PERIPHERAL NEUROPATHIES

The nonsystemic vasculitic neuropathies

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Abstract | Nonsystemic vasculitic neuropathy (NSVN) is an under-recognized single-organ vasculitis of peripheral nerves that can only be diagnosed with a nerve biopsy. A Peripheral Nerve Society guideline group published consensus recommendations on the classification, diagnosis and treatment of NSVN in 2010, and new diagnostic criteria for vasculitic neuropathy were developed by the Brighton Collaboration in 2015. In this Review, we provide an update on the classification, diagnosis and treatment of NSVN. NSVN subtypes include Wartenberg migratory sensory neuropathy and postsurgical inflammatory neuropathy. Variants include diabetic radiculoplexus neuropathy and — arguably — neuralgic amyotrophy. NSVN with proximal involvement is sometimes termed nondiabetic lumbosacral radiculoplexus neuropathy. Cutaneous polyarteritis nodosa and other skin–nerve vasculitides overlap with NSVN clinically. Three patterns of involvement in NSVN have been identified: multifocal neuropathy, distal symmetric polyneuropathy, and overlapping multifocal neuropathy (asymmetric polyneuropathy). These patterns lack standard definitions, resulting in inconsistencies between studies. We propose definitions and provide an up-to-date differential diagnosis of multifocal neuropathy. Available evidence suggests that NSVN and neuropathy-predominant systemic vasculitis might be controlled better by treatment with corticosteroids and an immunosuppressive agent than with corticosteroids alone. Treated NSVN rarely spreads to other organs, but 30% of patients experience a relapse. Long-term neurological outcome is favourable, but chronic pain is common.

The vasculitides are a clinically diverse group of diseases with the histopathological signature of blood vessel-centred inflammation that results in vascular damage and ischaemic injury to the affected tissues[1]. Vasculitis can be caused by drugs, infections and cancers, but diagnostic workup reveals no trigger in most patients. Autoimmune mechanisms are active in all vasculitides, except those caused by direct infection of vessel walls. Most vasculitides are systemic and involve multiple organs and tissues. Those affecting small- to medium-sized vessels often manifest with a vasculitic neuropathy. For example, neuropathies occur in 60–70% of patients with polyarteritis nodosa, eosinophilic granulomatosis with polyangiitis and cryoglobulinaemic vasculitis, and 40–50% of those with microscopic polyangiitis and rheumatoid vasculitis[2].

Vasculitic neuropathy can also occur without systemic vasculitis. This single-organ vasculitis of the PNS has commonly been referred to as nonsystemic vasculitic neuropathy (NSVN), but other forms of clinically isolated PNS vasculitis are now recognized and can be considered variants of NSVN[3]. Although NSVN is classically an acute, relapsing, multifocal neuropathy, it can present as a slowly progressive neuropathy without distinct asymmetries. As such, it should be considered as a possible cause of any progressive axonal neuropathy. NSVN can be diagnosed only with a nerve biopsy, with or without a concomitant muscle or skin biopsy; as nerve biopsies are seldom performed, the condition is under-recognized. The disorder must be distinguished from many other causes of multifocal neuropathy, the definition of which is itself not standardized and requires clarification.

A Peripheral Nerve Society guideline group reviewed the literature on vasculitic neuropathy and published consensus recommendations on the classification, diagnosis and immunosuppressive treatment of NSVN in 2010 (REF. 4), with the underlying evidence included in multiple online supplements. Since 2010, many new patients with NSVN have been reported, new diagnostic criteria for vasculitic neuropathy were developed by the Brighton Collaboration, and new evidence on treatment

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Key points

- Nonsystemic vasculitic neuropathy (NSVN) is typically multifocal or asymmetric, painful, sensory or sensorimotor, lower-limb predominant, and characterized by one or more acute attacks
- NSVN is usually distal-predominant, but can involve proximal nerves, a phenotype designated radiculoplexus neuropathy (diabetic or nondiabetic)
- The diagnostic gold standard for NSVN is vessel wall inflammation and damage identified by nerve biopsy; a probable diagnosis is possible if the biopsy findings are suspicious but not pathognomonic
- We propose a clinical definition and differential diagnosis of a multifocal pattern of neuropathy ('mononeuritis multiplex')
- NSVN and neuropathy-predominant systemic vasculitis should probably be treated with an immunosuppressive agent in addition to corticosteroids.

of small-to-medium vessel vasculitides and NSVN has emerged. In this Review, we provide an update on the classification, diagnosis and treatment of the NSVNs and propose definitions for multifocal neuropathy and asymmetric polyneuropathy.

Classification of the vasculitides

The names and definitions of the vasculitides were most recently updated at the Chapel Hill Consensus Conference in 2012 (CHCC2012) to harmonize the ever-evolving nomenclature, classification and diagnostic systems[1]. Vasculitides are broadly categorized according to the size of the predominantly affected vessels. The large-vessel vasculitides are giant cell arteritis and Takayasu arteritis, which primarily affect large arteries. The medium-vessel vasculitides are polyarteritis nodosa and Kawasaki disease, which affect small and medium-sized arteries but not the microvasculature. Small-vessel vasculitides primarily affect microvessels and small arteries and/or veins, although medium-sized vessels can also be involved. Small-vessel vasculitides are divided according to the extent of immune complex deposits in the vessel walls: those with sparse deposits are known as pauci-immune disorders and include the anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides microscopic polyangiitis, granulomatosis with polyangiitis (formerly Wegener granulomatosis) and eosinophilic granulomatosis with polyangiitis (formerly Churg–Strauss syndrome), while those with prominent deposits are known as immune complex small-vessel vasculitides, which include anti-glomerular basement membrane disease, IgA vasculitis (formerly Henoch–Schönlein purpura), hypocomplementaemic urticarial vasculitis, and cryoglobulinaemic vasculitis. Vasculitides that can affect a range of vessel sizes (referred to as variable vessel vasculitides) are Behçet disease and Cogan syndrome. Nonsystemic vasculitic disorders, such as NSVN, are designated as single-organ vasculitides. Secondary forms of vasculitis are classified as 'vasculitis associated with systemic disease' or 'vasculitis associated with probable aetiology'.

The 2010 Peripheral Nerve Society guideline included a classification of vasculitides associated with neuropathy[4]. We present an updated version of this classification in accordance with the consensus from CHCC2012, which includes a new formulation of single-organ vasculitic neuropathies based on evidence presented in this Review[1,4] (BOX 1). Systemic vasculitic neuropathies (SVNs) occur with varying degrees of frequency in numerous vasculitides[2,5–8]. Histopathologically proven vasculitic neuropathy has not been reported in Kawasaki disease, Takayasu arteritis, anti-glomerular basement membrane disease or Cogan syndrome[4]. The incidence and prevalence of NSVN are unclear, but studies that have provided data on the relative frequencies of different vasculitic neuropathies (Supplementary information S1 (table)) show that NSVN is the most commonly diagnosed vasculitic neuropathy.

In some reviews, NSVN has been classified as a microvasculitis[9]. Microvasculitis affects epineurial microvessels with diameters ≤40 μm, which includes small arterioles, small venules and capillaries. PNS microvasculitis without vascular damage is nonspecific and has been reported in many nonvasculitic conditions[10]. PNS microvasculitis with vascular damage is characteristic of the diabetic radiculoplexus neuropathies[11]. However, data from at least four studies that evaluated the size of vessels involved in NSVN[12–15] indicate that NSVN is not, in most circumstances, a microvasculitis.

The Peripheral Nerve Society guideline group derived consensus diagnostic criteria for distinguishing between NSVN and the SVNs based on the results of a literature review of differentiating clinical, laboratory and histopathological features[4]. Analyses revealed only two features with >95% specificity for SVN — ANCAs and erythrocyte sedimentation rate (ESR) ≥100 mm/h — which were consequently adopted as new exclusionary criteria for NSVN, supplementing the previously established exclusionary criteria of specific aetiology, extra-neurological involvement and a condition predisposing to systemic vasculitis. A duration of symptoms <12 months, high levels of rheumatoid factor, anaemia, leukocytosis, and fever were also associated with SVN, but were deemed insufficiently specific to exclude NSVN. In 2015, the Brighton Collaboration Vasculitic Peripheral Neuropathy (VPN) Working Group adapted these criteria with only one substantive change — the addition of "Brighton case definition for any form of vasculitis other than nerve or muscle" as a new but partially redundant exclusion criterion[16].

