National Consensus on Diagnosis and Treatment of Immune-mediated Polyneuritis and Polyneuropathies

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Initiated by:

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National Consensus Statement for diagnosis and treatment of immune mediated polyneuritis and polyneuropathies

Today, 21 February 2019, we, the undersigned experts reached consensus on diagnosis and treatment of immune mediated polyneuritis and polyneuropathies:

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Polyneuritis and polyneuropathies are disorders of the peripheral nervous system (PNS) that damage bilaterally and symmetrically two or more peripheral nerves affecting their motor, sensory, or autonomic nerve fibres. They may affect cranial nerves and/or spinal roots.

Epidemiology They affect 2-8% of adult population, and morbidity increases with age.

Classification - depends on the type of onset (acute, subacute and chronic) and on the type of dominant symptoms (sensory, motor, sensorimotor or autonomic), as well as on disease etiology and pathogenesis.

Table 1. Etiopathogenetic classification of polyneuropathy

Immune-mediated polyneuropathy ***Inflammatory demyelinating polyradiculoneuropathy*** Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) Multifocal motor neuropathy with conduction block ***CIDP associated with other disorders*** ***Idiopathic sensory and autonomic neuropathy*** ***Polyneuropathy associated with vasculitis and connective tissue disease***
Infectious polyneuropathy polyneuropathy associated with diphtheria, leprosy, infectious mononucleosis, neuroborreliosis or HIV
Metabolic polyneuropathy (associated with endocrinopathy) diabetic, hypoglycaemic, acromegalic or hypothyroid polyneuropathy
Polyneuropathy associated with systemic disease uremic, hepatic or gastrointestinal or critical illness polyneuropathy, or polyneuropathy associated with COPD or gout
Polyneuropathy associated with malignant neoplasm
Toxic polyneuropathy Drug-induced polyneuropathy, polyneuropathy associated with industrial, agricultural and other toxic substances or heavy metals
Deficiency polyneuropathy Polyneuropathy associated with vitamin deficiency, postgastrectomy syndrome, hypophosphatemia, and alcoholic polyneuropathy

Hereditary polyneuropathy

Based on pathomorhology, there are three types of peripheral nerve injury. *Distal axonal* retrograde degeneration (dying-back) is a process involving progressive distal to proximal axonal degeneration. It also involves myelin degeneration.

Wallerian degeneration (dying-forward) is a process involving axon and myelin degeneration distal to axonal lesion.

Segmental demyelination may be primary or secondary (to axon degeneration).

Clinical presentation - most often symmetrical, distal, sensory and motor polyneuropathy. Involving distal symmetrical sensory changes, combined with distal peripheral paresis with muscular hypotonia and depressed or absent tendon reflexes. Small-fibre neuropathy does not affect tendon reflexes, however it causes autonomic disorder and affects pain and temperature sensation. Symptoms of autonomic disorders include anhidrosis and orthostatic hypotension. Pupillary abnormalities, impaired lacrimation and salivation, sexual dysfunction, bladder disturbances, etc. may also occur. Large nerve fibre involvement with concomitant tendon areflexia result in deep sensory impairment. In such cases, sensory ataxia, pseudoathetosis (’dancing fingers’) or action tremor of the upper extremities may also appear. Sensory impairment is more common than motor impairment in toxic and metabolic neuropathies. In most cases, the lower extremities are most severely affected. This pattern of impairment affecting mainly the distal end of lower limbs and of more severe impairment in lower extremities is typical in axonal degeneration. The longest peripheral nerves are affected first and most severely. Denervated muscles gradually undergo atrophy.

More rare forms are proximal polyneuropathy and multiple mononeuropathy - asymmetric isolated dysfunctional involvement of multiple peripheral nerves, either simultaneously or sequentially. This pattern of impairment affecting the proximal end of extremities first is typical in demyelinating polyneuropathy. It does not cause muscular atrophy, as peripheral nerve axons are almost intact and muscles are not denervated.

The course of disease may vary. Polyneuropathies may have acute (days), subacute (weeks) and chronic (months or years) or chronic remitting course. Acute polyneuropathies may be inflammatory, immune-mediated, toxic or vascular. Most common types of subacute polyneuropathies are toxic, metabolic or associated with

systemic disease. Chronic polyneuropathies are hereditary or in rare cases - metabolic.

Diagnosis and differential diagnosis are based on patient's medical history, neurological status, electromyography (EMG), and cerebrospinal fluid analysis, histological and other laboratory tests. Various tests are required in order to clarify disease etiology – glucose tolerance, HbA1C, serum vitamin B_{12}, screening tests for systemic vasculitis and collagenosis, etc. EMG shows whether polyneuropathy is axonal or demyelinating, symmetrical or asymmetrical, severe or mild.

Treatment is focused on underlying disease, if possible. In most polyneuropathies, treatment can impact only pain. None of the medications available can reverse muscle weakness.

Metabolic (diabetic) polyneuropathy, deficiency (alcoholic) polyneuropathy and polyneuropathies associated with malignant or infectious diseases (AIDS), as well as hereditary sensory and autonomic neuropathies are mainly associated with neuropathic pain. These types of neuropathies are included in the National Consensus on Diagnosis and Treatment of Pain of Neurological Origin as their treatment can impact only pain.

Immune-mediate polyneuritis and polyneuropathy are a group of disease with common pathogenesis. They include a subgroup of inflammatory demyelinating polyneuropathies and CIDP associated with other disorders which are difficult to distinguish from chronic demyelinating polyneuropathy. This group includes rare idiopathic sensory and autonomic neuropathies, polyneuropathy associated with vasculitis or autoimmune connective tissue disorders.

I. Inflammatory demyelinating polyradiculoneuropathy

1. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)

Guillain-Barré syndrome (GBS) is an immune-mediated acute polyradiculoneuritis.

It has several subtypes with different histopathology, neurophysiology and clinical presentation.

Acute inflammatory demyelinating polyneuropathy (AIDP) is the most common (75%) subtype. It mainly affects motor nerves and nerve roots, and is

associated with good prognosis. It often results in secondary axonal degeneration.

Acute motor axonal neuropathy (AMAN) with axonal degeneration is affects 5-10% of all patients.

The third subtype is the rare form of *acute motor and sensory axonal neuropathy (AMSAN)* that affects motor and sensory nerve axons.

The fourth subtype of Guillain-Barré syndrome is *the Miller Fisher syndrome* described in 1956 as a triad of acute ophthalmoplegia, ataxia and areflexia.

Various *variants of the syndrome* have been also described, including pharyngeal-cervical-brachial variant, cranial polyneuritis and acute pandysautonomia. Miller-Fisher syndrome (in 5% of all cases), cranial polyneuritis and purely sensory variant constitute 15% of all cases.

The incidence is 1.2-1.9 cases per 100,000 individuals, and the incidence of Fisher variant is much lower - 0.1 per 100,000 people. Incidence increases with age, and reaches 4 cases per 100,000 people over 75 years old. Men are 1.5 times more likely to be affected than women. AMAN occurs more frequently in Asia (China and Japan) where they have summer epidemic affecting children in Mexico.

The etiology involves infection that triggers immune response damaging peripheral nerves by cross-reaction with axolemma and Schwann cell antigens. 75% of patients had a preceding infection 1-4 weeks prior GBS onset, such as common cold and more rarely gastroenteritis. Various viruses and bacteria have been identified as possible triggers of GBS, such as Campylobacter jejuni (66%), cytomegalovirus (15%), Epstein-Barr virus (10%) and Mycoplasma pneumoniae (5%). As a result of the immune response against the infectious microorganism, autoantibody are generated and cross react with epitopes on axons. Anti-GM1 ganglioside antibodies are found in the axon subgroup (in 50% of patients) and anti-GQ1b ganglioside antibodies - in Miller Fisher syndrome. Infections are not related to a certain subtype of clinical presentation, however more severe axonal degeneration is often observed following Campylobacter jejuni infection, and severe involvement of sensory nerve fibres - following cytomegalovirus infection.

The pathogenesis is multifactorial and associated with complex interactions involving humoral and cellular immunity, complement deposition, cytokines and other inflammatory mediators.

The pathogenesis of demyelinating GBS is associated with mononuclear cell infiltration into peripheral nerves. Macrophages invade myelin sheaths and denude axons. Activated macrophages are targeted to antigens on the surface of Schwann

cells or myelin sheaths by activated T lymphocytes. The initial invasion of the Schwann cell basement membrane is a consequence of matrix metalloproteinases, toxic nitric oxide radicals and other mediators released by activated macrophages. The initial event may be associated with the binding of antibodies to the surface of Schwann cells, fixation of complement, cell damage and subsequent vesicular dissolution of myelin in advance of cell invasion. In severe lesions, the axons are also damaged as a secondary consequence of the toxic enzymes and radicals released by the immune-mediated inflammatory response directed against myelin.

Axonal GBS may have various pathogenesis. Targeted by their Fc receptor-mediated binding of antibodies directed against ganglioside antigens on the axolemma, macrophages invade the nodes of Ranvier. They insert between the axon and the surrounding Schwann cell axolemma, leaving the myelin sheath intact. In severe cases, the axons are damaged in the ventral root, which may cause severe degeneration of the whole axon.

Motor and sensory neuropathy affects dorsal roots.

The clinical course is characterised by acute development (up to 4 weeks) of pain (radicular pain or dysesthesia in the lower extremities), motor and sensory impairment and symmetrical paresthesia in the extremities. Early and common symptoms include loss of tendon reflexes (70%) and pain. Neuropathic pain persists in the acute phase in 70% of cases. Pain is deep, especially in the lower extremities, accompanied by dysesthesia. Muscle weakness may be initially be proximal, distal or a combination of both. It affects earlier and more severely the lower extremities and spreads to the upper cranial nerves. 5-25% of patients develop weakness of the respiratory muscles, requiring mechanical ventilation. The facial nerves are often affected and less often the bulbar and ocular motor nerves. Autonomic involvement is also common (50%) and causes urine retention, ileus, sinus tachycardia, hypertension, cardiac arrhythmia and postural hypotension.

Symptoms reach their nadir within 2 to 4 weeks. The acute phase is followed by stable phase and reversal with return of proximal, followed by distal muscle strength. The rate of mortality is 4-8% and 20% of patients remain with some disability. Most (75%) of the patients who recover well experience chronic fatigue which can be explained by residual muscle weakness.

- *Acute motor axonal neuropathy (AMAN)* is more severe and characterised by muscle paresis and hypotrophy, more rapid progression to nadir, but recovery times are similar to those in patients with demyelinating neuropathy. The residual

neurological deficit is more prominent.

- *Acute motor and sensory axonal neuropathy (AMSAN)* is more severe, more often requires mechanical ventilation and is associated with poor prognosis, and residual neurological symptoms in 80% of patients.

- *Miller-Fisher syndrome* (MFS) is characterised by a triad of total external ophthalmoplegia, ataxia and areflexia, or only by ophthalmoplegia. It is often characterised also by facial and oropharyngeal weakness, internal ophthalmoplegia and central nervous system involvement. Bickerstaff's brainstem encephalitis (BBE) is a syndrome related to Miller-Fisher syndrome. It is characterised by ophthalmoplegia, ataxia, corticospinal tract abnormalities and impaired consciousness. Facial weakness and dysarthria are common symptoms in these two syndromes. Some of the patients with any of these syndromes also have GBS with flaccid quadriparesis. Anti-GQ1b antibodies are present in 95% of patients with acute MFS and in 75% of patients with BBE. For that reason and due to their specific clinical presentations, these two conditions are referred to as the 'anti-GQ1b antibody syndrome'. Their prognosis is favourable and usually patients achieve full recovery.

