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Olga Gumkowska-Sroka[1, 2], Przemysław Kotyla[1, 2]

[1]Department of Internal Medicine, Rheumatology and Clinical Immunology, Medical University of Silesia, Katowice, Poland
[2]Department of Rheumatology, Voivodeship Hospital No. 5, Sosnowiec, Poland

Peripheral neuropathy in systemic inflammatory connective tissue diseases

ABSTRACT

Peripheral neuropathy (PN) is a relatively common comorbidity of connective tissue diseases. It often represents a neurological presentation of systemic diseases, while complications of systemic treatment of systemic connective tissue diseases cause some cases.

This paper presents the current division and contemporary diagnostic and therapeutic strategies focusing on the most common systemic rheumatic diseases.

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KEY WORDS: polyneuropathy; systemic connective tissue diseases; diagnosis; treatment

INTRODUCTION

Peripheral neuropathy (PN) refers to damage to the peripheral nervous system, both structural and functional. The causes of this damage can be varied; in addition to systemic connective tissue diseases, it can also include infections, metabolic disorders, exposure to toxic substances, and complications from the therapies used [1].

Typical physical manifestations of polyneuropathy include sensory disturbances with a "stocking-and-glove" distribution, paresis of the distal muscles, primarily of the lower limbs and affecting extensors more than flexors (walking on heels is impaired earlier than walking on tiptoes), weakened or abolished tendon reflexes, abnormal vibration and position sensation, sensory ataxia, pseudoathetosis, and a positive Romberg's test [1, 2].

The diagnosis of nervous system involvement in systemic connective tissue diseases is a particular challenge for the clinician, as the symptoms of polyneuropathy may precede the full-blown manifestation of the systemic disease, may also be associated with an exacerbation of the disease but may also be due to causes unrelated to the underlying disease and be a complication of concomitant diseases or adverse effects of the drugs used.

Definitively determining that symptoms of nervous system damage are due to inflammatory connective tissue disease is not easy and requires extensive differential diagnosis [2].

DIVISION

This very diverse group of neurological conditions can be divided in terms of

— **the number** of nerve structures involved — a distinction is then made between:
  a) mononeuropathy — involving a single nerve;
  b) mononeuropathy multiplex — involving simultaneous or sequential damage to multiple nerves that are not anatomically connected;
  c) polyneuropathy — involving multiple nerves;
— **the type** of damaged structures: axonal damage, demyelinating damage, ganglionopathy and neuronopathy;
— **the function** of the nerve fibres: sensory, motor and autonomic neuropathy;
— **the anatomical location of the damaged area**: radiculopathy, plexopathy;

Address for correspondence:
Przemysław Kotyla,
Clinical Department of Rheumatology and Clinical Immunology, Voivodship Hospital No. 5, Sosnowiec;
e-mail: pkotyla@sum.edu.pl