Clinical features of NSVN

Since our reviews of NSVN in 2004 (REF. 17) and 2008 (REF. 18), many additional patients with NSVN have been reported or identified in the older literature[15,19–33]. Here, we combine these data with that included in the previous reviews to comprehensively analyse the clinical features of NSVN, and we tabulate specific features of the ten largest series of NSVN (Supplementary information S2 (table)). The mean age of onset is 60.0 ± 14.8 years (range 13–88 years), with a relatively even distribution between the sexes. No signs or symptoms are referable to non-PNS organs, but constitutional symptoms can occur; for example, 28% of patients lose weight and 13% develop fever. Most patients follow a stepwise or relapsing clinical

Box 1 | **Classification of vasculitides associated with neuropathy**

The classification is modified from the Peripheral Nerve Society guideline in accordance with the Chapel Hill Consensus Conference in 2012[4].

Primary systemic vasculitides

- Predominantly small-vessel vasculitis
  - Microscopic polyangiitis*
  - Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)*
  - Granulomatosis with polyangiitis (Wegener granulomatosis)*
  - Essential mixed cryoglobulinaemia (non-HCV)
  - IgA vasculitis (Henoch–Schönlein purpura)
  - Hypocomplementemic urticarial vasculitis
- Predominantly medium-vessel vasculitis
  - Polyarteritis nodosa
- Predominantly large-vessel vasculitis
  - Giant cell arteritis

Vasculitides associated with systemic diseases

- Connective tissue diseases
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Sjögren syndrome
  - Systemic sclerosis
  - Mixed connective tissue disease
- Dermatomyositis
- Sarcoidosis
- Behçet disease
- Inflammatory bowel disease

Vasculitides associated with probable aetiologies

- Infection (such as hepatitis B virus, hepatitis C virus, HIV, cytomegalovirus, leprosy, Lyme disease, human T cell-lymphotropic virus-I, parvovirus B19)
- Drugs
- Malignancy
- Vaccinations

Single-organ vasculitides of the peripheral nervous system

- Nonsystemic vasculitic neuropathy, including but not limited to the following subtypes
  - Wartenberg migratory sensory neuropathy (non-mechanical cases)
  - Postsurgical inflammatory neuropathy
- Neuralgic amyotrophy (probably)
- Painful diabetic radiculoplexus neuropathy
  - Predominantly lumbosacral
  - Predominantly thoracic (thoracic radiculoneuropathy)
  - Predominantly cervical
- Painless diabetic radiculoplexus neuropathy
- Nonsystemic skin/nerve vasculitis
  - Cutaneous polyarteritis nodosa
  - Other

*Usually anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides.

course, but the disease steadily progresses in 40%[3,19,34,35]. Approximately 5–10% of patients present with acute, rapidly progressive deficits and are diagnosed within 1 month, but most patients progress subacutely or chronically[30,31,35–37]. Median duration of symptoms at diagnosis is 2.5–12 months[13,19,31,35–38]. In one study, the median delay to diagnosis was 2 years; combined with the relatively mild neurological involvement in this cohort, this delay suggests a bias against inclusion of more severely affected patients[30]. Unusually long delays of 8–13 years have occurred in most series, highlighting the need for vigilance for NSVN in patients with long-standing neuropathies[23,30,35,36].

Three patterns of clinical involvement in NSVN have been identified: multifocal neuropathy, asymmetric polyneuropathy (also commonly known as overlapping multifocal neuropathy), and distal symmetric polyneuropathy. The reported frequencies of these phenotypes are disturbingly variable, owing to a lack of standardized definitions for these clinical patterns; to address this problem, we propose new definitions later in this Review. For example, in the 2003 Ohio State series, wherein no asymmetry was ignored, asymmetric polyneuropathy was the most common pattern (85%) followed by multifocal neuropathy (13%) and distal symmetric polyneuropathy (2%)[36], but combined data from all series and case reports yields a different prevalence: 45% asymmetric polyneuropathy, 33% multifocal neuropathy and 23% symmetric polyneuropathy. In vasculitis, symmetric polyneuropathies are necessarily overlapping multifocal neuropathies microscopically (all vasculitic lesions are distributed multifocally in peripheral nerve biopsies), suggesting that clinical findings in vasculitic neuropathy should always be at least somewhat asymmetric or multifocal.

Neurological deficits in NSVN are usually most noticeable distally, but proximal involvement is not uncommon. PNS vasculitis affects axons rather than neuronal cell bodies[39], so most patients present with weakness and sensory loss, although 15% of patients have purely or predominantly sensory signs and symptoms. Sensory loss usually involves both large-fibre and small-fibre modalities; a purely small-fibre neuropathy is exceptional. Pure motor presentations are also rare[30]. Vasculitic neuropathy is generally considered to be a painful neuropathy, but our review of the literature has identified that 20% of patients with NSVN have no pain.

NSVN is more likely to affect certain nerves than others, although by the time most patients see a neurologist, multiple overlapping nerves are usually affected[36,40]. Decomposing the neurological deficits seen in five NSVN series[3,15,19,35,36] into their constituent terminal nerves shows that the prevalence of individual motor nerve involvement is as follows: common peroneal (or peroneal division of sciatic) in 91% of patients, tibial (or tibial division of sciatic) in 61%, ulnar in 58%, femoral in 53%, superior gluteal in 42%, median in 41%, radial in 35%, axillary in 33%, and musculocutaneous in 26%. Cranial neuropathies occur in 6% of patients. The propensity of NSVN to affect certain nerves has generally been attributed to poor collateral vascular supply, but variability in vascular topography, antigen expression and adhesion molecules might also have a role[41].

Subtypes and variants of NSVN

Several syndromes that are currently known by other names should, on the basis of their clinical and/or histopathological characteristics, be classified as subtypes or variants of NSVN. Subtypes are conditions subsumed within the broad spectrum of NSVN but distinguished by characteristic clinical features or triggers. Variants

represent unique disease entities that overlap clinicopathologically with NSVN. NSVN with proximal involvement is neither a subtype nor a variant.

NSVN with proximal involvement

Most cases of NSVN affect the distal limbs, but some patients exhibit both distal and proximal involvement, a phenotype defined as a radiculoplexus neuropathy. NSVN with proximal involvement is sometimes referred to as nondiabetic lumbosacral radiculoplexus neuropathy, but the Peripheral Nerve Society guideline group concluded that this presentation is insufficiently distinguishable from distal-predominant forms of NSVN to warrant a separate designation — it is simply NSVN selected for proximal involvement. As revealed by standard distal cutaneous nerve biopsies, histopathological evidence of vasculitis in patients with proximal-predominant involvement is less definitive than that in distal NSVN, but is still consistent with vasculitis.

Extensive clinical overlap and variability exists between patients with proximal-predominant and distal-predominant NSVN, precluding a discrete nosologic demarcation. The only large study of NSVN with proximal involvement was conducted in a cohort of 57 patients with so-called nondiabetic lumbosacral radiculoplexus neuropathy[40]. In 2010, the Peripheral Nerve Society guideline group on NSVN compared this cohort with a cohort of 48 patients with NSVN[36]. Many phenotypic features were similar, but proximal lower limb weakness, weight loss and elevated CSF protein levels were more common in nondiabetic lumbosacral radiculoplexus neuropathy than NSVN, whereas elevated ESR, high levels of antinuclear antibodies, pure sensory involvement, and necrotizing vasculitis were more common in NSVN. Most patients with NSVN had diffuse, asymmetric, distally accentuated, lower-limb-predominant involvement, whereas four of 48 patients had a lumbosacral radiculoplexus neuropathy that was restricted to the lower limbs. The group's consensus was that nondiabetic lumbosacral radiculoplexus neuropathy is a form of NSVN characterized by proximal lower limb involvement, weight loss and microvascular damage, but that the nosological boundaries between this disorder and other phenotypes of NSVN were ambiguous[4]. As such, the condition was not classified as a distinct clinicopathological entity.

Subtypes

Wartenberg migratory sensory neuropathy. Wartenberg migratory sensory neuropathy is a purely sensory, chronic, relapsing multifocal neuropathy featuring episodes of sudden-onset sensory loss in the distribution of individual cutaneous nerves (commonly smaller branches than in other NSVNs), often, but not always, accompanied by pain and paraesthesia[42,43]. Symptoms usually resolve without treatment within several months, although numbness can persist indefinitely. Electrodiagnostic studies reveal no abnormalities except for low-amplitude or absent sensory nerve action potentials in the involved nerves. Laboratory studies are generally unrevealing. During long-term follow-up, deficits are fully reversible in 25–33% of patients[42,44].