- *Pharyngeal-cervical-brachial variant* is characterised by difficulty swallowing, neck and proximal upper limb muscle weakness. It may also include pupillary abnormalities, ptosis, ophthalmoplegia and ataxic gait.

- *Cranial polyneuritis* is characterised by multiple cranial nerve lesions. Patients have mild limb paresis or EMG shows only peripheral nerve involvement.

- *Acute pandysautonomia* is characterised by rapid development of combined sympathetic and parasympathetic failure: severe orthostatic hypotension, anhidrosis, miction disorders, sexual dysfunction and gastrointestinal atony. It is associated with favourable prognosis.

Diagnosis is based on mandatory clinical, cerebrospinal fluid and electrophysiological criteria.

Clinical features required for diagnosis – progressive weakness of more than one limb and tendon areflexia.

Supportive features:

- Progression within a few days to 4 weeks;
- Relatively symmetrical distribution of paresis;
- Mild sensory symptoms;
- Cranial nerve involvement;

- Recovery beginning 2-4 weeks after progression stops;
- Symptoms of autonomic dysfunction;
- Absence of fever at disease onset.

Features that do not rule out diagnosis:

- Bladder and/or bowel dysfunction;
- Positive Babinski sign;
- Ataxia;
- Dystonia.

Cerebrospinal fluid (CSF) features *strongly supportive of the diagnosis* include evidence of protein-cell dissociation in CSF (in 80% of cases) - elevated CSF protein > 0.46 g/L with underlying normocytosis (up to 10 mononuclear leukocytes x 10^6/L). In 10% of all cases, CSF protein may remain within the normal ranges over the entire course of disease. Within the first days of disease onset, protein levels may remain normal. The highest levels are reached during the second or the third week and their reversal to normal may take months. 10% of patients have mild lymphocytic pleocytosis (up to 50 x 10^6/L cells). If the mononuclear cell count exceeds these ranges, other conditions should be ruled out, such as HIV infection, Lyme disease, sarcoidosis and neoplasms.

Some of the patients have hypergammaglobulinorachia and elevated IgG levels in CSF, as well as evident oligoclonal bands in CSF protein electrophoresis.

EMG features required for diagnosis – signs of demyelination in more than two peripheral nerves. Presence of at least 3 of the following 4 EMG features:

- Slowed motor conduction in peripheral nerves
- Complete or partial motor conduction block (>20%) of peripheral nerves and/or abnormal temporal dispersion;
- Prolonged distal motor latencies;
- Prolonged F-wave latencies and/or reduced incidence of F-wave latencies.

EMG is very important for disease diagnosis and prognosis. Based on EMG, patient's condition may be classified as one of GBS subtypes depending on the evidence of demyelination, or axonal degeneration and either motor or sensory involvement. EMG testing should be performed as early as possible after disease onset, as patients develop secondary axonal degeneration over time which makes disease classification more difficult. It is difficult to classify the condition when the

initial EMG shows minimum changes or if the changes are so severe that peripheral nerves cannot be activated. In such cases, testing should be repeated in 1-2 weeks. Prognosis is estimated based on the presence and degree of axonal degeneration which is a sign of more severe involvement and slower recovery.

The first EMG signs of demyelination include prolonged or absent F-wave latency and H reflexes (in 50% of patients), slowed conduction in peripheral nerves and temporal dispersion of compound muscle action potential (CMAP). Axonal degeneration is characterised by reduced sensory and motor response amplitudes and denervation of the relevant muscles. The sensory forms usually affect the median and ulnar nerves, without affecting the sural nerve.

Differential diagnosis includes acute myelopathy due to transverse myelitis, acute spinal compression or spinal infarction. Rapidly progressive vasculitic multiple mononeuropathy or acute-onset chronic demyelinating polyneuropathy should also be considered. Acute intermittent porphyria, botulism, myasthenia gravis, Lyme neuroborreliosis, heavy metal intoxication, poliomyelitis and AIDS may also be considered, although more rarely.

Treatment includes general medical care, respiratory support and feeding, as the recovery is spontaneous. It is subdivided into care for patients with severe paralysis requiring intensive care and respiratory reanimation (25%), specific care (immunotherapy) focused on nerve recovery and symptomatic treatment.

Intensive care is most important because if patients survive the acute phase, their functions recover. Modern technological advancements have allowed the development of such medical ventilators and ventilation modes that if a patient dies from acute respiratory failure, nowadays this is considered as a major medical mistake. Modern intensive care has dramatically changed mortality rate which was reduced from 30% to 5-10%. This is mainly due to the positive pressure ventilation.

Symptoms may progress very rapidly and the patient may need endotracheal intubation and mechanical ventilation even within the first 24 hours from symptoms onset.

For that reason patients must be hospitalised and monitored for respiratory disorders, cranial nerve paresis or autonomic nervous system dysfunction.

Clinical symptoms suggestive of developing respiratory disorders include tachypnoea, diaphoresis (excessive sweating), anxiety, use of accessory respiratory muscles, asynchronous thoracoabdominal movement and tachycardia. The strength of diaphragm and respiratory muscles must be assessed and monitored. It correlates with

the strength of neck and trapezius muscles with overlapping segmental innervation. Lung capacity is roughly estimated as the patient is asked to take a deep breath and count quickly. The ability to count to 20 in one breath corresponds to a vital capacity > 1.5 L.

Endotracheal intubation and mechanical ventilation are required in patients with respiratory muscle weakness (mostly the diaphragm), worsening respiratory parameters (reduced vital capacity < 60% - 20 mL/kg, maximum inspiratory pressure < 30 cm H_2O, maximum expiratory pressure <40 cm H_2O), inability to cough/stand/flex the arms or head, and elevated liver enzymes. In some patients mechanical ventilation is required due to severe bulbar dysfunction causing difficulty with clearing secretions, increasing the risk of aspiration and impairing gas exchange. Mechanical ventilation is more often required in patients with demyelinating disease. The mean duration of mechanical ventilation is 2 to 6 weeks.

Tracheostomy is used in patients who need prolonged mechanical ventilation.

Mechanical ventilation carries a risk of tracheobronchitis, bronchopneumonia, pulmonary atelectasis, pulmonary embolism and bacteremia.

Respiratory infections may be reduced by minimal sedation, physical therapy and ventilation with end expiratory pressure to reduce atelectasis and so-called ‘elephant lung’.

Acute autonomic disorders, most frequently involving the heart affect 65% of patients. It should be noted that autonomic disorders may result from pulmonary embolism, sepsis, dehydration, unmanaged pain and electrolyte disturbances. In most cases, patients develop sympathetic overdrive with reduced parasympathetic activity.

Sinus tachycardia (120 bpm) is the most common predictor of dysrhythmia. Heart rhythm disorders are a common cause of death and may be reduced by ECG monitoring and temporary placement of pacemaker in patients with severe bradycardia that can be a predictor of cardiac asystole.

Cardiac rhythm disturbances are a common cause of death, and this can be reduced by ECG monitoring with prophylactic temporary pacing in cases of significant bradycardia, which may herald cardiac asystole.

Blood pressure should be monitored, as blood pressure is elevated in 25% of patients. Saline infusion should be used in patients with arterial hypotension. The fluid and electrolyte balance should be monitored.

Urinary retention due to parasympathetic dysfunction may occur in 25% of patients, especially in those with mechanical ventilation. It necessitates the placement

of urinary catheter.

Gastrointestinal motility disorders occur in 15% of patients. Transient (for days to weeks) ileus may occur during the acute or plateau phase. When ileus occurs during the early acute phase, it is caused by parasympathetic dysfunction, and if it occurs later - it is caused by mechanical ventilation and prolonged immobility. It requires parenteral feeding, enema, erythromycin or neostigmine.

Prolonged paralysis leads to other complications and appropriate prophylaxis should be performed.

Prophylaxis of deep venous thrombosis and pulmonary embolism with low dose Heparin (5000 U subcutaneously every 12 hours) or low-molecular-weight heparin (Clexane 20-40 mg/day, Fraxiparin 0.3-0.6 mL/day) is also required.

Specific treatment is not known yet, and patients recover spontaneously. In view of the evidence of immune dysregulation, treatment with steroids, plasma exchange, and intravenous immunoglobulin should be used. Immunotherapy is initiated as soon as motor symptoms appear, but is not required in milder cases without motor symptoms. Plasma exchange and high dose immunoglobulin only reduce the recovery period, the duration of hospital stay and mechanical ventilation. The American Academy of Neurology recommends plasma exchange and immunoglobulins in patients with lower limb paresis diagnosed within the first 2 weeks from onset, unable to walk, however they highlight that this is not the best treatment option yet. There have been no clinical trials on immunotherapy in patients with Miller-Fisher syndrome. 10% of patients have early deterioration (new episodes) after plasma exchange and immunoglobulin use, especially if initiated late after disease onset.

Plasma exchange is the only treatment that has been shown to be more effective (faster recovery) compared with placebo and intensive care, and currently it is the gold standard used as a comparator for all new treatments. Plasma exchange efficacy data is based on 6 open-label clinical trials. Most of these trials use 7-point disability scale. Four trials have shown that after 4 weeks the use of plasma exchange achieved mean improvement of < 1 point (0.89) compared with untreated patients. Five trials have shown 50% reduction in the number of patients (14%) requiring mechanical ventilation after 4 weeks. It also reduced hospital stay. Four trials have demonstrated that after the 1 year, the proportion of patients with full recovery increased from 55% to 68%. There was no change in mortality rates. Treatment should be initiated as early as possible, not later than 4 weeks. Patients should

undergo a total exchange of about five plasma volumes within 1-2 weeks. Plasma exchange removes circulating immune factors implicated in the pathogenesis of GBS. This approach is not cost effective, as the costs for plasma exchange exceed the costs saved from reduced hospital stay and intensive care.

Plasma exchange is indicated in patients with confirmed diagnosis and severe polyradiculoneuritis with motor impairment (unable to walk, respiratory disorders) whose condition continues to deteriorate and whose disease history does not exceed 3 weeks. It is recommended to remove 200-500 mL/kg plasma over 4-6 sessions every other day and replacement with 5% m albumin solution in saline. Disadvantages include technical difficulties, risks, adverse effects and unavailability in smaller towns and villages. Adverse effects include hypotension, septicemia, bronchopneumonia, abnormal clotting, complications from central venous access and hypocalcemia.

High-dose intravenous immunoglobulin has been used since 1988. Immunoglobulin is a biologic product derived from donor blood fractionation. There are 4 subclasses of immunoglobulin G - IgG_1, IgG_2, IgG_3, and IgG_4.

The mechanism of action of immunoglobulin involves modulation of expression and function of macrophage Fc receptor, suppression of cytokines, chemokines and adhesion molecules, interference with complement activation and T-cell regulation. Pathological antibodies bind to IgG and their clearance is increased. It activates CD8+ T cell function by unknown mechanism.

Adverse effects are observed more rarely compared to plasma exchange, affect only 10% of patients, and are associated with transient symptoms of common cold, vomiting, risk of anaphylactic shock, aseptic meningitis, neutropenia, renal failure and myocardial infarction.

