Chapter 23
Diagnosis and Therapy for Peripheral Vasculitic Neuropathy

Franz Blaes

Abstract Vasculitic neuropathy may occur as a part of systemic vasculitis or an isolated vasculitis of the peripheral nervous system. The typical clinical syndrome is mononeuropathia multiplex, but distal-symmetric neuropathy can also be observed. Neurophysiological examination reveals axonal damage in most cases and nerve biopsy shows inflammatory infiltrates together with vessel wall damage. Treatment includes steroids, cyclophosphamide, azathioprine, rituximab and other immunosuppressants. This chapter provides an overview about clinical, laboratory and histopathological diagnostic criteria and the current treatment options for vasculitic neuropathy.

Keywords Vasculitis • Neuropathy • Immunosuppressive treatment • Rheumatology

23.1 Introduction

Vasculitic neuropathies are a group of inflammatory neuropathies, characterised by inflammation of the vasa nervorum, mainly the epineural arteries of the nerve. They can occur as non-systemic vasculitis (non-systemic vasculitic neuropathy NSVN, exclusively affecting the peripheral nervous system) or part of a systemic vasculitis including the involvement of other organs (systemic vasculitic neuropathy) (Table 23.1). The differential diagnosis may be difficult, if the neuropathy is the first manifestation of vasculitis. The exact incidence of vasculitic neuropathy has never been investigated in bigger studies. However, the annual incidence of systemic vasculitis is 60–140/million, which includes a part of 30 % secondary systemic vasculitis [1, 2]. In nerve biopsy specimen obtained in neuropathy of unknown reason, about 1 % show vasculitic neuropathy [3, 4]. Some systemic vasculitic diseases are rarely associated with neuropathy, whereas in others, such as Churg-Strauss syndrome, it belongs to the diagnostic criteria (Table 23.2) [5].

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Table 23.1 Classification of vasculitic diseases according to [8, 9]

Primary systemic vasculitis
1. Small vessel vasculitis
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss-Syndrome)
Granulomatosis with polyangiitis (GPA)
Essential mixed cryoglobulinemia (non-Hepatitis C)
Henoch-Schönlein purpura
2. Medium vessel vasculitis
Polyarteritis nodosa
3. Large vessel vasculitis
Giant cell arteritis
Secondary systemic vasculitis
1. Connective tissue diseases
Rheumatoid arthritis
Systemic lupus erythematosus
Sjögren's syndrome
Systemic sclerosis
Dermatomyositis
Mixed connective tissue disease
2. Sarcoidosis
3. Behçet's disease
4. Infections (Hepatitis B and C, HIV, CMV and others)
5. Drugs
6. Malignancy
7. Inflammatory bowel disease
8. Hypocomplementemic urticarial vasculitis syndrome
Non-systemic or localised vasculitis
1. Non-systemic vasculitic neuropathy
2. Diabetic/non-diabetic radiculoplexus neuropathy (DRPLN/RPLN)
3. Localised cutaneous or neuropathic vasculitis

23.2 Classification

In 1990, the American College of Rheumatology presented classification criteria for PAN, CSS, GPA and others. However, this classification was criticized because (1) there was no discrimination between vasculitis from non-vasculitic disease and (2) ANCA testing was not included in the classification. The Chapel Hill consensus conference (CHCC) in 1994 proposed definitions for most vasculitic diseases according to the size and pathology of the involved vessels [6]. In 2007, a new classification incorporating both ACR and CHCC criteria was established and Wegener's

Table 23.2 Frequency of neuropathy in vasculitic diseases (according to [77, 85])

Disease	Frequency	Reference
Primary systemic vasculitis		
Giant cell arteritis	Rare	[101, 102]
Polyarteritis nodosa	65–85 %	[50, 103]
Churg-Strauss syndrome	65–80 %	[22]
Granulomatosis with polyangiitis	5–50 %	[50, 104]
Microscopic polyangitis	6–75 %	[50]
Cryoglobulinemia	30–70 %	[44, 105]
Secondary systemic vasculitis		
1. Connective tissue diseases		
Systemic lupus erythematosus	20–27 %	[106]
Rheumatoid arthritis	15–70 %	[107, 108]
Sjögren syndrome	30–45 %	[109, 110]
Systemic sclerosis (scleroderma)	5–30 %	[44, 111]
2. Others		
Infections (HBV, HCV, HIV)	5–70 %	[44, 50, 73]
Sarcoidosis	5–10 %	[68]
Malignancy	Rare	[112]
Drugs	Rare	[75, 113, 114]

granulomatosis was renamed granulomatosis with polyangiitis [7]. The 2012 second CHCC updated some of the diagnostic criteria for vasculitis. More recently, it has been proposed to divide the vasculitic neuropathies in two groups according to the size of the affected nerve vessels, distinguishing a nerve large arteriole vasculitis from a nerve microvasculitis. The latter involves arterioles <40 μm and endoneurial microvessels and includes the most non-systemic vasculitic neuropathy, Sjögren syndrome and some virus-associated vasculitic neuropathies [8]. Most neurologists also use the classification developed from the Peripheral Nerve Society Task Force. Vasculitic neuropathy is categorized in primary systemic vasculitis, secondary systemic vasculitis or non-systemic/localized vasculitis depending on the disease-associations (Table 23.1) [9].