Mechanical stretching of the involved nerve was the originally proposed mechanism, but in the largest prospective study, which involved 12 patients, only 50% described prodromal stretching[42]. Sural nerve biopsies in two patients revealed vasculitis in epineurial arteries[45]. Biopsy samples from three other patients raised suspicions of vasculitis but were not diagnostic[43,46,47]. The Peripheral Nerve Society guideline group concluded that nonmechanical cases of this syndrome are probably a benign, pure sensory form of NSVN[4].

Postsurgical inflammatory neuropathy. Postsurgical inflammatory neuropathy is a self-limited, acute, focal or multifocal axonal neuropathy that emerges within 30 days of a surgical procedure in the absence of trauma to affected nerves[48]. To qualify, the condition must develop after the immediate postoperative period or, if it develops within this period, involve nerves remote from the surgical field. In the largest series of biopsy-confirmed cases, which included 21 patients, the median age of onset was 65 (24–83) years. The median delay between surgery and onset of symptoms was 2 days. Almost all patients in the study had combined motor and sensory deficits, and 85% had pain. The most common patterns were diffuse radiculoplexus neuropathy, unilateral or bilateral lumbosacral radiculoplexus neuropathy and sciatic mononeuropathy. The neuropathy in most patients was self-limited, but one patient had three attacks. EMGs revealed axonal changes. Laboratory studies detected elevated ESR in 14% of patients, elevated levels of rheumatoid factor in 14%, the presence of perinuclear pattern ANCA (pANCA) in 10%, and elevated CSF levels of protein in 63%. MRI revealed increased T2-weighted signals in roots, plexus elements and/or peripheral nerves. Nerve biopsies revealed epineurial perivascular inflammation in all patients, microvasculitis in 38%, acute axonal degeneration in 75%, and asymmetric fibre loss, focal perineurial thickening and haemosiderin deposits in 50–60%. Sixteen patients were treated with corticosteroids. Fourteen patients were monitored for a median of 10.5 months. All improved, including two who were not treated. The combination of clinical and histopathological findings and the treatment responses suggest that postsurgical inflammatory neuropathy is a self-limited subtype of NSVN triggered by surgery.

Variants

The diabetic radiculoplexus neuropathies can be considered variants of NSVN. Unlike NSVN with proximal involvement, the diabetic radiculoplexus neuropathies are always self-limited and develop in a stereotypical manner, commencing in one region and spreading to another, even as the first site is resolving[11,49–58]. The mechanisms responsible for this distinctive behaviour of diabetes-related vasculitis are poorly understood. The diabetic radiculoplexus neuropathies are characterized by acute-onset, proximal and distal asymmetric involvement, severe pain, and weight loss. They can be subdivided into lumbosacral, thoracic and cervical subtypes, which are sometimes concurrent. Other possible variants of NSVN include neuralgic amyotrophy and nonsystemic skin–nerve vasculitis.

Diabetic lumbosacral radiculoplexus neuropathy. Diabetic radiculoplexus neuropathy has a propensity to affect lumbosacral nerve roots and peripheral nerve trunks and is then labelled as diabetic lumbosacral radiculoplexus neuropathy (DLSRPN)[11,49–58]. DLSRPN affects 1% of patients with diabetes mellitus[59], typically type 2. The median age of onset is 60 years, and the male:female ratio is 3:2. The initial symptom is usually severe pain in the thigh and/or hip that spreads to the distal lower limb; ipsilateral weakness emerges within days to weeks. Weakness usually starts proximally and evolves to affect multiple myotomes and peripheral nerves, resulting in distal weakness in 60% of patients. Pain and weakness are usually unilateral at onset but become bilateral in 85% of patients. Approximately 50% of patients lose weight and develop autonomic symptoms. Concurrent cervical radiculoplexus neuropathy occurs in 10% of patients. Electrodiagnostic studies reveal predominantly axonal changes with patchy active and chronic partial denervation involving multiple lumbosacral nerve roots and peripheral nerves. ESR is elevated in 20% of patients, and CSF protein levels are high in 85%. Symptoms progress for 1 week to 3 years (median four months), then recede over many months (median 15 months)[11,49–58]. Residual weakness persists, especially distally, in more than 50% of patients, and 10–15% of patients relapse. Nerve biopsies reveal T-cell predominant perivascular or vascular inflammation of epineurial microvessels and histopathological alterations associated with vasculitic neuropathy, such as asymmetric fibre loss, active axonal degeneration, haemosiderin, and complement deposits in vessel walls; necrotizing vasculitis, however, is rare[11,49,53–57,60]. Thus, DLSRPN seems to be a PNS microvasculitis. Currently, no treatments for DLSRPN have been identified, although an unpublished randomized trial of 75 patients, reported in an abstract, showed that pulsed methylprednisolone for 12 weeks was more effective than placebo at improving pain but not Neuropathy Impairment Score[61].

Pain is a key feature of DLSRPN, but 5–10% of patients described in the literature had no pain[11,49–58]. In a 2011 study of 23 patients with painless DLSRPN (also known as painless diabetic motor neuropathy), almost all had type 2 rather than type 1 diabetes mellitus[62]. Compared with painful DLSRPN, painless DLSRPN was characterized by a slower progression from onset, greater symmetry and greater upper limb involvement. 80% of patients lost weight, and electrodiagnostic testing indicated a patchy, axonal polyradiculoneuropathy. Median CSF protein levels were 89 mg/dl. As for painful DLSRPN, sural nerve biopsy samples from patients with painless DLSRPN exhibited changes consistent with ischaemic injury and microvasculitis.

Diabetic thoracic radiculoneuropathy. Similarly to DLSRPN, diabetic thoracic radiculoneuropathy usually affects patients in middle-to-late adulthood with type 2 diabetes mellitus[63–67]. Patients present with abrupt-onset pain extending from the back to the lateral torso, abdomen and/or chest. Multiple contiguous thoracic dermatomes, more commonly lower than upper, are usually affected. Within each dermatome, involvement is often incomplete. Pain is accompanied by paraesthesias, contact hypersensitivity, numbness and weight loss. Most cases begin unilaterally, but at least 50% spread to contralateral dermatomes. In a minority of patients, ventral nerve roots are also affected, resulting in focal abdominal outpouching. The disorder is self-limited and gradually resolves over several months to 2 years, but relapses can occur. EMG reveals fibrillation potentials in thoracic paraspinal and abdominal muscles. Thermoregulatory sweat testing identifies discrete areas of anhidrosis on the chest or abdomen[68]. No studies of intercostal nerve biopsy samples from patients with diabetic thoracic radiculoneuropathy have been published, but dorsal root ganglion biopsies have shown inflammatory infiltrates[58].

Diabetic cervical radiculoplexus neuropathy. Upper-limb involvement in DLSRPN is infrequent[69], but the existence of a diabetic cervical radiculoplexus neuropathy that predominates in the upper limbs was first proposed in 2012 (REF 70). This study included 85 patients. The median age of onset was 62 years, and the male:female ratio was 2:1. The most common initial symptom was pain, but 20% of patients had no pain. 60% of patients had hyperacute onset (<24 h) and reached a nadir within 1 week, but in 15%, the condition progressed for >1 month. In 80% of patients, symptoms were initially unilateral, but 47% developed bilateral deficits. 20% of patients had a thoracic radiculoneuropathy and 25% had a lumbosacral radiculoplexus neuropathy. 35% of patients lost weight. CSF protein levels were elevated in 90% of patients. MRI revealed abnormal T2-weighted signal in the brachial plexus cords and/or trunks in all patients. Electrodiagnostic studies revealed axonal changes affecting the upper plexus in 52% of patients, middle plexus in 45%, lower plexus in 54%, and the entire plexus in 28%. Nerve biopsies were performed in 22 patients (primarily cutaneous nerve biopsies in the lower (11) or upper (11) limbs); all revealed an active axonal neuropathy. Epineurial perivascular inflammation ($n = 21$), microvasculitis ($n = 5$), large-vessel vasculitis ($n = 1$), asymmetric fibre loss ($n = 15$), focal perineurial thickening ($n = 16$), and haemosiderin deposits ($n = 6$) were also reported.

Whether diabetic cervical radiculoplexus neuropathy represents a distinct entity is unclear. Most cases of the condition — those with hyperacute-onset and progression to maximal deficit within 1 week — could be classified as neuralgic amyotrophy. However, a minority of patients exhibited features that are not typical of neuralgic amyotrophy, such as a lack of pain (20%), progression over more than 1 month (15%), and lower plexus involvement (54%). Hence, a subset of these patients might have had a subacutely progressive form of diabetic radiculoplexus neuropathy with preferential cervical involvement.