Comparative studies do not show significant difference between immunoglobulin and plasma exchange in duration of mechanical ventilation, mortality, disability and time to recovery. There have been no clinical trials comparing intravenous immunoglobulin therapy and placebo. However, intravenous immunoglobulin is preferred than plasma exchange due to its easier administration. Efficacy studies were conducted only for acute inflammatory demyelinating polyneuropathy (AIDP). There are no efficacy data for AMAN, AMSAN, Miller-Fisher syndrome and other clinical variants. It is considered that immunoglobulin has the same efficacy as plasma exchange. The regimen of administration of intravenous immunoglobulin is typically 0.4 g/kg per day for five days. The most commonly used immunoglobulin in Bulgaria is Immunovenin-intact 5% IgG available in 5 mL

ampoules. It contains 50 g/L human immunoglobulins, of which at least 98% are immunoglobulin G. It contains traits of IgA.

Corticosteroids have been used in clinical practice since 1950. Intravenous corticosteroids (methylprednisolone 500 mg/day) have no impact on the course of disease as reported by 6 clinical trials. In certain cases, high-dose corticosteroids stop disease progression. Oral corticosteroid use even delays recovery. The prevalent opinion is that corticosteroids should be avoided due to lack of efficacy. However, corticosteroid use has very good effect in chronic demyelinating polyneuropathy. The reason for the lack of efficacy remains unclear - probably corticosteroids have beneficial effects on inflammation but delay recovery by inhibiting macrophage clearance of myelinating debris, thus hampering remyelination. The reason for the different clinical effect depending on the route of administration (oral or intravenous) also remains unclear and is probably associated with the dose administered.

One trial has demonstrated good efficacy of combination therapy with intravenous corticosteroids and immunoglobulin. However, these data have not been confirmed yet.

Paediatric patients recover faster than adults. Plasma exchange is a treatment of choice in patients with acute onset severe GBS (aged > 12 years), however corticosteroid therapy is preferred in patients with subacute GBS with milder symptoms. Intravenous immunoglobulin (0.2 g/kg) manages symptoms faster than corticosteroid therapy.

Symptomatic treatment includes neuropathic pain management, physical therapy and rehabilitation.

Pain management is important with regard to pain duration and incidence.

Anticonvulsants are medications of first choice in neuropathic pain management.

Gabapentin (900-1800 mg/day) is the most effective anticonvulsant for neuropathic pain management. It reduces the incidence and duration of pain episodes and may induce remission.

Pregabalin (300-600 mg/day) is a gabapentin analog, but with more rapid onset of action and superior bioavailability and linear pharmacokinetics. It manages peripheral and central neuropathic pain better than gabapentin. Its dose titration and onset of action are rapid (1 week) and it manages sleep disturbance. Adverse effects (in 11% of cases) include dizziness, somnolence, dry mouth, peripheral oedema and weight gain. In order to avoid adverse reactions, lower dose may be administered

(150-300 mg).

Antidepressants are medications of second choice. Serotonin and noradrenaline reuptake inhibitors (SNRI) are used: amitriptyline (12.5–75 mg/day), venlafaxine (75-150 mg/day), mirtazapine (30-60 mg/day) and duloxetine (60 mg/day).

Physical therapy rehabilitation are required in 40% of patients during the acute phase. Early initiation of physical therapy is required for prevention of contractures, peripheral nerve compression lesion, decubitus ulcers, bronchopneumonia and postural hypotension. After the acute phase, physical therapy and rehabilitation should be continued with focus on residual neurological symptoms.

No specific treatment for Guillain-Barre syndrome is available.

Patient care is most important, as the patient must survive the acute phase in order to enter the phase of spontaneous functional recovery.

Plasma exchange and intravenous immunoglobulin therapy are used in the acute phase only in patients with AIDP and lower limb paresis diagnosed within the first 2 weeks from onset, unable to walk, as they reduce the duration of mechanical ventilation in these patients.

Symptomatic treatment is focused on neuropathic pain.

Prognosis. Recovery is faster within the first 6 months and slower within 2 years from onset. Some degree of disability occurs in 30% of cases (muscle weakness and sensory impairment). Disability is more severe with axonal GBS. Fatigue is a sequela of GBS in 75% of patients. It can persist for years and is not associated with muscle weakness.

2. Chronic inflammatory demyelinating polyneuropathy (CIDP)

In 1958, Austin differentiated CIDP from AIDP based on disease evolution, treatment response and prognosis. It is characterised by progressive symmetrical muscle weakness in limbs over at least 2 months.

CIDP incidence is 2-7 cases per 100,000 individuals. It affects men twice as often as women. Prevalence ranges from 0.5 in children to 2 per 100,000 in adults. It may affect any age, however CIDP peak incidence is between 40 and 60 years.

Classification. CIDP is a heterogeneous disorder that includes several variants characterised by various clinical course and response to treatment. All acquired

demyelinating neuropathies of unknown etiology are considered to be CIDP. In 25% of patients, CIDP is associated with other disease (monoclonal gammopathy, paraproteinemia, lymphoma, systemic lupus, HIV infection, Waldenström macroglobulinemia, osteosclerotic myeloma, POEMS syndrome, chronic active hepatitis, inflammatory bowel disease, Hodgkin lymphoma, etc.). Asymmetrical variants of CIDP should be monitored more closely, as if they remain undiagnosed, the patient will lose the opportunity to benefit from immunosuppressive therapy (corticosteroids or intravenous immunoglobulin)

Table 2. CIDP classification

Idiopathic (classic form of) CIDP – no comorbidities
Atypical CIDP:
- Multifocal motor neuropathy (MMN) - asymmetrical, predominantly motor presentation;
- predominantly acquired demyelinating sensory and motor neuropathy (Lewis-Sumner syndrome) – asymmetrical, sensory and motor presentation;
- Distal acquired symmetrical demyelinating neuropathy – symmetrical, distal, sensory and motor presentation; abnormal gait; IgM paraproteinemia in 75% of cases.
- Cranial polyneuritis;
- Brachial or lumbosacral radiculoplexus neuropathy;
- Multiple mononeuropathy;
- Combined central and peripheral demyelination;
- Pure sensory neuropathy;
CIDP associated with other disorders:
- HIV infection;
- Lymphoproliferative disorders (Hodgkin lymphoma);
- Monoclonal or biclonal gammopathy (macroglobulinaemia, POEMS syndrome);
- Monoclonal gammopathy of undetermined significance of the IgM, IgG and IgA type;
- Systemic lupus erythematosus;
- Diabetes mellitus;
- Chronic active hepatitis B or C;
- Inflammatory bowel disease (Crohn's disease);

- Thyrotoxicosis;
- CNS demyelination.

Disease etiology is unknown. Triggering factors may include vaccination against influenza, diphtheria, pertussis, tetanus, hepatitis B, smallpox, rubella or mumps. In contrast to AIDP which often develops after viral infection, HLA-A1,-B8,-DRw3, and-Dw3 are found to be associated with CIDP.

The pathogenesis of macrophage-mediated demyelination is associated with antibody-mediated and T-cell mediated immune reactions - the same as with other inflammatory neuropathies.

Pathomorphological evidence is characterised by chronic demyelination of proximal peripheral nerve segments and nerve roots, and more rarely show signs of axonal degeneration. Its features are predominantly axonal.

Clinical presentation is characterised by gradually and slowly progressive weakness in proximal and distal muscle groups in the lower and more rarely in the upper extremities Peak neurological deficit is reached within ≥ 8 weeks of the onset of neurological symptoms. In 15% of patients, the disease has an acute onset similar to AIDP, and then its clinical course changes. It may start with asymmetrical symptoms or may affect upper extremities first. It may involve mild muscle hypotrophy. Sensory impairment is more prominent compared with AIDP, although pain is not a leading symptom. Back pain may also be present. Sensory impairment in CIDP is usually greater for vibration sense and position sense than for pain and temperature sense, reflecting the involvement of larger myelinated fibres. In some cases dysesthesias can occur. Cranial nerve involvement is rare (10-15% of cases). Peripheral autonomic disorders occur in 20% of cases, and focal neurological symptoms involving CNS are observed in 10% of cases. Some patients experience hand tremor.

Clinical course of CIDP is chronic, progressive, stepwise progressive or relapsing.

Diagnosis is based on clinical, cerebrospinal fluid (CSF), electrophysiological and pathomorhological criteria. Depending on these criteria, diagnosis can be possible, probable or definite.

Clinical features required for diagnosis: symmetrical proximal or distal muscle weakness in more than one limb, combined with tendon hyporeflexia to areflexia, and disease progression longer than 2 months.

Features supportive of the diagnosis: evidence of predominantly distal weakness, sensory loss and/or excitability symptoms.

- ***CSF features*** – evidence of protein-cell dissociation in CSF (protein > 0.45 g/L, cells < $10x10^6$/L). According to the American Academy of Neurology (AAN) these criteria must be met for definite diagnosis.

- ***Electromyographic features*** are required for diagnosis. In contrast to GBS, patients with CIDP have significantly slowed motor conduction in peripheral nerve, more prominent partial motor conduction block of peripheral nerves or abnormal temporal dispersion, prolonged F-wave and distal latencies. Needle EMG often shows denervation and more scarce findings.

- ***Histological features*** – evidence of demyelination, remyelination and inflammatory infiltration. According to AAN these criteria are must be met for definite diagnosis. In patients with probable diagnosis (EMG and CSF criteria have not been met), peripheral nerve biopsy is recommended to rule out other diseases.

Differential diagnosis requires many examinations: serum glucose, glucose tolerance test, glycated hemoglobin, thyroid function studies, liver and renal function tests, hepatitis tests, HIV antibodies, serum and urine electrophoresis to detect paraprotein, complete blood count, Borrelia burgdorferi serology, C-reactive protein, antinuclear antibodies, angiotensin converting enzyme, antibodies to extractable nuclear antigens, chest and bone X-ray (if paraprotein is detected).

Differential diagnosis. Patients who meet the criteria for CIDP are further subdivided into idiopathic CIDP or CIDP associated with other disorders. Hereditary motor and sensory neuropathy must be ruled out.

CIDP should be differentiated from other forms associated with underlying disease.

This requires CSF analysis, CSF, serum and urine electrophoresis to detect paraprotein, as well as many other examinations and tests.

Treatment is based on *immune-modulating therapy* with corticosteroids, plasma exchange and intravenous immunoglobulin. These therapies are used in patients with severe neurological deficit that outweighs the risk associated with therapy, especially in case of corticosteroid therapy.

Continuous treatment with prednisone (dehydrocortison) at initial dose of 80-120 mg/day daily or alternate-day dosing of 7.5 mg on alternate days, is the treatment

of first choice. Every month the daily dose is reduced by 20 mg until the minimum effective dose is achieved - usually 20-40 mg/day. Treatment should be initiated as early as possible and continue at least 9 months. Early termination of treatment results in recurrence. Maintenance dose of 0.5- 0.75 mg/kg/day can be used in long-term treatment. The most common complications caused by long-term corticosteroid therapy include osteoporosis with vertebral compression fractures and cataract.

Combination therapy with prednisone and plasma exchange is indicated in patients whose condition does not improve after 4-week treatment with prednisone, or whose condition continues to worsen, or who develop adverse reactions. This therapy is administered twice weekly for 3-6 weeks, and may be repeated depending on the patient's condition.

Intravenous immunoglobulin therapy has a transient effect. Treatment is initiated at dose of 0.5-2 g/kg/day for 4-5 days. Patients with adequate response may receive 0.5g/kg/day single-dose infusion at intervals depending based on their condition. Serious adverse reactions are rare, however patients with renal failure should be treated with caution.

