III/9.6. Polyneuropathies

Polyneuropathy is the generalized disorder of the peripheral nervous system. Its prevalence is approximately 2.4%, but reaches 8% above the age of 55 years. Polyneuropathies are generally caused by a systemic disease, thus polyneuropathy should always be considered as a symptomatic diagnosis and a search for etiology is mandatory.

Symptoms and clinical forms of polyneuropathies

Most of the polyneuropathies are chronic, of predominantly sensory type, and a slowly progressive course. It is typical that the longest nerves are affected first, therefore first symptoms appear symmetrically on the distal aspects of the lower limbs, on the toes and soles, most often in the form of ‘positive’ sensory symptoms (paresthesias, allodynia or neuropathic pain). Paresthesias may present in a variable way, and patients use variable terms to describe them: e.g. patients may report of numbness, tingling, ice cold or burning feeling, feeling of ants crawling or tightness (‘as if I had tight boots on’), feeling of having an extra layer of skin on the soles, feeling of having socks on when really not, or feeling of walking on pillows, etc. These paresthesias ascend with time, but rarely above the knee. Later the hands are also affected and the classic stockings-gloves distribution of sensory symptoms develops (Fig. 22).

In addition to the ‘positive sensory symptoms’ described above, ‘negative sensory symptoms’ (sensory loss) may also occur or may even be the predominant symptom. Upon neurological examination, symmetric distally increasing hypesthesia is found on the limbs involving all or some of the sensory modalities. Patients may be unaware of hypesthesia or may describe it as numbness or lack of feeling. Trophic ulcers, non-healing wounds, and gait disorder may be the consequence of sensory loss. Gait disorder reflects sensory ataxia as the result of loss of sensory feedback needed for movement. This problem may be described as ‘dizziness’ by the patient that can cause confusion as to its origin.

Neurological signs of polyneuropathies include hyporeflexia or areflexia and fasciculation. Motor symptoms may appear with time, which also have a distal symmetric distribution: atrophy and weakness of small foot and leg muscles. This contributes to the gait problem already present due to sensory loss. In severe polyneuropathy, steppage gait is characteristic as a result of bilateral weakness of the tibialis anterior muscles. Patients are unable to stand on their heels or on tip-toes.

Fig. 22: Distribution of sensory symptoms in polyneuropathies
The most common and typical clinical form of polyneuropathy is the one described above: chronic, symmetric, distal and predominantly sensory. Less frequently, polyneuropathies may be asymmetric or take the form of multiple mononeuropathy when individual peripheral nerves are affected simultaneously or consecutively. Some polyneuropathies may involve only the sensory or motor fibers, or may have a subacute or acute course with symptoms developing within days or weeks.

**Classification and causes of polyneuropathies**

Polyneuropathies may be classified based on several factors, e.g. clinical form, etiology or pathological form (demyelinating-axonal). A short classification of polyneuropathies based on etiology is given here below. Table 6 shows the main groups of causes leading to polyneuropathy.

### Table 6: Causes of polyneuropathies

<table>
<thead>
<tr>
<th>Causes of polyneuropathy</th>
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<tr>
<td>1. Metabolic-endocrine</td>
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<td>2. Vitamin-deficiency</td>
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<td>3. Toxic-exposure</td>
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<td>4. Dysimmune–paraneoplastic</td>
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<td>5. Infections</td>
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<tr>
<td>6. Hereditary</td>
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<td>7. Other</td>
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<td>8. Idiopathic</td>
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Among polyneuropathies of **metabolic-endocrine** origin, polyneuropathy as a complication of **diabetes mellitus** must be emphasized. Diabetes mellitus is the most common cause of neuropathy in the developed world and affects 20-30 million people worldwide. Neuropathy is the most common complication of diabetes, which develops in 45-50% of diabetic patients; in approximately 10% of patients, neuropathy is present already at the time of diagnosis. Risk factors include inadequate glycemic control, duration of diabetes and age. It should be underlined that latent diabetes, impaired glucose tolerance (IGT) can also cause neuropathy.