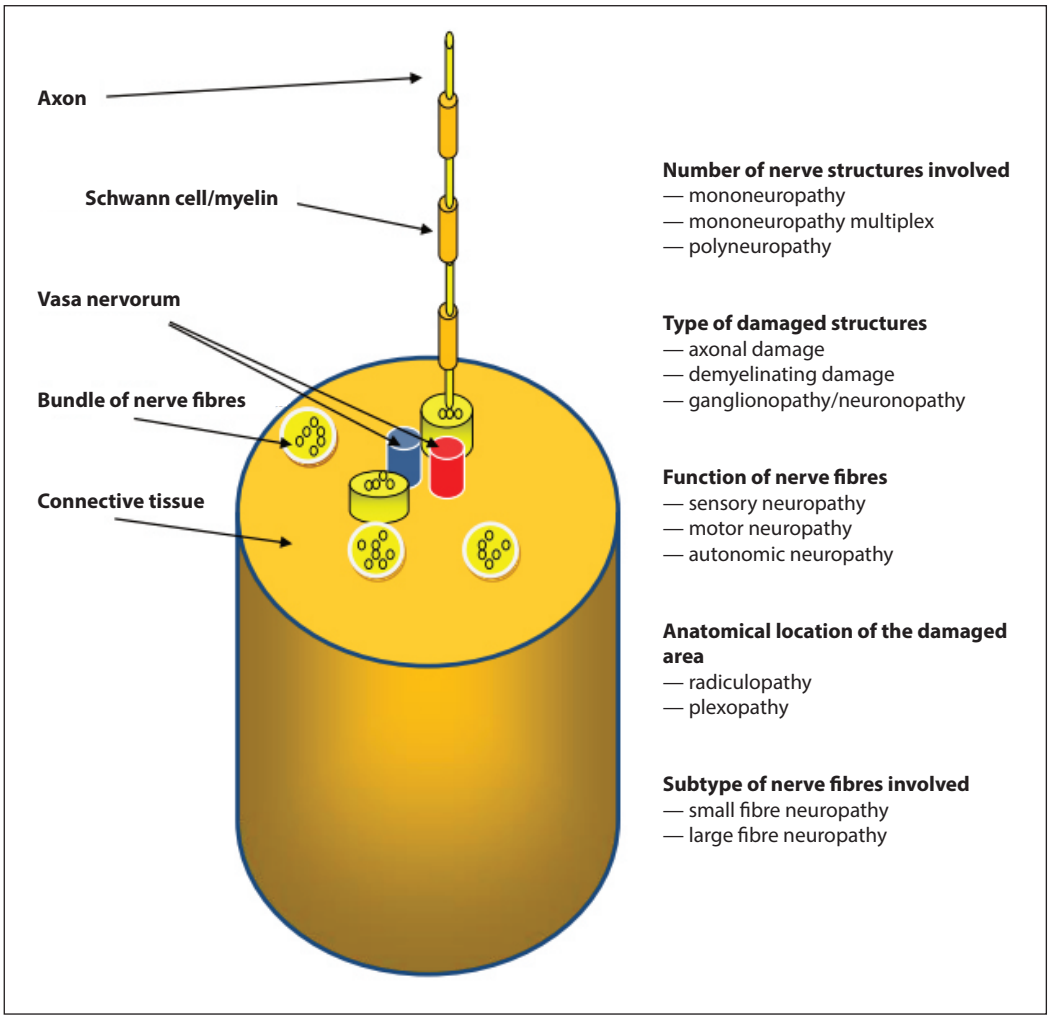

Figure 1. Division of peripheral neuropathies

— **the subtype of nerve fibres involved**: small fibre neuropathy, large fibre neuropathy.

The symptoms of neuropathy can also be divided into positive ones, e.g. positive sensory symptoms (paraesthesias), as well as allodynia (pain resulting from stimuli that in healthy people do not cause pain, such as blowing, touch — stimulation below the threshold of pain), hyperalgesia (excessive sensitivity to pain) and neuropathic pain.

Negative sensory symptoms include weakness or loss of superficial sensation (touch, temperature, pain). Deep (proprioceptive) sensibility disorders involve a lack of orientation in positioning body parts without visual control.

Motor symptoms usually first appear in the distal parts of the limbs with distal propagation, e.g. weakness of the ankle extensors causes the foot to drop.

Damage to the autonomic system is manifested by dizziness, orthostatic drops in blood pressure, impaired sexual function, and sphincter disorders [3].

The division of PN is shown in Figure 1.

PATHOGENESIS

The pathogenesis of peripheral nervous system fibre damage in autoimmune diseases is complex. Neurogenic inflammatory mechanisms, an immunological mechanism involving autoantibodies, an ischaemic and metabolic mechanism, and, in recent years, an allergic inflammatory mechanism resulting in the development of neuropathic pain are considered [4].

