Neurology: Hereditary and Acquired Polyneuropathies

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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

It refers to the diseases affecting peripheral nerves including dorsal and ventral root ganglions. The term polyneuropathy (PNP) summarizes different systemic diseases of the peripheral nervous system. The nomenclature corresponds with the number of nerves involved:

- **Mononeuropathy**: a single nerve is affected
- **Mononeuropathia 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 at 2.5%; in individuals over the age of 55, this number climbs to 8%. The number of causes of polyneuropathies is estimated at approximately 100; in approximately 20% of patients the cause remains undetermined.

Classification of polyneuropathies

It can be done based on:

- Anatomical classification
- Pathological classification. They are divided into axonopathies, demyelinating diseases and mixed lesions
- Aetiopathological classification
- Clinical classification. Divides them into acute, subacute, chronic polyneuropathies and the relapsing types

Polyneuropathies can also be classified as follows:

<table>
<thead>
<tr>
<th>Classification according to</th>
<th>Subforms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of disturbance</td>
<td>Sensory, motor, sensorimotor, autonomic</td>
</tr>
<tr>
<td>Type of damage</td>
<td>Axonal, demyelinating, mixed axonal-demyelinating</td>
</tr>
<tr>
<td>Progression</td>
<td>Acute (up to four weeks after onset of symptoms), subacute (between four and eight weeks), chronic (progression more than eight weeks)</td>
</tr>
<tr>
<td>Cause</td>
<td>Hereditary, acquired</td>
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</table>

This article will provide you with information about hereditary and acquired polyneuropathies. You can read everything about Guillain-Barré syndrome as well as Miller-Fisher syndrome in the article regarding inflammatory and immune-mediated polyneuropathies.

Key Symptoms of Polyneuropathies

Even though the cause and severity of polyneuropathy can be very different, there are certain typical key symptoms:

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

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

The 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 overview shows possible causes in order:

- Genetic: hereditary motor and sensory polyneuropathy, hereditary polyneuropathy with liability to pressure palsy, Friedreich ataxia, amyloidosis
- Metabolic disorders: diabetes mellitus, uremia, hypothyroidism,
- **Exogenous toxic:** alcohol, medications (frequently chemotherapeuticals), heavy metals, solvents
- **Infectious:** Borrelia, HIV, leprosy, typhoid, paratyphoid
- **Immunological:** Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy (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 with bronchial, ovarian, stomach, colon carcinoma, 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 time and again. For the past year, he has been experiencing slight sensory disturbances in his toes and the foot soles. The skin is becoming dry. After a longer 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 skin care, the patient will be able to walk normally again.

Now he is experiencing morning sensory disturbances in his right hand, whereby predominantly the fingertips of the first three fingers fall asleep. Some mornings, pain and clumsiness in the hand occurs. The treating general practitioner wonders if the sensory disturbance is the result of a PNP.

**Clinical signs of damage to sensory nerve fibers**

As described in the case study, symptoms usually begin to occur slowly. In many cases, the feet are affected simultaneously 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 vegetative nervous system**

If vegetative 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 of distribution of peripheral neuropathy]

#### Diagnosing Polyneuropathy

As far as the patient’s medical history is concerned, you should be looking for **familial predisposition**.

Various laboratory parameters will narrow down possible causes. The following levels should be examined via laboratory/chemical testing in order to determine the likely cause of PNP:

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Disease/cause</th>
</tr>
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<tbody>
<tr>
<td>Fasting glucose, HbA1c</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Blood sedimentation rate (ESR), CRP</td>
<td>Inflammation, vasculitis</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Paraneoplastic, exogenous toxic</td>
</tr>
<tr>
<td>Liver and kidney tests, electrolytes, creatine kinase</td>
<td>Metabolic disorder</td>
</tr>
<tr>
<td>Protein and immunoelectrophoresis</td>
<td>Dysproteinemia/paraproteinemia</td>
</tr>
<tr>
<td>Thyroid function</td>
<td></td>
</tr>
<tr>
<td>Vitamin B12 levels, methylmalonic acid in urine</td>
<td>Deficiency/malnutrition</td>
</tr>
<tr>
<td>Molecular genetic tests</td>
<td>Genetic causes</td>
</tr>
</tbody>
</table>

**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 widening of the CMAP duration.

In axonal diseases, the overall muscle action potential is reduced. Thus, reduces CMAP and SNAP amplitudes.

- **Electromyography** (EMG): determines muscle involvement
- **Somatosensory evoked potentials (SEP), transcranial magnetic stimulation**: determines central 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 (n. suralis); for muscle biopsy, a moderately affected muscle is preferred.

D = demyelinating in cases of diabetic PNP.
A = axonal in cases of asymmetric diabetic PNP and alcoholic PNP.

