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Diagnosis and therapeutic options for peripheral vasculitic neuropathy

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***Abstract*:** Vasculitis can affect the peripheral nervous system alone (nonsystemic vasculitic neuropathy) or can be a part of primary or secondary systemic vasculitis. In cases of pre-existing systemic vasculitis, the diagnosis can easily be made, whereas suspected vasculitic neuropathy as initial or only manifestation of vasculitis requires careful clinical, neurophysiological, laboratory and histopathological workout. The typical clinical syndrome is mononeuropathia multiplex or asymmetric neuropathy, but distal-symmetric neuropathy can frequently be seen. Standard treatments include steroids, azathioprine, methotrexate and cyclophosphamide. More recently the B-cell antibody rituximab and intravenous immunoglobulins have shown to be effective in some vasculitic neuropathy types.

Keywords: autoantibodies, polyneuropathy, rheumatic diseases, treatment, vasculitic neuropathy

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Introduction

Vasculitic neuropathies are a heterogeneous group of peripheral nerve disorders associated with vasculitis, either nonsystemic (only affecting the peripheral nerve) or systemic vasculitis (Table 1). Systemic vasculitis can occur as primary vasculitis with no other reason for the vasculitis, or secondary vasculitis as a complication of other autoimmune or infectious disease [Collins, 2012]. The common feature of all vasculitic neuropathies is an inflammation of the vasa nervorum, mainly the epineural arteries of the nerve, leading to thrombosis and subsequently to ischaemic damage.

If the neuropathy is part of an already known systemic vasculitis, diagnosis is not difficult to make. However, if the neuropathy is the first manifestation of vasculitis, diagnosis may be difficult, since only a part of the vasculitic neuropathies shows the typical clinical picture of mononeuritis multiplex. Therefore, if vasculitic neuropathy is suspected, an extensive diagnostic pathway is necessary to confirm or to exclude the diagnosis.

There are no studies, which investigated the incidence or prevalence of vasculitic neuropathy. Systemic vasculitic diseases themselves have an annual incidence of about 60–140/million, including about 30% secondary systemic vasculitis [Watts *et al.* 1995; Gonzalez-Gay and Garcia-Porrua, 1999]. In all patients who undergo nerve biopsy because of unclear neuropathy, about 1% overall have vasculitis [Kissel *et al.* 1985; Davies *et al.* 1996]. In some systemic vasculitis, especially large vessel vasculitic diseases, neuropathy is rare; in others neuropathy even belongs to the diagnostic criteria (Table 2) [Basu *et al.* 2010].

Pathogenesis

Inflammation of the walls of nutrient and epineural arteries is the main pathophysiological feature in vasculitic neuropathy. However, since the underlying vasculitic diseases have different aetiologies, the common final path in the vasa nervorum is thrombosis and ischaemic damage. Although the nerve is diffusely affected by the vasculitic process, the tissue at risk is a border zone in the proximal to middle section of the nerve, where the most axonal damage occurs [Dyck *et al.* 1972; Morozumi *et al.* 2011]. In cryoglobulinemia, a direct pathogenic role of frequently detectable antisulfatide antibodies is discussed [Alpa *et al.* 2008]. The pain in vasculitic neuropathies may be associated with an increased expression of nerve growth factor (NGF) in the affected nerves [Yamamoto *et al.* 2003].

Table 1. Classification of vasculitides associated with neuropathy (according to Collins *et al.* [2010]).

Primary systemic vasculitis
1. Small vessel vasculitis
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
Granulomatosis with polyangiitis (GPA)
Essential mixed cryoglobulinemic (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. Behcet's disease
4. Infections (hepatitis B and C, HIV, cytomegalovirus and others)
5. Drugs
6. Malignancy
7. Inflammatory bowel disease
8. Hypocomplementemic urticarial vasculitis syndrome
Nonsystemic or localized vasculitis
1. Nonsystemic vasculitic neuropathy
2. Diabetic radiculoplexus neuropathy (DRPLN)
3. Localized cutaneous or neuropathic vasculitis

Clinical features and diagnostic procedures

About 35–65% of the vasculitic neuropathy patients show the typical clinical picture of a mononeuropathia multiplex. However, half of the patients show other clinical types, mostly painful sensorimotor axonal neuropathy or, rarely, pure sensory neuropathy, mostly with an asymmetric pattern. About 10–40% of biopsy-proven vasculitic neuropathies can occur as distal-symmetric neuropathy [Davies *et al.* 1996; Claussen *et al.* 2000; Bennett *et al.* 2008]. There is no association of a distinct clinical picture with the underlying vasculitic disease. Most affected nerves are the peroneal and/or tibial nerve, on the upper extremity ulnar nerve seems to be involved most frequently. Almost all vasculitic neuropathies develop acutely or subacutely, a chronic development over years can occur in rare cases. Unspecific symptoms, such as weight loss, fever or fatigue, have been reported in 80% of neuropathy with systemic vasculitis and in about 50% of patients with nonsystemic vasculitic neuropathy (NSVN).

Neurographic examination reveals multifocal axonal neuropathy with reduced compound muscle action potential (CMAP) amplitudes. In electromyography, one can see a neurogenic pattern including spontaneous muscle fibre activity, polyphasic, extended and/or high-amplitude motor unit action potentials.

If a systemic vasculitis or another underlying reason for the neuropathy has not been detected yet, a variety of laboratory tests should be performed. This includes a routine testing in all patients with neuropathy of yet unknown reason and, if inflammatory or vasculitic neuropathy is suspected, a more detailed laboratory investigation (Table 3).

If there is no evidence of a systemic vasculitis by other parameters (clinical manifestations, autoantibodies, etc.) nerve biopsy is required. Usually, sural nerve biopsy with or without muscle biopsy has been used to detect vasculitic neuropathy. An interesting alternative is the combined biopsy of the superficial peroneal nerve together with the peroneus brevis muscle [Agadi *et al.* 2012]. Although controlled trials are lacking, peroneal nerve/muscle biopsy could be more effective since in the case of muscle involvement, the more distal peroneus brevis muscle may be more frequently involved than the gastrocnemius muscle.