23.3 Pathogenesis

Blood supply in the peripheral nervous system is secured by the regional vasa nervorum, which feed an extensive network between the epineurial and the endoneurial vessels. This allows a functionality of the peripheral nerve even under anaerobic conditions and makes the nerve quite resistant to ischemic damage [10]. The underlying etiology of the vasculitic disease may be different, and, in some diseases, not completely understood. However, occlusion of vessels by vascular inflammation leading to ischemic nerve damage is the common final path in vasculitic neuropathy.

This ischemic damage occurs diffusely in the whole nerve, but with a maximum effect in the proximal and middle parts of the nerves, which is the most vulnerable zone to ischemia [11]. In cryoglobulinemia, anti-sulfatide antibodies can be found, which may be involved in the pathogenesis [12]. An increased expression of nerve growth factor (NGF) may be involved in the pain development of vasculitic neuropathy [13].

23.4 Clinical Features and Diagnostic Procedures

The typical clinical presentation of vasculitis is mononeuropathia multiplex. However, about 30–60 % of patients with vasculitis have other clinical types of neuropathy including painful sensorimotor axonal neuropathy or pure sensory neuropathy or asymmetric neuropathy. Pain is a regular symptom in most vasculitic neuropathies. In biopsy-proven vasculitic neuropathy, 10–40 % are distal-symmetric pattern [14–16]. The peroneal and tibial nerves on the lower and the ulnar nerve on the upper limb are most frequently involved in vasculitic neuropathy. However, there is no association of a distinct clinical pattern with a special type of vasculitic disease. The majority of vasculitic neuropathies develop subacute within days to weeks and only in a few cases, a chronic, slowly progressing neuropathy has been observed. About 80 % of neuropathies associated with systemic vasculitis, but also 50 % of patients with non-systemic vasculitic neuropathies have general symptoms (weight loss, fever, myalgia, or fatigue).

The neurophysiological examination shows multifocal axonal neuropathy including reduced CMAP amplitudes with only slightly reduced nerve conduction velocities (NCV) in neurography [14, 17, 18]. However, if the CMAP amplitudes are massively reduced, the NCV can also be reduced because of the loss of thick myelinated fibres. A transient nerve conduction block can be observed early after symptom onset and represents an ongoing Wallerian degeneration, which has not been completed distal of the affected nerve; however, within 1–2 weeks, this phenomenon disappears. Electromyography reveals neurogenic pattern including spontaneous muscle fiber activity, and polyphasic, extended, or high-amplitude motor unit action potentials (MUAP). However, if an additional vasculitic myopathy is also present, myopathic and neurogenic changes can be observed at the same time [9, 19].

Whenever systemic vasculitis or another reason for the neuropathy is not known, a variety of laboratory investigations should be performed. As a first step, routine laboratory investigations should be performed in neuropathies with unknown reason. If an inflammatory neuropathy is suspected, a more detailed laboratory investigation should be performed (Table 23.3). Analysis of the cerebrospinal fluid will not increase the sensitivity to detect vasculitic neuropathy, but can be an important investigation in the differential diagnosis of an as yet unclear neuropathy. Other routine technical diagnostic procedures depend on the suspected diagnosis (Table 23.4).

Table 23.3 Laboratory investigations in suspected vasculitic neuropathy (modified according to [85])

Basic neuropathy screening	Vasculitis suspected
Full blood count	Antinuclear antibodies (ANA)
Erythrocyte sedimentation rate	Anti-neutrophil cytoplasmic antibodies (ANCA,
Vitamin B6, B12	including exact determination of the antibody)
C-reactive protein	Extractable nuclear antigens (ENA)
Fasting glucose (2 consec. days)	Rheumatoid factor
Electrolytes	Anti-CCP antibodies
Renal and liver function	Cryoglobulins
Creatinkinase	HIV serology
Serum protein immunofixation	Urine analysis (microalbuminuria ?)
Hepatitis B and C serology	Cerebrospinal fluid analysis
Thyroid function	Angiotensin-converting enzyme
	Soluble interleukin-2 receptor
	Antineuronal antibodies
	Serum complement C3, C4