NEUROGENIC INFLAMMATION

Nociceptors located in nerve endings in response to inflammatory cytokines such as interleukin-1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α) induce activation of mitogen-activated protein kinase (MAPK), resulting in increased excitability of the cell mem-

brane, and leading to the release of a variety of neuropeptides such as substance P, calcitonin gene-related protein (CGRP) and a number of chemokines that cause vasodilation, increased vascular permeability and cell movement. These mediators activate the innate and acquired immune system, including T cells. There is also a release of nerve growth factor (NGF) and prostaglandin E2 (PGE2), the primary inflammatory mediators inducing peripheral sensitisation and involved in hyperalgesia [5].

IMMUNOLOGICAL MECHANISM

Damage to nervous system structures also occurs as a result of a number of autoantibodies, including anti-neuronal, anti-neurotrophin, anti-ganglioside, NGF, and antibodies to proteins responsible for the normal functioning of the nervous system [6].

Onconeuronal antibodies are used in the diagnosis of paraneoplastic neurological syndromes, in which the nervous system involvement that occurs in patients with cancer is not due to metastases or local tumour activity. Clinical manifestations may include subacute sensory neuropathy, subacute motor neuropathy, sensorimotor neuropathy, Lambert-Eaton myasthenic syndrome. Detection of these antibodies helps differentiate paraneoplastic lesions from systemic connective tissue diseases with nervous system involvement. Anti-Hu antibodies are found in patients with small-cell lung cancer but also those with breast, ovarian and testicular cancer. Anti-Ri antibodies are found in patients with breast and lung cancer. Anti-Yo antibodies are observed in breast, ovarian, gastric, oesophageal and salivary gland cancers [7].

ISCHAEMIC MECHANISM

Local ischaemia and neuronal hypoxia resulting from vasculitis of *vasa nervorum* and *epineurium* are other important mechanisms that lead to damage to the fibres of the peripheral nervous system. Ischaema is further exacerbated by flow abnormalities in the small vessels associated with both impaired blood rheological function and the presence of antiphospholipid antibodies and cryoglobulins, which may accompany systemic connective tissue diseases.

ALLERGIC INFLAMMATION LEADING TO NEUROPATHIC PAIN

The mechanism of allergic inflammation-related neuropathic pain (NeP) was first described in patients with eosinophilic granulomatosis with polyangiitis (EGPA) without antineutrophil cytoplasmic antibodies (ANCA) — negative myeloperoxidase antineutrophil cytoplasmic antibodies negative (MPO-ANCA negative). In patients with a predisposition to develop allergic reactions, increased humoral activity may lead to the induction of anti-plexin D1 antibodies (*anti-plexin D1*) via a molecular mimicry mechanism with environmental allergens. These antibodies are thought to play an important role in neuropathic pain development [8]. In addition, overproduction of endothelin 1 (ET-1) can induce blood-brain barrier permeability and activate microglia.

Various components of neural structures can be a point of attack by immune mechanisms. One such structure is the nodes of Ranvier—the gaps between the cells of the myelin sheath. In these strictures, the axon's cell membrane is not sheathed in myelin, so it comes into contact with extracellular fluid.

In chronic inflammatory demyelinating polyneuropathy (CIPD), antibodies against neurofascin 155 (NF155), which is expressed in glial cells, have been described [9].

DIAGNOSTIC PROCEDURE

The basis of the diagnostic procedure is a detailed history and physical examination. Differential diagnosis and exclusion of other conditions that may lead to nervous system involvement, such as infections with human immunodeficiency virus (HIV), Epstein-Barr virus (EBV) varicella-zoster virus (VZV), endocrine disorders, toxic damage, effects of drugs (cisplatin, pyridoxine), deficiencies (B vitamin and folic acid deficiencies), and cancer (small-cell lung cancer) [2].

A complete neurological examination should include examination of the cranial nerves, assessment of tendon reflexes, all types of sensation, assessment of gait, Romberg's test and examination of the eye fundus. Additional neurophysiological tests are also necessary.