Neuralgic amyotrophy. Neuralgic amyotrophy (also known as acute brachial plexus neuropathy) is a clinical syndrome characterized by acute-onset pain in the shoulder and arm followed by focal or multifocal weakness

with slow recovery over months to years[71–73]. Most cases are idiopathic, but an autosomal dominant hereditary form exists, which is usually linked to the *SEPT9* gene[74]. The incidence of idiopathic and hereditary neuralgic amyotrophy in the primary care setting is 1 in 1,000 per year in the Netherlands[73]. In the largest series, which included 199 patients with idiopathic neuralgic amyotrophy and 47 with hereditary neuralgic amyotrophy, the median age of onset was 41.3 (10–80) years for the idiopathic cohort and 28.0 (3–56) years for the hereditary cohort, with a 2:1 male:female ratio for both groups[72]. Clinical and electrodiagnostic assessments usually reveal multiple mononeuropathies rather than root, trunk or cord lesions. The condition has its major effect on motor nerves, especially those derived from the upper plexus, such as long thoracic, suprascapular, axillary, musculocutaneous, dorsal scapular, pronator teres motor branch and anterior and posterior interosseous nerves. Almost all patients experience acute, severe, continuous pain that is bilateral and asymmetric in 30%. Acute pain lasts a median of 20 days, but two-thirds of patients subsequently develop musculoskeletal pain. Weakness generally follows pain within 1–2 weeks but can develop up to 4 weeks. Sensory loss occurs in 80% of patients. Nerves outside of the brachial plexus are affected in 56% of patients with hereditary neuralgic amyotrophy and 17% with the idiopathic condition. Recovery is often incomplete: of 49 patients monitored for ≥3 years, only two reported a full recovery at the end of follow-up, 24 had pain and 48 had variable degrees of weakness.

The pathogenesis of neuralgic amyotrophy is unknown. To our knowledge, the findings from only five nerve biopsies performed during attacks of neuralgic amyotrophy have been reported in two studies[75,76]. In one of these reports, two patients had typical idiopathic neuralgic amyotrophy, and their brachial plexus biopsy samples revealed conspicuous mononuclear perivascular inflammation in the epineurium and endoneurium; no other histopathological features were detailed. In the other study, three patients with hereditary neuralgic amyotrophy underwent superficial radial nerve biopsies that revealed epineurial mononuclear and perivascular inflammation in all three patients, disruption of vessel walls in two patients, marked axonal degeneration in two patients, multifocal fibre loss in one patient, and no necrotizing vasculitis. These findings were consistent with histopathologically probable vasculitic neuropathy. On the basis of this histopathological evidence and the clinical phenotype of acute, painful, axonal, multifocal sensorimotor neuropathy, neuralgic amyotrophy might represent a self-limited variant of NSVN. More neuropathological investigations are needed.

Nonsystemic skin/nerve vasculitis. Cutaneous polyarteritis nodosa is a necrotizing, nonsystemic skin–nerve vasculitis of small-to-medium-sized arteries in the dermis and hypodermis that manifests with painful nodules, livedo racemosa, ulcers, atrophie blanche, purpura, indurated plaques and necrosis[77–81]. The condition predominates in the lower limbs, but the arms and trunk are also affected in 10–50% patients. Patients experience recurrent relapses of skin lesions over years, and some develop myalgia, arthralgia or fevers. Most patients have a mildly to moderately elevated ESR, but are negative for ANCAs. The mainstays of treatment are short courses of nonsteroidal anti-inflammatories or corticosteroids, but immunosuppressive agents can be used to permit corticosteroid tapering. On the basis of data from numerous reports, 40–45% of patients develop a lower-limb neuropathy, more commonly a multifocal neuropathy than a distal polyneuropathy[78,80–85]. Reports of nerve biopsies in patients with cutaneous polyarteritis nodosa are rare, but one revealed vasculitis[86]. The incidence of myopathy has not been adequately investigated, but in one study, all five muscle biopsy samples demonstrated necrotizing vasculitis[77]. On the basis of this evidence, cutaneous polyarteritis nodosa can be classified as a lower-limb-predominant vasculitis that manifests with skin and, to a lesser extent, neuromuscular involvement.

Analogous to cutaneous polyarteritis nodosa, some cases reported as NSVN have also predominated in the lower limbs and been accompanied by cutaneous vasculitis[14,87–89]. Prospective investigations have shown that NSVN is often associated with subclinical perivascular inflammation in adjacent cutaneous tissues[90,91]. Rarely, NSVN starts in the PNS and spreads to the skin[23,36]. Similarly to this local skin involvement, peroneus brevis muscle biopsies in patients with NSVN reveal vasculitis in 25% of patients[14,19,34,92]. Hence, NSVN can be viewed as a lower-limb-predominant vasculitis with nerve and occasional subclinical skin and muscle involvement. Some patients with NSVN accompanied by overt skin involvement will also satisfy diagnostic criteria for cutaneous PAN.

Diagnosis of NSVN

The clinical and histopathological features of the neuropathy in NSVN are essentially identical to those in SVN, so diagnostic approaches to NSVN and SVN overlap. As such, discussion that relates to SVN below also applies to NSVN.

Histopathological diagnosis

Definite vasculitic neuropathy. The gold standard for diagnosis of NSVN is nerve biopsy evidence of definite vasculitis. In 2010, the Peripheral Nerve Society guideline group derived consensus criteria for histopathologically definite vasculitic neuropathy[4]. The group's consensus was that vascular wall inflammation must be accompanied by vascular damage to qualify as definite vasculitis. Microvasculitis, defined as inflammation of microvessels without vascular damage, was deemed nonspecific, as it can occur in many non-vasculitic neuropathies[10]. Moreover, analyses of two class II studies showed that clinicopathological surrogates of vasculitic neuropathy were generally not associated with microvasculitis[14,93]. Definite vasculitis was divided according to the presence of active or chronic lesions, which coexist in most vasculitic neuropathies. The Peripheral Nerve Society guideline group's definition has been adapted without substantive changes by the Brighton Collaboration VPN Working Group[16].

Probable vasculitic neuropathy. Nerve biopsies that fail to satisfy criteria for definite vasculitis can meet less-specific criteria to enable a diagnosis of histopathologically probable vasculitic neuropathy; the Peripheral Nerve Society guideline group formulated such criteria after reviewing the evidence on histopathological findings associated with definite vasculitic neuropathy[4]. Given the dearth of data on NSVN, the group reviewed studies that enrolled patients with SVN or NSVN. Eighteen articles were selected, six class II and twelve class III (all case–control studies, except one retrospective cohort survey)[14,34,54,60,94–107], which were analysed to identify variables associated with vasculitic neuropathy. By combining evidence from this review with that from class IV studies that showed active axonal degeneration to be increased in all vasculitic neuropathy series, the guideline group designed consensus diagnostic criteria for histopathologically probable vasculitic neuropathy. These criteria required predominantly axonal alterations together with either perivascular inflammation and histopathological signs of vascular damage, or perivascular or vascular inflammation accompanied by one of five class II and III histopathological predictors of vasculitic neuropathy (vascular deposits of complement, IgM or fibrinogen detectable with direct immunofluoresence; haemosiderin deposits detectable with Perls' stain; asymmetric nerve fibre loss or degeneration; prominent active axonal degeneration; and myofibre necrosis and regeneration or infarcts revealed by concomitant peroneus brevis muscle biopsy and not explained by underlying myopathy)[4].

The evidence from the selected studies suggested that epineurial neovascularization was not a reliable predictor of vasculitic neuropathy. The guideline group consequently concluded that neovascularization, endoneurial haemorrhage, focal perineuritis, focal perineurial damage or thickening, injury neuroma, and swollen dark axons deserved further investigation. With the exception cited below, these investigations have not been done.

A PubMed search of the years 2008–2016 yielded two additional studies with information on histopathological predictors of vasculitic neuropathy[19,91] (Supplementary information S3 (table)). The first was a class II retrospective cohort study of 43 patients undergoing biopsy of the superficial peroneal nerve and peroneus brevis muscle for suspected vasculitis. In this study, four histopathological variables were associated with vasculitis: asymmetric nerve fibre loss, active axonal degeneration, Perls' stain for haemosiderin in nerve or muscle, and Perls' stain for haemosiderin in nerve alone[19]. A fifth variable — epineurial neovascularization — was not associated. These findings corroborated those previously reviewed by the Peripheral Nerve Society guideline group[4].

The second investigation was a class III case–control study in which inflammatory aggregates in skin biopsy samples from 17 patients with untreated NSVN were compared with those in biopsy samples from patients in two control groups: 10 patients with noninflammatory axonal neuropathies, and nine healthy controls[91]. The key finding was that vessel-bound $CD3^+$ T cells and $CD68^+$ macrophages were significantly more prevalent in samples from patients with NSVN than those from controls. On the basis of this evidence, the Brighton Collaboration case definition of vasculitic neuropathy included "perivascular mononuclear inflammation in skin biopsy obtained concurrently with nerve biopsy" as a sixth criterion to support the diagnosis of histopathologically probable vasculitic neuropathy[16].

