Curr Treat Options Neurol (2015) 17: 44
DOI 10.1007/s11940-015-0374-1

Neuromuscular Disorders (SA Rudnicki, Section Editor)

Vasculitic Neuropathies

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Published online: 7 September 2015

This article is part of the Topical Collection on *Neuromuscular Disorders*

Keywords Vasculitic neuropathy · Necrotizing vasculitis · Nerve large arteriole · Microvasculitis · Microscopic polyangiitis · Polyarteritis nodosa · Churg-Strauss syndrome · Wegener's granulomatosis · Rheumatoid vasculitis · Sjögren's syndrome · Hepatitis C vasculitic neuropathy · Cryoglobulinemia · HIV-associated vasculitic neuropathy · Non-systemic vasculitic neuropathy · Diabetic lumbosacral radiculoplexus neuropathy · Lumbosacral radiculoplexus neuropathy · Diabetic cervical radiculoplexus neuropathy · Painless diabetic motor neuropathy

Opinion statement

From pathological standpoint, we divide vasculitic neuropathies in two categories: nerve large arteriole vasculitides and nerve microvasculitis. It is also important to determine whether a large arteriole vasculitis has an infectious etiology as it entails different treatment approach. Treatment of non-infectious large arteriole vasculitides consists initially of induction therapy with corticosteroids. Adding an immunosuppressant, mainly cyclophosphamide, is often needed. Treatment of infectious large arteriole vasculitides needs a multidisciplinary approach to target both the underlying infection and the vasculitis. Corticosteroids are the first-line therapy for classic non-systemic vasculitic neuropathy. Stable or improving patients without biopsy evidence of active vasculitis can be either observed or treated. Currently, adding an immunosuppressant is only indicated for patients who continue to progress on corticosteroids alone or patients with a rapidly progressive course. The treatment of the radiculoplexus neuropathies such as diabetic lumbosacral radiculoplexus neuropathy, lumbosacral radiculoplexus neuropathy (in non-diabetic patients), and diabetic cervical radiculoplexus neuropathy, as well as painless diabetic motor neuropathy, is not well established yet. We treat patients, if they present early on in the disease course or if they have severe disabling symptoms, with IV methylprednisolone 1 g once a week for 12 weeks.

Introduction

Vasculitides are a group of disorders caused by inflammation and destruction of blood vessels of different sizes and affecting different organs resulting in ischemic injury to the involved tissue. Vasculitis can be a systemic process or confined to a single organ such as the peripheral nervous system.

Classification of vasculitides has been an evolving topic with varying features being considered [1–3]. In 2010, Peripheral Nerve Society issued a guideline where vasculitic neuropathies were classified into primary systemic vasculitides, secondary systemic vasculitides, and non-systemic/localized vasculitis. Primary systemic

vasculitides can be further divided based on the size of the vessels involved, into predominantly large vessel, medium vessel, and small vessel vasculitis. However, only small vessels are found in the peripheral nerves; hence, vasculitic neuropathies can be simply divided into large arteriole vasculitis affecting epineurial and perineurial vessels of 75–300 μm in diameter and microvasculitis involving predominantly the endoneurial microvessels and venules [4••]. Even though there is an overlap in vessel size, primary and secondary systemic vasculitic neuropathies usually affect large arterioles, and non-systemic vasculitic neuropathy more commonly affects microvessels.

Clinically, vasculitic neuropathy should be suspected when a patient presents with an acute to subacute painful neuropathy. It can manifest as a mononeuropathy, multiple mononeuropathies, or an asymmetric polyneuropathy with a marked impact on patient's life [5]. However, vasculitic neuropathy can also present as a slowly progressive process, can be symmetric, sensory or sensorimotor, painless, or even asymptomatic [4••, 6].

Hence, the possibility of a vasculitic neuropathy should always be entertained. Nerve conduction studies and electromyography help to well delineate the nature of the neuropathic process and it is symmetry. In most cases, tissue diagnosis is required. It is important to choose a nerve that is affected by the disease. Doing a muscle biopsy in addition to the nerve biopsy is thought to increase the yield by about 15 % [7]. It is difficult to tell the sensitivity of a nerve biopsy for definite vasculitis as there is no gold standard test to compare to; nonetheless, it is estimated to be about 50 % [8].