The main pathological feature of vasculitis is a wall-damaging intramural infiltration [Collins *et al.* 2010] (Figure 1). The guideline on NSVN from the Peripheral Nerve Society provides diagnostic criteria for probable and definite vasculitic neuropathy. The diagnosis of definite vasculitic neuropathy includes (1) inflammatory cells in the vessel wall accompanied by pathologic evidence of acute or chronic vascular wall damage, and (2) no evidence of another primary disease that mimics vasculitis pathology (lymphoma, lymphomatoid granulomatosis or amyloidosis) [Collins *et al.* 2010]. Probable vasculitic neuropathy can be suspected, if (1) the criteria for definite vasculitic neuropathy are not completely fulfilled, (2) the neuropathy is predominantly axonal and (3) perivascular inflammation plus signs of vascular damage or pathological predictors of vasculitic neuropathy [Collins *et al.* 2010].

Table 2. Frequency of neuropathy in vasculitic diseases.

Disease	Frequency	Reference
Primary systemic vasculitis		
Giant cell arteritis	Rare	[Chia *et al.* 1996; Koike *et al.* 2013]
Polyarteritis nodosa	65–85%	[Schaublin *et al.* 2005; Ohyama *et al.* 2013b]
Churg–Strauss syndrome	65–80%	[Hattori *et al.* 1999; Zwerina, 2008]
Granulomatosis with polyangiitis	5–50%	[Schaublin *et al.* 2005; De Souza *et al.* 2010]
Microscopic polyangiitis	6–75%	[Hattori *et al.* 2002; Schaublin *et al.* 2005]
Cryoglobulinemia	30–70%	[Cacoub *et al.* 2008; Collins and Periquet, 2008]
Secondary systemic vasculitis		
1. Connective tissue diseases		
Systemic lupus erythematosus	20–27%	[Vital *et al.* 2006; Servioli *et al.* 2007]
Rheumatoid arthritis	15–70%	[Voskuyl *et al.* 2003; Agarwal *et al.* 2008; Muramatsu *et al.* 2008]
Sjögren's syndrome	30–45%	[Delalande *et al.* 2004; Terrier *et al.* 2007]
Systemic sclerosis (scleroderma)	5–30%	[Dyck *et al.* 1997; Collins and Periquet, 2008]
2. Others		
Infections (hepatitis B virus, hepatitis C virus (HCV), HIV)	5–70%	[Said and Lacroix, 2005; Schaublin *et al.* 2005; Cacoub *et al.* 2008; Collins and Periquet, 2008, Ohyama *et al.* 2013b]
Sarcoidosis	5–10%	[Chen and McLeod, 1989; Allen *et al.* 2003; Vital *et al.* 2008]
Malignancy	Rare*	[Oh *et al.* 1991; Fain *et al.* 2007]
Drugs	Rare	[Schapira *et al.* 2000; Thaisetthawatkul *et al.* 2011]

Table 3. Laboratory investigations in suspected vasculitic neuropathy.

Basic neuropathy screening	Vasculitis suspected
Full blood count	Antinuclear antibodies (ANA)
Erythrocyte sedimentation rate	Antineutrophil cytoplasmic antibodies (ANCA)
C-reactive protein	Extractable nuclear antigens (ENA)
Fasting glucose (2 consecutive days)	Rheumatoid factor
Electrolytes	Anti-CCP antibodies
Renal and liver function	Cryoglobulins
Creatine kinase	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

Primary systemic vasculitis

Primary systemic vasculitis has been classified according to the diameter of the affected vessels, including three groups of vasculitis: small-vessel, medium-vessel and large-vessel vasculitis. The frequency of neuropathy in the different diseases varies between 5% and 80% (Table 2). However, since the most frequent diameters in nerves and muscles are between 50 and 300 μm, vasculitic neuropathy occurs mainly in the small- and medium-sized vasculitides (Table 2).

Large vessel vasculitis

The large vessel vasculitis includes two disease entities: giant cell arteritis and Takayasu arteritis.

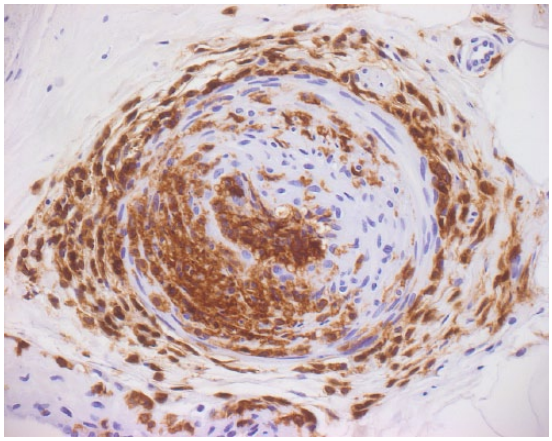

Figure 1. Immunohistochemistry of peripheral nerve vasculitis. Epineural vessel with extensive lymphocyte infiltration and subtotal stenosis. Staining of lymphocytes with anti-LCA (lymphocyte common antigen) antibody. (Courtesy of J. Weis, Aachen.)

Both diseases are normally not associated with neuropathies, but with central nervous system involvement.

Medium-sized vessel vasculitis

This group includes classic polyarteritis nodosa (PAN), Kawasaki disease and thromboangiitis obliterans. Both latter diseases are not associated with neuropathy, whereas in PAN, involvement of the peripheral nervous system can frequently be seen.