Clinical diagnosis

Evidence of histopathologically definite vasculitic neuropathy from a nerve biopsy enables diagnosis irrespective of clinical phenotype. Without such evidence, patients can still be diagnosed with clinically probable vasculitic neuropathy if their clinicopathological profile matches that of a typical biopsy-proven case of vasculitic neuropathy. To facilitate this process, a case definition of clinically probable vasculitic neuropathy is required.

The Peripheral Nerve Society guideline group on NSVN designed such a case definition by consensus after reviewing the evidence on clinical and laboratory predictors of definite vasculitic neuropathy[4]. Clinical and laboratory variables associated with definite vasculitic neuropathy in class II or III studies were electrodiagnostic evidence of multifocal or asymmetric neuropathy, clinically-defined multifocal or asymmetric neuropathy, rapidly progressive neuropathy (symptom onset within 1 month of biopsy), pain, elevated ESR, and elevated levels of C-reactive protein, rheumatoid factor, myeloperoxidase-pANCA, β-2 microglobulin, and vascular endothelial growth factor (VEGF) (Supplementary information S4 (table)).

Our PubMed search of the years 2008–2016 yielded no new articles on clinical predictors and only one new article on a laboratory predictor (Supplementary information S4 (table)). This publication was a small, unblinded case–control study that showed plasma VEGF levels to be higher in five patients with polyarteritis nodosa-associated vasculitic neuropathy than in eight healthy controls, confirming a previously identified study that compared patients with disease controls[108].

Following their initial analysis, the guideline group analysed 22 uncontrolled NSVN and SVN series to determine the typical phenotype of a vasculitic neuropathy[4]. Features with high sensitivity for vasculitic neuropathy were electrodiagnostically-revealed axonal neuropathy (100%), distal predominance (90%), electrodiagnostic evidence of asymmetric or multifocal process (85%), clinically asymmetric or multifocal neuropathy (81%), pain (78%), fibrillation potentials in at least one muscle as detected by EMG (70%), and a clinical course characterized by at least one acute attack (67%). Conversely, factors with very low sensitivity were electrodiagnostic evidence of primary demyelinating neuropathy (0%), pure motor involvement (0.6%), upper-limb predominance (5%), CSF pleocytosis (4%) and CSF protein levels >110 mg/dl (2%). From experience, the group reached a consensus that a distal symmetric polyneuropathy with no asymmetry was also rare in vasculitic neuropathy, despite the reported 15–20% prevalence of symmetric polyneuropathy. These clinical features and class II and III clinical predictors were used to construct a consensus case definition of clinically probable vasculitic neuropathy.

Box 2 | **Brighton Collaboration case definition of vasculitic neuropathy**

Level 1 definition (gold standard)

- Biopsy of peripheral nerve meets criteria for histopathologically definite vasculitis.

Level 2 definition

- Clinical features are suggestive of vasculitic neuropathy*; and
- Histopathological support for the existence of vasculitis: biopsy of peripheral nerve meets criteria for histopathologically probable vasculitis; or diagnosis of systemic vasculitis confirmed by biopsy; or biopsy of skin or muscle meets criteria for histopathologically definite vasculitis.

Level 3 definition (minimum acceptable evidence)

- Biopsy of peripheral nerve or muscle not done or does not meet criteria for definite or probable vasculitis; and
- Clinical features are suggestive of vasculitic neuropathy*.

Definitions adapted from Hadden *et al.*[16] *Clinical features that are suggestive of vasculitic neuropathy are: electrodiagnostic or clinical examination evidence of peripheral neuropathy and a clinical presentation that is typical for vasculitic neuropathy (multifocal or asymmetric, involving sensory or sensory–motor nerves, lower limb-predominant, painful and with one or more acute attacks). Full details are available in the Brighton Collaboration case definition[16].

Brighton Collaboration case definition of vasculitic neuropathy. The Brighton Collaboration case definition was developed in 2015 as a practical clinical tool to help nonspecialists identify patients with vasculitic neuropathy[16]. Although intended for use in epidemiological studies of adverse effects of vaccination, the definition is equally suitable for vaccination-unrelated cases. The case definition specifies three levels of clinical certainty (BOX 2); the highest level requires evidence of definite vasculitis from a nerve biopsy, using criteria only minimally changed from those of the Peripheral Nerve Society.

A novel feature of the Brighton Collaboration case definition was the lowest level of certainty, which allowed a diagnosis of clinically probable vasculitic neuropathy based on history and examination alone, without any laboratory tests, and was therefore suitable for use in resource-poor countries. In addition to clinical or electrodiagnostic evidence of peripheral neuropathy, this definition specified features with the greatest sensitivity for vasculitic neuropathy adapted from the work of the Peripheral Nerve Society. The criteria for time course and anatomical distribution were modified to improve clarity; they are analogous to 'dissemination in time and space' in the diagnosis of multiple sclerosis. The criterion for multifocal or asymmetric distribution was defined as any deviation from perfect symmetry at any time by history, examination, electrophysiology or imaging, and not attributable to compression of nerves or roots, the most common mimics of this pattern. Alternative non-vasculitic causes of an asymmetric or multifocal distribution were listed as exclusions. Although highly sensitive for vasculitic neuropathy, distal predominance was deleted to permit inclusion of patients with a radiculoplexus neuropathy phenotype. The intermediate level of certainty requires support from biopsy evidence of definite vasculitis in another organ (especially muscle or skin) or a nerve biopsy that shows histopathologically probable vasculitic neuropathy.

Nerve and nerve–muscle biopsies. Considering the broad differential diagnosis of multifocal or asymmetric neuropathy (see Multifocal neuropathy: definition) and the absence of specific biomarkers for NSVN, diagnosis in patients with clinically suspected NSVN requires a nerve biopsy. Indeed, given the 20% prevalence of distal symmetric polyneuropathy among reported patients with NSVN, nerve biopsy should be considered in all patients with progressive axonal neuropathies, irrespective of symmetry. That said, among patients with an idiopathic, chronic, symmetric polyneuropathy, nerve biopsy yields a diagnosis of definite vasculitis in only 3%[109–111], much lower than the 20% yield among patients with a clinical phenotype that raises suspicion of vasculitis[112–114]. This low yield must, therefore, be weighed against the risks of biopsy.

An accessible, clinically and electrophysiologically affected sensory nerve should be selected for a biopsy. The most commonly biopsied nerves are the sural and superficial peroneal nerves. If clinically indicated, other sensory nerves can be biopsied, such as the saphenous, intermediate femoral cutaneous, lateral antebrachial cutaneous, dorsal ulnar, and superficial radial nerves. Although a nerve biopsy is more often diagnostic than a muscle biopsy, especially in NSVN, a meta-analysis showed that a concomitant muscle biopsy increases the histopathological diagnosis of definite vasculitis by 15% among patients with a final diagnosis of vasculitic neuropathy[115]. Superficial peroneal nerve biopsy is always combined with peroneus brevis muscle biopsy through the same incision. Sural nerve biopsies can be combined with anterior tibialis, gastrocnemius, soleus or quadriceps muscle biopsies. One study reported that a biopsy of the quadriceps did not increase diagnosis of definite vasculitis, suggesting that distal muscles are more commonly involved[35].

The true sensitivity of nerve or nerve–muscle biopsy for NSVN cannot be determined in the absence of an independent reference standard; however, patients for whom nerve biopsy does not provide proof of vasculitic neuropathy can still be diagnosed with clinically probable vasculitic neuropathy by recourse to the Peripheral Nerve Society or Brighton Collaboration case definitions, permitting derivation of an estimated sensitivity. On the basis of data from multiple studies, the estimated sensitivities of sural nerve biopsy alone and superficial peroneal nerve biopsy combined with peroneus brevis muscle biopsy for definite NSVN are both ~50%[3,13,14,19,35–37,116–119].

Radiographic studies. No radiographic techniques have been established for diagnosing or monitoring NSVN. A single case report documented the use of magnetic resonance angiography of the lower limbs in NSVN and suggested that this procedure might be a reliable marker of disease activity[120], but no further studies have been published. MRI guidance before targeted fascicular biopsies of proximal nerves and plexuses is routinely performed at the Mayo Clinic, but comparison of its diagnostic accuracy in vasculitic neuropathy with that of conventional distal lower

limb cutaneous nerve biopsies has not been done[121]. No series dedicated to peripheral nerve MRI findings in patients with histopathologically proven vasculitic neuropathy has been published.