**Table 7 shows the different forms of diabetic neuropathies.**

### Table 7: Different forms of neuropathies due to diabetes mellitus

<table>
<thead>
<tr>
<th>Acute reversible biphasic sensory neuropathy</th>
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<tr>
<td>Chronic symmetric polyneuropathy</td>
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<tr>
<td>• Distal symmetric, predominantly sensory nerve polyneuropathy (micro-axonal and small fibers)</td>
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<tr>
<td>• Autonomic neuropathy</td>
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<td>• Total foot neuropathy</td>
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<tr>
<th>Focal and multifocal neuropathies</th>
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<tr>
<td>• Cranial neuropathes</td>
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<tr>
<td>• Mononeuropathies (pressure palsades, entrapment neuropathies)</td>
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<td>• Peroneal diabetic neuropathy (diabetic entrapment neuropathy)</td>
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<tr>
<td>• Thoraco-lumbar entrapment neuropathy</td>
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<tr>
<td>• Multifocal diabetic neuropathy</td>
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There are two major forms of diabetic neuropathies: distal symmetric predominantly sensory neuropathy, and focal or multifocal neuropathies. Eighty percent of diabetic polyneuropathies are of the **distal symmetric**
**predominantly sensory type**, which affects primarily sensory fibers and the longest axons. Therefore, its symptoms are similar to those described above. Very characteristic is the 'burning feet' symptom, which is often the first manifestation of diabetic neuropathy. Furthermore, autonomic symptoms (dry skin, erectile dysfunction, tachycardia at rest, gastroparesis, urinary disturbance, etc.) are also common in this type of polyneuropathy. A very important clinical consequence of diabetic polyneuropathy is **diabetic foot** with non-healing ulcers, gangrene, eventually leading to amputations (Fig. 23). Eighty-five percent of non-traumatic amputations are due to diabetic foot. Diabetic distal symmetric neuropathy is irreversible, but progression may be stopped or slowed by adequate glycemic control.

**Fig. 23: Foot ulcers in diabetic neuropathy (diabetic foot)**

Focal diabetic neuropathies are less frequent, affect primarily older patients with type II diabetes mellitus, and show less connection to the metabolic state of the patient. Among the focal neuropathies, compression neuropathies (e.g. carpal tunnel syndrome, ulnar nerve lesion at the elbow, meralgia paresthetica, compression palsy of the common peroneal nerve at the fibular head) and cranial neuropathies of probably vasculitic origin (oculomotor or abducens nerve lesion) are seen most often. Some of the focal-multifocal diabetic neuropathies show spontaneous recovery (e.g. diabetic cranial nerve lesion, diabetic proximal neuropathy-plexopathy).

Among polyneuropathies due to **vitamin deficiency**, vitamin B1 deficiency is to be mentioned first. In Hungary and the developed world, vitamin B1 deficiency is mainly seen in connection with chronic **alcoholism**, thus it is a very common cause of polyneuropathy. Malnourishment and malabsorption may also cause vitamin B1 deficiency. It causes typical chronic symmetric predominantly sensory type polyneuropathy. Vitamin B12 deficiency may also cause polyneuropathy, but it leads more commonly to central nervous system symptoms, demyelination of the posterior columns of the spinal cord. Vitamin B6 deficiency or overdose may also be a cause of polyneuropathy.

Various exogenous agents (**toxic substances, drugs**) may induce chronic axonal polyneuropathies. Among industrial toxins, organic solvents (e.g. n-hexane) and heavy metals (e.g. lead, mercury) are known causes of polyneuropathies and constitute an occupational hazard. Polyneuropathy may develop as a side effect of many therapeutic drugs, including phenytoin, INH, vincristine, cisplatin, nitrofurantoin, chloroquine, thalidomide, disulfiram, metronidazole, and bortezomib. Furthermore, it is likely that polyneuropathy associated with alcoholism is not only caused by vitamin B1 deficiency, but also by the direct toxic effect of
A very large group of polyneuropathies are those of dysimmune origin, occurring as a consequence of abnormal immune response or other disorders of the immune system. Some of them involve only the peripheral nervous system, such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP) and the very rare multifocal motor neuropathy with conduction blocks (MMN).