Polyarteritis nodosa

The PAN is a rare systemic vasculitis (annual incidence in European countries 0.1–1.6 cases/million inhabitants) of the medium-sized arteries and not associated with glomerulonephritis [Hernandez-Rodriguez *et al.* 2014]. According to the definition of the Chapel Hill consensus conference, arterioles, capillaries and venules are not affected [Hiemstra *et al.* 2010]. PAN is an immune complex vasculitis and in about one third of the PAN patients, hepatitis B is involved in the pathogenesis. Interestingly, other chronic infections, such as parvovirus B19, hepatitis C, HIV or streptococci can also led to PAN. An observed reduction of incidence may be due to the widespread vaccination against hepatitis B. In contrast to the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides, there are no typical autoantibodies in PAN. Histological features include infiltration of vessel walls with polymorphonuclear neutrophils, predominantly in branching points. In active lesions, fibrinoid necrosis is frequently seen. The clinical symptoms include weight loss, livedo reticularis, testicular pain, myalgia, kidney involvement and visceral artery aneurysms. PAN is mostly a monophasic disease and the prognosis depends on the involved organ systems. If the heart or the central nervous system is involved, prognosis is poor. Recently, the French vasculitis group proposed a revised five-factor score to estimate the prognosis of PAN [Guillevin *et al.* 2011]. Up to 75% of the PAN patients have neuropathy, which led to the inclusion of neuropathy into the American college of rheumatology diagnostic criteria [Basu *et al.* 2010]. Clinically, the neuropathy presents mainly as painful mononeuropathia multiplex, but typical chronic inflammatory demyelinating polyneuropathy (CIDP) has also been described in association with PAN.

Small vessel vasculitis

Churg–Strauss syndrome. Churg–Strauss syndrome (CSS) is a vasculitis of the small vessels and was first described in 1951 by Churg and Strauss. After years of prodromi (asthma, rhinitis), most patients develop an intermittent phase of eosinophilia and eosinophilic infiltrates (mainly pulmonary), then vasculitic manifestation with cutaneous, gastrointestinal, sinusitis, arthralgia and neuropathy. Involvement of PNS occurs in about 75–80% of patients, and the neuropathy is mainly mononeuropathy multiplex, less often pure sensory or axonal sensorimotor neuropathy. The histopathological picture includes granulomatous vasculitis of the small and medium-sized arteries, arterioles, capillaries and venules with eosinophilic infiltrates in the peripheral blood. Blood examination reveals eosinophilia and 40–70% of the patients have pANCA.

Granulomatosis with polyagiitis. Granulomatosis with polyagiitis (GPA) is a granulomatous disease of the upper and/or lower respiratory tract (localized), often associated with rapid-progressive glomerulonephritis and a subsequent development of systemic vasculitic disease. Rhinitis can also be observed and many patients develop fully generalized syndrome with pulmonary and renal involvement including alveolar haemorrhage. Almost all patients are positive for c-ANCA, which are mainly directed against proteinase 3. The pathophysiology of GPA is quite well understood: there is a necrotizing vasculitis of smaller vessels (arterioles, capillaries, venules), in which

the ANCA induce activation and degranulation of granulocytes with consecutive endothelial damage. During this process, tumour necrosis factor (TNF)-alpha and interleukin (IL)-1 induce the translocation of proteinase 3 to the endothelial surface and adherence of neutrophils to endothelial cells, followed by degranulation of the neutrophils (→ANCA-cytokine-sequence mechanism). About 20–25% of GPA patients develop neuropathy, mostly mononeuritis multiplex or, rarely, mononeuropathy of a cranial nerve. In rare cases, the neuropathy may be the first symptom of GPA.

IgG4-related disease

IgG4-related systemic disease is a recently recognized systemic disease, which can include a variety of organ systems [Beyer *et al.* 2014]. This syndrome is mainly characterized by elevated IgG4 serum levels and an increased level IgG4+ plasma cells in biopsy (see the review by Perez Alamino and colleagues [Perez Alamino *et al.* 2013]). An IgG4-associated neuropathy has been described in single case reports, but the incidence of neuropathy in this syndrome has not been established yet [Ohyama *et al.* 2013a; Yokoi *et al.* 2014].

Microscopic polyangiitis

Microscopic polyangiitis (MPA) is a necrotizing vasculitis mainly of lung and kidney capillaries and is associated with pANCA, or, less frequently, cANCA [Schonermarck *et al.* 2001]. Clinically, the patients show glomerulonephritis, lung involvement, abdominal pain and skin purpura. Neuropathy has been found in 10–50% and mononeuropathia multiplex is the most common feature [Agard *et al.* 2003; Ribi *et al.* 2010; Suppiah *et al.* 2011].

Secondary systemic vasculitis

This is a heterogeneous group including vasculitis associated with infectious diseases, connective tissue diseases or malignancies as well as drug-induced vasculitides.

Connective tissue diseases

Systemic lupus erythematosus. Neurological involvement in systemic lupus erythematosus (SLE) includes cerebral vasculitis, transverse myelitis and peripheral neuropathy. About 20% of SLE patients have neuropathy, which can be classical distal-symmetric or mononeuropathia multiplex [Andrade *et al.* 2004; Collins and Periquet, 2008]. Neurophysiological studies show an axonal type in 70–80% and a more demyelinating type in 20% [Florica *et al.* 2011]. One third have autonomic involvement [Rafai *et al.* 2007].

Systemic sclerosis

Polyneuropathy in systemic sclerosis (SSc) seems to be more frequent than initially suspected. Up to 30% of the SSc patients have neuropathy, mostly sensory symptoms and small fibre dysfunction [Collins and Periquet, 2008]. Interestingly the gut motility disturbance in these patients is caused by an autonomic neuropathy of the gastrointestinal tract [Di Ciaula *et al.* 2008].

Sjögren's syndrome

Sjögren's syndrome is clinically characterized by a sicca syndrome (dry eyes/dry mouth) since the exocrine glands are affected by the autoimmune process. SS-A and/or SS-B antibodies can be found in the most patients [Beyer *et al.* 2014]. Sjögren's syndrome can occur as a primary disease, but can also be a part of another connective tissue disease as secondary Sjögren's syndrome. The incidence of neuropathy has been reported between 2% and 64%, but only a smaller part of them are vasculitic neuropathies. Clinically, symmetric and asymmetric neuropathies as well as small fibre neuropathies can be seen [Birnbaum, 2010]. In addition, the trigeminal nerve can be affected and autonomic neuropathies have been reported.

