Review

Isolated vasculitis of the peripheral nervous system

M.P. Collins, M.I. Periquet

Department of Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin, USA.

Michael P. Collins, MD, Ass. Professor; M. Isabel Periquet, MD, Ass. Professor.

Please address correspondence and reprint requests to:
Michael P. Collins, MD, Department of Neurology, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Milwaukee, WI 53226, USA.
E-mail: mcollins@mcw.edu

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ABSTRACT

Vasculitis restricted to the peripheral nervous system (PNS), referred to as nonsystemic vasculitic neuropathy (NSVN), has been described in many reports since 1985 but remains a poorly understood and perhaps under-recognized condition. There are no uniform diagnostic criteria. Classification is complicated by the occurrence of vasculitic neuropathies in many systemic vasculitides affecting small-to-medium-sized vessels and such clinical variants as nonsystemic skin/nerve vasculitis and diabetic/non-diabetic lumbosacral radiculoplexus neuropathy. Most patients present with painful, stepwise progressive, distal-predominant, asymmetric or multifocal, sensory-motor deficits evolving over months-to-years. NSVN is identical to but less severe than systemic vasculitis-associated neuropathies (SVNs). All vasculitic neuropathies are axonal by electrodiagnostic/pathologic criteria. Laboratory testing is unremarkable except for mildly elevated erythrocyte sedimentation rate (ESR) in 50%. Highly elevated ESRs, leukocytosis, rheumatoid factors, and anti-neutrophil cytoplasmic antibodies (ANCAs) raise concern for underlying systemic vasculitis. Without a specific clinical/laboratory marker, the condition depends on nerve biopsy for diagnosis. Biopsies showing necrotizing vasculitis are about 50% sensitive, mandating reliance on "suspicious" changes in many patients. Vasculitic lesions predominate in smaller epineurial vessels and are milder than those in SVNs. The disorder is often accompanied by subclinical involvement of adjacent muscles and skin. NSVN has the potential to spontaneously relapse and remit but neurologic deficits accumulate. No randomized controlled trials have been performed, but one retrospective cohort survey showed combination therapy to be more effective than prednisone alone. Although most patients have a good outcome, more than 30% relapse and 60% have residual pain. Many nosologic, pathogenic, diagnostic, and therapeutic questions remain unanswered.

Introduction

The vasculitides comprise a broad spectrum of diseases which exhibit, as their primary feature, inflammation and destruction of vessel walls, with secondary ischemic injury to the involved tissues (1). They are generally classified based on sizes of involved vessels and histopathologic and clinical features. Two classification systems have gained wide acceptance. In 1990, the American College of Rheumatology (ACR) proposed classification criteria for seven forms of vasculitis designed to discriminate between patients with pre-established diagnoses (2), and in 1994, the Chapel Hill Consensus Conference (CHCC) published definitions for ten type of vasculitis (3). Significant discordance results when these two systems are applied to the same cohorts of patients (4). For this reason, a consensus methodology for classification of ANCA-associated vasculitides (AAV) and polyarteritis nodosa (PAN) was recently proposed, which incorporates both the ACR classification criteria and CHCC definitions (5).

Except for cutaneous leukocytoclastic angiitis, these systems do not address the nonsystemic or localized vasculitides. Localized vasculitis affects vessels in a single tissue or organ, without clinical evidence of more widespread involvement (6, 7). Anatomically restricted vasculitis has been described in almost all organs, including the CNS (8), skin (9), kidneys (10), eyes (11), muscles (12), heart (13), lungs (14), GI tract (15), and genital tract (16). In these disorders, progression to systemic

disease is unusual and excision can be curative. A recent study comparing localized with systemic PAN showed that the pathologic process was less destructive to the vascular wall in the localized variant (17).

Systemic vasculitides involving small-to-medium-sized vessels often affect the PNS. For example, neuropathies occur in 60% of patients with PAN diagnosed pre-CHCC, 80% with hepatitis B-associated PAN, 60% with microscopic polyangiitis (MPA) diagnosed post-CHCC, 65-70% with Churg-Strauss syndrome (CSS), and 15% with Wegener's granulomatosis (WG) (18-21). On the other hand, vasculitic neuropathies are vanishingly rare in large-vessel vasculitides such as giant cell arteritis (Table I). A proposed classification of vasculitides associated with vasculitic neuropathy is found in Table II.