**Guillain-Barré syndrome** is an acute polyneuropathy (polyradiculoneuropathy) with an immunological mechanism, where extensive perivascular lymphocyte-macrophage infiltration and consequent macrophage-mediated segmental (uneven) demyelination occurs in the peripheral nervous system. Guillain-Barré syndrome is preceded by an intercurrent infectious disease by 1-2 weeks in two-thirds of cases. Due to the similarity in antigens of the infectious agent and the peripheral nerves, the immune response produced against the infectious agent also attacks the peripheral nerves. The incidence of Guillain-Barré syndrome is 1.5-2/100,000/year. The clinical picture is characteristic: ascending flaccid paresis develops within days or 1-2 weeks that may progress to loss of ambulation, tetraplegia, dysphagia and respiratory insufficiency. The risk of respiratory insufficiency necessitates close monitoring of the patient. Sensory disturbance is usually milder, but radicular pain and autonomic symptoms are common. EMG shows typical signs of segmental demyelination, and the protein content of the cerebrospinal fluid is increased with a normal cell count. Spontaneous recovery usually occurs within months, but plasma exchange or administration of intravenous immune globulins (IVIG) is recommended in more severe cases. Corticosteroids are ineffective. Supportive care is particularly important because the outcome of Guillain-Barré syndrome is determined primarily by the complications of a bed-bound state.

**CIDP** (chronic inflammatory demyelinating polyneuropathy) is a subacute chronic sensory-motor polyneuropathy also with an immunological mechanism. Its course is typically relapsing-remitting, and asymmetrical symptoms and cranial nerve involvement are common. Cerebrospinal fluid examination shows an elevated protein content with a normal cell count. CIDP may be effectively treated with repeated courses of IVIG, long-term oral corticosteroid treatment, or repeated courses of plasma exchange.

Polyneuropathies are often associated with conditions with paraproteinemia, such as benign monoclonal gammopathy (anti-MAG IgM), cryoglobulinemia (e.g. associated with HCV infection), multiple myeloma, etc. These polyneuropathies are usually of demyelinative nature.

**Systemic vasculitis** (e.g. polyarteritis nodosa, Churg-Strauss syndrome, SLE, rheumatoid arthritis, Sjögren’s syndrome, etc.) and connective tissue diseases involve many organs, and the peripheral nervous system is also frequently affected. Generally, other manifestations of the disease precede the development of polyneuropathy, but rarely it may be first or predominant manifestation, e.g. in polyarteritis nodosa. In vasculitis, polyneuropathy may take the form of multiple mononeuropathy or show asymmetric signs, and it may also follow an acute, fulminant course triggered by an immune stimulus.

Polyneuropathy may occur as a distant effect of various tumors, also with an immunological mechanism. These are called paraneoplastic polyneuropathies. Due to the similarity in antigens of the tumor and the alcohol.
peripheral nerves, the immune response produced against the tumor also attacks the peripheral nerves. The polyneuropathy may precede other signs and diagnosis of the tumor by years. Small cell lung cancer is a tumor commonly causing paraneoplastic polyneuropathy or other paraneoplastic nervous system disorders. Paraneoplastic polyneuropathies may be of various clinical forms, but the most typical form is a purely sensory polyneuropathy with severe pain and very unpleasant paresthesias.

Polyneuropathies of infectious origin in the developed world are of minor significance in comparison to the causes described above. Worldwide, however, polyneuropathy associated with HIV infection and leprosy is a major health issue. Lyme disease should also be mentioned, which may be a common cause of facial palsy in children in endemic regions. Typical polyneuropathy caused by Lyme disease is however distinctly rare.