Some use of peripheral nerve ultrasonography in vasculitic neuropathy has been reported. One study assessed ultrasonography as a means to evaluate clinically involved tibial nerves in the ankles of eight patients with SVN[122]. Compared with those in healthy controls, tibial nerves in patients with SVN had a significantly larger mean cross-sectional area. In another study of 14 patients with SVN (proven by sural nerve biopsy in eight patients), ultrasonography of 31 clinically involved nerves revealed focal enlargements in 22 (REF. 123). Mean cross-sectional areas of the tibial, peroneal and — to a lesser extent — median and ulnar nerves were larger than those in healthy controls. In a third study, ultrasonography was used to assess the sural, superficial peroneal, tibial and deep peroneal nerves in six patients with biopsy-proven vasculitic neuropathy (four with NSVN), six with chronic inflammatory demyelinating polyneuropathy (CIDP), five with non-immune neuropathies and 26 healthy controls[124]. In patients with vasculitic neuropathy, the cross-sectional area of the sural nerve was significantly greater than that in healthy and disease controls, and the longitudinal diameter of the superficial peroneal nerve was greater than that in healthy controls. Hence, focal nerve enlargements revealed by ultrasonography could have a role in directing nerve biopsies and monitoring disease activity in NSVN, but further study is necessary.

Multifocal neuropathy: definition

Vasculitic neuropathies, whether systemic or nonsystemic, typically have a multifocal distribution. The term mononeuritis multiplex was originally synonymous with SVN, but has since evolved into a nonspecific label for all neuropathies that involve multiple single nerves in the extremities, which can result from numerous aetiologies, many of which are noninflammatory. As such, more aetiologically neutral designations are preferable; for example, mononeuropathy multiplex, multiple mononeuropathies or (our preference) multifocal neuropathy.

As noted above (see Clinical features of NSVN), three patterns of vasculitic neuropathy are usually distinguished: multifocal neuropathy, distal symmetric polyneuropathy, and a transitional phenotype known as overlapping, confluent or extensive multifocal neuropathy, or asymmetric polyneuropathy (FIG. 1). Unfortunately, definitions for these patterns are not standardized, resulting in heterogeneity between studies. Definitions for multifocal neuropathy and distal symmetric polyneuropathy should be straightforward, but the broad middle ground is less easily compartmentalized. For example, it remains unclear when, at the focal end of the spectrum, a true multifocal neuropathy transitions into an overlapping multifocal neuropathy, and, at the diffuse end, when a distal symmetric polyneuropathy becomes an asymmetric polyneuropathy, thereby raising suspicion of an underlying multifocal neuropathy.

To address this uncertainty, we reviewed numerous articles, reviews and book chapters for published definitions, the most salient of which are here cited[12,114,125–137], and identified key elements of a complete and unambiguous definition of multifocal neuropathy. These elements are as follows: involvement of two or more individual, named peripheral nerves and not unnamed nerve twigs; limitation to the sensorimotor somatic and not the autonomic PNS; involvement defined clinically by distribution of weakness or sensory loss; no overlap or contiguity between affected nerves; applicability of

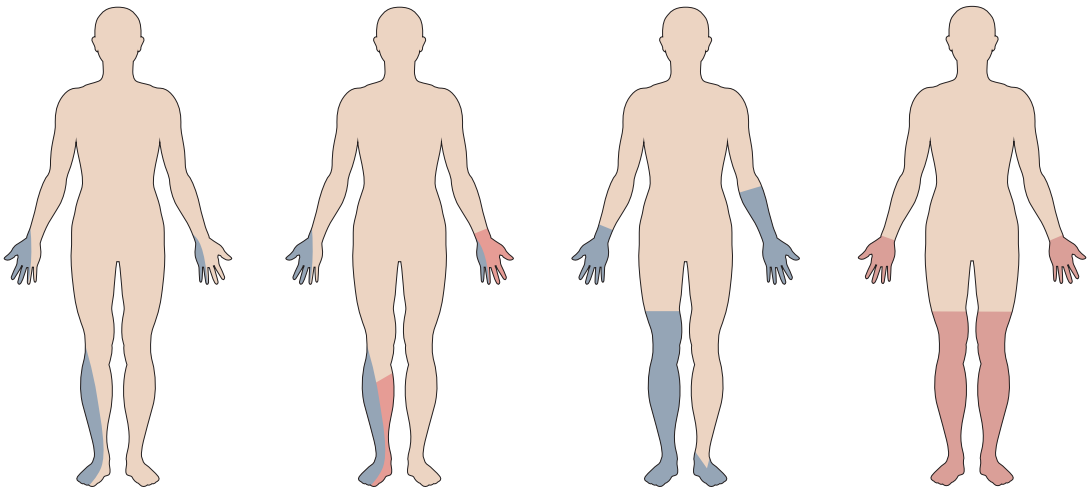

Figure 1 | **Anatomical patterns of neuropathy.** The distinct patterns of involvement indicate diagnosis of each of the conditions. In multifocal neuropathy and early overlapping multifocal neuropathy, the two colours differentiate between the distributions of different cutaneous nerves. In late overlapping multifocal neuropathy and distal symmetric polyneuropathy, the single colour highlights involvement of multiple overlapping cutaneous nerves.

Table 1 | **Lower limit of normal interside amplitude ratio in assessment of asymmetry in nerve conduction studies**

Nerve	Bromberg (1989)[139]	Buschbacher (2016)[140]
Median motor	0.50	0.50
Ulnar motor (abductor digiti minimi)	0.70	0.75
Peroneal motor (extensor digitorum brevis)	0.20	0.40
Peroneal motor (anterior tibialis)	Not determined	0.50
Tibial motor	0.40	0.50
Median sensory	0.60	0.50
Ulnar sensory	0.50	0.50
Sural sensory	0.40	0.30

the definition to any peripheral or cranial nerve; and allowance for nerves to be affected either sequentially or simultaneously.

On the basis of these elements, we define multifocal neuropathy as an anatomical pattern of peripheral neuropathy that affects two or more noncontiguous, individual, named, somatic, sensory, motor or sensorimotor peripheral or cranial nerves simultaneously or sequentially. Conversely, we define distal symmetric polyneuropathy as an anatomical pattern of length-dependent peripheral neuropathy that affects multiple somatic nerves diffusely and symmetrically, commencing distally and spreading proximally with continued distal predominance.

If a multifocal neuropathy progresses, anatomically contiguous nerves will eventually be affected. Distinguishing contiguous involvement of two or more distal nerves from a single, more proximal lesion involving the brachial plexus, lumbosacral plexus or sciatic nerve with clinical and electrodiagnostic criteria alone can be challenging. Peripheral nerve MRI has the potential to resolve this issue, but this technology and the necessary expertise are not widely available. Autopsy studies in microscopic polyangiitis have shown that vasculitis affects peripheral nerves both distally and proximally, resulting in distally accentuated ischaemic damage to axons, sparing the spinal cord, nerve roots and ganglia[39]. Hence, in vasculitis, a combined distal and proximal pattern in one limb generally implies involvement of multiple contiguous, distal and proximal nerves, rather than a single proximal nerve.

On the basis of the aforementioned clinical arguments, an early overlapping multifocal neuropathy can be defined as a multifocal neuropathy in which contiguous cranial or individual peripheral nerves distal to the plexuses are involved. In a late overlapping multifocal neuropathy, there is more extensive involvement of contiguous nerves, generally in a distally accentuated pattern, to the extent that individual mononeuropathies are no longer distinguishable and the anatomical pattern loses its multifocal features. The neuropathy then appears as a diffuse process, mimicking a distal symmetric polyneuropathy, but can be identified by residual asymmetries. On this basis, a late overlapping multifocal neuropathy is an asymmetric polyneuropathy, although what constitutes a clinically relevant asymmetry remains unclear.

Data exist to aid the identification of significant asymmetries from nerve conduction studies, but not from clinical examinations. An asymmetry in amplitude of ≥50% is generally taken as significant in motor and sensory nerve conduction studies, but evidence suggests that the cutoff should be higher for the ulnar motor nerve and lower for the peroneal motor and sural sensory nerves[138–140] (TABLE 1). Other findings in nerve conduction studies that suggest a non-length-dependent process are significant amplitude differences between nerves of similar length in one limb, and significantly lower amplitudes in upper-limb nerves than lower-limb nerves that cannot be explained by entrapment or pre-existing radiculopathies. In an overlapping multifocal neuropathy, needle EMG usually reveals active and/or chronic partial denervation in a non-length-dependent distribution, such as conspicuous interside differences in denervation between homologous muscles, a greater extent of denervation in proximal muscles than distal muscles, disproportionate involvement of a single nerve in one limb, and a greater extent of denervation in upper-limb muscles than in lower-limb muscles.