Electrophysiological testing plays an important role in the diagnosis of polyneuropathy. This examination aims to confirm polyneuropathy, allows the identification of damaged fibres, assessment of the extent and severity of the process, determination of the pathophysiology of the damage (axonopathy versus myelinopathy) and its dynamics.

Tests include:

— electroneurography (ENG) — sensory and motor conduction study, fundamental in the diagnosis of neuropathy. It enables assessment of the peripheral neurons. It confirms PN, allows identification of the damaged fibres, assesses the extent and severity of the process, and determines the pathophysiology of the damage and its dynamics. For this purpose, a motor and sensory conduction study is performed for several peripheral nerves with evaluation of parameters such as terminal latency, response amplitude, conduction velocity, F-wave latency.

The examination result enables assessment of peripheral nerve damage with determination of its extent (sensory nerves, motor nerves) and type (demyelinating neuropathy, axonal neuropathy);

— electromyography (EMG) — important for the assessment of primary muscle disorders (myopathies);

— evoked potential tests — the signals generated by the nervous system in response to sensory or motor stimuli.

Skin biopsy aids the diagnosis of small fibre sensory neuropathy by revealing density defects in the intra-epidermal nerve endings.

Autonomic neuropathy involves the dysfunction of the sympathetic and parasympathetic systems. Clinical manifestations include bladder and bowel dysfunction, orthostatic hypotension, impaired sweating, reduced pupil reactivity.

Assessment of autonomic function involves:

— evaluation of heart rate variability in response to the Valsalva manoeuvre and rhythmic deep breathing (cardiac reflex assessment);

— evaluation of arterial pressure variation in response to the Valsalva manoeuvre and orthostatic stress (assessment of adrenergic responses);

— sympathetic skin response (assessment of sweat secretion);

— quantitative sudomotor axon reflex test (QSART) — a quantitative test to assess C-fibre neuropathy. It is difficult and time-consuming to perform;

— assessment of electrochemical skin conductance using a SUDOSCAN+, a non-invasive method to identify patients at increased risk of developing clinically overt neuropathy. SUDOSCAN+ is a tool for the non-invasive assessment of sweat gland function based on the electrochemical response of chlorine ions released in sweat when exposed to a low-voltage current;

— examination of cerebrospinal fluid (CSF), which excludes infection and bleeding.

Protein concentrations, cytosis and the presence of antibodies are assessed.

Guillain-Barré syndrome presents with albuminocytologic dissociation and significantly elevated protein concentrations with normal cell numbers and composition.

The presence of oligoclonal bands may be associated with an inflammatory or immunological process in the nervous system. Specific oligoclonal bands are found in more than 90% of multiple sclerosis patients.

PMR may show immunoglobulins (Ig): IgG, IgA, IgM against Borrelia antigen, onconeuronal antibodies [3, 10].

PERIPHERAL NERVOUS SYSTEM INVOLVEMENT IN SYSTEMIC CONNECTIVE TISSUE DISEASES

PRIMARY SJÖGREN'S SYNDROME

Peripheral nervous system lesions in primary Sjögren's syndrome (pSS) are more common than those in the central nervous system and, according to current literature, affect 5–15% of patients [11]. Peripheral nervous system involvement may be the first or even the only symptom of pSS or occur before the clinical diagnosis.

Neurological symptoms precede the onset of pSS in approx. 81% of patients, sometimes by 3–5 years. Furthermore, only 21% of patients have typical ANAs (Ro and La) at the onset of neurological symptoms, which develop over the following 7 years [11, 13].