Table 23.4 Technical investigations in suspected vasculitic neuropathy

Method	Neuropathy
Chest X-Ray	Sarcoidosis, paraneoplastic neuropathy
CT Chest/Abdomen	Paraneoplastic neuropathy
Visceral angiography	Polyarteritis nodosa (PAN)
Salivary gland biopsy	Sjögren syndrome, Mikulicz syndrome

If a patient develops subacute asymmetrical neuropathy or mononeuropathia multiplex without evidence for systemic vasculitis, nerve biopsy should be performed. In most cases, the sural nerve is used with or without muscle biopsy. The combined biopsy of the superficial peroneal nerve together with the peronaeus brevis muscle is an alternative to the sural nerve biopsy [20]. Although controlled studies are lacking, the combined nerve/muscle biopsy has a slightly higher sensitivity to detect vasculitis and the biopsy of the peronaeus brevis muscle may be more effective than the gastrocnemius muscle. One study used a proximal muscle for biopsy (quadriceps) and showed no increased yield for vasculitic neuropathy compared to nerve biopsy alone, indicating that distal muscles are more suitable for biopsy in suspected vasculitis [14].

23.4.1 Pathology

The histopathological diagnosis of vasculitic neuropathy requires different criteria, which have been set up in detail in a guideline of the Peripheral Nerve Society [9]. The definite diagnosis of vasculitis includes both intramural inflammation (Fig. 23.1)

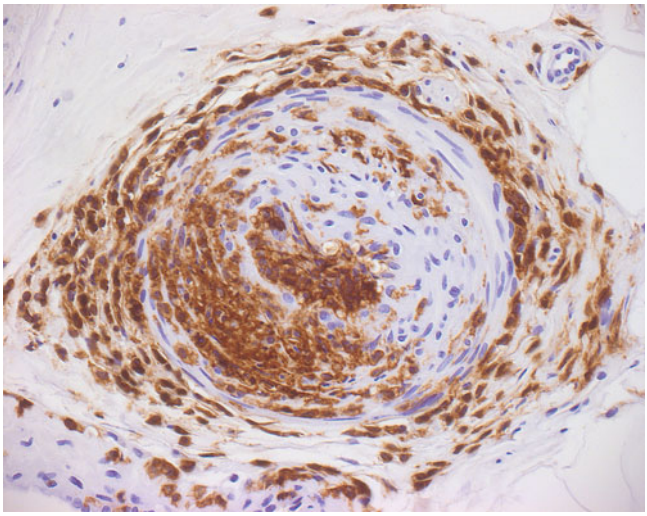

Fig. 23.1 Peripheral nerve vasculitis. Epineurial vessel with lymphocyte infiltration and subtotal stenosis. Lymphocytes stained with anti-LCA (lymphocyte common antigen) antibody (Courtesy of Prof. J. Weis, Aachen)

Table 23.5 Diagnostic criteria for definite vasculitic neuropathy (according to [9])

1. Active lesion: nerve biopsy showing collection of inflammatory cells in vessel wall and one or more signs of acute vascular damage:
(a) Fibrinoid necrosis
(b) Loss/disruption of endothelium
(c) Loss/fragmentation of smooth muscle cells in media
(d) Acute thrombosis
(e) Vascular/perivascular hemorrhage
(f) Leucocytoclasia
2. Chronic lesion with signs of healing/repair: nerve biopsy showing collection of mononuclear inflammatory cells in vessel wall and one or more signs of chronic vascular damage with repair:
(a) Intimal hyperplasia
(b) Fibrosis of media
(c) Adventitial/periadventitial fibrosis
(d) Chronic thrombosis with recanalisation

and additionally vessel damage (Table 23.5). It can be distinguished between findings in active lesions and chronic lesions. However, not all patients meet the criteria for definite vasculitic neuropathy, although vasculitis is clinically highly suspected. For these cases, criteria for probable vasculitic neuropathy have been established (Table 23.6). The histopathological picture shows mainly axonal damage, and the predominant blood vessels affected are epineurial more than peri- or endoneurial. The cellular infiltrates include mainly T-lymphocytes and macrophages, B-cells are rarely seen. In PAN and CSS eosinophils may also be present. Immune complex

Table 23.6 Diagnostic criteria for probable vasculitic neuropathy (according to [9])

1. Pathologic criteria for definite vasculitic neuropathy not fulfilled and
2. Predominantly axonal changes and
3. Perivascular inflammation accompanied by signs of active or chronic vascular damage; or Perivascular/vascular inflammation plus at least one additional class II or III pathologic predictor of definite vasculitic neuropathy:
(a) Vascular deposition of complement, IgM, or fibrinogen by direct immunofluorescence
(b) Hemosiderin deposits
(c) Asymmetric nerve fibre loss or degeneration
(d) Prominent active axonal degeneration
(e) Myofiber necrosis, regeneration or infarcts in peronaeus brevis muscle biopsy

deposits consisting of complement proteins, immunoglobulins and fibrinogen may be present [21, 22].