General Polyneuropathy Therapy

If the etiology is known, it should obviously be attempted to treat the underlying disease. The pain that develops due to neuropathy can be treated with different types of medications that are listed below:

- **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** = Hereditary Motor and Sensory Neuropathies

Hereditary motor and sensory neuropathies are divided into seven types. Only the first three 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 five and 20.

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

- Strongly reduced nerve conduction velocity
- Distal symmetric paresis, frequent failure of the ulnar (n. ulnaris) and the peroneal (n. peroneus) nerve
- 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
Diagnosing and treating Charcot-Marie-Tooth syndrome (HMSN I)

In most cases, positive family history and high arches result in the diagnosis of suspected Charcot-Marie-Tooth syndrome. Biopsies find onion-bulb-like arrangement of Schwann cells with simultaneous axonal degeneration. Demyelinisation extremely slows down the nerve conduction velocity which can be seen in neurography imaging (> 20 m/s). In approximately 70 % of all cases, molecular genetic diagnostics shows 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, *healing has been impossible so far.*

Neuronal Peroneal Muscular Atrophy (HMSN II)

Autosomal dominant inheritance is also the case with HMSN II.

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

Dejerine-Sottas disease (HMSN III)

The clinical picture of HMSN III is also that of *autosomal dominant* inheritance. The clinical picture of this neuropathy is also very similar to HMSN I, but it is much more grave. 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

**Pathogenesis of diabetic polyneuropathy**

The genesis of diabetic neuropathy has not been determined in detail so far; as of 2015, multifactorial genesis is widely assumed. These factors include:

- **Vascular** involvement, a 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 adjusted well.
- **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

The clinical picture of a patient with diabetic neuropathy offers a wide spectrum of symptoms. The following table will provide you with an overview of common symptom groups. The most frequent one is the **symmetric distal sensorimotor polyneuropathy**.

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

### Diagnosing diabetic polyneuropathy

The clinical signs will lead you to the diagnosis: **nocturnal paresthesia, weakened reflexes, reduced vibration sensation** and **anhidrosis** are particularly typical. In lab tests, you will determine the **blood sugar levels** of glucose and HbA1c and conduct a 3 hour oral glucose tolerance test (OGTT). Another diagnostic tool being used is neurography or a simpler monofilament test to represent innervation lesions (see table).

### Diabetic polyneuropathy therapy

The diabetic **metabolism** must be normalized in the best possible way! Here, you can read everything about how to treat **diabetes mellitus**. If the glucose levels are well adjusted, it is possible to halt the progression of the symmetric form. Furthermore, **α-lipoic 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 the vitamin B deficiency usually occurring simultaneously (due to malnutrition) causes 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.

**Diagnosing alcoholic polyneuropathy**

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

**Note:** Carbohydrate-deficient transferrin (CDT) in connection with alcohol abuse is a favorite of the IMPP for the medical exam!

**Alcoholic Polyneuropathy Therapy**

Absolute alcohol abstinence is of the utmost therapeutic priority. Furthermore, vitamin B complex should be prescribed. Axonal reinnervation is possible with abstinence but will be delayed for some time.

**Critical Illness Polyneuropathy**

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

**Pathogenesis and clinical signs of critical illness polyneuropathy**

Septic inflammatory reactions are suspected but the pathogenesis of CIP has not been determined to its full extent yet.

Affected individuals suffer from symmetrical flaccid atrophic paresis beginning from the distal side. Respiratory muscles may be affected as well.

**Diagnostics, therapy and prognosis for critical illness polyneuropathy**

Unfortunately, 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 only difficult due to the fact that the patient is indeed suffering from CIP. The EMG will reveal pronounced pathological spontaneous activity.

Once patients recover from their severe underlying disease, complete remission from CIP is possible and frequent. With regard to the patient’s intensive care, however, problems may develop due to their prolonged time on the respirator.

**Review Questions**

The answers can be found below the references.

1. In cases of alcoholic neuropathy, neurography imaging will show the following damage:
A. demyelinating
B. axonal
C. demyelinating-axonal
D. axonal-demyelinating
E. none

2. Which symptoms are typical for autonomic polyneuropathy in the context of diabetic polyneuropathy?

A. Disturbances of sweat secretion (distal anhidrosis, proximal hyperhidrosis).
B. Lancing pain in the groin/ilioinguinal region.
C. Paralysis of the abdominal wall.
D. Painful paresthesia („burning feet“).
E. Damage to the motor portion of the lumbosacral plexus (plexus lumbosacralis).

3. Charcot-Marie-Tooth disease is the most common form of hereditary neuropathy. Aside from stork legs, which foot deformity belongs to the clinical picture of an autosomal dominant inheritance disease?

A. Splayfoot (pes transversoplanus)
B. Valgus deformity (pes valgus)
C. Clubfoot (pes equinovarus)
D. Hollow foot (pes excavatus)
E. Pigeon toes (pes adductus)

References


Correct answers: 1B, 2A, 3D

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