Most commonly, sensory neuropathy clinically manifests as:

— distal axonal sensory polyneuropathy — the most common form of peripheral nervous system involvement. The lesions are localised symmetrically and distally, more often in the lower limbs; there are symmetrical peripheral paraesthesias in the form of tingling, numbness and dysesthesias associated with hypersensitivity. Symptoms are often restricted to the lower limbs and accompanied by a burning sensation in the feet. Tendon reflexes are weakened or abolished; there is weak surficial sensation or skin hyperaesthesia. Muscle strength is preserved. ENG shows no or weakened nerve poten-

tials, and conduction velocity is normal. The nerve biopsy is non-characteristic;
— small fibre sensory neuropathy — a painful sensory neuropathy caused by the involvement of small unmyelinated C-fibres that conduct nociceptive stimuli and damage to poorly myelinated A-δfibres. It is marked by painful paraesthesias in the proximal and distal limbs, trunk and face, exacerbated at night. Neurological examination reveals impaired responses to tactile and temperature stimuli. The ENG result is normal. It is the most typical neuropathy for pSS;
— distal sensorimotor polyneuropathy, which results from damage to thick nerve fibres. It is distal. Consequently, there is progressive and symmetrical muscle weakness (most commonly affecting the foot extensors). On examination, deep tendon reflexes may be weakened or absent. This type of polyneuropathy is associated with cryoglobulinaemia, reduced complement component 4 and the risk of developing lymphoma;
— mononeuropathy multiplex (*mononeuritis multiplex*) — simultaneous or consecutive asymmetrical damage to at least two nerves that are not connected. In its course, sensory and motor fibres are affected, but trigeminal and intercostal nerves may also be involved. The underlying mechanism is *vasa nervorum* vasculitis, which leads to nerve damage in an ischaemic mechanism;
— sensory ganglionopathy — a chronic sensory neuropathy with ataxia and involvement of nerve cell bodies in the dorsal root ganglion, which is associated with deep sensation and vibration disorders. The main symptom is gait instability. Romberg's test is positive, and deep tendon reflexes are absent;
— chronic inflammatory demyelinating polyneuropathy (CIDP) — a rare sensorimotor neuropathy. Clinically, it is characterised by symmetrical weakness of the proximal and/or distal muscles of the upper and lower limbs with weakness of the deep tendon reflexes;
— cranial neuropathy — most commonly involves the trigeminal nerve and is caused by damage to the trigeminal ganglion [11, 12].

SENSORY NEUROPATHY WITH ATAXIA

Patients with Sjögren's syndrome also have peripheral nervous system damage in the form of painful sensory neuropathy with ataxia, associated with abnormalities of deep sensation and vibration. Patients are found to have gait abnormalities (shaky gait, on a wider base), clumsiness of upper limb movements and impaired execution of rapid alternating movements. On neurological examination, vibratory and position sensations are absent, Romberg's test is positive, and deep tendon reflexes are absent. Muscle strength is usually preserved; only in advanced stages may it be reduced due to muscle atrophy. Electrophysiological examination shows decreased amplitude or absence of sensory fibre potentials. In cases of significant nerve root damage, F-wave latencies are prolonged. A nerve biopsy shows a substantial reduction in thick myelinated axonal fibres. Histopathological examination of the dorsal root ganglia shows degeneration of large sensory neurons and CD8+ T-cell infiltration. This presentation, like the aforementioned painful sensory neuropathy secondary to ganglionopathy, is also an indication for IVIG or plasmapheresis. There are reports of successful treatment with infliximab, interferon-α and rituximab [13].

AUTONOMIC NEUROPATHIES

Impairment of the autonomic nervous system occurs with varying frequency, from 50% to approx. 3% of patients. It predominantly develops with sensory ataxia or ganglioneuronopathy. Antibodies against muscarinic receptor type 3, cytokines and CD8+ T cells infiltrating the ganglia are involved in the development of autonomic dysfunction, known as dysautonomia. The main symptoms of autonomic nervous system involvement are tachycardia, orthostatic hypotonia, bowel dysfunction, impaired sweat secretion (*anhidrosis*) and pupillary rigidity (Adie's pupil). The last symptom is due to inflammation of the ciliary ganglion neurons. In addition, it has been shown that autonomic system dysfunction is more common in patients with fibromyalgia symptoms and mood disorders in the form of depression. Treatment is usually symptomatic; if it coincides with other types of neuropathy, combination treatment is used, which is indicated for the type of peripheral nervous system damage.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disorder with a wide range of clinical manifestations and abnormalities in laboratory results. Nervous system involve-