In vasculitic neuropathies, nerve biopsy shows evidence of either large arteriole vasculitis (Fig. 1) or microvasculitis (Fig. 2); hence, we prefer the simplistic dichotomous classification into nerve large arteriole vasculitis and nerve microvasculitis [4••].

The next step is to determine whether there is evidence of a systemic disease versus a non-systemic vasculitic neuropathy. Sometimes, the history alone can coin the diagnosis as could be the case in diabetic lumbosacral radiculoplexus neuropathy where tissue diagnosis may not be needed. Otherwise, the neurologist should evaluate for evidence of other organ involvement (such as lung, kidney, GI tract, and skin) and for systemic markers and specific antibodies. As management of different types of vasculitic neuropathies may be different, it is important to differentiate between systemic vs non-systemic, primary systemic vs secondary systemic, and infectious vs non-infectious as will be detailed below.

Treatment response should be monitored based on pre-established objective clinical, electrodiagnostic, or laboratory measures.

The 1996 Five-Factor Score (FFS) help prognosticating patients with polyarteritis nodosa (PAN), microscopic polyangiitis (MPA), or eosinophilic granulomatosis with polyangiitis or Churg-Strauss (EGPA) [9]. The revised 2009 FFS can be applied to PAN, MPA, EGPA, and granulomatosis with polyangiitis or Wegener's (GPA) [10]. It consists of four factors each allocated one point: age>65, renal insufficiency, cardiomyopathy, and severe gastrointestinal manifestations. The fifth factor, ENT involvement, is considered protective so the absence of ENT involvement is allocated one point. The fifth factor is only used for GPA and EGPA. Five-year survival rate is estimated to be 9 % for FFS=0, 21 % for FFS=1, and 40 % for FFS≥2. Vasculitic neuropathy by itself does not significantly affect survival; nonetheless, it has major impact on the patient daily life activities and level of function.

For treatment discussion, we will divide the vasculitides into three categories that share approximately the same treatment approach: non-infectious large arteriole vasculitides that include primary systemic vasculitides and secondary non-infectious systemic vasculitides, infectious large arteriole vasculitides, and non-systemic vasculitic neuropathy (mostly microvasculitis).

Treatment of non-infectious large arteriole vasculitides

As mentioned before, primary systemic vasculitides can be classified based on vessel size. The predominantly small vessel vasculitis (SVV) includes anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (MPA, EGPA, and GPA) as well as immune complex SVV.

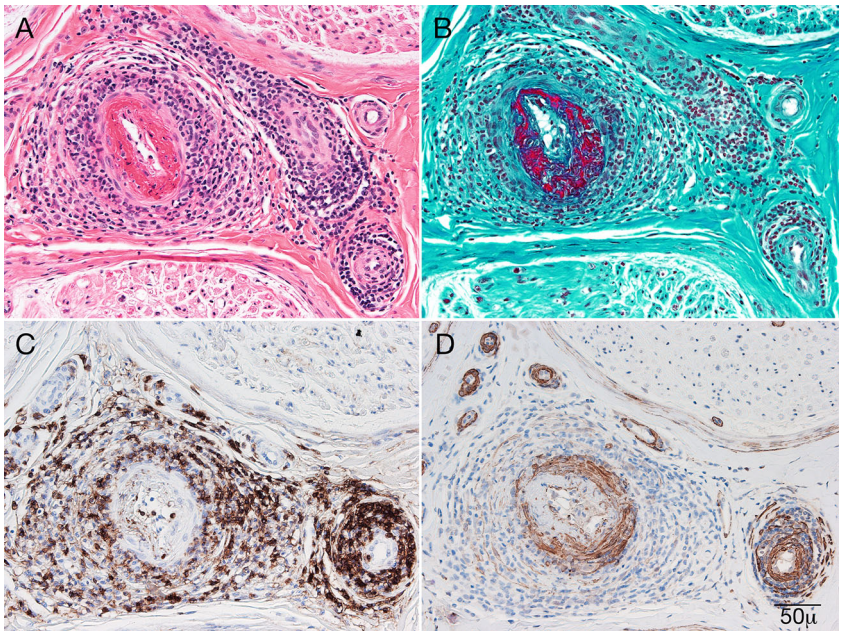

Fig. 1. Serial transverse paraffin sections showing nerve large arteriole vasculitis. Panels **a** (hematoxylin and eosin stain) and **b** (trichrome stain) show inflammatory infiltration and vessel wall destruction as well as fibrinoid necrosis of the mural elements. Panel **c** (CD 45) demonstrates the lymphocytic infiltration. Panel **d** (smooth muscle actin) shows the fragmentation of the muscle layers.