Azathioprine 3 mg/kg/day for 3 months may be used in case of treatment failure. If the patient's response to azathioprine therapy is also inadequate, intravenous cyclophosphamide 50 mg/kg/day should be administered for 4 days.

Treatment with *alpha or beta interferon* may have transient effect in some patients.

Symptomatic management of neuropathic pain.

Prognosis includes long-term neurological dysfunction and smaller likelihood of spontaneous remission compared with the more favourable prognosis in AIDP. After treatment completion, 95% of patients achieve transient improvement. Afterwards, only 40% of patients remain in complete or partial remission with no background therapy. Prognosis is more favourable in patients with spontaneous remission compared with those with progressive disease.

CIDP should be treated with corticosteroids for 9 months. Symptomatic treatment is focused on neuropathic pain.

3. Multifocal motor neuropathy (MMN) with conduction block was first described in 1985.

Incidence is very low, more than 300 cases worldwide. It mainly affects men

(80%) at the age of 20-50 years (80%).

It is subdivided into two forms – multifocal motor neuropathy (MMN) and multifocal conduction block. These two forms have clinical, EMG and immunologic differences, however their differentiation is difficult.

Disease etiology is unknown. 50% of patients have elevated IgM anti-GM1 ganglioside antibodies to peripheral myelin. This gives rise to discussion whether it belongs to paraproteinemic polyneuropathies. The reason of selective involvement of peripheral nerve motor fibres is still unclear. It may be due to the different antigen expression in motor and sensory fibres, or various predisposition to impairment.

Pathomorphological features show demyelination and remyelination - very similar to those observed in CIDP.

The clinical course is very similar to that observed in amyotrophic lateral sclerosis (ALS), with chronic remitting course and more often with slow chronic-progradient course. It is characterised by acute or subacute distal motor mononeuropathy in the upper and more rarely in the lower extremities (wrist or foot drop). In 10% of patients, upper extremities and proximal muscle groups are involved. Another peripheral nerve may also be affected. Cranial nerve involvement is not typical. Asymmetrical, predominantly distal weakness and muscle hypotrophy, single fasciculations and cramping, more often in the upper extremities. The distribution of paretic muscles correlates to the innervation area of a single peripheral nerve. Tendon reflexes are decreased or normal. Clinical and EMG examinations show absence of sensory deficit. The presence of paresthesia does not rule out diagnosis. Some patients with multifocal conduction block show clinical and EMG evidence of sensory impairment in the motor block are, and the clinical presentation is similar to that in CIDP. There is no pain, autonomic disorders or central motor neuron involvement.

Diagnosis is based on clinical, cerebrospinal fluid (CSF) and EMG criteria.

Neurographic evidence of demyelination – persistent multifocal partial motor conduction block in peripheral nerve (in MMN) or mixed nerve conduction block. This is a major differentiating diagnostic feature that distinguishes the condition from motoneuron diseases. Partial motor conduction block is characterised by disproportionate reduction in CMAP area and amplitude in proximal compared with distal electrical stimulation of peripheral motor nerve. There should be no temporal dispersion of CMAP. Another criteria is reduction in proximal CMAP area and amplitude by > 20% compared with distal CMAP. Nerve stimulation at short intervals (2-2.5 cm), the so called inching technique is recommendable. It allows to detect

whether CMAP amplitude drops at a certain segment of the nerve, which is a diagnostic criteria if the drop is not within the common compression sites of the nerve. Progressive amplitude drop is typical for other conditions associated with chronic demyelination or axonal degeneration. Conduction block may occur in any segment of the peripheral motor nerve, but more often affects the ulnar and the median nerves in the forearm, and more rarely the armpit or the axilla. The peroneal and tibial nerves are more rarely affected. The conduction velocity of peripheral motor nerves is usually within the normal range or mildly reduced. Sensory fibres are intact. Often needle EMG does not show any pathological changes. It may show fasciculations, fibrillations and motor action potentials with increased duration or amplitude confined to the muscles innervated by the affected nerve. By contrast, in case of spinal motoneuron involvement, changes affect many muscular groups.

CSF protein concentration is within the normal reference range in 90% of patients, or slightly elevated in the rest of the patients (up to 0.8 g/L).

Good therapeutic effect of intravenous immunoglobulin or cyclophosphamide is supportive of the diagnosis.

Differential diagnosis requires to ruled out ALS, spinal muscle atrophy and CIDP. The presence of distinct sensory impairment within the affected peripheral nerves (EMG evidence of reduction in the sensory amplitude or in the conduction velocity of sensory fibres) in patients with asymmetrical paresis is indicative of other diagnoses. Such diagnoses may include Lewis-Sumner syndrome, which is a variant of CIDP, multiple mononeuropathy due to vasculitis or multiple compression syndromes of peripheral nerves in hereditary neuropathy with predisposition to paralysis caused by compression or neurofibromas.

Treatment with cyclophosphamide 1 g/m^2/month for 6 months is a method of first choice, but only in patients with severe disability due to the risk of adverse reactions.

Intravenous immunoglobulin therapy (at dose of 0.4-0.5 up to 2 g/kg/day for 4-5 days) achieves transient and partial effect in most patients, and does not stop disease progression. Treatment should be repeated. It has no effect on the levels of anti-glycolipid antibodies.

Corticosteroid therapy and plasma exchange do not improve patient’s condition.

Prognosis is favourable.

4. CIDP associated with other disorders

Polyneuropathy associated with gammopathy (monoclonal proteins)

Serum monoclonal proteins can be detected, even if no symptoms are present. Monoclonal gammopathy of undetermined significance of various isotypes (IgM, IgG or IgA) affect 3% of the population older than 65 years. Gammopathies may be the primary and single manifestation of the pathological process. The presence of monoclonal immunoglobulin paraprotein (M-component) in blood may be primary detected or in relation to other concomitant diseases, such as neoplasm, slow viral infections, AIDS, syphilis, etc. Polyneuropathies affect 29-71% of patients with gammopathies. They have clinical, histological and neuro-physical differences. They may involve demyelination or axonal degeneration.

Etiology of polyneuropathies is associated with abnormal serum immunoglobulin. Polyneuropathies occur in primary (benign monoclonal gammopathy and cryoglobulinemia) and secondary gammopathies, especially in (solitary or multiple) myeloma, plasmocytoma and Waldenström macroglobulinaemia.

Pathogenesis of polyneuropathies is associated with immune-mediated peripheral nerve injury. There are probably several different mechanisms of impairment that cause predominant demyelination or axonal degeneration.

The clinical course of polyneuropathy may vary.

Benign monoclonal gammopathy (monoclonal gammopathy of undetermined significance /MGUS/) is common, an M-protein is found in 1.5% of the population older than 50 years and in 3% of the population older than 70 years. It most often affects men aged 60-70 years. The condition is defined as gammopathy of undetermined significance, as 25% of patients with MGUS develop myeloma over time. Some of the patients with IgM paraproteinemia develop Waldenström macroglobulinemia over time.

It is characterised by the presence of an abnormal spike in the β-γ region of serum protein electrophoresis, variably called paraprotein, monoclonal protein or M-protein (consisting of immunoglobulins of the same isotype), all produced by a single clone of abnormally proliferating lymphocyte and plasma cells. Immunoglobulins detected in relation to neuropathy are most often IgM (60%), IgG (30%) or IgA (10%). Kappa light chain component is detected in most of the patients. In some cases, only light immunoglobulins chain synthesised by plasma cells are detected in urine.

Multiple specific polyclonal and monoclonal antibodies to peripheral nerve myelin and its components have been detected (chondroitin sulfate, GM1 and GD1b - ganglioside, glycolipids and sulfatides). The most important antibody (in 75% of patients with IgM-related neuropathy) reacts with myelin-associated glycoprotein (MAG) and glycolipids (sulfatide components of myelin).

Pathoanatomical evidence of demyelination and remyelination.

Clinical course - chronic-progressive course. Most patients with anti-MAG neuropathy have distal symmetrical limb involvement with predominant sensory excitability (numbness) and sensory loss symptoms. They initially involve in the lower extremities and cause ataxic gait. Later, they also involve upper extremities and MAG-positive patients develop postural tremor. Motor fibres are less severely involved, and paretic symptoms and muscle hypotrophy are mild and develop later over time. Tendon reflexes are impaired in the late course of disease.

Only 3-5% of patients with ***multiple myeloma*** develop polyneuropathy.

Clinical presentation - mild sensory and motor or pure sensory neuropathy with subacute or chronic-remitting course.

Osteosclerotic myeloma, a form of multiple myeloma, has a very low incidence – 0.5-3% of patients. Polyneuropathy is often detected (50%) in patients with osteosclerotic myeloma.

Solitary or multiple osteosclerotic myeolma is often associated with chronic inflammatory demyelinating, predominantly motor polyneuropathy.

POEMS (polyneuropathy, osteosclerotic myeloma, organomegaly, endocrinopathy, M-protein and skin changes) syndrome in patients with osteosclerotic myeloma is associated with abnormal monoclonal globulin with lambda light chain. It is more common in Japan, and is also called Crow-Fukase syndrome. 50% of patients develop polyneuropathy.

Clinical presentation - moderate sensory and motor polyneuropathy. Skin changes include hypertrichosis (excessive hair growth), skin thickening and hyperpigmentation. Patients may also develop papilloedema, hepatosplenomegaly, oedema and hyperthyroidism. Lymphadenopathy due to angiofollicular hyperplasia is also often observed in patients with Castleman’s disease.

CSF analysis shows elevated protein levels in CSF. Immune electrophoresis detects IgG and IgA paraprotein.

Blood tests identify monoclonal, biclonal or multiclonal immunoglobulin peak and lambda light chain.

EMG shows demyelination, and in the late course of disease - axonal degeneration.

Bone marrow biopsy shows normal morphology of plasma cells which produce paraproteins; plasma cell count is sometimes mildly elevated.

Radiologic features of POEMS - osteosclerotic lesions in long bones, vertebrae, ribs, pelvis and skull.

Waldenström macroglobulinemia is caused by a monoclonal elevation of IgM fraction. It is a rare disease, accounting only for 2% of monoclonal gammopathies. Men aged 50-70 years are more commonly affected. 50% of patients have anti-MAG antibodies. It causes polyneuropathy in 5% of patients.

Clinical presentation - chronic polyneuropathy with asymmetrical onset. Over time, polyneuropathy becomes symmetrical, sensory and distal, predominantly affecting lower extremities. Patients develop sensory ataxia. No knee and Achilles reflexes.

Elevated CSF protein and globulin fraction. IgM monoclonal protein > 3 mg/L. In 80% of patients, monoclonal proteins are associated with kappa (κ) light chain.

EMG shows demyelinating sensory and motor impairment. Needle EMG shows fibrillations, positive sharp waves and reduced motor action potentials.

Cryoglobulinemia may be essential or secondary to multiple myeloma, lymphoma, connective tissue disease, chronic infection and hepatitis C. Cryoglobulin is a serum protein that precipitates on exposure to cold. It is IgM or IgG type and more often polyclonal. Cryoglobulins are circulating immune complexes, consisting of immunoglobulins directed against polyclonal immunoglobulins. They are three main types. Type I is the result of monoclonal immunoglobulins, usually IgM, directed against polyclonal IgG. Type I cryoglobulins are detected most often in patients with plasma cell dyscrasia. Type II cryoglobulins comprise a combination of monoclonal IgM and polyclonal immunoglobulins directed against polyclonal IgG. Type III cryoglobulins are a mixture of polyclonal IgM, IgG and IgA, directed against polyclonal IgG. Types II and III are referred to as mixed cryoglobulinemias. Mixed cryoglobulinemias may also be associated with other conditions, such as lymphoproliferative disorders, connective tissue disorders, hepatitis B and C. Polyneuropathy is developed by 25-90% of patients with primary and symptomatic form of disease.