Some patients with a vasculitic neuropathy exhibit no clinical evidence of systemic involvement despite long-term follow-up, indicative of another localized vasculitis. Isolated PNS vasculitis was first reported by Kernohan and Woltman in 1938 (22). The concept was revitalized and established as a distinct clinicopathologic entity by Kissel *et al*. in 1985 and Dyck *et al*. in 1987 (23, 24). Dyck coined the term nonsystemic

Table I. Prevalence of vasculitic neuropathy types.

Series	NSVN	PAN*/ MPA**	RV	CSS	UCTD	WG	SLE	Cancer	SS	EMC /HCV	Other
Kissel, 1985 (23)	7	3	0	0	5	0	1	0	0	0	0
Harati, 1986 (62)	21	2	2	0	4	0	0	3	0	0	Scl-1
Dyck, 1987 (24)	20	32	2	4	0	1	1	0	3	0	Scl-1, HIV-1
Said, 1988 (25)	25	26	26	6	6	0	1	1	2	0	Scl-1. HIV-3, Sarcoid-1, GCA-1, PM-1
Panegyres, 1990 (84) Hawke, 1991 & (54)	7	0	5	3	0	1	0	0	1	0	MGUS-1
McCombe, 1987 (148)	2	11	7	3	8	1	3	1	1	0	0
Midroni, 1995 (60)	4	3	8	3	10	0	2	0	1	0	HV-1
Nicolai, 1995 (149)	2	2	1	4	7	0	0	0	0	3	HIV-1
Singhal, 1995 (150)	7	6	0	2	0	1	4	0	0	0	0
Ohkoshi, 1996 (151)	1	6	1	3	0	0	2	0	0	0	0
Collins, 2000 (52)	11	6	8	0	0	2	1	2	0	0	MGUS-3, VZV-1, HV-2
Sanchez, 2001 (152)	5	12	0	3	0	2	2	1	0	0	Sarcoid-1
Vital, 2006 & Vital, 2006 (32, 153) §	35	28	9	17	0	4	1	0	3	6	Skin/nerve-5, HIV-4, Sarcoid-2, Eos-2, DM-2, EBV-1
Bennett, 2007 (37) †	22	10	3	3	2	3	0	3	2	2	HIV-2, Scl-1
Mathew, 2007 (34)	11	27	12	22	6	14	4	4	0	4	HSP-1, meningioma-1
Oka, 2007 (35)	8	13	3	6	0	0	1	0	3	0	0
Zivkovic, 2007 (36)	9	4	6	0	1	2	4	4	1	2	DM-4, Scl-1, Sarcoid-1, MCTD-1
Total (percent)	197 (26)	191 (25)	93 (12)	79 (10)	49 (6.4)	31 (4.0)	27 (3.5)	19 (2.5)	17 (2.2)	17 (2.2)	HIV-11 (1.4) DM-6 (.8) MGUS-4 (.5) Scl-5 (.7) Sarcoid-5 (.7) Nerve/skin-5 (.7) HV-3 (.4) Eos-2 (.3) HSP-1 (.1) GCA-1 (.1) PM-1 (.1) VZV-1 (.1) MCTD-1 (.1) EBV-1 (.1) Meningioma-1 (.1)

CSS: Churg Strauss Syndrome; DM: diabetes mellitus; EBV: Epstein-Barr virus; EMC: essential mixed cryoglobulinemia; Eos: hypereosinophilia without lung involvement; GCA: giant cell arteritis; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HSP: Henoch Schonlein Purpura; HV: hypersensitivity vasculitis; MCTD: mixed connective tissue disease; MGUS: monoclonal gammopathy of undetermined significance; MPA: microscopic polyarteritis, NSVN: nonsystemic vasculitic neuropathy; PAN: polyarteritis nodosa; PM: polymyositis; RV: rheumatoid vasculitis; sarcoid: sarcoidosis; Scl: scleroderma; SLE: systemic lupus erythematosus; SS: Sjögren's syndrome; UCTD: undifferentiated connective tissue disease; VZV: varicella zoster virus, WG: Wegener's granulomatosis.