A large number of hereditary polyneuropathies is known. The most common inherited polyneuropathy is Charcot-Marie-Tooth’s disease, which is also one of the most common genetic conditions; many of its genetic subtypes have been recognized during the last 10-15 years. The demyelinating type I of Charcot-Marie-Tooth’s disease is encountered most frequently, caused by a mutation (duplication) in the PMP22 gene, which is responsible for the myelin sheath of peripheral nerves. Penetrance is very variable, even within a family. The disease shows a very slow progression, involving the longest nerves first: initial symptoms include small foot muscle then later leg muscle atrophy and weakness with consequent foot deformity (high arch [cavus] foot) and the stork-like appearance of the legs (Fig. 24). Sensory disturbance is not pronounced.

![Fig. 24: Severe distal muscle atrophy in Charcot-Marie-Tooth’s disease](image)

HNPP (hereditary polyneuropathy with liability to pressure palsies) is caused also by a mutation in PMP22 gene, but the type of mutation is deletion rather than duplication. This is also a generalized demyelinating polyneuropathy as shown by EMG, but the clinical picture and course is completely different from Charcot-Marie-Tooth’s disease type I. These patients do not have clinical signs of a generalized polyneuropathy, but suffer pressure palsies even after minor external pressure on the nerves (e.g. leg-crossing causing peroneal nerve palsy). These pressure palsies show spontaneous recovery.

**Other** polyneuropathies. Critical illness polyneuropathy (CIP) occurs in critically ill, ventilated patients with sepsis and multi-organ failure, treated in intensive care units. About seventy percent of such patients show signs of critical illness polyneuropathy or myopathy. CIP is a severe axonal polyneuropathy with generalized muscle atrophy,
weakness and sensory loss, which may become manifest first in the
difficulty of weaning the patient from the ventilator.

*Celiac disease* (gluten-sensitive enteropathy) may also be a cause of
sensory polyneuropathy. *Sarcoidosis* typically causes multiple
mononeuropathy or facial palsy. Polyneuropathy caused by *amyloidosis*
is associated with autonomic symptoms and focal neuropathies (e.g.
carpal tunnel syndrome).

*Idiopathic*. Unfortunately, the cause of polyneuropathy remains
unknown in a significant portion of cases (up to 40-50%) even after
thorough evaluation. This is especially true for the slowly progressive,
predominantly sensory, axonal polyneuropathies seen in the elderly.

Special consideration should be given to the so called *small-fiber
neuropathy*, because of diagnostic difficulties associated with it. In
small-fiber neuropathy, only sensory nerve fibers with the smallest
diameter (unmyelinated C and myelinated A\(\delta\) fibers) - conveying light
touch, pain and temperature - are affected. It may be the initial stage of
diabetic neuropathy, or it may be the only manifestation of IGT.
Small-fiber neuropathy is also often idiopathic, which occurs
characteristically in elderly women. Patients complain of burning pain,
unpleasant tingling sensation, but other sensory modalities (vibration,
joint position) and deep tendon reflexes are normal because thick
sensory fibers remain intact. Motor fibers are also normal, so there is no
weakness or gait disorder. Therefore, very few objective signs of
polyneuropathy are present, which may question the organic nature of
the complaints. Furthermore, EMG is also normal because it can
evaluate only thick nerve fibers.

**Diagnosis of polyneuropathy**

The diagnosis of polyneuropathy is a complex task, which is based on
the integrated assessment of history, clinical signs and symptoms (time
course, distribution, affected nerve fibers), and electrodiagnostic data.

As a first step, polyneuropathy should be confirmed with objective
methods, such as EMG. EMG also gives information about the axonal
or demyelinative nature of the disease, about the type of fibers involved,
and its duration (chronic, acute-subacute). Furthermore, EMG may
detect subclinical polyneuropathy when patients are still free of
symptoms. A subclinical polyneuropathy is a predisposing factor for
pressure palsies and tunnel syndromes.