Pathogenesis is associated with paraprotein which plays the role of antineural

antibody. Its intravascular deposition in epineural vessels may possible cause peripheral nerve injury.

Clinical presentation - chronic, distal, symmetrical, sensor and motor polyneuropathy. In more rare cases, it may show typical symptoms of multiple mononeuropathy. Initially, symptoms include only pain and paresthesia on exposure to cold. Gradually patients develop muscle weakness and hypotrophy in the lower extremeties, later affecting also the upper extremities. Patients may develop Raynaud phenomenon and purple skin rash on extremities.

Cryoglobulins are detected in blood.

EMG shows axonal degeneration. Sensory fibres are impaired, predominantly in the lower extremities. Needle EMG shows fibrillations, positive sharp waves and reduced motor action potentials in the distal muscle groups.

Non-familial primary amyloid polyneuropathy is not associated with other diseases. In some cases, it may trigger multiple myeloma. Secondary amyloidosis is induced by chronic inflammatory or noninflammatory disease. It is induced by monoclonal (rarely polyclonal) protein in blood. Macrophages release enzymes that break down large immunoglobulin molecules, and their light chains aggregate and form amyloid deposits in tissues and peripheral nerves. Plasma cells can also produce light chains directly. Lambda light chains are predominant in idiopathic amyloidosis, and kappa light chains - in myeloma.

Clinical symptoms are manifested in patients aged around 65 years with pain and paresthesia, symmetrical hypesthesia to pain and temperature, autonomic disorders due to involvement of small peripheral nerve fibres. Over time patients develop muscle weakness in the lower extremities, which may also affect upper extremities. Large nerve fibres may also be affected causing deep sensory loss. 25% of patients develop carpal tunnel syndrome. The condition is characterised by autonomic disorders - gastrointestinal, bladder, pupillary, etc. Disease progression is fast and survival is 2 years.

CSF analysis shows normal results or mild elevation in protein levels. Paraprotein is detectable in serum and urine.

EMG shows predominantly sensory fibre involvement in the lower extremities. Needle EGM shows positive sharp waves and muscle fibrillations, predominantly in the lower extremities.

Diagnosis is confirmed by biopsy of the sural nerve and amyloid detection.

Differential diagnosis includes familial form of disease, paraneoplastic or

other polyneuropathy with small-fibre involvement.

Treatment of patients with IgA, IgG and IgM (MAG-negative) gammopathy of undetermined significance and neuropathy includes corticosteroid therapy (the same as in CIDP). Plasma exchange and intravenous immunoglobulin therapy are not effective.

Patients with IgM (MAG-positive) gammopathy and neuropathy are treated with cyclophosphamide 0.1-0.2 mg/kg/day for 4 weeks. Another treatment option is chlorambucil (300 mg/m^2 q.i.d.) for 4 weeks.

Treatment of patients with POEMS is prescribed after consultation with a hematologist (radiotherapy, dehydrocortison in combination with melphalan or cyclophosphamide).

Treatment of macroglobulinemic polyneuropathy includes prednisone, chlorambucil, cyclophosphamide and repeated plasma exchange.

Immunosuppressive therapy is not effective in non-familial primary amyloid polyneuropathy. Symptomatic management of pain.

5. Idiopathic sensory and autonomic neuropathies

5.1. Idiopathic sensory neuropathies (gangliopathies)

Epidemiology. Approximately 100 cases have been described worldwide. Women are affected a bit more often. Disease onset around the age of 40.

Disease etiology is unknown. Some patients experienced flu-like symptoms or diarrhoea before disease onset.

Pathogenesis. Disease is induced by autoimmune attack against dorsal root ganglia. CD8+ T-cell mediated cytotoxic attack against spinal ganglion neurons. The target antigen is probably ganglioside GD1b localised in the dorsal root ganglion neurons.

Histopathological evidence of reduction in small- and large-myelin fibres. Wallerian degeneration and reduced neuron number are detected in spinal ganglia.

Clinical presentation - the disease may have very rapid (hours) or slow (months, years) progression. The course of disease may be monophasic, remitting, chronic-progressive or chronic-remitting. Disease onset is asymmetrical hypesthesia of the face, body, upper or lower extremities. Over time patients develop hypesthesia with pain. Hypesthesia may remain asymmetrical, or may later become symmetrical. It predominantly involves large fibres and results in unstable gait and clumsy hands. Vibration sense and position sense are impaired. Temperature and pain sense are less

impaired. Changes affect predominantly the upper that the lower extremities. Muscle strength is retained, but impaired proprioception causes clumsiness. Patients develop pseudoathetosis of upper limbs, dysmetria, positive Romberg's sign and difficulty walking in the dark. Tendon reflexes are decreased or absent.

Tests and examinations. *CSF analysis* shows normal results or mild elevation in protein levels. Some patients have IgM, IgG or IgA monoclonal gammopathy. Anti-ganglioside antibodies (anti-GF1b) are detectable in some patients with IgM monoclonal gammopathy. Anti-neuronal nuclear (anti-Hu and anti-Purkinje cell) antibodies should be examined to rule out paraneoplastic syndrome. Anti- SS-A and SS-B antibodies should be examined to rule out Sjögren syndrome.

Neurographic evidence of low amplitude or absent sensory nerve action potentials (SNAP). Distal sensory and motor latencies are normal or slightly prolonged. CMAP amplitudes are mildly reduced (<20%). The conduction velocity of peripheral motor nerves are normal or slightly reduced. H-reflexes are absent. Needle EMG shows normal results.

Differential diagnosis includes paraneoplastic polynephropathy with anti-Hu antibodies and sensory ganglionitis with underlying Sjogren syndrome. The diagnosis is established by ruling out toxic and paraneoplastic polyneuropathy, connective tissues diseases (Sjögren syndrome) and Epstein-Barr virus infection.

Treatment may include corticosteroids, plasma exchange or immunoglobulin. Treatment efficacy is not high and regeneration is not possible in case of permanent impairment of sensory neurons.

5.2. Idiopathic autonomic neuropathies

Described by Young, et. al. Later a few more cases have been described.

Pathogenesis is associated with autoimmune attack directed against peripheral autonomic fibres or ganglia. In some cases, antibodies are directed against calcium channels in presynaptic autonomic nerve terminals.

Pathohistological evidence of reduction in small myelinated nerve fibres.

Clinical course - heterogeity with regard to disease onset, type of automic deficiency, presence or absence of somatic involvement and degree of recovery. Idiopathic autonomic neuropathies may involve autonomic deficiency and presence or absence of somatic nerve fibre involvement. Selective cholinergic dysfunction is identified in 20% of patients, whereas the rest of the patients have various degree of diffuse sympathetic and parasympathetic dysfunction. Most patients (80%) experience

orthostatic dizziness. Gastrointestinal symptoms (nausea, vomiting, diarrhoea, ileus or postprandial bloating) are the second most common symptoms (70%). Most patients have impaired thermoregulation with heat intolerance and abnormal sweating. Patients often have blurred vision, dry eyes, dry mouth, urinary retention or incontinence, sexual dysfunction. 30% of patients experience tingling, impaired sensory function and dysesthesia in the upper and lower extremities. Muscle strength is retained.

The course of disease is monophasic, progression followed by plateau phase and slow recovery. Most patients achieve full recovery.

Tests and examinations. *CSF analysis* shows mild elevation in protein levels and no pleocytosis.

Autonomic nervous system tests show orthostatic hypotension and reduced heart rate variability during deep inspiration breath-holds, in 60% of patients. 40% of patients have abnormal response to Valsalva manoeuvre – larger blood pressure drop during the early secondary response phase, lack of recovery in systolic and diastolic blood pressure in the late secondary phase, or reduction or no increase in systolic and diastolic blood pressure during Phase IV. 85% of patients have abnormal score calculated by using the Quantitative Sudomotor Axon Reflex Test (QSART). Most patients have abnormal results from thermoregulatory sweat test, with areas of anhidrosis in 12–97% of the body. Patients have gastroesophageal hypermobility everywhere from the esophagus to the rectum.

EMG and neurographic evidence show normal results. Sympathetic skin response may be absent.

Symptomatic management of orthostatic hypotension, gastrointestinal and bladder disorders. Fludrocortisone administered in the morning and at noon manages plasma volume. The initial dose of 0.1 mg/day is increased by 0.1 mg every 3-4 days. Gastrointestinal hypomobility is managed with metoclopramide. Laxatives are used in patients with constipation. Bladder disorders are managed by urologist by using urinary catheter or cholinergic agonists.

Immune-modulating therapy with corticosteroids, plasma exchange or immunoglobulins does not achieve significant effect.

6. Polyneuropathy in primary or secondary vasculitis

Peripheral nerves are often damaged in some types of vasculitis and connective tissue disorders.

They are classified based on the size of damaged blood vessels (small, medium and large sized). Another classification criteria is based on whether they are systemic or isolated in the peripheral nervous system. The third classification criteria is based on whether vasculitis is primary (polyarteritis nodosa, Churg-Strauss disease, Wegener granulomatosis, cryoglobulinemia) or secondary to other systemic diseases (connective tissue disorders, infections, adverse drug reactions, malignancies).

Histopathology. Vasculitis is a chronic condition characterised by transmural inflammatory-cell infiltration and necrosis of the vessel wall. Immunohistological tests show immunoglobulin deposition (IgM and/or IgG) and complement in blood vessels. Patients experience asymmetrical nerve fibre loss and active Wallerian degeneration, if vasculitis caused nerve infarction. Inflammation is unspecific symptom and is not always associated with vasculitis. Necrotising vasculitis is developed as a result of ischaemia of tissues supplied by the damaged vessels.

Clinical presentation - vasculitis has a few common symptoms with certain variations depending on the type of damaged vessels. Each specific disease has its own typical systemic symptoms, however peripheral nervous system symptoms are the same.

There are three patterns of involvement of the peripheral nervous system: The first pattern is a multiple mononeuropathy involving several nerves which causes asymmetrical symptoms. The second pattern is overlapping multiple mononeuropathy where individual nerves are bilaterally involved to a different extent, and various muscle groups are affected. This causes generalised asymmetrical involvement. Over time, involvement may become more symmetrical with the so called ’stocking-glove’ distribution of symptoms as typical for most distal symmetrical polyneuropathies. These two types of multiple mononeuropathy are seen in 60–70% of patients, and distal symmetrical polyneuropathy – in 30–40%.

The most common symptom is burning dysesthesia pain along the anatomical innervation of affected nerves. Motor and sensory nerve fibres are affected causing motor and sensory impairment. In case of distal symmetrical involvement, sensory and motor impairment has stocking-glove distribution.

Tests and examinations. Peripheral nerve *biopsy* to study histopathological findings. *Ultrasound diagnostic imaging* can be used to detect the localisation and severity of vasculitis, and structural changes of the peripheral nerve and muscle architecture.