23.5 Primary Systemic Vasculitides

Neuropathies associated with primary systemic vasculitides have been classified according to the diameter of the affected blood vessels into three groups: large-vessel-, medium-vessel-, and small-vessel vasculitis. Vasculitic neuropathy can be observed predominantly in the small-vessel- and medium-vessel vasculitides, since the vessel diameters in nerves and muscles are mainly in a range between 50 and 300 μm.

23.5.1 Large Vessel Vasculitides

The large vessel vasculitides include Takayasu arteritis and giant cell arteritis. Takayasu arteritis is normally not associated with neuropathies, but shows significant central nervous system involvement, mainly strokes. Giant cell arteritis patients often have central nervous system involvement, in some rare cases, neuropathies have been described [23].

23.5.2 Medium-Sized Vessel Vasculitides

23.5.2.1 Polyarteritis Nodosa (PAN)

The polyarteritis nodosa is a very rare disease, the annual incidence decreased to 0.1–1.6 cases/million in developed countries after establishment of hepatitis B vaccination [24]. The histopathological features have been revised in the CHCC. PAN

is a disease of the small and medium-sized arteries, sparing arterioles, capillaries and venules. The vascular inflammation is segmental, often predominantly seen in branching points with mixed inflammatory infiltrates [25]. In later stages vascular remodelling with intima hyperplasia and diffuse fibrotic changes can be found. PAN can develop as idiopathic form, but also associated with viral infections. Hepatitis B was the main virus inducing PAN, but hepatitis C virus, cytomegalovirus, HIV, parvovirus B19 and even streptococci can also trigger the disease. The clinical symptoms include constitutional symptoms, such as fever, weight loss and arthralgia, but also organ involvement of different organ symptoms, of which skin symptoms and nervous system involvement are the most frequent. In contrast to other primary systemic vasculitides, PAN is a typical monophasic disease with a relapse rate of less than 10 %. Heart and central nervous system involvement determines a poor prognosis. The French vasculitis group proposed a five factor score for estimation of the prognosis of PAN. Neuropathies can be found in about 75 % of PAN patients [26]. The typical manifestation is a painful mononeuropathia multiplex, but distal-symmetric sensorimotor neuropathies and even chronic inflammatory demyelinating polyneuropathy (CIDP) can be observed as peripheral nervous system involvement in PAN [5]. There is no typical laboratory abnormality, blood sedimentation rate and C-reactive protein are often elevated and PAN is not associated with ANCA. The diagnosis can be confirmed by the typical histological features in biopsy and/or the detection of microaneurysms in the intestinal angiography.

23.5.3 Small Vessel Vasculitides

23.5.3.1 Churg-Strauss Syndrome (CSS)

This vasculitis type was first described in 1951 by Churg and Strauss. A development over different phases can be observed: (1) a prodromal phase with asthma or rhinitis, which can last for years before the vasculitic symptoms develop, (2) an intermittent phase with eosinophilia and pulmonary eosinophilic infiltrates, and (3) the main vasculitic manifestation including cutaneous, gastrointestinal symptoms, sinusitis, arthralgia and vasculitic neuropathy. PNS involvement is frequent (75–80 % of patients) and neuropathy can be the initial manifestation in a substantial proportion of patients [27]. The main clinical syndrome is mononeuropathia multiplex, some patients may have pure sensory or sensorimotor distal neuropathy [28, 29]. Neurophysiological examination shows typically an axonal damage. Eosinophilia in the peripheral blood can be found regularly and in 40–70 % of patients, pANCA are positive [30]. Eosinophilic infiltrates are present in biopsy specimen of nerve and other tissues [29]. One study suggests two different histopathological types of neuropathy in CSS patients. In this study, ANCA-positive CSS patients have predominantly necrotizing vasculitis in the nerve biopsy, whereas ANCA-negative CSS nerve biopsies show a large number of eosinophilic infiltrates in the epineurium [29].

23.5.4 Granulomatosis with Polyagiitis (GPA)

GPA is a vasculitic disease, regularly associated with c-ANCA, which are directed against proteinase 3. Mostly, patients have granulomatous involvement of the upper and lower respiratory tract and additional rapid-rapidly progressive glomerulonephritis. Subsequent development of vasculitic disease is common and many patients show the full-generalised form including pulmonary and renal involvement. Interestingly, the c-ANCA seems to be directly involved in the physiopathology by activation and degranulation of granulocytes. The cANCA bind to surface-expressed proteinase-3, which has been translocated from inside the cell by the proinflammatory cytokines TNF-α and IL-1. The degranulation of the granulocytes then induces a necrotizing vasculitis with endothelial damage.