Rheumatoid arthritis

Neuropathy occurs in 15–50% of rheumatoid arthritis (RA) patients. Peripheral neuropathy in RA can have different origins, therefore, nonvasculitic neuropathy, such as entrapment mononeuropathy and drug-induced polyneuropathy must be recognised. The main clinical feature is a distal symmetric sensorimotor neuropathy [Schaublin *et al.* 2005].

Paraneoplastic vasculitic neuropathy

The typical paraneoplastic neuropathy is a pure sensory neuronopathy (Denny–Brown) associated with antineuronal autoantibodies (mostly anti-Hu). However, every other clinical type of neuropathy has been described as paraneoplastic.

The most associated tumours are small cell lung cancer, gynaecological cancer and lymphoma. The first descriptions of paraneoplastic vasculitic neuropathy came from Torvik and Berntzen in 1968 and from Johnson and colleagues in 1979 [Torvik and Berntzen, 1968; Johnson *et al.* 1979]. These patients had vasculitic neuropathy associated with renal cell carcinoma, small cell lung cancer or lymphoma. A bigger series was reported by Oh, who described the clinical features of 26 patients with paraneoplastic vasculitic neuropathy, mainly associated with SCLC and lymphoma [Oh, 1997]. High cerebrospinal fluid protein content and high erythrocyte sedimentation rate were suggestive of vasculitic paraneoplastic neuropathy. Most patients with paraneoplastic vasculitic neuropathy present clinically with mononeuropathia multiplex or asymmetric polyneuropathy. In case of suspected paraneoplastic vasculitic neuropathy, the examination of antineuronal autoantibodies, especially anti-Hu, may be helpful. Anti-Hu has a high specificity for paraneoplastic aetiology and more than 90% of anti-Hu positive patients have small cell lung cancer. In contrast to most other paraneoplastic neuropathies, vasculitic neuropathies seem to respond to immunosuppressive treatment with steroids or cyclophosphamide (CYC).

Hepatitis C/cryoglobulinemia

Various chronic infections can be associated with cryoglobulinemia. Cryoglobulins are immunoglobulins that precipitate at temperatures $<37°C$. The cryoglobulinemia can be asymptomatic or induces a small-vessel, immune-complex-mediated vasculitis. Most cases occur in hepatitis C infections. Although most of the hepatitis C patients develop cryoglobulinemia, only 15% of them show clinical signs of vasculitic disease. Purpura of the skin, renal involvement and arthralgia are the main clinical features and 30–70% of the patients develop neuropathy [Cacoub *et al.* 2008]. Most of the neuropathies are mononeuropathia multiplex or symmetric sensorimotor neuropathy. In rare cases, a pure sensory neuropathy could be observed [Schaublin *et al.* 2005]. In some patients, autoantibodies against the GM1-ganglioside or antisulphatide antibodies could be detected [Alpa *et al.* 2008]. It is unclear, whether these autoantibodies are a bystander phenomenon or directly involved in the pathophysiology of the axonal damage. In infection-associated vasculitis, antigen removal by antiviral treatment is as important as immunosuppression and patients with hepatitis C virus HCV and cryoglobulinemia will receive antiviral treatment in the first line. If no improvement can be seen, combination of antiviral and immunosuppressive treatment is necessary (see treatment).

Other secondary systemic vasculitides

In sarcoidosis, mononeuropathia multiplex and typical CIDP have been described [Vital *et al.* 2008]. Most neuropathies respond to steroids, and (in CIDP types) to intravenous immunoglobulins.

Inflammatory bowel disease (IBD) is rarely associated with neuropathy. Figueroa and colleagues just recently reported a 20-year incidence of 0.7% in a population-based study [Figueroa *et al.* 2013]. Most of the IBD-associated neuropathies seem to be nonvasculitic [Kararizou *et al.* 2012].

Behcet's disease is characterized by recurrent oral aphthae and several systemic clinical features, such as ocular disease, skin lesions, arthritis and genital aphthae. In most Behcet's patients with neurological complications, central nervous system involvement is much more frequent than neuropathy [Noel *et al.* 2013].

Drug-induced vasculitis has been reported in a variety of drugs. Naproxene has induced a leukocytoclastic vasculitis including neuropathy [Schapira *et al.* 2000]. Minocycline, an antibiotic has been reported to induce a NSVN [Thaisetthawatkul *et al.* 2011]. Treatment with propylthiouracil, an antithyroid drug, led to an ANCA-positive vasculitis including neuropathy [Frigui *et al.* 2008]. Other drugs with induction of vasculitis are penicillin, cocaine, heroin, phenytoin, all in which discontinuation improved the vasculitis [Schapira *et al.* 2000].

Nonsystemic vasculitis of the peripheral nervous system

Vasculitic neuropathy can occur without any systemic involvement and is then called NSVN. This type of neuropathy often develops subacute, although at least one third of the patients show a progressive course. Even there is no histological examination, NSVN should be suspected if an axonal neuropathy is asymmetric, progressive and painful and is associated with disabling paresis. Neurophysiological examination reveals axonal motor or sensorimotor neuropathy. Nerve biopsy

should be performed in the case of suspected NSVN. However, about 50% of patients with suspected vasculitic neuropathy are lacking histological examination. If biopsy has been performed, the main histopathological finding is intramural infiltration with vascular wall damage. The Peripheral Nerve Society recently published a guideline on the diagnosis, investigation and treatment of NSVN [Collins *et al.* 2010]. In this consensus report, criteria for definite, probable and possible vasculitic neuropathy have been established.

As already stated in neuropathies associated with systemic vasculitis, no randomized controlled treatment trials are available for the treatment of NSVN. There is a recommendation to treat NSVN patients with corticosteroids (start with prednisolone 1 mg/kg/day) with a slow tapering over months. Alternatively, a treatment regimen with initial high-dose prednisolone pulse (500–1000 mg prednisolone for 3–5 days), followed by tapering the dose can be used. In rapid progressive neuropathy, CYC pulse therapy can be used, followed by long-term immunosuppression with methotrexate or azathioprine. CYC should be used together with mesna to reduce the probability of haemorrhagic cystitis. For toxicity reasons, CYC should not be used for more than 6–12 months. Two cohort studies suggest that combination therapy may be more effective [Davies *et al.* 1996; Collins *et al.* 2003]. Although there is only evidence in primary vasculitis and not on NSVN, in treatment-resistant cases, rituximab, plasma exchange or intravenous immunoglobulins could be used [Levy *et al.* 2005; Stone *et al.* 2010].

