor and sensory neuropathies are divided into 7 types. Only the first 3 are of clinical relevance and will be discussed in the following paragraphs.

- **HMSN I: Charcot-Marie-Tooth disease**
- **HMSN II: Neuronal peroneal muscular atrophy**
- **HMSN III: Dejerine-Sottas disease**
- HMSN IV: Refsum disease
- HMSN V: Hereditary spastic paraplegia
- HMSN VI: HMSN with optic atrophy
- HMSN VII: HMSN with retinitis pigmentosa

Charcot-Marie-Tooth syndrome (HMSN I)

Charcot-Marie-Tooth disease is the most common hereditary neuropathy. This autosomal dominant-type inheritance is among the demyelinating neuropathies. Affected individuals fall ill between the ages of 5 and 20 years.

Symptoms of Charcot-Marie-Tooth syndrome (HMSN I)

- Strongly reduced nerve conduction velocity
- Distal symmetric **paresis**, frequent failure of the ulnar and peroneal nerves
- Motor: inactivity atrophy with high arches and stork legs
- Peripheral nerves are thickened and can be felt
- Autonomous nerve system: trophic disorders, pupillary disorders, reduced heart rate variability
- Painful muscle cramps, predominantly at night



Image: The foot of a person with Charcot-Marie-Tooth. The lack of muscle, a high arch, and hammertoes are signs of genetic

Diagnosing and treating Charcot-Marie-Tooth syndrome (HMSN I)

In most cases, positive family history and high arches result in the diagnosis of Charcot-Marie-Tooth syndrome. Biopsies find an onion-bulb-like arrangement of **Schwann cells** with simultaneous axonal degeneration. Demyelination extremely slows down the nerve conduction velocity which can be seen in neurography imaging (> 20 m/s). In approx. 70% of all cases, molecular genetic diagnostics show a duplication of the *PMP22* gene.

Note: The normal nerve conduction velocity is > 40 m/s for the legs and > 45 m/s for the arms.

Therapy focuses on treating the symptoms, **as a cure is currently impossible.**

Neuronal peroneal muscular atrophy (HMSN II)

Autosomal dominant inheritance also occurs with HMSN II.

The reduction of the nerve conduction velocity in individuals with HMSN II is less pronounced. Clinically, there are few differences between HMSN I and II; however, their **biopsy findings** are clearly different. HMSN II does not exhibit onion-bulb-like arrangements but rather displays **axonal degeneration with secondary demarcation**. Therefore, HMSN II is sometimes referred to as an **axonal form of Charcot-Marie-Tooth disease**.

Dejerine-Sottas disease (HMSN III)

HMSN III also exhibits an **autosomal dominant** inheritance. The clinical picture of this neuropathy is also very similar to HMSN I but is much more serious. Affected individuals only have a nerve conduction velocity of **10 m/s**, and the disease already begins in the first decade of life.

Acquired Polyneuropathies

Polyneuropathy and diabetes mellitus



[Image:](#) Diabetic foot syndrome. By ApoPfleger, License: [CC BY 3.0](#)

Pathogenesis of diabetic polyneuropathy

The genesis of diabetic neuropathy has not been determined in detail. As of 2015, a multifactorial genesis is widely assumed. These factors include:

- **Vascular involvement**, microangiopathy of the vasa nervorum occurs, resulting in multifocal fiber loss.
- **Metabolic** involvement can be deduced from the fact that the symptoms improve if blood glucose levels are well adjusted.
- **Immunological** genesis could be proven by showing inflammatory infiltrates in the autonomic ganglia.

The above factors are thus intertwined to formulate the theory that, uncontrolled sugars in diabetics leads to non-enzymatic glycosylation that causes accumulation of advanced glycation end-products. This induces cytokine and adhesion molecules release that may damage nerves leading to neuropathies.

Clinical signs of diabetic polyneuropathy

A patient with diabetic neuropathy displays a wide spectrum of symptoms. The following table provides an overview of common symptom groups. The most frequent is **symmetric distal sensorimotor polyneuropathy**.