*Includes cases of hepatitis B-associated PAN

**MPA combined with PAN because these disorders were not distinguished in vasculitic neuropathy series prior to 1997

§Drs. Claude and Anne Vital provided additional clinicopathologic information on the 216 patients in their series, which was used to classify patients by clinical diagnosis and pathologic category (using criteria from Collins *et al*., 2003).

†Diagnoses from poster presentation on July 15, 2007 at the meeting of the Peripheral Nerve Society and confirmed by Dr. David L. Bennett in e-mail communication on December 15, 2007.

vasculitic neuropathy, which is now the accepted name for the disorder. Some investigators have argued that NSVN is a mild form of systemic vasculitis with clinical involvement predominating in the PNS (25), whereas others have concluded that the disease is a unique, organ-specific vasculitis (24, 26). In support of this theory, some patients with isolated vasculitic neuropathy have remained free of systemic involvement over decades of follow-up (24, 27). Moreover, the PNS is relatively resistant to ischemia and thus should not be particularly susceptible to a systemic ischemic process (28).

Since this topic was last reviewed in 2004 (29), many additional patients with NSVN have been reported or identified in the pre-existing literature, including two detailed retrospective cohorts (30,31), articles/abstracts providing more limited information on many patients (32-37), and several smaller series or case reports (38-47). Other case reports are not considered due to inadequate or absent pathologic findings, insufficient clinical information, or evidence of an underlying systemic disease. Table III itemizes clinicopathologic attributes of the seven largest series of NSVN. Diagnostic criteria vary between studies, but our criteria are as follows:

1. Clinical and electrodiagnostic evidence of an axonal neuropathy;
2. Nerve or muscle biopsy diagnostic of or suspicious for vasculitis;
3. No clinical, laboratory, or pathologic evidence of tissue involvement beyond nerves or muscles;
4. No identified etiology (including infections or drugs); and
5. No systemic disease potentially predisposing to vasculitis (*e.g.*, connective tissue disease, diabetes mellitus, malignancy, mixed cryoglobulinemia, and sarcoidosis).

Table II. Proposed classification of vasculitides associated with neuropathy.

1. Primary systemic vasculitides
   - a. Predominantly large vessel vasculitis
     - i. Giant cell arteritis
   - b. Predominantly medium vessel vasculitis
     - i. Polyarteritis nodosa
   - c. Predominantly small vessel vasculitis
     - i. Granulomatous
       - Churg Strauss Syndrome*
       - Wegener's granulomatosis*
     - ii. Non-Granulomatous
       - Microscopic polyarteritis*
       - Essential mixed cryoglobulinemia (non-HCV)
       - Henoch Schönlein Purpura
2. Secondary systemic vasculitides
   - a. Vasculitis secondary to connective tissue diseases
     - i. Rheumatoid arthritis
     - ii. Systemic lupus erythematosus
     - iii. Sjögren's syndrome
     - iv. Scleroderma
     - v. Dermatomyositis
     - vi. Mixed connective tissue disease
   - b. Sarcoidosis-related vasculitis
   - c. Behçet's disease
   - d. Infection-related vasculitis (such as HBV, HCV, HIV, CMV, leprosy, Lyme disease, HTLV-I)
   - e. Drug-induced vasculitis
   - f. Malignancy-related vasculitis
   - g. Vasculitis associated with inflammatory bowel disease
3. Nonsystemic/localized vasculitis
   - a. Nonsystemic vasculitic neuropathy
   - b. Diabetes mellitus-related vasculitis
     - i. Diabetic radiculoplexus neuropathy (proximal-predominant)
     - ii. Diabetic multifocal neuropathy (distal-predominant)
   - c. Non-diabetic lumbosacral radiculoplexus neuropathy
   - d. Localized cutaneous/neuropathic vasculitis
     - i. Cutaneous polyarteritis nodosa
     - ii. Others

*ANCA-associated vasculitides.
CMV: cytomegalovirus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HTLV: human T-lymphotropic virus.