ment (central and/or peripheral) is usually associated with a more severe course and unfavourable prognosis. Neurological symptoms are thought to be caused by the closure of a blood vessel lumen or direct damage to nerve cells by circulating antibodies.

Symptoms of peripheral nervous system damage manifest most commonly as peripheral polyneuropathy, i.e. symmetrical damage to the distal parts of the fibres, mononeuropathy, i.e. damage to a single fibre, and rarely as acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome). Less commonly, cranial nerve neuropathy or autonomic nervous system disorders, cranial nerve neuropathy (the most commonly involved nerves are II, VIII, oculomotor nerves (III, IV, VI), trigeminal nerve V and facial nerve VII [14].

GUILLAIN-BARRÉ SYNDROME — ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

It occurs in less than 2% of SLE patients. The disease begins with sensory impairment (numbness) and weakness in the lower limbs. Subsequently, it involves the upper limbs; sometimes, there is damage to nerve VII. Swallowing disorders also occur, followed by respiratory failure. The prognosis is reasonably good, with symptoms gradually subsiding. A variant of Guillain-Barré syndrome, Miller-Fisher syndrome is characterised by ataxia, ophthalmoplegia, and areflexia; it is associated with a worse prognosis [15].

A major problem is the neuropathic symptoms that appear before the clinical manifestations of SLE, i.e. those found in a person without a diagnosis of SLE. According to some publications, in more than 50% of patients with nervous system involvement, neurological symptoms were observed before the diagnosis of the underlying disease. For this reason, after the diagnosis of neuropathy, diagnostic tests for connective tissue diseases, including lupus, are performed in the absence of clinical symptoms of these diseases. Neurological symptoms, including neuropathy in a patient with suspected SLE, make it necessary to expand the diagnosis and sometimes start immunosuppressive treatment, even though the diagnostic criteria of the underlying disease are not met.

SYSTEMIC SCLEROSIS

In the course of systemic sclerosis, polyneuropathy is more common than central nervous system involvement. Carpal tunnel syndrome is relatively common. Some patients develop trigeminal neuralgia and autonomic system disorders (mainly related to the cardiovascular and gastrointestinal systems). Severe polyneuropathies (usually sensorimotor) and mononeuropathies are relatively rare [16].

SYSTEMIC VASCULITIS

Peripheral nervous system involvement is also an important part of the clinical picture of diseases with systemic vasculitis. In the course of these diseases, including microscopic polyangiitis (MPA), peripheral nervous system involvement affects 14–36% of patients and, according to other authors, even 55–79% [17].

PN is the most common (and for a long time may be the only) manifestation of the disease. Necrotising vasculitis causes nerve ischaemia, leading to nerve damage. The neuropathy can be acute or slowly progressive. The most common manifestation is mononeuropathy multiplex, which involves the fibular nerve (89%), sural nerve (84%), tibial nerve, ulnar nerve, and median nerve. The second most common is symmetrical peripheral polyneuropathy. It usually affects the distal part of the lower limbs. Asymmetric sensory neuropathy is rare. Cranial nerve involvement is also frequent, generally in the facial nerve, less commonly in nerve III or VI. Of all types of PN, systemic vasculitic neuropathy (SVN) occurs in 85% of patients, 60% of whom have primary systemic vasculitis, and the remaining 15% represent non-systemic vasculitic neuropathy (NSVN) [17, 18].