The next step is to search for the *cause* of polyneuropathy. It is evident
from the previous section that a very large number of conditions may be
associated with polyneuropathy. It is naturally unfeasible and
unreasonable to look for all possible causes, but evaluation should be
focused based on the following considerations.

A thorough and detailed history is the most important help in the search
for etiology. Questions should be asked concerning underlying diseases,
occupation and work environment, drugs, and family history. The time
course, clinical form and axonal or demyelinative nature are also
important pieces of information (*Table 8*).
Auxiliary examinations. After consideration of the information mentioned above, the search for etiological diagnosis can usually be limited to a few directions. However, routine laboratory tests are recommended, including ESR, blood glucose, renal and hepatic function, serum electrophoresis. As IGT can also cause polyneuropathy, oral glucose tolerance test should be considered in polyneuropathies of unknown origin. Depending on the supposed diagnosis, auto-antibodies, serological tests, toxicological tests, and blood vitamin B12 level measurement may be warranted. If paraneoplastic polyneuropathy is suspected, a tumor search should be carried out. Cerebrospinal fluid examination is needed only when certain polyneuropathies is suspected. Protein content is elevated with normal cell count in Guillain-Barré syndrome from the second week, and in CIDP. Protein content may be elevated also in diabetic neuropathy. Pleocytosis is seen in Lyme disease, HIV infection and sarcoidosis. Sural nerve biopsy is rarely needed, it is mainly indicated to confirm vasculitis. Genetic tests are indicated when there is a strong suspicion of hereditary neuropathy.

Treatment of polyneuropathies

The primary aim is to treat and remove the cause of polyneuropathy. It is important to consider that with a successful treatment improvement is to be expected within weeks in demyelinating neuropathies, whereas only after months or even years in axonal polyneuropathies.

As the cause of polyneuropathy often remains elusive, symptomatic treatment is very important. Patients may suffer significantly from ‘positive’ sensory symptoms, paresthesias and neuropathic pain. Both of these may be alleviated by pharmacological treatment (Table 3).

Vitamins. It is a common practice that vitamin B1 and B12 is administered in neuropathies. However, this is justified only conditions with true vitamin deficiencies, such as chronic alcoholism, malabsorption and malnourishment.

Immunological treatment. From the group of dysimmune neuropathies, Guillain-Barré syndrome and CIDP respond to plasma exchange and IVIG treatment. CIDP also responds to chronic corticosteroid treatment. Likewise, chronic corticosteroid treatment is needed in polyneuropathies associated with systemic vasculitis and connective tissue diseases.

Other. Physical therapy is important if weakness is present, to prevent contractures. Assistive devices may be needed if gait is affected (e.g. ankle foot orthosis for foot drop, walking canes, etc.). If sensory loss is present, proper foot care, appropriate shoes, prevention of injuries, and

### Table 8: Demyelinating and axonal polyneuropathies

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<tr>
<th>Demyelinating</th>
<th>Axonal</th>
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<tr>
<td>- Diabetic polyneuropathy</td>
<td>- Diabetic polyneuropathy</td>
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<tr>
<td>- Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
<td>- Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
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<tr>
<td>- Hereditary sensory and autonomic polyneuropathy (HSAN)</td>
<td>- Hereditary sensory and autonomic polyneuropathy (HSAN)</td>
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<td>- Diabetic polyneuropathy</td>
<td>- Diabetic polyneuropathy</td>
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<tr>
<td>- Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
<td>- Chronic inflammatory demyelinating polyneuropathy (CIDP)</td>
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<td>- Diabetes insipidus polyneuropathy</td>
<td>- Diabetes insipidus polyneuropathy</td>
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<td>- Hereditary sensory and autonomic polyneuropathy (HSAN)</td>
<td>- Hereditary sensory and autonomic polyneuropathy (HSAN)</td>
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<td>- Diabetic polyneuropathy</td>
<td>- Diabetic polyneuropathy</td>
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avoidance of persistent external pressure are of paramount importance. These serve to prevent ulcers and to reduce the risk of amputation.