Vasculitic neuropathy can be observed in 20–25 % of GPA patients [31, 32]. Most of them show mononeuritis multiplex, in a few patients, cranial nerve involvement has been described [33]. The neuropathy may be the first symptom of GPA in some patients, which underlines the importance of ANA/ANCA diagnostic tests in patients with newly diagnosed asymmetric neuropathy [27].

23.5.5 Microscopic Polyangiitis (MPA)

MPA is a systemic, necrotizing vasculitis of the small vessels, mainly in older patients with a slight male predominance. Patients have lung involvement, glomerulonephritis, skin lesions and abdominal pain. In 50–75 % of patients p-ANCA can be found, some patients can have c-ANCA [34]. About 10–50 % of MPA patients develop neuropathy. The most frequent clinical manifestation is mononeuropathia multiplex, mainly affecting the peroneal, median and ulnar nerves [33, 35, 36].

23.6 IgG4-Related Disease

Immunoglobulin G4-related disease was recently recognized as a common pathophysiology in a heterogeneous group of diseases and can affect a variety of organ systems [37]. One of the first diseases described is the Mikulicz syndrome, an inflammatory disease of the salivary gland, which was already described in the late nineteenth century [38]. The main finding is an infiltration of the affected tissue with IgG4+ plasma cells; the IgG4 level in the serum may be elevated [39]. Single cases of an IgG4-associated neuropathy were reported, but the incidence of IgG4-related neuropathy is unknown yet [40].

23.7 Secondary Systemic Vasculitis

Secondary systemic vasculitis is a heterogeneous disease group. Infectious diseases, connective tissue diseases, malignancies and drugs can cause vasculitis including vasculitic neuropathy.

23.7.1 Systemic Lupus Erythematosus (SLE)

A variety of neurological disturbances can be observed in SLE, including cerebral vasculitis, which often leads to stroke, cerebral venous thrombosis, transverse myelitis, or peripheral neuropathy. The latter can be observed in about 10–20 % of SLE patients [41, 42]. Clinically, the neuropathy in SLE is mainly distal-symmetric sensory or sensorimotor neuropathy and less frequent mononeuropathia multiplex or small fibre [41]. Neurophysiological investigation reveals axonal type in 80–90 % and demyelinating type in 10–20 % of SLE-associated neuropathy. Autonomic disturbances are present in one third of the neuropathy patients, including both sympathetic and parasympathetic nervous system involvement [43].

23.7.2 Systemic Sclerosis (SSc)

About 30 % of systemic sclerosis patients have neuropathy, predominantly sensory or small-fibre type [44]. Additionally, autonomic dysfunction causes mainly gut motility disturbances in these patients [45]. In some cases of systemic sclerosis, neuropathy can be the initial presentation of the disease.

23.7.3 Sjögren's Syndrome

Due to an affection of the exocrine glands, Sjögren's syndrome is clinically defined by the so-called sicca complex (dry eyes/dry mouth). Anti-SSA and –SSB autoantibodies, a subgroup of ENA can be found regularly in these patients [46]. Interestingly, autoantibodies against the muscarinic M3 receptor seem to have an important pathophysiological role in the sialoadenitis and could also be involved in the nervous system manifestations of these patients [47]. Both central and peripheral nervous system involvement including trigeminal nerve affection has been described [48]. Neuropathies have been found in 2–64 % of the patients. These neuropathies can be symmetric or asymmetric or resemble small fibre neuropathy and only a small part of them are vasculitic [49].

23.7.4 Rheumatoid Arthritis (RA)

About 15–50 % of RA patients develop neuropathy. However, peripheral nervous system disease in RA can have a variety of origins, such as drug-induced neuropathy or entrapment mononeuropathy. The main form of polyneuropathy is an axonal, distal-symmetric sensorimotor neuropathy [50].