POLYARTERITIS NODOSA

In polyarteritis nodosa, peripheral nervous system involvement predominates (60–70% of patients). This arteritis manifests as mononeuropathy, mononeuritis multiplex or polyneuropathy, which results from inflammation of the vessels supplying the nerves. The most commonly involved are the fibular, sural, radial, ulnar and median nerves. Peripheral nervous system involvement is apparent early in the course of the disease. CNS involvement is less common, develops later and has a poorer prognosis [19].

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS

Peripheral nervous system involvement is relatively common and affects 10–60% of

Table 1. Predisposing factors for peripheral neuropathy (PN) in patients with systemic connective tissue diseases. Based on [27]

Systemic connective tissue disease	Factors associated with PN development
Systemic lupus erythematosus	Older age at diagnosis
	High activity of the disease
	Concomitant vasculitis
Sjögren's syndrome	Salivary gland enlargement
	Hypocomplementemia
Eosinophilic granulomatosis with polyangiitis	ANCA antibodies
	Skin, muscular, cardiovascular system involvement
Rheumatoid arthritis	High DAS-28
	High inflammatory parameters
	Increased platelet count

ANCA — antineutrophil cytoplasmic antibodies; DAS-28 — Disease Activity Score

Table 2. Effects of rheumatologic drugs on peripheral nervous system function

Drug	Side effects
Allopurinol	Paraesthesias, neuropathy
Chloroquine	Confusion, myopathy, **peripheral neuropathy**
Cyclosporine	Paraesthesias, myalgia, **rarely peripheral neuropathy**
Leflunomide	**Peripheral neuropathies** most commonly within the first three months, with motor and axonal damage (on ENG)
Mycophenolate mofetil	Lambert-Eaton myasthenic syndrome, headaches, increased muscle tension
TNF-α inhibitors	Cases **of peripheral demyelinating polyneuropathies**

TNF-α — tumour necrosis factor alpha; ENG — electroneurography

patients. Mononeuritis multiplex is most common, with distal symmetrical sensory polyneuropathy and asymmetrical polyneuropathy less common. Early symptoms include painful paraesthesias and tingling, especially in the lower limbs. Nervous system involvement often occurs early in the disease. Nerve conduction study shows features of axonal degeneration.

CRYOGLOBULINAEMIA (INCLUDING FORMS ASSOCIATED WITH HEPATITIS B AND C).

Most often described is chronic, distal symmetrical sensory polyneuropathy due to axon damage caused by vasculitis. Autonomic neuropathy is less common [17, 18].

Predisposing factors for PN in patients with systemic connective tissue diseases are shown in Table 1.

Many rheumatologic drugs affect nervous system function, as shown in Table 2.

TREATMENT

Polyneuropathies involving systemic connective tissue diseases are mainly associated with immunological abnormalities and small-vessel vasculitis. Most authors recommend oral prednisone at a dose of 1 mg/kg. In severe cases, intravenous methylprednisolone pulses at a dose of 1 g for 3–5 days are administered. Treatment should be continued for 6–8 weeks, and then the dose of corticosteroids should be gradually reduced. In severe forms of polyneuropathy, glucocorticosteroids are combined with immunosuppressive treatment. Cyclophosphamide appears to be the most effective drug for inducing remission. Cyclophosphamide induction therapy lasts 3–12 months followed by maintenance treatment (azathioprine, methotrexate, mycophenolate mofetil). Intravenous immunoglobulin (IVIG) is a safe treatment option for severe systemic polyneuropathies.

Current recommendations for the management of peripheral nervous system involvement in Sjögren's syndrome were published in 2020 [20]. In mononeuritis multiplex, oral corticosteroids and disease-modifying immunosuppressants (methotrexate, azathioprine, cyclosporine) are used. In severe cases, rituximab and cyclophosphamide are used. In life-threatening vasculitis with cryoglobulinae-

mia, plasmapheresis is used. Intravenous immunoglobulin regimens for 5 consecutive days are also employed, with the option of repeating the therapy after a month.