Diabetic and nondiabetic lumbosacral radiculoplexus neuropathy

A mostly painful affection of lower limb nerve roots, lumbosacral plexus and peripheral nerves can occur in diabetic (diabetic lumbosacral radiculoplexus neuropathy [DLRPN]) or nondiabetic (lumbosacral radiculoplexus neuropathy [LRPN]) patients has been identified as a form of microvasculitis. Interestingly, DLRPN is not associated with increased severity of the diabetes, but affects also patients with stable diabetic situation. The disease is usually monophasic and spontaneous recovery can be seen, but is often incomplete, leaving the patients with weakness and sensory symptoms. It typically develops acute or subacute and shows an asymmetric distribution of affected nerves, plexus and/or roots, leading to the picture of a mononeuropathia multiplex of the lower limbs. Histological examination revealed nerve ischaemia, caused by microvasculitis [Dyck *et al.* 1999]. Upper limb involvement can occur in DLRPN/LRPN. However, a separate upper limb variant has recently been described [Massie *et al.* 2012].

Treatment

Primary systemic vasculitis and NSVN

In general, neuropathy associated with systemic vasculitis should be treated according to the guidelines of the disease. However, standard treatment of systemic vasculitic neuropathy (SVN) and classical NSVN are corticosteroids. A dose of 1 mg/kg daily is mostly recommended. During the following months, there should be a reduction of 5–10 mg every other week, until a maintenance therapy using 5–10 mg prednisolone daily is achieved. Osteoporosis prophylaxis should be initiated for every steroid treatment longer than 2 weeks. If patients have severe neuropathy, high-dose corticosteroids (1000 mg daily) can be initiated for 3–5 days, followed by 1 mg/kg daily. If the patient has axonal damage, a strong improvement will not be seen in the first few weeks. In patients with SVN, systemic parameters, such as erythrocyte sedimentation rate or C-reactive protein can be used as a control for effective treatment. In NSVN, no surrogate parameter has been identified yet to control treatment success. In a recent study, neuropathy has been reported to occur in about 15% of ANCA-associated vasculitis and improvement has been seen in 40% of the patients [Suppiah *et al.* 2011].

In many severe cases, CYC has been used additionally or subsequently to corticosteroids. Since daily orally CYC has substantial side effects, pulse therapy is recommended, mostly in dosages 0.6–0.75 g/m^2 every 2–4 weeks. To avoid bladder toxicity mesna should be added to treatment. The classical long-term treatment to maintain remission includes methotrexate (20–25 mg/weekly) or azathioprine (1–2 mg/kg/day). In GPA patients, leflunomide can be used in the long-term treatment [Metzler *et al.* 2007].

Mycophenolate mofetil (MMF) is another immunosuppressant that has been used to treat vasculitis patients. In an open-label pilot trial MMF could induce maintained remission in 13 out of

17 patients with GPA with only mild side effects [Silva *et al.* 2010]. However, in another study, relapses have been more frequent and occurred more quickly using MMF treatment, when compared with azathioprine [Hiemstra *et al.* 2010]. Therefore, MMF use in vasculitis is still under debate and there are no data on its effect on vasculitic neuropathy. In lupus, MMF has been equally effective to azathioprine with fewer side effects [Maneiro *et al.* 2014].

Recently, rituximab was established as an effective treatment in patients with MPA and GPA and has been licensed for ANCA-associated vasulitis recently. Rituximab is an anti-CD20 monoclonal antibody, targeting mainly B cells. In the meantime, Rituximab is considered as first-line treatment of ANCA-associated vasculitis. In a recent study, rituximab was as effective as CYC in the treatment of ANCA-associated vasculitis (197 patients, more effective in induction of remission after relapse) [Stone *et al.* 2010]. Rituximab was also effective in the treatment of cryoglobulinemic vasculitis [De Vita *et al.* 2012]. Normal dosage is 375 mg/m^2 four times every week.

Intravenous immunoglobulins (IvIg) have been described to be effective in some patients with NSVN and SVN in single case reports and smaller case series [Levy *et al.* 2003, 2005]. If steroids and/or CYC show no treatment effect, IvIg may be a suitable alternative.

Vasculitis associated with infections

If vasculitic neuropathy is associated with hepatitis C, antiviral treatment including pegylated interferon-alpha, ribavirin, and/or telaprevir and boceprevir [Chiche *et al.* 2012]. Ferri and colleagues [Ferri *et al.* 2011] reported 87 patients with cryoglobulinemic vasculitis, independent of hepatitis C status, which responded well to rituximab. In this study, skin purpuric lesions improved in 74%, vasculitic leg ulcers in 87%, nephropathy in 95% and neuropathy in 44% and rituximab was considered as a safe and effective treatment.

Plasma exchange is used in mixed cryoglobulinemia, since it is able to remove circulating cryoglobulins. However, no randomized controlled trials have been reported and only some of the patients seem to respond [Rockx and Clark, 2010; Ramos-Casals *et al.* 2012].

Concluding remarks

About 30–50% of all vasculitis patients exhibit signs of peripheral neuropathy. Neuropathies associated with systemic vasculitis should be treated according to the guidelines of the underlying disease. NSVN will be treated with steroids, or in severe/progressive cases, CYC pulse therapy. Some patients need long-term immunosuppression. Rituximab is an effective alternative to cyclophosphamide in the treatment of vasculitic neuropathies and is licensed for ANCA-associated vasculitis.

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Conflict of interest statement

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References

Agadi, J., Raghav, G., Mahadevan, A. and Shankar, S. (2012) Usefulness of superficial peroneal nerve/peroneus brevis muscle biopsy in the diagnosis of vasculitic neuropathy. *J Clin Neurosci* 19: 1392–1396.