Epidemiology

No study has determined the incidence or prevalence of NSVN or, for that matter, any other type of vasculitic neuropathy. One review article on immune-mediated neuropathies stated that PNS vasculitis has an annual incidence of 0.6-1.2 per 100,000 (48), and a publication from the Neuropathy Association® noted NSVN to have an annual incidence of 5 cases per million (49), but neither of these assertions were referenced. On the other hand, there is abundant data on the *relative frequency* of different types of vasculitic neuropathy compiled from series dedicated to such patients. An updated compilation of diagnoses from series with a wide spectrum of patients is found in Table I.

Clinical features

Combining data from the 2004 review of NSVN with more recently ascertained series and case reports, the mean age of onset is 59.5 years (standard deviation 15.3; range 13-88). Reported women outnumber men by a factor of 5:4 (177 women; 143 men). In reports for which these attributes are not explicitly excluded, weight loss occurs in ~30% of patients and fevers in ~15%. Although some patients present with acute mononeuropathies or multiple mononeuropathies, most exhibit a more subacutely or chronically progressive, sometimes stepwise clinical course and slowly accrue multifocal/asymmetric damage to multiple peripheral nerves. Accordingly, the diagnosis is typically delayed for months. The median duration of symptoms before diagnosis ranged from 5-7.5 months in four series (26, 31, 50, 51), but patients reported by Kararizou *et al*. were symptomatic for a median of 60 months, suggesting

Table III. Nonsystemic vasculitic neuropathy cohorts: clinicopathologic characteristics.

	Dyck 1987 (24)	Said 1988 (25), 1996 (141)	Davies 1996 (26)	Collins 2003 (51)	Kararizou 2005 (30)	Sugiura 2006 (31)	Bennett 2007 (37)
Number of patients	20	32	25	48	22	23	22
Age (mean ± SD, years)	62.4 ± 12.3	61 ± 14	61 ± 13.2	61.8 ± 14.5	54.1 ± 14.5	58.4 ± 14.5	59 ± 12.7
Gender (women: men)	13:7	18:14	13:12	30:18	10:12	9:14	13:8
Constitutional symptoms exclusionary	No	No	Yes	No	No	Yes	No
Selected for absence of systemic spread on FU	Yes	No	Yes	No	No FU	No FU	No FU
Median duration of symptoms before diagnosis (months)	?	?	6	5	60	7.5	23.5
Median duration of FU after diagnosis (months)	?	60	33.5	63	No FU	No FU	No FU
Pain (% of patients)	?	19/32 (75)	?	46/48 (98)	19/22 (86)	17/23 (74)	19/22 (86)
Cranial nerve involvement (% of patients)	?	?	?	4/48 (8)	2/22 (9)	0/23 (0)	2/22 (9)
Pure sensory (% of patients)	2/20 (10)	?	?	6/48 (13)	?	3/23 (13)	4/22 (18)
Asymmetric findings (% of patients)	16/20 (80)	24/32 (75)	17/25 (68)	47/48* (98)	13/22 § (59)	18/23 (78)	18/22 (82)
Mean modified Rankin score	?	?	?	3.25	3.2	2.7	?
ESR elevation (% of patients)	10/19 (53)	19/32 (59)	10/16 (63)	31/48 (65)	4/22 (18)	7/23 (30)	6/21 (29)
Definite vasculitis in nerve (% of patients)	5/20 (25)	13/32 (41)	19/25 (76)	26/48 (54)	22/22 (100)	11/23 (48)	8/22 (36)
Definite vasculitis in muscle (% of patients)	NA	26/32 (81)	NA	3/19 (16)	NA	NA	2/7 (29)
Spread of vasculitis to non-neuromuscular organs (% of patients)	0†	11/32 (34)	0†	3/48 (6)	No FU	No FU	No FU
Relapse rate (% of total patients)	?	7/32 (31)	9/25 (36)	18/48 (38)	No FU	No FU	No FU
Overall mortality (% of patients)	3/20 (15)	10/32 (31)	1/25 (4)	10/48 (21)	No FU	No FU	No FU
5-year survival (% of patients)	?	85	?	87	No FU	No FU	No FU

*Mild asymmetries not discounted; §Mild asymmetries discounted; †Absence of spread during FU a selection criterion; ESR: erythrocyte sedimentation rate; SD: standard deviation; FU: follow-up.

that some patients in this series might have had an alternate condition (30).