Neurography shows asymmetrical reduction in SNAP amplitude or loss of

SNAP. The same changes are also observed in CMAP. Distal motor latencies are normal or slightly prolonged. Motor conduction velocity is normal. Some patients may have conduction block. Needle EGM shows positive sharp waves and fibrillations in muscles innervated by the affected nerves. Over time, the duration and amplitude of motor unit action potentials may increase.

Treatment of systemic vasculitis - combination therapy with corticosteroids and cyclophosphamide. Hypersensitivity vasculitis and isolated vasculitis should be treated only with corticosteroids.

Methylprednisolone is administered intravenously at initial dose of 1 g for 3 days, followed by oral prednisone 1.5 mg/kg/day (maximum daily dose: 100 mg/day) administered as a single dose in the morning. After 2–4 weeks, treatment should be continued with 100 mg on alternate days. Concurrent treatment with supplemented calcium, vitamin D and bisphosphonates is recommended for osteoporosis prevention.

Oral or intravenous *cyclophosphamide* is initiated along with the corticosteroid therapy. Oral cyclophosphamide at a dose of 1.0–2.0 mg/kg achieves more effective immune suppression, but is associated with higher rate of adverse reactions (haemorrhagic cystitis). Intravenous pulse cyclophosphamide is administered as a single dose of 500–1000 mg/m^2 body area once monthly. Sodium 2-mercaptoethane sulfonate (mesna) is added to reduce bladder toxicity and ondansetron is added to reduce nausea. Patients should be well hydrated to reduce bladder toxicity. Maximum reduction in WBC levels is observed 7-18 days after intravenous administration. The risk of infection is highest during that period.

Therapy should be continued until achieving improved or stable condition; treatment duration is usually 4-6 months. Then prednisone dose is gradually reduced by 5 mg every 2-3 weeks. Pulse cyclophosphamide therapy should continue at least 1 year. In case that the intravenous cyclophosphamide therapy is not effective, patients should be switched to oral therapy. Patients with Churg-Strauss syndrome need more continuous prednisone therapy due to the presence of asthma. New episodes may appear in 50% of patients with Wegener granulomatosis. These patients may need life-long immunosuppressive therapy.

In patients refractory to therapy, treatment with methotrexate (0.15–0.3 mg/kg/week) in combination with corticosteroids, azathioprine, cyclosporine, tacrolimus or chlorambucil, can be attempted.

In patients with hepatitis B or C, standard therapy with high-dose corticosteroids and cyclophosphamide causes virus replication and persistence, and is

associated with high risk of hepatic impairment. Corticosteroids should be used only in the first weeks to manage life-threatening symptoms of systemic vasculitis. Afterwards, corticosteroid therapy should be discontinued. Patients undergo plasma exchange and receive antiviral therapy with vidarabine or α-interferon (3 million units 3 times a week).

6.1. Primary systemic vasculitis affecting medium and large-sized blood vessels

There are two forms of **giant-cell vasculitis** – temporal and Takayasu's arteritis. Peripheral neuropathy is developed only in temporal arteritis. It affects medium and large-sized arteries, especially aortic arch and its branches.

Clinical presentation - patients have headache, myalgia and lower jaw clicking. 8-23% of patients have ischaemic optic neuropathy with secondary vision loss. Ischaemic strokes are another important complication. In 14% of cases, peripheral nervous system is affected as a result of multiple mononeuropathy, radiculopathy, plexopathy or generalised sensory and motor neuropathies. Temporal artery tenderness and thickening are detected on palpation.

Tests and examinations. Elevated erythrocyte sedimentation rate (ESR) is observed in all patients.

Temporal artery biopsy shows negative results in 30% of patients. Inflammatory infiltration with giant-cells in vessels are detected in the rest of the patients.

Treatment with corticosteroids (prednisone) or cyclophosphamide is effective. Plasma exchange is used in case of cryoglobulinemia.

6.2. Primary systemic vasculitis affecting small and medium-sized blood vessels

Polyarteritis nodosa is the most common type of necrotsing vasculitis. The disease is systemic and predominantly affects medium sized compared to small sized arteries in multiple organs. 70% of patients develop polyneuropathy - most often multiple mononeuropathy. Most often the disease affects the sciatic nerve and its branches - the peroneal and tibial nerves. Cranial neuropathies and nervous system involvement are rare (less than 2% of patients).

Incidence of polyarteritis nodosa is 2 to 9 per 1,000,000.

Pathogenesis is unknown. It probably involves endothelial cell-mediated T-

cell process. Complement-mediated vessel damage plays a secondary role.

Clinical presentation - affects patients aged between 40 and 60 years, with symptoms of fever, loss of appetite and weight loss. Patients develop multisystem dysfunction involving kidneys, liver, muscles, skin and gastrointestinal tract. Myalgia and arthralgia are common symptoms (up to 70%). Skin changes (25-60% of patients) include petechiae, papules, subcutaneous nodules, livedo reticularis and distal gangrene. Gastrointestinal vasculitis are characterised by symptoms of abdominal pain and bleeding. Renal ischaemia causes renal failure. Orchitis is a typical symptom. Patients may develop Raynaud phenomenon or rarely mixed polyclonal cryoglobulinemia.

Tests and examinations. Elevated ESR > 60 mm/h Elevated rheumatoid factor, C-reactive protein and α_2 globulin levels. Leucocytosis and normochromic anemia. Hepatitis B antigenemia is detected in 30% of patients. Some patients may have hepatitis B or HIV infection. Abdominal angiography may detect vasculitic aneurysm.

Biopsy - infiltrates are predominantly comprised of CD8+ T-cells and macrophages. Polymorphonuclear cells associated with fibrinoid necrosis. Immunohistological tests show IgM, IgG and complement deposition in blood vessels. In contrast to Churg-Strauss syndrome, there are no granuloma or eosinophilic infiltration.

Churg-Strauss syndrome (allergic angiitis/granulomatosis) is a rare disease.

Incidence - 30% less prevalent compared with polyarteritis nodosa, but affects the peripheral and central nervous system as often as in polyarteritis nodosa.

Clinical presentation - patients have respiratory disorders, in contrast to polyarteritis nodosa. Patients develop allergic rhinitis, nasal polyposis and sinusitis, followed by asthma. Asthma develops at older age as compared to idiopathic asthma. 50% of patients have pulmonary infiltrates due to asthma and hypereosinophilia. The first symptoms of systemic vasculitis occur averagely 3 years after asthma onset. 16-49% of patients develop necrotising glomerulonephritis, in contrast to patients with ischaemic nephropathy and polyarteritis nodosa. Polyarteritis nodosa and Churg-Strauss syndrome have the same symptoms, with the exception only of pulmonary and renal symptoms. 75% of patients develop multiple mononeuritis.

Tests and examinations. Patients have eosinophilia (often > 10^9/L), leukocytosis, elevated ESR, C-reactive protein, rheumatoid factor, and serum IgG and IgE levels. Antineutrophil cytoplasmic antibodies (ANCA) and primary myeloperoxidase (p-ANCA) are detected. The combination of eosinophilia and

asthma is a pathognomonic sign of Churg-Strauss syndrome.

Biopsy shows evidence of necrotising vasculitis of small and medium-sized arteries and veins. Inflammatory infiltrates contain CD8+ cytotoxic T-cells and CD4+ helper T-cells, as well as not so many eosinophils.

Wegener granulomatosis is a rare disease with necrotising granulomatous infiltrations and lesions in the upper and lower respiratory tract, glomerulonephritis and antineutrophil cytoplasmic antibodies. It affects medium and small-sized blood vessels.

Clinical presentation - early respiratory symptoms include nasal discharge, cough, hemoptoe and dyspnea. Patients also develop facial pain. 30-50% of patients have nervous system involvement, but only 15-20% have multiple mononeuropathy or symmetrical polyneuropathy. The presence of neuropathy correlates with renal impairment severity. Cranial neuropathy is observed in 10% of patients as a result of nasal and paranasal granulomas (the 2nd, 6th and 7th cranial nerves).

Tests and examinations. Proteinase 3 specific antineutrophil cytoplasmic antibodies (c-ANCA) are detected. Biopsy shows absence of eosinophilia or eosinophil infiltrates.

Microscopic polyangiitis affects small arterioles, venules and capillaries. In contrast to polyarteritis nodosa, immune deposits are not detected in blood vessels.

This is a rare condition and affects only 30% of patients with polyarteritis nodosa.

Clinical presentation - average onset at the age of 50 years. The course of disease is similar to polyarteritis nodosa, but often affects lungs. The inflammation of pulmonary capillaries causes alveolar damage and interstitial fibrosis. 14-36% of patients develop polyneuropathy. Renal function is affected in most of the cases (haematuria, elevated urea and creatinine levels). Biopsy shows focal segmental thrombosis and necrotising glomerulonephritis.

Tests and examinations. p-ANCA and more rarely c-ANCA antibodies are detected.

Behcet's disease is of unknown etiology.

Men are more often affected.

Clinical presentation - characterised by recurrent oral and genital ulcers associated with eye inflammation. Other symptoms include arthritis, thrombophlebitis, skin lesions and vasculitis of medium and small-sized arteries. CNS is involved more rarely than the peripheral nervous system with brain-stem

stroke, meningoencephalitis and psychosis. Patients develop multiple mononeuropathy or sensory and motor generalised polyneuropathy.

6.3. Secondary systemic vasculitis

Vasculitis associated with connective tissue disorders is most often affects patients with rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome or systemic sclerosis. Neuropathies are common complications. Neuropathy is a common complication of connective tissue disorders, but they are rarely induced by vasculitis.

Clinical, histological and neuro-physical manifestations are similar to those observed in periarteritis nodosa.

Infectious vasculitis with peripheral nervous system involvement may be induced by a viral infection, such as herpes varicella zoster, cytomegalovirus (CMV), HIV, hepatitis B and C. Multiple mononeuropathy in HIV or CMV infection occurs in 3% of patients with AIDS. Hepatitis B and C may induce polyarteritis nodosa or vasculitis in small blood vessels associated with cryoglobulinemia. Lyme disease caused by the spirochete Borrelia burgdorferi is also associated with various vasculitis-induced neuropathies.

Vasculitis associated with malignancies with peripheral nervous system involvement is caused by small-cell lung carcinoma or lymphoma, and more rarely by renal, bile duct, prostate or stomach cancer. Vasculitic neuropathies are rare.

Pathogenesis - in most cases the pathogenesis is not associated with necrotising vasculitis, but rather with transmural and perivascular inflammation of small blood vessels, without necrosis. Complications of small-cell lung cancer may be due to anti-Hu antibodies.

Clinical presentation - the impairment of the peripheral nervous system may involve symptoms of symmetrical or asymmetrical sensory impairment, dysesthesia and motor weakness. Complications in lymphomas may include paraneoplastic non-vasculitic neuropathy, or lymphomatous infiltration of peripheral nerves may induce multiple mononeuropathy or generalised neuropathy.

Drug-induced hypersensitivity vasculitis is a self-limiting disease.

Pathogenesis is associated with complement-mediated leukocytoclastic reaction.

Clinical presentation - predominant skin manifestations. It affects the CNS more often in patients who use amphetamines, cocaine or opioids. The peripheral

nervous system is more rarely affected.

Treatment - corticosteroid therapy.

Vasculitis associated with essential mixed cryoglobulinemia. This type of cryoglobulinemia is diagnosed in case of absence of other systemic disease, different from viral hepatitis. Most cases are associated with hepatitis C antigenemia.

Incidence of polyneuropathies in various types of cryoglobulinemia ranges from 25% to 90%.