23.7.5 Paraneoplastic Vasculitic Neuropathy

Until now, every clinical type of neuropathy was found in paraneoplastic (tumor-associated) neuropathy. However, pure sensory neuronopathy (Denny-Brown) is the most classical type of paraneoplastic neuropathy, and this special neuropathy is mainly associated with small cell lung cancer (SCLC) and anti-Hu antibodies can be found (Fig. 23.2). In general, SCLC, breast and ovarian cancer as well as lymphoma are the most frequent tumors found in paraneoplastic neuropathy [51]. Patients with vasculitic paraneoplastic neuropathy have mostly mononeuropathia multiplex or asymmetric neuropathy. Torvik and Berntzen in 1968 and Johnson et al. 1979 described the first patients with vasculitic neuropathy associated with tumors (renal cell carcinoma, SCLC or lymphoma) [52, 53]. Oh described 26 patients with paraneoplastic vasculitic neuropathy, mainly associated with SCLC and lymphoma. Many of them had elevated CSF protein and high ESR [54]. Clinically, mononeuritis multiplex and distal-symmetric sensorimotor neuropathy can be observed. If paraneoplastic vasculitic neuropathy is suspected, antineuronal autoantibodies, as well as antinuclear antibodies (ANA) and ANCA should be examined. In some patients with paraneoplastic neuropathies, both vasculitic and non-vasculitic, only ANA can be found [55]. Non-vasculitic paraneoplastic neuropathies, such as the anti-Hu positive sensory neuronopathy Denny-Brown, do not respond to immunotherapy, whereas vasculitic paraneoplastic neuropathy may respond to immunosuppressants (steroids, cyclophosphamide) in the majority of patients.

23.7.6 Hepatitis C/Cryoglobulinemia

Cryoglobulinemia can occur essential or in the context of chronic infections or lymphoproliferative diseases. The cryoglobulins are mono- or polyclonal immunoglobulins, that precipitate at cool temperatures and these proteins can induce vascular damage by occlusion of microvessels or induction of immune complex deposits in small vessels [56–58]. Fifty per cent of hepatitis C patients have mixed cryoglobulinemia, but only 15 % of them develop the clinical syndrome of mixed cryoglobulinemic vasculitis (MCV). About 80 % of MCV lacking other reasons are caused by

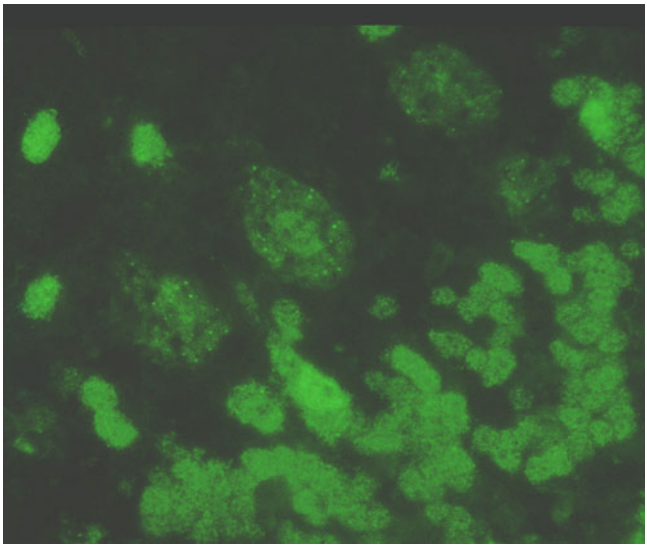

Fig. 23.2 Antineuronal antibody (antu-Hu) from a patient with vasculitic neuropathy and small cell lung cancer. Staining of neuronal nuclei and (to a lesser extent) cytoplasm of cerebellar neurons

chronic hepatitis C. The clinical symptoms consist of skin lesions (purpura), neuropathy, glomerulonephritis, ulcers, arthritis, and sicca syndrome. Rheumatoid factor can be found in more than 80 % and decreased complement factors C3 and C4 occur in 70 % of MCV patients [56]. The pathophysiological role of anti-sulfatide and anti-ganglioside antibodies, which can be detected in a part of MCV-associated neuropathy, is still not elucidated yet [12].

Neuropathy can be asymmetric, mononeuropathia multiplex or distal-symmetric, the latter often showing a slowly progressive course, whereas the others develop acute or subacute [59, 60]. Pure sensory neuropathy has also been described [50]. Pain occurs in 50 % of MCV-associated neuropathy and predominant small-fibre neuropathies have also been observed [59]. Neurophysiological examination reveals axonal neuropathy and even without clinical symptoms, most patients with MCV show at least neurophysiological abnormalities suggestive of neuropathy [61–63]. Nerve biopsy studies show axonal damage, perivascular infiltration with mononuclear cells predominantly in the epineurium and IgM and complement deposits in the affected vessel walls [59, 63, 64].

23.7.7 Other Secondary Systemic Vasculitides

Sarcoidosis can be associated with mononeuropathia multiplex, small fibre neuropathy or typical CIDP. The latter shows a good response to intravenous immunoglobulins (IVIg), the others respond regularly to steroids [65–68].

Behcet's disease and inflammatory bowel disease both are rarely associated with neuropathy and most of them are non-vasculitic. In both diseases, central nervous system involvement is much more frequent [69, 70].