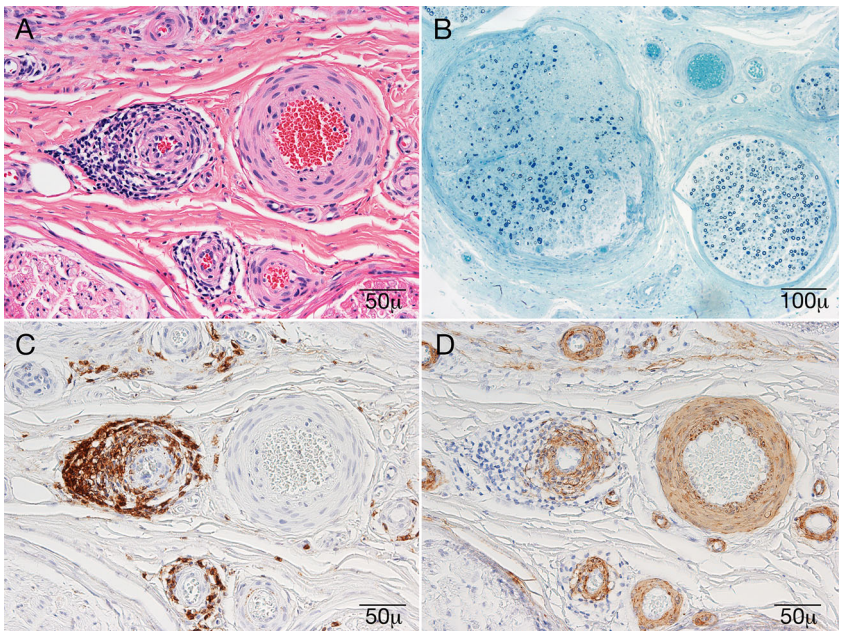

Fig. 2. Serial transverse paraffin sections showing microvasculitis. Panel **a** (hematoxylin and eosin stain) shows inflammation surrounding and involving the vessel wall of a microvessel with a nearby, intact, larger arteriole. Panel **b** (methylene blue stain) shows the multifocal fiber loss (the left fascicle has multifocal areas devoid of myelinated fibers, while the right fascicle has normal myelinated fiber density). These findings indicate an ischemic injury as seen in vasculitis. Panel **c** (CD 45) demonstrates the lymphocytic infiltration. Panel **d** (smooth muscle actin) shows the fragmentation of the muscle layers.

Microscopic polyangiitis (nerve large arteriole vasculitis)

The key pathologic feature of MPA is the lack of granulomatous tissue. The kidney is commonly involved (75–90 %), and 40–50 % of patients have peripheral nervous system (PNS) involvement. ANCAs are present in 75–85 % of patients, more commonly myeloperoxidase (MPO) or perinuclear ANCA (pANCA) subtype.

Eosinophilic granulomatosis with polyangiitis (nerve large arteriole vasculitis)

The main clinical feature of EGPA is respiratory tract involvement and the association with asthma. Nasal polyps recurring after surgery, rhinosinusitis, and eosinophilia are all key features that should raise the suspicion for the diagnosis. Sixty-five percent of patients have PNS involvement [11•, 12] and 30–40 % have ANCAs (MPO>proteinase 3 or PR3) [13, 14]. EGPA patients with positive ANCAs have more PNS and kidney involvement and less cardiac involvement when compared with ANCA-negative patients [11•, 13–16]. Overall, kidney involvement is less common in EGPA than in MPA and GPA [11•, 13]. Seven- to 10-year survival rate in appropriately treated patients is 90 % [12, 17].