Symmetric distal sensorimotor polyneuropathy	Asymmetric distal sensorimotor polyneuropathy	Diabetic radiculopathy	Autonomic polyneuropathy
Distal symmetric paresis (fatigue with plegia, atrophy, and contractures)	More uncommon than the symmetric form	Manifesting on the lower thoracic segments	Trophic disturbances occur
Sensory failures	Damage to the motor portion of the lumbosacral plexus, especially the femoral nerve, obturator nerve, and gluteal nerves		Disturbances of sweat secretion (distal anhidrosis, proximal hyperhidrosis)
Painful paresthesia ("burning feet")		Paralysis of the abdominal wall	
Muscle cramps in the upper and lower leg	Pronounced atrophies (diabetic amyotrophy)	Trunk pain and sensory disorders	Bladder and bowel dysfunction
Lancing pains in the groin and ilioinguinal region			Impotence
Weakened Achilles tendon reflex			Circulatory disorders
Neurography imaging: Image of demyelinating polyneuropathy	Neurography imaging: Image of axonal damage		

Diagnosing diabetic polyneuropathy

Nocturnal paresthesia, weakened reflexes, reduced vibration sensation, and **anhidrosis** are particularly typical of diabetic polyneuropathy. For laboratory tests, determining the **blood sugar levels** and HbA1c levels, and a 3-hour oral glucose tolerance test (OGTT) is important. Another diagnostic tool is neurography or a simpler monofilament test to represent innervation lesions (see table).

Therapy for diabetic polyneuropathy

Diabetic **metabolism** must be **normalized** in the best possible way (see treatments for **diabetes mellitus**). If the glucose levels are well adjusted, it is possible to prevent the progression of the symmetric form. Furthermore, **α-lipoid acid** can be used to counter nerve damage. Pain therapy consists of opioids and antidepressants, and anticonvulsants are used as co-analgesics.

In order to retain motor function, **physiotherapy** is important and useful.

Polyneuropathy and Alcohol Abuse

The pathogenesis of alcoholic polyneuropathy

The combination of the direct **toxic effect of alcohol** and **vitamin B deficiency** usually occurs simultaneously (due to malnutrition) causing polyneuropathy. Characteristic signs are primary axonal damage and secondary demyelination.

Clinical signs of alcoholic polyneuropathy

Affected individuals suffer from **symmetric distal failure** impacting the sensory and motor system. Typical signs are 'burning feet', weakened reflexes, reduced vibration sensation, and ataxic gait. Palmar and plantar hyperhidrosis as signs of autonomous system disorder are rare.

Diagnosis of alcoholic polyneuropathy

Laboratory tests show the typical values pointing toward alcohol abuse: elevated liver enzymes, elevated MCV values, as well as elevated **carbohydrate-deficient transferrin (CDT)**. Neurography shows signs of axonal damage.

Note: CDT in connection with alcohol abuse is an important exam question.

Therapy for alcoholic polyneuropathy

Absolute alcohol abstinence is pertinent. Furthermore, vitamin B complex should be prescribed. Axonal reinnervation is possible with abstinence but will be delayed.

Critical illness polyneuropathy

Approximately 70% of the patients with **sepsis and multi-organ failure** will develop critical illness polyneuropathy (CIP).

Pathogenesis and clinical signs of critical illness polyneuropathy

Septic inflammatory reactions are suspected to give rise to CIP but the pathogenesis of CIP has not been fully determined.

Affected individuals experience **symmetrical** flaccid atrophic paresis beginning from the **distal** side. Respiratory muscles may also be affected.

Diagnostics, therapy, and prognosis for critical illness polyneuropathy

CIP is frequently overlooked in intensive care as **electromyography** and measuring the **nerve conduction velocity** is required in order to make the diagnosis. In most cases, weaning the patient off the respirator is difficult because of CIP. EMG will reveal pronounced pathological spontaneous activity.

Once patients recover from the severe underlying disease, complete remission from CIP is possible and common. However, in intensive care, problems may develop due to prolonged time on the respirator.

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