A vasculitic neuropathy in HIV has been described in association with cytomegalovirus (CMV) or with lymphoma. This disease may be the result of immune complex deposition more than direct HIV infection of the nervous system [71–73]. However, there is an increased risk for HIV patients to develop other secondary vasculitides, including PAN or MPA.

23.7.8 Drug-Induced Vasculitic Neuropathy

A variety of drugs can induce vasculitis, both ANCA-positive and –negative. These drugs include many of the new biologicals (etanercept, adalimumab, infliximab and others) as well as other medications, such as carbimazole or levamisole. Some drugs have especially been reported to induce vasculitic neuropathy. However, to prove a causal relationship is sometimes difficult, since some of the drugs are given as a treatment of vasculitic diseases. The antibiotic minocycline can induce a non-systemic vasculitic neuropathy [74, 75]. Other drugs, such as naproxen, penicillin or the antiepileptic phenytoin induced systemic vasculitis including neuropathy, and the discontinuation of the drug resulted in an improvement of the vasculitis [76]. Table 23.7 gives an overview about drugs, which can induce vasculitic neuropathy.

23.8 Non-systemic Vasculitis of the Peripheral Nervous System

If vasculitic neuropathy occurs without detectable systemic involvement, the term non-systemic vasculitic neuropathy (NSVN) is used. About 25 % of all vasculitic neuropathies belong to this group [44]. The course of NSVN is often subacute, but about one third of the patients show progressive disease. The typical clinical picture is an asymmetric, progressive and painful neuropathy with severe paresis [77]. The neurophysiological examination shows axonal sensorimotor or motor neuropathy. Mostly, NSVN remains a localized vasculitis; however, in some cases additional skin manifestations or generalization was observed and the neuropathy tends to relapse, when immunosuppressive treatment is reduced [78, 79]. Nerve biopsy

Table 23.7 Drugs inducing vasculitic neuropathy

Drug	Disease	Reference
Valacyclovir	Mononeuritis multiplex	[115]
Minocycline	Non-systemic vasculitic neuropathy	[75, 113, 114]
Ipililumab	Biopsy-proven vasculitic neuropathy	[116]
Bortezomib	Microvasculitic motor predominant neuropathy	[117]
Rituximab	Mononeuritis multiplex	[118]
Naproxene	Leukocytoclastic vasculitis including neuropathy	[76]
Propylthiouracil	ANCA-positive vasculitis including neuropathy	[119]

should be performed, if NSVN is suspected and histopathology shows nerve microvasculitis. Recently, the main clinical and histopathological features were published in a guideline of the peripheral nerve society, describing criteria for definite, probable and possible vasculitic neuropathy [9].

Treatment of NSVN includes corticosteroids, cyclophosphamide, methotrexate and azathioprine in the first line and is described in detail in the treatment section. In a recent single-center cohort of 60 patients with histologically proven NSVN, initially all patients improved after iv methylprednisolone. However, after 4 years, 48 % of the patients still had immunosuppressive treatment and an age <64 years was associated with a better prognosis [80].

23.9 Diabetic and Non-Diabetic Lumbosacral Radiculoplexus Neuropathy (DLRPN/LRPN)

In patients with diabetes, the lumbosacral plexus including roots and peripheral nerves can be affected in a often painful disease, termed diabetic lumbosacral radiculoplexus neuropathy (DLRPN) [81]. The disease starts often with acute, severe neuropathic pain, followed by asymmetric paresis of the lower limbs, which become disabling during the acute stage. DLRPN is a monophasic disease, but half of the patients have walking difficulties or become wheelchair bound in this stage [8]. Autonomic symptoms can be found in 50 % of DLRPN patients. Spontaneous recovery may occur, but most patients have incomplete recovery including weakness and sensory disturbances. Interestingly, it mainly affects patients with mild diabetes mellitus in a stable situation; a non-diabetic form (LRPN) has also been described. Although upper limb nerves can be involved in DLRPN, a separate upper limb variant exists (DCRPN) [82]. Moreover, an overlap with CIDP has been described in some patients [83]. The histopathological picture is a focal nerve ischemia, caused by microvasculitis [84]. Neurophysiological examination shows axonal involvement of the lumbosacral plexus and very often

includes paraspinal denervation. The cerebrospinal analysis reveals elevated total protein and a normal cell count in most patients.