We propose a new definition of significant inter-side differences in examination findings (BOX 3) based on our clinical experience. Clearly, this definition requires prospective validation in patients with a broad spectrum of neuropathic phenotypes and aetiologies to gauge its predictive value for vasculitic and other multifocal neuropathies.

Numerous aetiologies need to be considered in patients with an asymmetric or multifocal neuropathy. The full differential diagnosis is extensive (Supplementary information S5 (box)). Among the more common or important conditions to consider in

Box 3 | **Proposed clinical definition of asymmetric polyneuropathy**

Any of the following would indicate that a polyneuropathy is asymmetric:

- Motor examination criteria: a difference of ≥1 grade in strength between homologous muscles, measured with the Medical Research Council grading system (0–5) or Rasch-built Medical Research Council system (0–3) (REF. 153).
- Reflex examination criteria: a difference of ≥1 grade between homologous tendon reflexes, measured with the standard 0–4 grading system (0, absent; 1, reduced; 2, normal; 3, increased; 4, clonus).
- Sensory examination criteria: an inter-side difference of ≥50% in perceived intensity in any sensory modality.

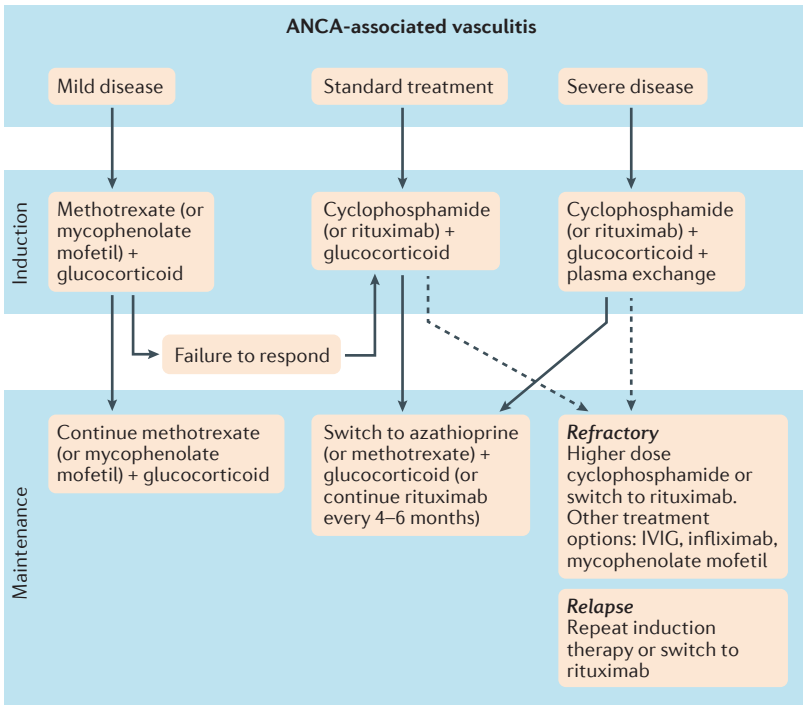

Figure 2 | **Algorithm for immunosuppressive treatment of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides.** Standard induction treatment is with cyclophosphamide and glucocorticoids, with alternatives for milder or more severe disease. Standard maintenance treatment is with azathioprine or methotrexate, which should be continued for longer than the glucocorticoids. Modified with permission from Nature Publishing Group © Schönermarck, U. *et al. Nat. Rev. Nephrol.* **10**, 25–36 (2014).

an asymmetric or multifocal neuropathy are the many vasculitic neuropathies, multiple entrapments of nerves or roots, Lewis–Sumner syndrome (multifocal CIDP), sarcoidosis, sensory neuronopathy (paraneoplastic or Sjögren syndrome-related), leprosy, Lyme disease, HIV infection (with secondary cytomegalovirus infection, varicella-zoster virus infection, or diffuse infiltrative lymphocytosis syndrome), amyloidosis, neoplastic cell infiltration, other paraneoplastic neuropathies, and motor neuron disease with sensory involvement.

Treatment

Evidence from systemic vasculitis

Owing to the absence of treatment trials in NSVN, treatment is typically extrapolated from the evidence available for systemic vasculitis. However, in treatment trials of systemic vasculitis, the presence of neuropathy was not associated with overall mortality or life-threatening organ involvement, and neuropathy outcome measures were unreliable[141]. Therefore, to assume that the best treatment for life-threatening forms of systemic vasculitis, such as those that affect the kidneys or lungs, are best for SVN or NSVN would be incorrect. Extensive historical evidence on the treatment of systemic vasculitis that affects small and medium vessels was reviewed in detail in the Peripheral Nerve Society guideline (online supplements 3 and 4)[4]. The introduction of corticosteroids and then cyclophosphamide in the 1950s transformed the survival rate of patients with polyarteritis nodosa and granulomatosis with polyangiitis from only 10–15% at 1 year to 85–90% at 5 years[4]. The serious adverse effects of continuous oral cyclophosphamide have been greatly reduced by a pulse regime or by substituting less-toxic immunosuppressive agents for induction and/or maintenance treatment, albeit at the expense of a higher relapse rate.

Since publication of the 2010 Peripheral Nerve Society guideline[4], evidence has shown that rituximab is at least as efficacious as cyclophosphamide for induction of remission and more efficacious than azathioprine in the maintenance of remission in the ANCA-associated vasculitides[142–144]. The most up-to-date guidelines on the treatment of the ANCA-associated vasculitides were published by the British Society for Rheumatology in 2014 (REF. 145) and the European League Against Rheumatism in 2016 (REF. 146) (FIG. 2).

NSVN and neuropathy-predominant SVN

When the Peripheral Nerve Society guideline group on NSVN reviewed the literature on treatment of NSVN in 2009, searches yielded no class I or II trials, but two class III retrospective cohort surveys were identified[4]. The larger of the two cohort studies analysed treatment responses to corticosteroid monotherapy or combination therapy with corticosteroid and oral cyclophosphamide; 48 patients were included, with a median follow-up of 63 months[36]. The study concluded that combination therapy was significantly more effective than corticosteroid monotherapy in inducing sustained improvement at 6 months and reducing disability. Similarly, the second cohort study, in which improvement in disability was analysed in 22 patients with NSVN, revealed a compelling trend that favoured combination therapy with corticosteroids and either cyclophosphamide, azathioprine or methotrexate over corticosteroid monotherapy[37].

In 2015, the French Vasculitis Study Group (FVSG) reported preliminary findings from treatment of their NSVN cohort[33]. Of the 41 patients initially treated with corticosteroids alone, 20 required second-line immunosuppressive therapy (cyclophosphamide, azathioprine or methotrexate) owing to an inadequate response to corticosteroid monotherapy, relapse or other issues. Hence, only 50% of patients had a sustained response to corticosteroids, consistent with observations in the two retrospective cohort studies[36,37].

A nearly identical outcome emerged from an FVSG study of patients with a form of systemic vasculitis that primarily affects skin and nerve, which is similar, but not identical, to NSVN. This prospective study of 124 patients with polyarteritis nodosa or microscopic polyangiitis and no poor-prognostic factors (renal, gastrointestinal, cardiac or CNS involvement) was conducted between 1993 and 2005 (REF. 147). Vasculitis affected skin in 79% of patients and nerve in 66% of patients. Additional manifestations were uncommon (5–30% of patients). All patients were initially treated with 1 mg/kg prednisone per day. Prednisone induced remission in 79% of patients, but the disease could not be controlled

Box 4 | **2010 Peripheral Nerve Society guideline Good Practice Point treatment recommendations for NSVN**

- All patients with progressive NSVN or for whom a biopsy indicates active vasculitis should be treated.
- Corticosteroid monotherapy (1.0 mg/kg prednisone daily tapered to 10 mg daily at 6 months) is preferred unless the neuropathy is rapidly progressive (new deficits within 4 weeks)*.
- Combination therapy (corticosteroids with cyclophosphamide, methotrexate or azathioprine‡) should be used for patients with rapidly progressive NSVN, and for those in whom corticosteroid monotherapy has failed*.
- For severe NSVN, cyclophosphamide§ is preferred, administered as 0.6 g/m^2 body surface every two weeks for three doses, followed by 0.7 g/m^2 body surface every three weeks for three to six doses (the dose should be adjusted downwards in elderly people and people with renal dysfunction).
- Once remission is achieved (improvement in at least one objective measure and no worsening by any measure after 6 months), prednisone can be stopped or continued at 5.0–7.5 mg daily for 18 months while initial combination therapy is replaced with maintenance immunosuppressive therapy with 1.0–2.0 mg/kg azathioprine daily or 20–25 mg methotrexate weekly for 18–24 months‖.
- Options for patients whose condition is refractory to cyclophosphamide include intravenous immunoglobulin, rituximab and plasma exchange.