Granulomatosis with polyangiitis (nerve large arteriole vasculitis)

GPA is characterized by necrotizing granulomatous inflammation of the lungs. GPA can be localized to the lungs or be associated with systemic disease with kidney involvement commonly manifesting as a necrotizing glomerulonephritis [18, 19]. About 90 % of patients with the systemic form have ANCAs more commonly cytoplasmic or PR3 subtype [19]. PR3-ANCA positivity is a risk factor for recurrence or persistence of severe disease [20]. Before cyclophosphamide, survival of patients with GPA averaged a few months [21].

Fifteen to 25 % of patients have PNS involvement, most commonly a multiple mononeuropathy [22]. If a patient with suspected vasculitic neuropathy has a cranial neuropathy, GPA should be suspected [18, 23].

Polyarteritis nodosa (nerve large arteriole vasculitis)

PAN is a predominantly medium vessel vasculitis that is not associated with ANCAs. Imaging of abdominal vessels is often abnormal and might help with the diagnosis [24, 25]. PAN can be associated with hepatitis B infection [26]. It is essential to screen patients with suspected PAN for hepatitis B as treatment is different (please refer to the infectious large arteriole vasculitides section). PNS is involved in about 25 % of cases [26].

Giant cell arteritis is the main, predominantly large vessel, primary systemic vasculitis. PNS involvement is uncommon [27].

Non-infectious secondary systemic vasculitides (nerve large arteriole vasculitis)

Non-infectious secondary systemic vasculitides could be associated with connective tissue diseases (rheumatoid arthritis, systemic lupus erythematous, Sjögren's syndrome, systemic sclerosis, dermatomyositis, or mixed connective tissue disease), sarcoidosis, Behçet disease, drugs, malignancy, inflammatory bowel disease, or hypocomplementemic urticarial vasculitis syndrome.

Rheumatoid vasculitis happens usually in patients with long-standing severe seropositive rheumatoid arthritis [28, 29]. The clinician has to be aware that not

every polyneuropathy associated with rheumatoid arthritis is a vasculitic neuropathy. Rheumatoid vasculitis is associated with poor outcome and about 26 % 5-year mortality rate [29, 30].

Sjögren's syndrome may be associated with a vasculitic neuropathy, trigeminal sensory neuropathy, distal sensorimotor polyneuropathy, sensory neuronopathy, or an autonomic neuropathy [31–33]. The reported symptoms of keratoconjunctivitis sicca (dry eyes and dry mouth) should raise the suspicion of the syndrome. Only about 25 % have positive anti-SSA or anti-SSB antibodies [34]. Lymphocytic infiltration on minor salivary gland biopsy helps establishing the diagnosis of Sjögren's syndrome especially in seronegative patients. Salivary gland ultrasonography could be a useful alternative diagnostic tool [35, 36].

Treatment of non-infectious large arteriole vasculitides consists initially of induction therapy with corticosteroids. Adding an immunosuppressant is often needed. The goal is to induce remission that is achievable in over 90 % of ANCA-associated vasculitis cases by 6 months [37]. However, about half of the patients relapse [38]; thus, maintenance therapy is needed.

Majority of patients achieve remission in 3 to 6 months. Most of refractory cases are associated with PR3-ANCA [20]. As almost half of the patients relapse after remission [38], maintenance therapy should be initiated and continued for 18–24 months [39]. Maintenance therapy usually consists of switching CYC to a less toxic medication (often azathioprine) with a slow taper of oral corticosteroids. Other options will be addressed as well in further details when discussing individual therapy options.

Corticosteroids

Corticosteroids are the mainstay of induction therapy. Oral prednisone or prednisolone is usually given at the dose of 1 mg/kg/day. IV methylprednisolone (1,000 mg/day for 3–5 days) followed by oral prednisone is believed to have a faster effect. Weekly IV methylprednisolone instead of daily oral prednisone may have a better side effect profile. After 1–2 months, depending on patient's response, tolerance of side effects, and clinical stability, slow tapering should be initiated.