23.10 Treatment

23.10.1 Treatment of Non-Systemic Vasculitic Neuropathy (NSVN)

There are no randomized controlled studies (RCT) for NSVN yet. However, the Peripheral Nerve Society published recommendations for the treatment of NSVN [9]. It is recommended to treat NSVN patients with corticosteroids (initially prednisolone 1 mg/kg/day) with a slow tapering over months. Initial high-dose prednisolone pulses (500–1000 mg prednisolone for 3–5 days) can be used alternatively, followed by daily treatment with 1 mg/kg. Osteoporosis prophylaxis should be given; it is unclear yet, whether steroid treatment increases the risk of peptic ulcers and whether patients should be treated with proton pump inhibitors prophylactically. In case of rapid progressive neuropathy, cyclophosphamide (CYC) pulse treatment should be considered and long-term immunosuppression with methotrexate or azathioprine is necessary [85]. To reduce the risk of hemorrhagic cystitis, mesna should always be used in CYC pulse therapy and for toxicity reason, CYC should only be given for 6–12 months. There are two cohort studies, which implicate a better efficiency of a combination therapy [16, 79]. Other treatment regimens are poorly investigated. Intravenous immunoglobulins have been used successfully in a few otherwise treatment-resistant vasculitis patients [86]. Plasma exchange seems to have little effect, even in combination treatment [87–89]. Since rituximab treatment shows a good effect also on the neuropathic symptoms in generalized vasculitic diseases, it may also be used for NSVN in otherwise treatment-refractory patients [90]. Since vasculitic neuropathies usually are predominantly axonal, no significant improvement may be seen in the first weeks or even months. However, there is no surrogate marker, by which the treatment efficacy during the treatment can be verified. The first symptom, which may improve under sufficient immunosuppression, is the neuropathic pain.

23.10.2 Treatment of Non-Viral Systemic Vasculitic Neuropathy (SVN)

The treatment of vasculitic neuropathy associated with systemic vasculitis (SVN) should be performed according to the guidelines of the underlying systemic disease. As in NSVN, corticosteroids are used as initial treatment of SVN in the same dosages. Improvement of SVN may last weeks or months because of the axonal

damage of the nerves. Therefore, erythrocyte sedimentation rate or C-reactive protein can be used to control the efficacy of the treatment. Suppiah and colleagues recently reported a rate of 15 % clinical apparent neuropathy in a cohort of ANCA-associated vasculitis and 40 % improved after treatment [33]. In severe SVN cases, cyclophosphamide (CYC) is used either additionally or subsequently to corticosteroid treatment. Daily oral cyclophosphamide shows serious side effects, therefore pulse therapy (0.6–0.75 g/m^2 every 2–4 weeks) should be preferred and mesna should be given to avoid hemorrhagic cystitis. Cyclophosphamide treatment should be limited to 6–12 months, since there are a variety of long-term immunosuppressive drugs with less toxic side effects. Methotrexate (20–25 mg weekly) or azathioprine (1–2 mg/kg daily) are the classical long-term immunosuppressants to maintain remission. Leflunomide can be used in the long-term treatment of GPA [91].

Another immunosuppressant in the treatment of vasculitis is mycophenolate mofetil (MMF): However, its effectiveness is not completely clear. One open-label pilot trial showed remission maintenance in 13 out of 17 patients with GPA, in another study relapses were more frequent and earlier in comparison to azathioprine [25, 92]. In lupus treatment, MMF is equally effective to azathioprine but has less side effects [93]. However, no data are available regarding its effect on vasculitic neuropathy.

Rituximab, an anti-CD20 monoclonal antibody, targets mainly B-cells and is established as an effective treatment in MPA and GPA. It has recently been licensed for ANCA-associated vasculitis. In the meantime, rituximab is a first-line therapy of ANCA-associated vasculitis and is as effective as cyclophosphamide [90]. It is also effective in cryoglobulinemic vasculitis and is usually given in a weekly dosage of 375 mg/m^2 for four times [94].

23.10.3 Vasculitis Associated with Infections

Neuropathy associated with mixed cryoglobulinemia/HCV infection includes both antiviral and immunosuppressive treatment. Antiviral treatment includes pegylated interferon-α, ribavirin, telaprevir and boceprevir and, more recently, the direct-acting antiviral agents. Interferon- α (IFN- α) alone or in combination with ribavirin may improve neuropathic symptoms in a smaller part of patients [64, 95, 96]. However, IFN- α is also able to induce inflammatory neuropathies and can also exacerbate other symptoms of mixed cryoglobulinemic vasculitis [97, 98]. Therefore, corticosteroids, cyclophosphamide or plasma exchange should be added in patients with severe neuropathy or if neuropathic symptoms do not improve under antiviral treatment. To remove circulating cryoglobulins, plasma exchange is used in MCV, although there are no RCT yet and only a part of MCV patients respond.

Ferri and collegues reported a cohort of MCV patients responding to rituximab, independently of HCV status [99]. In their study, 95 % of the neuropathic symptoms improved and rituximab was considered safe and effective. In HCV-associated MCV, additional rituximab showed a better response than antiviral treatment alone [100].

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