Information from Collins *et al.*[4] *We now suggest initial treatment of most patients with combination therapy (corticosteroids combined with cyclophosphamide, methotrexate or rituximab). ‡We now do not recommend azathioprine for induction therapy. §Or possibly rituximab adminstered as 375 mg/m^2 body surface area every week for 4 weeks. ‖Or, if rituximab is used to induce remission, maintenance rituximab 500 mg every 6 months for 18–24 months.

with corticosteroids alone in 45%, and 40% of patients were treated with second-line agents. Five-year survival was 92%. Long-term (median 98.2 months) follow-up of this cohort was reported in 2014 (REF. 148): corticosteroid monotherapy induced remission in 82% of patients, but 53% experienced a relapse. Throughout follow-up, 47% of patients required treatment with a second agent. Five-year survival was still 93%, but 78% of patients had chronic sequelae, most frequently neuropathy (49%) and corticosteroid-related morbidity. The investigators concluded that initial corticosteroid monotherapy commonly resulted in relapses and long-term sequelae.

In a subsequent study, the FVSG analysed 118 patients from the same cohort in combination with 75 patients with eosinophilic granulomatosis with polyangiitis who had no poor-prognostic factors and received similar treatment in order to identify patient characteristics at inclusion that were associated with the need for immunosuppressive agents[149]. Corticosteroids induced remission in 87% of patients, but add-on therapy was required in 45%, of which 60% developed chronic neuropathy. The only factor associated with the need for add-on therapy identified by univariate and multivariate analyses was multifocal neuropathy, suggesting that patients with multifocal neuropathy are more likely to fail corticosteroid monotherapy, and indicating the need for prospective evaluation of initial combination therapy (corticosteroids combined with another immunosuppressive agent).

Information about the treatment of NSVN with azathioprine is provided by a 2015 study that involved 60 patients with NSVN[30]. Nineteen of the 60 patients were initially treated with pulsed intravenous methylprednisolone, combined with an oral corticosteroid taper in nine patients, followed by 150 mg azathioprine daily. On the basis of multiple tabulated outcome measures, nine of the 19 patients clearly improved, 14 improved at least slightly, and 12 improved according to assessment with the Prineas disability scale. However, azothioprine failed in seven additional patients owing to adverse effects or disease progression. Inclusion of these seven treatment failures in the tabulation causes the azathioprine response rate to become disappointingly low: 35% with clear improvement, 56% with at least slight improvement, and 46% with improved disability.

The evidence described above suggests that patients with NSVN or neuropathy-predominant SVN who receive combination therapy (corticosteroids and a second immunosuppressive agent) at baseline might have a lower risk of treatment failure and sequelae than patients treated with corticosteroids alone. Moreover, cyclophosphamide might be more effective than azathioprine in inducing remission.

The 2010 Peripheral Nerve Society guideline included Good Practice Point treatment recommendations for NSVN (BOX 4). On the basis of our above updated review of therapy for NSVN and systemic vasculitis, we recommend two modifications to these recommendations. First, we suggest initial treatment of most, if not all, patients with combination therapy (corticosteroids combined with cyclophosphamide or methotrexate) until better evidence, such as that from a randomized controlled trial, is available. Second, extrapolating the results of recent trials in ANCA-associated vasculitis to NSVN, rituximab might be a first-line alternative to cyclophosphamide for induction therapy of severe NSVN, followed by maintenance infusions every 6 months for 18–24 months.

Treatment of neuropathic pain can be challenging[150]. Neurorehabilitation of patients with disability can include physiotherapy, occupational therapy, and ankle–foot orthoses for foot-drop.

Monitoring of disease activity in NSVN depends on neurological examination (weakness and sensory loss) and assessment of functional abilities. No laboratory biomarker of disease activity is available. Pain sometimes worsens with resolution of nerve ischaemia and

is, therefore, not a reliable measure of disease activity. Clinical improvement can take months owing to the slow speed of nerve regeneration.

Outcomes of NSVN treatment

In the most detailed cohort study of NSVN, relapses occurred 6–47 months after initiation of treatment in 18 of 39 patients who responded to initial treatment[36]. Patients who experienced relapses had discontinued treatment or their treatment had been tapered to low-dose prednisone. No patient experienced a relapse while taking cyclophosphamide. Combining data from all series and case reports of patients who were followed-up for at least 12 months after initiation of treatment, the relapse rate among all patients treated is ~30%; the relapse rate among treatment responders is likely to be higher, but cannot be calculated owing to insufficient data.

NSVN rarely spreads to other organs or tissues in patients who are properly screened for underlying systemic vasculitis at baseline and treated with immunosuppressive agents. Final neurological outcome in long-term survivors is reasonably favourable: 13% are essentially asymptomatic, 41% have mild symptoms but no restrictions in activities of daily living, 28% have mild-to-moderate restrictions but are independent, 14% require assistance with ambulation or activities of daily living, and 3% are non-ambulatory[30,31,36,37]. 82% of patients regain or retain the ability to ambulate without assistance. In the only study to have analysed mortality, 5-year survival was 87%[36]; in this cohort, all patients were treated with corticosteroids or corticosteroids combined with other immunosuppressive agents. However, studies have shown that chronic pain occurs in 60% of patients who survive more than 24 months in a cohort of severely affected patients and in 37% in a cohort of patients that were less severely affected[30,36].

Conclusions and future

Progress in clinical research of vasculitic neuropathy would be greatly assisted by better outcome measures and a comprehensive registry. The neuropathy measures used in current vasculitis clinical trials — the Birmingham Vasculitis Activity Score and Vascular Damage Index — are over simplistic, insensitive to change, and potentially misleading, yet traditional neurological examination is intimidating for nonspecialists. We plan to conduct a multicentre study to develop a Rasch-derived overall disability scale for vasculitic neuropathy[151]. The scale would be a simple patient-completed questionnaire about the difficulty of performing daily activities, yet have powerful statistical properties to enable detection of neurological change, similar to existing scales for other neuropathies[152]. This scale should be useful both for routine clinical monitoring and to improve analysis of neurological outcomes in future treatment trials.

A registry of patients with vasculitic neuropathy would permit acquisition of prospective data that would better define the incidence, clinical spectrum, natural history, treatment and outcomes of various types of vasculitic neuropathy. The UK & Ireland Vasculitis Study Group online registry will have more-detailed questions on neuropathy added to the next version and include patients with NSVN. These projects are important steps towards answering questions regarding the associations between nerve and non-nerve vasculitis pathogenesis, biomarkers, disability, and outcomes.

New investigations of immunological and non-immunological pathogenic mechanisms of NSVN are also essential. As knowledge of the pathophysiology of NSVN increases, better and more specific treatments can be developed. An important goal of future treatment trials will be to significantly reduce chronic pain in survivors.

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Both authors researched the data for the article, provided substantial contributions to discussions of its content, wrote the article and undertook review and/or editing of the manuscript before submission.

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Review criteria

We used many articles identified during our work as co-authors of the Peripheral Nerve Society Guideline, which was a formal systematic review of literature on NSVN and all other vasculitic neuropathies, searching MEDLINE, EMBASE and the Cochrane Library in all languages from all dates up to February 2008. The formal search strategies employed in the Peripheral Nerve Society review are detailed in Web Supplement 5 of the corresponding article[4]. The present Review was not a formal systematic review. We searched PubMed from 2008 to June 2016 with multiple combinations of search terms for new articles on vasculitic neuropathies of all types and treatment of systemic vasculitis. For multifocal neuropathy, we searched PubMed for articles in all languages from all dates up to June 2016 using the search terms "multifocal neuropathy" or "mononeuritis multiplex" or "mononeuropathy multiplex" or "multiple mononeuropathy" or "multiple mononeuritis" or "multifocal polyneuropathy" or "multifocal radiculoneuropathy." For all sections included in this Review, we also accessed our extensive personal files and searched the reference lists of newly identified articles for further leads.

FURTHER INFORMATION

The UK & Ireland Vasculitis Study Group online registry: http://www.vasculitis.org.uk/professionals/registry

SUPPLEMENTARY INFORMATION

See online article: S1 (table) | S2 (table) | S3 (table) | S4 (table) | S5 (box)

ALL LINKS ARE ACTIVE IN THE ONLINE PDF