Cyclophosphamide

Cyclophosphamide (CYC) is the classically used add-on immunosuppressant for vasculitis. Initial therapy with CYC is recommended for cases of GPA and MPA as well as severe cases of EGPA and PAN [40]. The severity of EGPA and PAN could be determined using the five-factor score (detailed above). Despite the fact that EGPA and PAN patients without poor prognostic factor have good long-term survival, they are at high risk for relapses and morbidity from vasculitic neuropathy sequelae [17]. Hence, they might still benefit from initial combined treatment with corticosteroids and CYC [41]. CYC can be given orally or as intravenous pulse therapy. Intravenous pulse therapy has been shown to be as effective as oral therapy in inducing remission with fewer side effects, given the less cumulative dose, and lower mortality [42–46]. However, intravenous pulse therapy was associated with a higher relapse rate upon long-term follow-up [47]. Oral CYC dose is 2 mg/kg/day. Pulse intravenous

CYC dose is 15 mg/kg or 0.6–0.7 g/m [2] every 2–3 weeks and should be adjusted according to age and renal function [46].

Cyclophosphamide has many potential side effects including bone marrow suppression, hemorrhagic cystitis, gonadal toxicity, opportunistic infections, and renal impairment. It is also associated with increased risk of malignancy such as lymphoma, leukemia, non-melanomatous skin cancer, and transitional cell carcinoma of the bladder [48–50]. A complete blood count should be monitored weekly initially then every 2 weeks with subsequent CYC dose adjustment [51, 52]. The use of Mesna and proper hydration is recommended to reduce urotoxicity. Monitoring for non-glomerular hematuria with a urinalysis should be performed every 3–6 months [52, 53].

Rituximab

Rituximab was shown to be as effective as cyclophosphamide for remission induction [54] and azathioprine for remission maintenance [54, 55] in severe ANCA-associated vasculitis. It is also used to treat relapses and cases refractory to conventional therapy [56–59] as well as cases of rheumatoid vasculitis [60]. Rituximab is usually given as 375 mg/m [2] once a week for 4 weeks.

Rituximab side effects include hypotension, fever, nausea, vomiting, dyspnea, angioedema, headache, urticaria, pulmonary disease, and infection such as progressive multifocal leukoencephalopathy.

Azathioprine

Replacing CYC with azathioprine (AZT) after remission has been shown to be effective [37]. It is the drug of choice for maintenance therapy. If thiopurine methyltransferase (TPMT) activity is within normal limits, azathioprine can be started at 50 mg/day and increased by 50 mg every 3–5 days to a goal of 2 mg/kg/day.

Side effects include an acute hypersensitivity reaction, bone marrow suppression, liver toxicity, pancreatitis, increased risk of infection, and malignancy [51, 61]. Complete blood count and liver enzymes should be monitored weekly for the first month then monthly for 6 months then every 3 months.

Methotrexate

Methotrexate (MTX) can be used in combination with steroids to induce remission in mild cases of non-infectious large arteriole vasculitis with higher rate of relapses after discontinuation of therapy when compared to cyclophosphamide therapy [62]. MTX can subsequently be continued as maintenance therapy for 18–24 months. It can also be used as an alternative to azathioprine for remission maintenance therapy after induction with cyclophosphamide. MTX is started at 7.5–15 mg/week and can be gradually titrated up to 20–25 mg/week.

MTX side effects include bone marrow suppression, liver toxicity, gastrointestinal toxicity, rash, and increased risk of infection. Liver enzymes

and complete blood count should be closely monitored. Interstitial pneumonitis is an uncommon side effect. Hence, if the patient were to develop any respiratory symptoms, further assessment with chest imaging, pulmonary function tests, and pulmonology consultation is recommended.

Weekly folic acid has been shown to reduce the incidence of gastrointestinal and liver toxicity. A weekly dose of at least 5 mg is recommended.

Intravenous immunoglobulin (IVIG)

IVIG has been used in treatment-refractory cases of systemic vasculitis [63–65]. It has also been reported beneficial to treat relapses in patients with MPA and GPA [66]. IVIG can also be considered in patients with EGPA in remission who have evidence of residual peripheral neuropathy [67, 68]. IVIG is usually dosed at 2 g/kg divided over 2–5 days. The frequency and dosing of subsequent maintenance treatment need to be individualized depending on response and relapses.

IVIG side effects include anaphylactic reaction, aseptic meningitis, headache, flu-like reaction, renal insufficiency, neutropenia, rash, and rarely a hyperviscosity syndrome. IgA levels should be checked prior to initiating therapy to reduce the risk of anaphylactic reaction.