Pathogenesis is associated with ischaemia due to hyperviscosity or vasculitis associated with immune complex deposition in small epineural blood vessels.

Clinical presentation - the course of disease is similar to painful distal symmetrical polyneuropathy and more rarely to multiple mononeuropathy.

Tests and examinations. Neurography shows reduction in SNAP and CMAP amplitude or loss of SNAP and CMAP, predominantly in the lower extremities. Needle EMG shows positive sharp waves, fibrillations and reduction in motor unit action potentials, predominantly in distal muscle groups.

6.4. Nonsystemic vasculitis

Nonsystemic or isolated vasculitis of the peripheral nervous system causes 30-58% of vasculitic neuropathies.

The etiology of this type of selective vasculitis is unknow.

Pathogenesis is associated with involvement of medium and small-sized arteries in the epineurium and the perineurium where immune complexes are deposited. T-cells are the main source of matrix metalloproteinases (MMP) MMP-2 and MMP-9, and the stroma of endoneurium and perineurium is an additional source. MMP-2 and MMP-9 metalloproteinases (A and B gelatinases) belong to the family of endopeptidases and have affinity to various extracellular matrix proteins. Their levels in the peripheral nerves are elevated in patients with nonsystemic vasculitis. MMP can degrade subendothelial basement membrane components, allowing inflammatory cells to to break down the blood-nerve barrier and invade peripheral nerves.

Clinical presentation - the course of disease is similar to neuropathy in polyarteritis nodosa, without internal organ involvement. It may involve multiple mononeuropathy or distal symmetrical polyneuropathy.

Tests and examinations. Patients have elevated ESR and low ANA titres.

Treatment with corticosteroids or cyclophosphamide is effective.

Prognosis is more favourable than in systemic vasculitis.

7. Neuropathy associated with autoimmune connective tissue disorders

Sjögren syndrome is characterised by the sicca complex - a combination of xerophthalmia (dry eye), xerostomia (dry mouth) and dryness of other mucous membranes.

Epidemiology. Women are affected much more often. It usually develops in middle-aged adults.

Pathohistological evidence of axonal degeneration in peripheral nerves and secondary segmental demyelination in patients with sensory and motor polyneuropathy. Nonspecific perivascular inflammation of perineural and endoneural blood vessels is often detected. Necrotising vasculitis is detected more rarely. Reduced number of large myelinated fibres is observed in patients with sensory neuropathy. Patients may have perivascular lymphocytic inflammation (CD8 T-cells) of perineural and endoneural blood vessels. Lymphocytic (predominantly CD8 T-cells) infiltration is detected in dorsal root ganglia.

Disease etiology and specific triggers are unknown.

Pathogenesis - autoimmune pathogenesis, but antigens are unknown. Sensory neuropathy is due to autoimmune attack directed against sensory ganglia. Some cases (30%) are induced by necrotising vasculitis.

Clinical presentation - may include symptoms of CNS involvement, similar to those observed in transverse myelitis or multiple sclerosis.

Neuropathy occurs in 10–50% of patients and may be the first symptom of the disease. In most cases, patients develop axonal sensory and motor neuropathy with sensory impairment and tingling in distal ends of extremities. Patients may have symptoms of burning and paresthesia. Muscle weakness is mild or absent. Autonomic neuropathy is rare.

Some patients develop sensory neuropathy (ganglionitis). Disease onset may be acute or gradual with progressive tingling and sensory impairment in extremities and sometimes affective the face. Hands are affected more often than lower extremities, and symptoms are asymmetrical, and may even be unilateral. Reduction in all sensory modalities, especially vibration sense and position sense. Patients may develop sensory ataxia or pseudoataxia. Patients with lower limb involvement have positive Romberg’s sign. Some patients may have reduced sensory function in the area innervated by the trigeminal nerve. Symptoms of autonomic failure with Adie’s pupil, anhidrosis, tachycardia and orthostatic hypotension are common. Tendon

reflexes are decreased or absent. Muscle strength is preserved, but sensory impairment may cause clumsiness.

Tests and examinations. SS-A/Ro and SS-B/La antibodies are often detected in serum. No CSF abnormalities.

Biopsy confirms diagnosis if it detects lymphocyte invasion in salivary glands or lips.

Neurography in patients with distal sensory and motor neuropathy shows reduction in SNAP amplitude and in the conduction velocity of sensory fibres. Needle EMG shows fibrillations, positive sharp waves, increased duration or amplitude of motor unit action potentials.

Reduction in SNAP amplitude or loss of SNAP in the lower extremities is detected in patients with sensory neuropathy. Upper extremities are more severely affected, and asymmetrical involvement is also possible. Motor fibres are not affected.

Treatment includes immunosupressive therapy but its effect is not sufficient.

Rheumatoid arthritis affects 1% of the population and 50% of patients develop polyneuropathy. Vasculitis affects 8-25% of patients, thus rheumatoid arthritis is the third most common cause of vasculitic neuropathies, preceded by polyarteritis nodosa and isolated vasculitis of the peripheral nervous system.

Clinical presentation - vasculitic neuropathy manifests 10–15 years after the onset of the rest of disease symptoms. It is rarely the first symptom of disease. It may be manifested as multiple or overlapping multiple mononeuropathy or generalised symmetrical polyneuropathy.

Laboratory tests detect antinuclear antibodies (ANA), elevated ESR and elevated serum rheumatoid factor.

Neurography shows changes similar to those observed in other forms of necrotising vasculitis. 75% of patients with rheumatoid arthritis have mild sensory neuropathy, with no evidence of necrotising vasculitis.

Biopsy shows thickening of epineural and endoneural blood vessels and perivascular inflammation in patients with no evidence of necrotising vasculitis.

Systemic lupus erythematosus (SLE) is a common connective tissue disorder.

Incidence - 1 case per 2,000 adults.

Pathogenesis - autoimmune. Mononuclear inflammatory infiltrates and increased expression of Class II antigens are detected in nerve fascicles and

endothelial cells.

Clinical presentation - affects multiple organs and systems. It affects the CNS more often, but may also affect the peripheral nervous system. Neuropathy is observed in 2-27% of patients. It most often involves slowly progressive distal sensory impairment. Patients often have mild autonomic neuropathy. Some patients may develop secondary multiple mononeuropathy due to necrotising vasculitis. Over time and with disease progression, multiple mononeuropathies may overlap and resemble symmetrical neuropathy. Generalised sensory and motor polyneuropathy similar to AIDP or CIDP is more rarely observed.

Tests and examinations. Neurography shows generalised, predominantly sensory axonopathy with low amplitude or absent SNAP. Mild reduction in CMAP amplitude and mild reduction in motor conduction velocity may also be observed. In patients with necrotising vasculitis. EMG shows typical evidence related to this type of mononeuropathy. Neurography shows signs of demyelination in patients with generalised sensory and motor polyneuropathy.

Treatment includes immunosuppressive therapy. Treatment is effective in patients with vaculitis-induced neuropathy, and less effective in patients with generalised sensory or sensory and motor polyneuropathy with no evidence of vasculitis. Patients with polyneuropathy that resembles AIDP should undergo the same treatment as used in AIDP.

Systemic sclerosis (scleroderma) involves progressive fibrosis affecting skin, gastrointestinal tract, kidneys and lungs.

5-14% of patients develop neuropathy.

Pathogenesis of neuropathy is unknown, and vasculitic genesis is extremely rare.

Clinical presentation - the course of disease is similar to distal, symmetrical, predominantly sensory polyneuropathy. The course of disease may also resemble cranial mononeuropathy. It most often affects the trigeminal nerve with sensory impairment, dysesthesias, electric shock-like pain or pinprick pain in the face. The 2nd and 9th cranial nerves are more rarely affected.

CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) is a limited form of scleroderma. 1–2% of patients have multiple mononeuropathies. Clinical, EMG and histological manifestations show evidence of necrotising vasculitis which causes neuropathy.

Mixed connective tissue disease (MCTD) is a syndrome involving SLE,

scleroderma and polymyositis. This type of neuropathy has not been studied in detail. 10% of patients have mild distal axonal sensory and motor polyneuropathy.

8. Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease that affects the liver, spleen, mucous membranes, parotid gland, muscle tissue, CNS and the peripheral nervous system.

Women are more often affected.

Histopathology. Noncaseating granulomas in various tissues are the main finding. In case of peripheral nerve involvement, biopsy of the affected nerve shows profuse infiltration with multiple sarcoid tubercles which affect all supporting nerve structures (endoneurium, perineurium and epineurium) and are associated with lymphocytic angiitis. Both axonal loss and demyelination are detected.

Disease etiology is unknown.

Pathogenesis - sarcoidosis is autoimmune disease but its pathological mechanism is not very clear. Neuropathy may be caused by direct compression, ischaemia, or by both, or may be due other unknown factors. Cranial nerve involvement and peripheral nerve mononeuropathies are probably due to direct invasion and nerve compression. Neuropathies that resemble AIDP or CIDP are caused by diffuse infiltration of the nerve and the nerve root or by immunological disorders associated with sarcoidosis.

Clinical presentation - individual course of disease that ranges from incidental detection of hilar adenopathy on chest x-ray to severe functional impairment and death. Most patients have unspecific symptoms, such as fever, weight loss, fatigue. Prior erythematous subcutaneous nodules in the pretibial region, accompanied by arthralgia. Palpable peripheral lymph nodes. Disease often begins with acute granulomatous uveitis that can progress to serious vision impairment and blindness. Mucosal lesions are often found in the nose and sinuses.

The peripheral nervous system (PNS) and CNS are affected in 5% of patients. In case of CNS involvement, the meninges, hypothalamus and hypophysis are affected most often. In case of PNS involvement, the cranial and peripheral nerves are affected most often, especially the spinal root region. The disease is often manifested as relapsing remitting multiple mononeuropathy of the cranial nerves. It may affect any cranial nerve. The 7th cranial nerve is affected most often, sometimes bilaterally. The 2nd and 11th cranial nerves are often affected.

In some patients, the clinical presentation resembles radiculopathy of one or more nerve roots. In case of generalised root involvement, symptoms resemble AIDP or CIDP. PNS is most often affected in the form of asymptomatic multiple mononeuropathy which can be detected by neurography. More rarely, the clinical presentation is in the form of slowly progressive primary sensory, motor, or sensory and motor neuropathy.

Tests and examinations. In patients with asymptomatic neuropathy, neurography shows reduction in SNAP amplitude or loss of SNAP in affected nerves. CMAP and motor conduction velocity are normal. EMG shows normal findings.

Reduction in SNAP amplitude or loss of SNAP is observed in patients with symmetrical sensory and motor neuropathy. Sensory conduction velocity is reduced by 20%. More significant reduction in conduction velocity is observed in patients with axonal degeneration and demyelination. Motor conduction velocity in the lower extremities is reduced by 20%. Patients have reduction in CMAP amplitude or loss of CMAP in lower extremities and normal CMAP in the upper extremities. Patients with polyradiculopathy have normal SNAP and abnormal CMAP. Needle EMG in patients with long-term disease and symptomatic sensory and motor neuropathy or polyradiculopathy shows axonal loss. Positive sharp waves and fibrillations and detected. The duration, amplitude and number of motor unit action potentials is increased.

Treatment - neurosarcoidosis with cranial nerve involvement is well managed with corticosteroid therapy. Patients refractory to therapy should receive immunosuppressive therapy (cyclosporine). Treatment discontinuation leads to recurrence.