Agard, C., Mouthon, L., Mahr, A. and Guillevin, L. (2003) Microscopic polyangiitis and polyarteritis nodosa: how and when do they start? *Arthritis Rheum* 49: 709–715.

Agarwal, V., Singh, R., Wiclaf, Chauhan, S., Tahlan, A., Ahuja, C. *et al.* (2008) A clinical, electrophysiological, and pathological study of neuropathy in rheumatoid arthritis. *Clin Rheumatol* 27: 841–844.

Allen, R., Sellars, R. and Sandstrom, P. (2003) A prospective study of 32 patients with neurosarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 20: 118–125.

Alpa, M., Ferrero, B., Cavallo, R., Naretto, C., Menegatti, E., Di Simone, D. *et al.* (2008) Anti-neuronal antibodies in patients with HCV-related mixed cryoglobulinemia. *Autoimmun Rev* 8: 56–58.

Andrade, R., Moya Machado, A., Gomez Conde, S., Garcia Espinosa, A., Molina Diaz, M., Machado Rojas, A. *et al.* (2004) [Neuropathies due to vasculitis in infancy]. *Rev Neurol* 38: 619–624.

Basu, N., Watts, R., Bajema, I., Baslund, B., Bley, T., Boers, M. *et al.* (2010) EULAR points to consider in the development of classification and diagnostic criteria in systemic vasculitis. *Ann Rheum Dis* 69: 1744–1750.

Bennett, D., Groves, M., Blake, J., Holton, J., King, R., Orrell, R. *et al.* (2008) The use of nerve and muscle biopsy in the diagnosis of vasculitis: a 5 year retrospective study. *J Neurol Neurosurg Psychiatry* 79: 1376–1381.

Beyer, G., Schwaiger, T., Lerch, M. and Mayerle, J. (2014) IgG4-related disease: a new kid on the block or an old aquaintance? *United European Gastroenterol J* 2: 165–172.

Birnbaum, J. (2010) Peripheral nervous system manifestations of sjogren syndrome: clinical patterns, diagnostic paradigms, etiopathogenesis, and therapeutic strategies. *Neurologist* 16: 287–297.

Cacoub, P., Delluc, A., Saadoun, D., Landau, D. and Sene, D. (2008) Anti-CD20 monoclonal antibody (rituximab) treatment for cryoglobulinemic vasculitis: where do we stand? *Ann Rheum Dis* 67: 283–287.

Chen, R. and McLeod, J. (1989) Neurological complications of sarcoidosis. *Clin Exp Neurol* 26: 99–112.

Chia, L., Fernandez, A., Lacroix, C., Adams, D., Plante, V. and Said, G. (1996) Contribution of nerve biopsy findings to the diagnosis of disabling neuropathy in the elderly. A retrospective review of 100 consecutive patients. *Brain* 119: 1091–1098.

Chiche, L., Bataille, S., Kaplanski, G. and Jourde, N. (2012) The place of immunotherapy in the management of HCV-induced vasculitis: an update. *Clin Dev Immunol* 2012: 315167.

Claussen, G., Thomas, T., Goyne, C., Vazquez, L. and Oh, S. (2000) Diagnostic value of nerve and muscle biopsy in suspected vasculitis cases. *J Clin Neuromuscul Dis* 1: 117–123.

Collins, M. (2012) The vasculitic neuropathies: an update. *Curr Opin Neurol* 25: 573–585.

Collins, M., Dyck, P., Gronseth, G., Guillevin, L., Hadden, R., Heuss, D. *et al.* (2010) Peripheral nerve society guideline on the classification, diagnosis, investigation, and immunosuppressive therapy of non-systemic vasculitic neuropathy: executive summary. *J Peripher Nerv Syst* 15: 176–184.

Collins, M. and Periquet, M. (2008) Isolated Vasculitis of the Peripheral Nervous System. *Clin Exp Rheumatol* 26: S118–130.

Collins, M., Periquet, M., Mendell, J., Sahenk, Z., Nagaraja, H. and Kissel, J. (2003) Nonsystemic vasculitic neuropathy: insights from a clinical cohort. *Neurology* 61: 623–630.

Davies, L., Spies, J., Pollard, J. and McLeod, J. (1996) Vasculitis confined to peripheral nerves. *Brain* 119: 1441–1448.

De Souza, F., Radu Halpern, A., Valente Barbas, C. and Shinjo, S. (2010) Wegener's granulomatosis: experience from a Brazilian tertiary center. *Clin Rheumatol* 29: 855–860.

De Vita, S., Quartuccio, L., Isola, M., Mazzaro, C., Scaini, P., Lenzi, M. *et al.* (2012) A randomized controlled trial of rituximab for the treatment of severe cryoglobulinemic vasculitis. *Arthritis Rheum* 64: 843–853.

Delalande, S., De Seze, J., Fauchais, A., Hachulla, E., Stojkovic, T., Ferriby, D. *et al.* (2004) Neurologic manifestations in primary Sjogren syndrome: a study of 82 patients. *Medicine (Baltimore)* 83: 280–291.

Di Ciaula, A., Covelli, M., Berardino, M., Wang, D., Lapadula, G., Palasciano, G. *et al.* (2008) Gastrointestinal symptoms and motility disorders in patients with systemic scleroderma. *BMC Gastroenterol* 8: 7.

Dyck, P., Conn, D. and Okazaki, H. (1972) Necrotizing angiopathic neuropathy. Three-dimensional morphology of fiber degeneration related to sites of occluded vessels. *Mayo Clin Proc* 47: 461–475.

Dyck, P., Hunder, G. and Dyck, P. (1997) A case-control and nerve biopsy study of crest multiple mononeuropathy. *Neurology* 49: 1641–1645.

Dyck, P., Norell, J. and Dyck, P. (1999) Microvasculitis and ischemia in diabetic lumbosacral radiculoplexus neuropathy. *Neurology* 53: 2113–2121.