In ganglionopathy or chronic inflammatory demyelinating polyneuropathy, intravenous immunoglobulin, methylprednisolone pulse and cyclophosphamide therapies are administered [21].

Symptomatic treatment of sensory neuropathies includes gabapentin and pregabalin. In trigeminal neuralgia, carbamazepine is used. Tricyclic antidepressants (amitriptyline) are recommended for patients with severe pain.

Patients with painful polyneuropathy respond to drugs known to be effective in neuropathic pain: antidepressants [tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (SNRIs) and various antiepileptic drugs such as gabapentin and pregabalin. Most clinical studies have shown that the efficacy of SNRIs is lower than that of tricyclic antidepressants. However, tricyclic antidepressants have a higher incidence of side effects in the elderly and are contraindicated in patients with glaucoma, prostatic hypertrophy or certain cardiac conduction disorders. Venlafaxine is an SNRI that has been shown to be effective in the treatment of painful polyneuropathies of various origins [22].

Attention is drawn to the efficacy of monoclonal antibodies directed against the CD20 antigen on B cells, such as rituximab, and TNF inhibitors, such as adalimumab, in the treatment of the small fibre neuropathies that occur in Sjögren's syndrome [23].

Reports on the efficacy of immunoglobulin therapy in sensorimotor and non-ataxic sensory associated with Sjögren's syndrome are available.

In chronic inflammatory demyelinating polyneuropathy, intravenous immunoglobulin is administered in the absence of effective steroid therapy. This treatment regimen is 0.4 g/kg/day for 5 days and then booster doses every 2–4 weeks (0.4–1 g/kg) [24].

Subcutaneous immunoglobulin (SCIG) is another option. This therapy can be considered in case of any systemic side effects of IVIG and poor venous access. SCIG is usually administered at a lower dose of 100 to 200 mg/kg every one to two weeks. SCIG can be administered at home, ensuring better patient compliance [25].

Plasmapheresis is the first choice in patients with severe disease. Four to six plasma exchange procedures are performed over 5–7 days (approx. 200 ml plasma/kg) [26].

In small fibre neuropathy, gabapentin (daily dose 900–2700 mg) and pregabalin (150–300 mg) are recommended as first-line therapy, which can be supplemented or replaced by duloxetine (60–90 mg) or venlafaxine (75–150 mg). IVIG at a dose of 0.4 g/kg/day for 5 days with booster therapy every 4–6 weeks is also used. Steroid therapy and rituximab have not proved effective in this group of patients.

In Poland, there is an IVIG transfusion treatment programme reimbursed by the National Health Fund in patients with the following indications (according to detailed criteria):

1. Chronic inflammatory demyelinating polyneuropathy (CIDP);
2. Multifocal motor neuropathy (MMN);
3. Myasthenia gravis (MG) while meeting certain conditions specified in the therapeutic programme;
4. Paraneoplastic syndromes: Lambert-Eaton myasthenic syndrome, limbic encephalitis, motor or sensorimotor polyneuropathy with documented additional tests indicated in the therapeutic programme;
5. Inflammatory myopathies: dermatomyositis and polymyositis in case of ineffective corticosteroid treatment;
6. Guillain-Barré syndrome;
7. Neuromyelitis optica (NMO);
8. Encephalitis with antibodies against neuronal antigens.

CONCLUSIONS

Nervous system involvement may appear late in the course of systemic inflammatory connective tissue disease but may also precede the onset of full-blown disease. Neuropathic symptoms in a patient without a diagnosis of systemic inflammatory connective tissue disease are always a major diagnostic challenge. For this reason, diagnostic tests for systemic connective tissue diseases should be performed after diagnosing neuropathy, even without clinical symptoms of these diseases.

Nervous system involvement is always a poor prognostic and indicates an aggressive course of the disease, requiring intensive treatment.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the final shape of the paper.

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CONFLICT OF INTEREST

Authors declare no conflict of interests.

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