9. Idiopathic perineuritis

Perineuritis is a nonspecific histological abnormality characterised by inflammation and thickening of the perineurium. It can be detected by nerve biopsy in patients with diabetes mellitus-induced neuropathy, connective tissue disorders, ulcerative colitis, vasculitis (including cryoglobulinemia), lymphoma and other malignancies. It is also observed in patients with AIDP or CIDP. It is not associated with a certain type of neuropathy. Idiopathic perineuritis is the main histological finding in patients without systemic disease.

Pathohistological evidence of inflammation and thickening of the perineurium. Chronic inflammatory cell infiltrates in the perineurium contain

lymphocytes and macrophages. Patients may have mild perivascular inflammation and loss of myelinated fibres due to axonal degenerations. Perineuritis, thickened perineurium and nerve fibre loss may by asymmetrical in separate bundles of nerve fibre which is indicative of ischaemic impairment.

Pathogenesis - probably autoimmune. It is still discussed whether perineuritis is a separate disease. Perineuritis can cause peripheral nerve injury due to ischaemia, impaired metabolism and toxin release from nerve fibres back and forth to the endoneurium, direct humoral or cell-mediated autoimmune attack directed against nerve fibres.

Clinical presentation - variable. Patients with perineuritis associated with diabetes or vasculities develop multiple mononeuropathy with sensory impairment, dysesthesias, hyperpathia and muscle weakness in the area innervated by multiple affected peripheral nerves. Some patients develop chronic progressive symmetrical motor and sensory loss which cannot be differentiated from AIDP or CIDP. Another group of patients with idiopathic perineuritis may have different clinical presentation with migrating areas of sensory loss, hypesthesia, hyperpathia, dysesthesia and pain caused by nerve trunk extension. Affected nerves show positive Tinel's sign. Small sensory fibres are more strongly affected than large ones. Tendon reflexes and muscle strength are preserved.

The course of disease is relapsing remitting.

Tests and examinations. Laboratory tests, including ANA, ESR, liver tests, serum protein electrophoresis and vasculitis tests show normal results. CSF protein is normal in patients with sensory neuropathy. Abnormal laboratory parameters are indicative of systemic disease, such as vasculitis. Elevated CSF protein is detected in patients whose disease resembles AIDP and in patients with diabetes-induced multiple mononeuropathy or lumbosacral polyradiculoplexopathy.

Neurographic evidence of reduction in SNAP amplitude or loss of SNAP. Needle EMG findings and motor conduction velocity are normal, except in patients with multiple mononeuropathy or radiculoplexopathy with sensory and motor impairment.

Treatment includes immunotherapy. Patients with true vasculitis or AIDP should receive immunosuppressive therapy, intravenous immunoglobulin or plasma exchange. Prednisone manages pain in patients with idiopathic sensory neuropathy.

10. Hypereosinophilic syndrome

Hypereosinophilic syndrome is characterised by eosinophilia with various skin, cardiac, hematologic and neurological abnormalities.

Pathogenesis - probably autoimmune, but no vasculitic component, except with regard to skin changes. The impaired function of multiple organs is associated with eosinophilia and several eosinophil breakdown products.

Clinical presentation 6–14% of patients develop neuropathy. It manifests as generalised polyneuropathy or multiple mononeuropathy. Some patients develop inflammatory myopathy.

Neurographic changes typical of axonal sensory and motor neuropathy.

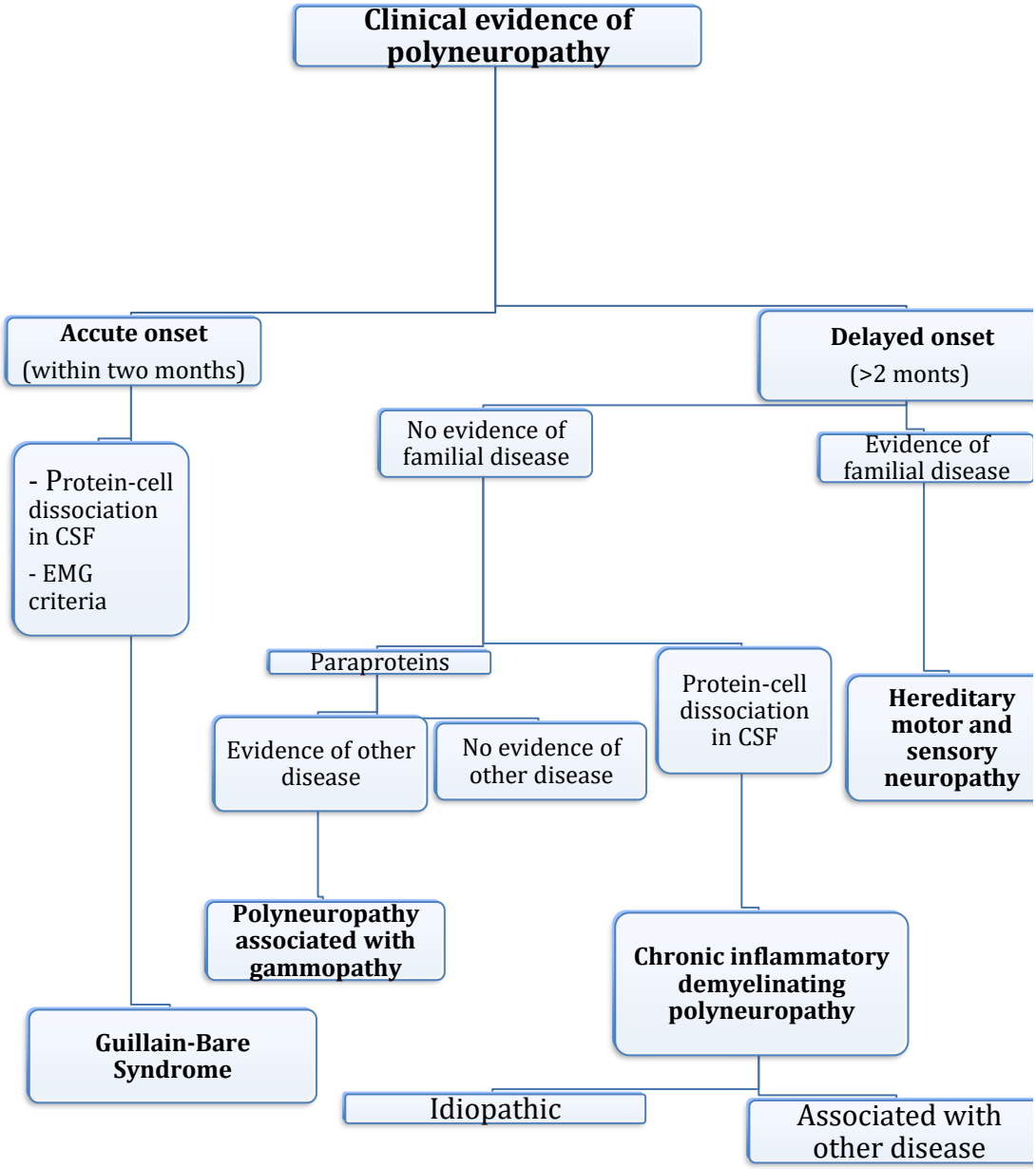
11. Isaacs Syndrome

Also known as neuromyotonia or continuous muscle fibre activity. It is sporadic in most cases, and more rarely hereditary.

Etiology - paraneoplastic etiology in patients with malignancy. Autoantibodies against voltage-dependant calcium channels in the peripheral nerves are detected in some patients with acquired form of disease. Mutations in these channels are detected in patients with hereditary episodic ataxia and generalised myokymia.

Clinical presentation - muscular contractions (myokymia) at rest, muscle cramps and high muscle tone which increase during exercise and excessive sweating. Some patients have symptoms of neuropathy. Patients with acquired form of disease may also have other autoimmune disorders, such as myasthenia gravis, CIDP, thymoma or cancer (lymphoma or small-cell lung carcinoma).

Figure 1. Diagnostic Algorithm in Immune-mediated Polyneuropathy


Clinical evidence of polyneuropathy
Accute onset
(within two months)
Delayed onset
(>2 monts)
- Protein-cell dissociation in CSF
- EMG criteria
No evidence of familial disease
Evidence of familial disease
Paraproteins
Protein-cell dissociation in CSF
Hereditary motor and sensory neuropathy
Evidence of other disease
No evidence of other disease
Polyneuropathy associated with gammopathy
Chronic inflammatory demyelinating polyneuropathy
Guillain-Bare Syndrome
Idiopathic
Associated with other disease

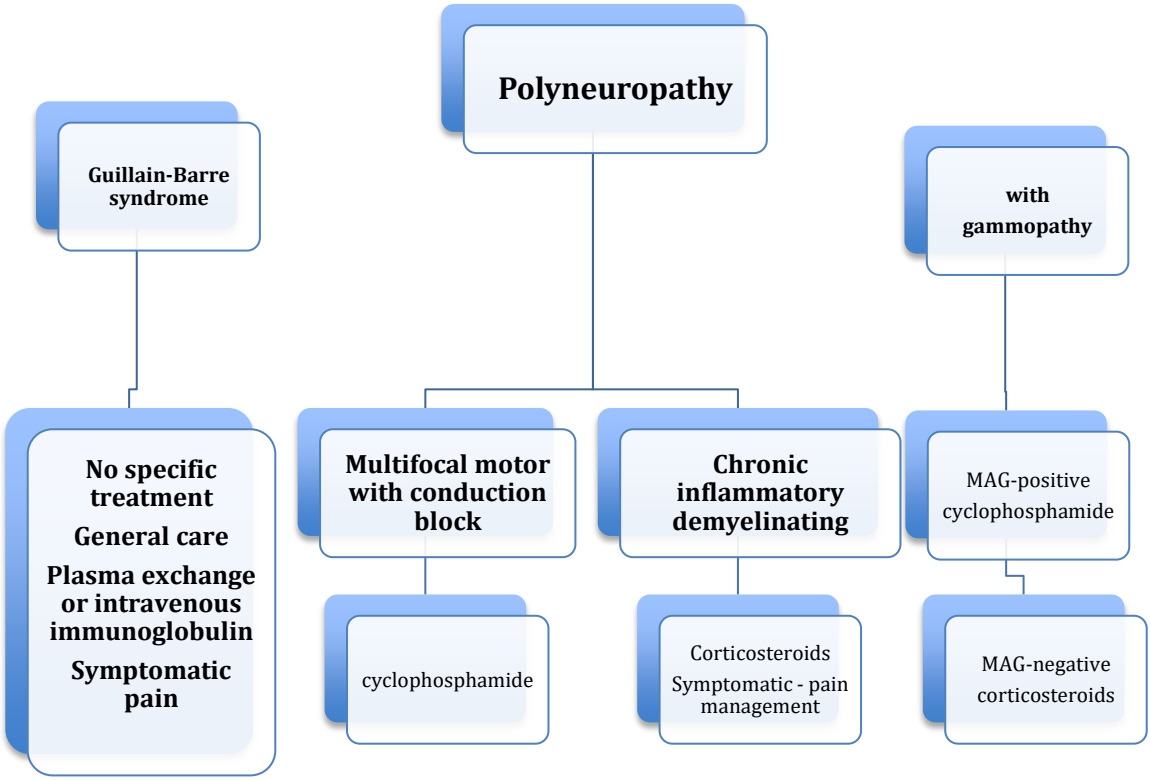



Figure 2. Treatment Algorithm in Immune-mediated Polyneuropathy