Fain, O., Hamidou, M., Cacoub, P., Godeau, B., Wechsler, B., Paries, J. *et al.* (2007) Vasculitides associated with malignancies: analysis of sixty patients. *Arthritis Rheum* 57: 1473–1480.

Ferri, C., Cacoub, P., Mazzaro, C., Roccatello, D., Scaini, P., Sebastiani, M., *et al.* (2011) Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: result of a multicenter cohort study and review of the literature. *Autoimmun Rev.* 11: 48–55.

Figueroa, J., Loftus, E., Jr, Harmsen, W., Dyck, P. and Klein, C. (2013) Peripheral neuropathy incidence in inflammatory bowel disease: a population-based study. *Neurology* 80: 1693–1697.

Florica, B., Aghdassi, E., Su, J., Gladman, D., Urowitz, M. and Fortin, P. (2011) Peripheral neuropathy in patients with systemic lupus erythematosus. *Semin Arthritis Rheum* 41: 203–211.

Frigui, M., Kechaou, M., Haddouk, S., Masmoudi, A., Kaddour, N., Masmoudi, H. *et al.* (2008) [Benzylthiouracil induced ANCA-positive vasculitis: study of three cases and review of the literature]. *Ann Endocrinol (Paris)* 69: 517–522.

Gonzalez-Gay, M. and Garcia-Porrua, C. (1999) Systemic vasculitis in adults in Northwestern Spain, 1988–1997. Clinical and epidemiologic aspects. *Medicine (Baltimore)* 78: 292–308.

Guillevin, L., Pagnoux, C., Seror, R., Mahr, A., Mouthon, L. and Le Toumelin, P. (2011) The five-factor score revisited: assessment of prognoses of systemic necrotizing vasculitides based on the French Vasculitis Study Group (FVSG) cohort. *Medicine (Baltimore)* 90: 19–27.

Hattori, N., Ichimura, M., Nagamatsu, M., Li, M., Yamamoto, K., Kumazawa, K. *et al.* (1999) Clinicopathological features of churg-strauss syndrome-associated neuropathy. *Brain* 122: 427–439.

Hattori, N., Mori, K., Misu, K., Koike, H., Ichimura, M. and Sobue, G. (2002) Mortality and morbidity in peripheral neuropathy associated Churg–Strauss syndrome and microscopic polyangiitis. *J Rheumatol* 29: 1408–1414.

Hernandez-Rodriguez, J., Alba, M., Prieto-Gonzalez, S. and Cid, M. (2014) Diagnosis and classification of polyarteritis nodosa. *J Autoimmun* 48–49: 84–89.

Hiemstra, T., Walsh, M., Mahr, A., Savage, C., De Groot, K., Harper, L. *et al.* (2010) Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA* 304: 2381–2388.

Johnson, P., Rolak, L., Hamilton, R. and Laguna, J. (1979) Paraneoplastic vasculitis of nerve: a remote effect of cancer. *Ann Neurol* 5: 437–444.

Kararizou, E., Davaki, P., Speggos, K. and Stamboulis, E. (2012) Rare association of polyneuropathy and Crohn's disease: a clinicopathological study of 4 cases. *Pol J Pathol* 63: 261–266.

Kissel, J., Slivka, A., Warmolts, J. and Mendell, J. (1985) The clinical spectrum of necrotizing angiopathy of the peripheral nervous system. *Ann Neurol* 18: 251–257.

Koike, H., Yoshida, H., Ito, T., Ohyama, K., Hashimoto, R., Kawagashira, Y. *et al.* (2013) Demyelinating neuropathy and autoimmune hemolytic anemia in a patient with pancreatic cancer. *Intern Med* 52: 1737–1740.

Levy, Y., Uziel, Y., Zandman, G., Rotman, P., Amital, H., Sherer, Y. *et al.* (2005) Response of vasculitic peripheral neuropathy to intravenous immunoglobulin. *Ann N Y Acad Sci* 1051: 779–786.

Levy, Y., Uziel, Y., Zandman, G.G., Amital, H., Sherer, Y., Langevitz, P. *et al.* (2003) Intravenous immunoglobulins in peripheral neuropathy associated with vasculitis. *Ann Rheum Dis* 62: 1221–1223.

Maneiro, J., Lopez-Canoa, N., Salgado, E. and Gomez-Reino, J. (2014) Maintenance therapy of lupus nephritis with mycophenolate or azathioprine: systematic review and meta-analysis. *Rheumatology (Oxford)* 53: 834–838.

Massie, R., Mauermann, M., Staff, N., Amrami, K., Mandrekar, J., Dyck, P. *et al.* (2012) Diabetic cervical radiculoplexus neuropathy: a distinct syndrome expanding the spectrum of diabetic radiculoplexus neuropathies. *Brain* 135: 3074–3088.

Metzler, C., Miehle, N., Manger, K., Iking-Konert, C., De Groot, K., Hellmich, B. *et al.* (2007) Elevated relapse rate under oral methotrexate versus leflunomide for maintenance of remission in Wegener's granulomatosis. *Rheumatology (Oxford)* 46: 1087–1091.

Morozumi, S., Koike, H., Tomita, M., Kawagashira, Y., Iijima, M., Katsuno, M. *et al.* (2011) Spatial distribution of nerve fiber pathology and vasculitis in microscopic polyangiitis-associated neuropathy. *J Neuropathol Exp Neurol* 70: 340–348.

Muramatsu, K., Tanaka, H. and Taguchi, T. (2008) Peripheral neuropathies of the forearm and hand in rheumatoid arthritis: diagnosis and options for treatment. *Rheumatol Int* 28: 951–957.

Noel, N., Drier, A., Wechsler, B., Piette, J., De Paz, R., Dormont, D. *et al.* (2013) [Neurological manifestations of Behcet's disease.]. *Rev Med Interne*, in press.

Oh, S. (1997) Paraneoplastic vasculitis of the peripheral nervous system. *Neurol Clin* 15: 849–863.