Plasma exchange

Plasma exchange (PLEX) has been used in cases of severe systemic vasculitis associated with severe glomerulonephritis or alveolar hemorrhage. However, a recent study done by the European Vasculitis Study Group showed no long-term benefit [69]. Adding plasma exchange to steroids in severe cases of PAN or EGPA did not yield any additional benefit [70].

Other immunosuppressants

Mycophenolate mofetil was found to be less effective than AZA for maintaining disease remission in GPA and MPA [71]. Leflunomide use remains controversial given its association with toxic neuropathy [72]. Mepolizumab and INF-α have been used in refractory EGPA [73, 74].

Treatment of infectious large arteriole vasculitides

It is important to determine if a vasculitic neuropathy has an underlying infectious etiology as immunosuppression might lead to the exacerbation of viremia.

Vasculitic neuropathy may be associated with various infections such as HBV, HCV, HIV, CMV, leprosy, Lyme disease, and HTLV-1.

Mixed cryoglobulinemia is mainly caused by chronic hepatitis C infection (80–90 % of patients). Hepatitis C-related cryoglobulinemic neuropathy can manifest as a distal symmetric or asymmetric polyneuropathy or a multiple mononeuropathy. Patients may have elevated rheumatoid factors or sicca syndrome that might lead to an erroneous diagnosis.

HIV is rarely associated with a vasculitic neuropathy especially in the era of more efficient antiretroviral therapy. HIV-associated vasculitides are usually

self-limited [75]. In HIV patients, vasculitic neuropathy could also be due to CMV infection, hepatitis B-associated PAN, MPA, and lymphoma.

Treatment of hepatitis C-related cryoglobulinemia neuropathy (CRYOVASC) (nerve large arteriole vasculitis)

Treatment of CRYOVASC consists of a combination of antiviral therapy with immunosuppression. The classically used antiviral combination therapy is pegylated interferon-α (Peg-IFN-α) plus ribavirin [76, 77]. In severe or refractory cases, protease inhibitors (telaprevir or boceprevir) may be added [78, 79]. Peg-INF-α plus ribavirin plus a protease inhibitor is a highly effective regimen but with a high rate of side effects including severe bone marrow suppression.

Antiviral therapy is the mainstay of treatment for mild to moderate CRYOVASC associated with a mild peripheral neuropathy [80•]. Rituximab plus corticosteroids can be added to severe or refractory cases [56, 81, 82]. In life-threatening situations, plasma exchange combined with cyclophosphamide may be considered [83]. The use of low-dose interleukin 2 in cases refractory to conventional therapy has been reported in a prospective open label, phase 1–phase 2a study [84].

Treatment of CRYOVASC should be managed by a hepatologist with the neurologist assessing clinical response and monitoring for relapse.

Treatment of hepatitis B-associated PAN (nerve large arteriole vasculitis)

Hepatitis B-associated PAN is initially treated with 2 weeks of corticosteroids to address the life-threatening organ damage. It is then followed by plasma exchange to remove the immune complexes and antiviral therapy to decrease the viral load [40, 85].

Treatment of non-systemic vasculitic neuropathy (nerve microvasculitis)

Non-systemic vasculitic neuropathy (NSVN) share similar but relatively milder clinical features with systemic vasculitic neuropathy (SVN) [86]. By definition, there is no evidence of other organ involvement even though systemic symptoms such as fever and weight loss are not uncommon [5]. A small proportion of patients with NSVN might evolve into SVN. Patients with NSVN have usually a slower progression and less frequent attacks. NSVN is usually non-fatal and has a better prognosis when compared to SVN [5, 87, 88].

Diabetic lumbosacral radiculoplexus neuropathy (DLRPN), in contrast to diabetic distal polyneuropathy, often happens early on in diabetes, in patients with few or no long-term microvascular complications. Occasionally, diabetes is discovered during the workup of a lumbosacral radiculoplexus neuropathy (LRPN) [89]. DLRPN usually starts unilaterally with severe pain followed by progressive weakness, initially proximal and then may spread to involve the

whole limb. The contralateral side often follows and sometimes there is concomitant thoracic radiculopathy or upper limb involvement [90]. Patients frequently have concomitant weight loss. During the acute illness, about half of the patients become wheelchair bound [89]. Even though it is usually a monophasic process with spontaneous resolution and subsequent improvement, recovery is often incomplete and distal weakness or foot drop is a common long-term problem [89]. Histopathological findings include perivascular epineurial inflammation resulting in ischemic injury with multifocal nerve fiber loss, injury neuroma, perineurial thickening, neovascularization, and other signs of ischemic injury. About half of the patients have features suggestive of or diagnostic of microvasculitis [89].

Diabetic cervical radiculoplexus neuropathy (DCRPN) [91] and lumbosacral radiculoplexus neuropathy (in non-diabetic) share similar clinical profiles and histopathology findings [92–95]. Painless diabetic motor neuropathy usually has an insidious onset of bilateral distal weakness (foot drop) followed by proximal weakness with occasional upper limb involvement [96].

Treatment of classic NSVN (nerve microvasculitis)

According to the Peripheral Nerve Society guideline published in 2010 [97], patients with progressive NSVN or with definite, active vasculitis demonstrated in a recent biopsy should be treated. Stable or improving patients without biopsy evidence of active vasculitis can be either observed or treated.

Corticosteroids are the first-line therapy. Prednisone is usually started at 1 mg/kg/day. Extrapolating from systemic vasculitis treatment, prednisone should be tapered down to 25 mg at 3 months and 10 mg at 6 months. Low-dose prednisone (5 to 7.5 mg/day) might further reduce relapses. In patients with severe, rapidly progressive NSVN, pulse therapy with IV methylprednisolone can be considered.

Combination therapy with an immunosuppressant may be more effective than corticosteroid monotherapy [5, 87]. Currently, it is recommended for patients who continue to progress on corticosteroids alone or patients with a rapidly progressive course [97]. Options include CYC, MTX, and AZA. CYC is usually the immunosuppressant of choice in severe cases.

Treatment of DLRPN and LRPN (nerve microvasculitis)

There is no proof yet that immunotherapy significantly improves neurological outcome in patients with DLRPN or LRPN [98]. A prospective, randomized, double-blind, multicenter controlled study [99], published as an abstract, showed no significant difference in primary outcome of improvement in Neuropathy Impairment Score in the lower limbs between patients treated with IV methylprednisolone vs placebo. Nonetheless, IV methylprednisolone group had significantly better control of their neuropathic symptoms, especially pain. Otherwise, published case series reported improvement with methylprednisolone treatment [100–105]; however, it is difficult to draw conclusions without patients being compared to controls given the natural history of the disease.

No controlled clinical trials using IVIG or PLEX in either DLRPN or LRPN have been reported. Case series showed that IVIG can improve pain and

strength in patients with DLRPN [101, 103, 106]. One case series showed improvement with plasma exchange in five patients [102].

Given the paucity of clinical trials to guide treatment of DLRPN and LRPN, the inflammatory findings on histopathology, and the fact that pain is commonly severe and disabling, we tend to treat patients if they present early on in the disease course or if they have severe disabling symptoms. We usually treat with IV methylprednisolone 1 g once a week for 12 weeks. For long-term pain management, neuropathic pain medications such as anti-epileptics (such as gabapentin, pregabalin, or topiramate) and anti-depressants (such as tricyclics, SSRIs, and SNRIs) are often needed.

Conclusion

Vasculitic neuropathies can be a part of a primary systemic vasculitis or a secondary systemic vasculitis caused by infectious or non-infectious disorders. Furthermore, the vasculitic process might be confined to the peripheral nervous system known as non-systemic vasculitic neuropathy. These different entities share many clinical similarities. Thus, when a patient is found to have a vasculitic neuropathy, it is crucial to appropriately classify the underlying process as it may entail different treatment approaches and prognosis. The treatment of the radiculoplexus neuropathies such as DLRPN, LRPN, and DCRPN as well as painless diabetic motor neuropathy is not well established yet. Consequently, further studies are needed to help the clinician with treatment decisions.

Acknowledgments

We thank Janean Engelstad for her assistance with the figures.

Compliance with Ethics Guidelines

Conflict of Interest
Elie Naddaf and P. James Bonham Dyck declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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