Oh, S., Slaughter, R. and Harrell, L. (1991) Paraneoplastic vasculitic neuropathy: a treatable neuropathy. *Muscle Nerve* 14: 152–156.

Ohyama, K., Koike, H., Iijima, M., Hashimoto, R., Tomita, M., Kawagashira, Y. *et al.* (2013a) IgG4-related neuropathy: a case report. *JAMA Neurol* 70: 502–505.

Ohyama, K., Yasui, K., Hasegawa, Y., Morozumi, S., Koike, H. and Sobue, G. (2013b) Differential recovery in cardiac and vasomotor sympathetic functional markers in a patient with acute autonomic sensory and motor neuropathy. *Intern Med* 52: 497–502.

Perez Alamino, R., Martinez, C. and Espinoza, L. (2013) IgG4-associated vasculitis. *Curr Rheumatol Rep* 15: 348.

Rafai, M., Fadel, H., Boulaajaj, F., Gam, I., El Moutawakkil, B., Karkouri, M. *et al.* (2007) [Peripheral neuropathy in systemic lupus erythematosus with epineural vasculitis and antiphospholipid antibodies]. *Rev Neurol (Paris)* 163: 103–106.

Ramos-Casals, M., Stone, J., Cid, M. and Bosch, X. (2012) The cryoglobulinaemias. *Lancet* 379: 348–360.

Ribi, C., Cohen, P., Pagnoux, C., Mahr, A., Arene, J., Puechal, X. *et al.* (2010) Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: a prospective randomized study of

one hundred twenty-four patients. *Arthritis Rheum* 62: 1186–1197.

Rockx, M. and Clark, W. (2010) Plasma exchange for treating cryoglobulinemia: a descriptive analysis. *Transfus Apher Sci* 42: 247–251.

Said, G. and Lacroix, C. (2005) Primary and secondary vasculitic neuropathy. *J Neurol* 252: 633–641.

Schapira, D., Balbir-Gurman, A. and Nahir, A. (2000) Naproxen-induced leukocytoclastic vasculitis. *Clin Rheumatol* 19: 242–244.

Schaublin, G., Michet, C., Jr, Dyck, P. and Burns, T. (2005) An update on the classification and treatment of vasculitic neuropathy. *Lancet Neurol* 4: 853–865.

Schonermarck, U., Lamprecht, P., Csernok, E. and Gross,W. (2001) Prevalence and spectrum of rheumatic diseases associated with proteinase 3-antineutrophil cytoplasmic antibodies (ANCA) and myeloperoxidase-ANCA. *Rheumatology (Oxford)* 40: 178–184.

Servioli, L., Perez, C., Consani, S., Suarez, A., Sehabiaga, G., Collazo, C. *et al.* (2007) Prevalence and characteristics of immunomediated neuropathies in a group of patients with autoimmune diseases. *J Clin Neuromuscul Dis* 9: 285–290.

Silva, F., Specks, U., Kalra, S., Hogan, M., Leung, N., Sethi, S. *et al.* (2010) Mycophenolate mofetil for induction and maintenance of remission in microscopic polyangiitis with mild to moderate renal involvement - a prospective, open-label pilot trial. *Clin J Am Soc Nephrol* 5: 445–453.

Stone, J., Merkel, P., Spiera, R., Seo, P., Langford, C., Hoffman, G. *et al.* (2010) Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 363: 221–232.

Suppiah, R., Hadden, R., Batra, R., Arden, N., Collins, M., Guillevin, L. *et al.* (2011) Peripheral neuropathy in ANCA-associated vasculitis: outcomes from the European Vasculitis Study Group trials. *Rheumatology (Oxford)* 50: 2214–2222.

Terrier, B., Lacroix, C., Guillevin, L., Hatron, P., Dhote, R., Maillot, F. *et al.* (2007) Diagnostic and prognostic relevance of neuromuscular biopsy in primary Sjogren's syndrome-related neuropathy. *Arthritis Rheum* 57: 1520–1529.

Thaisetthawatkul, P., Sundell, R., Robertson, C. and Dyck, P. (2011) Vasculitic neuropathy associated with minocycline use. *J Clin Neuromuscul Dis* 12: 231–234.

Torvik, A. and Berntzen, A.E. (1968) Necrotizing vasculitis without visceral involvement. postmortem examination of three cases with affection of skeletal muscles and peripheral nerves. *Acta Med Scand* 184: 69–77.

Vital, A., Lagueny, A., Ferrer, X., Louiset, P., Canron, M. and Vital, C. (2008) Sarcoid neuropathy: clinico-pathological study of 4 new cases and review of the literature. *Clin Neuropathol* 27: 96–105.

Vital, C., Vital, A., Canron, M., Jaffre, A., Viallard, J., Ragnaud, J. *et al.* (2006) Combined nerve and muscle biopsy in the diagnosis of vasculitic neuropathy. A 16-year retrospective study of 202 cases. *J Peripher Nerv Syst* 11: 20–29.

Voskuyl, A., Hazes, J., Zwinderman, A., Paleolog, E., Van Der Meer, F., Daha, M. *et al.* (2003) Diagnostic strategy for the assessment of rheumatoid vasculitis. *Ann Rheum Dis* 62: 407–413.

Watts, R., Carruthers, D. and Scott, D. (1995) Epidemiology of systemic vasculitis: changing incidence or definition? *Semin Arthritis Rheum* 25: 28–34.

Yamamoto, M., Ito,Y., Mitsuma, N., Hattori, N. and Sobue, G. (2003) Pain-related differential expression of NGF, GDNF, IL-6, and their receptors in human vasculitic neuropathies. *Intern Med* 42: 1100–1103.

Yokoi, S., Kawagashira, Y., Ohyama, K., Iijima, M., Koike, H., Watanabe, H. *et al.* (2014) Mononeuritis multiplex with tumefactive cellular infiltration in a patient with reactive lymphoid hyperplasia with increased immunoglobulin G4-positive cells. *Hum Pathol* 45: 427–430.

Zwerina, J. (2008) [Churg–Strauss syndrome]. *Z Rheumatol* 67: 137–143; quiz 144.