Neurological deficits (weakness and sensory loss) are almost always distally accentuated, but proximal involvement is not uncommon. In the largest reported cohort, assembled by workers at Ohio State University (OSU), examination revealed proximal lower limb weakness in 60% of patients and proximal upper limb weakness in 40% (51). The three most common clinical patterns are multifocal neuropathy (multiple mononeuropathy), asymmetric polyneuropathy ("overlapping" multifocal neuropathy), and distal symmetric polyneuropathy. In the OSU series, wherein no asymmetries were discounted, the frequency of these patterns was as follows: Asymmetric polyneuropathy 85%, multifocal neuropathy 13%, and distal symmetric polyneuropathy 2%. However, cumulative incidences from all reported series and cases with available data are quite different: Multifocal neuropathy 45%, asymmetric polyneuropathy 30%, and distal symmetric polyneuropathy 25%. The necessary inference is that many investigators use a more inclusive definition of multifocal neuropathy and discount minor asymmetries.

The most commonly affected nerves in NSVN are a diffuse admixture of lower limb nerves derived from the lumbosacral plexus. The most frequently involved *individual* nerve is the common peroneal or peroneal division of the sciatic. In the upper limbs, the ulnar nerve is more vulnerable than the median, radial, and more proximal nerves. Vasculitis is an *axonopathy* and thus tends to affect mixed (sensory-motor) and purely sensory cutaneous nerves. Hence, most patients with NSVN exhibit mixed motor and sensory deficits, but 15% have purely sensory signs and symptoms (24, 31, 37, 50, 51). Vasculitis-related sensory loss typically involves all modalities with occasional large fiber predominance. Eighty percent of reported patients have had pain. At presentation, most patients are still independent in activities of daily living. Approximately 50% can walk without assistance, 35% require walking aids, and 15% are nonambulatory (26, 30, 31, 51).

The clinical presentation of NSVN is similar to that of a SVN (23, 24, 52). Sugiura *et al*. compared 23 patients with NSVN to 40 with MPA-associated neuropathy and found no significant differences in gender, initial symptoms, rate of progression, clinical pattern, presence and distribution of weakness or sensory loss, functional involvement, pain, and cranial nerve involvement, but as a group, the MPA cohort was more disabled (31). A cohort of patients with CSS-related neuropathy reported by the same group was also more severely affected (53). Bennett *et al*. compared 22 patients with NSVN to 31 with various SVNs (37). The groups were similar in gender, pain, clinical pattern, and cranial nerve involvement, but patients with NSVN were symptomatic for a longer period of time prior to diagnosis than those with SVN (mean 23.5 versus 8.5 months), suggestive of slower progression. Median duration of symptoms was also longer in a cohort of patients with NSVN ascertained in Sydney than in a SVN cohort reported by the same center (26, 54) but not for cohorts reported by OSU (52). In summary, NSVN is clinically identical to a SVN except for reduced severity and – possibly – more indolent progression.

Table IV. Differential diagnosis of acute/subacute multifocal or asymmetric neuropathy.

- Vasculitic Neuropathies (see Table II)
- Other Inflammatory Conditions
  - Sarcoidosis
  - Multifocal acquired demyelinating sensory and motor neuropathy (Lewis-Sumner syndrome)
  - Neuralgic amyotrophy, brachial or lumbosacral
  - Multifocal variants of Guillain-Barre syndrome
  - Hypereosinophilic syndrome
  - Graft versus host disease
  - Hashimoto thyroiditis
- Infectious neuropathies
  - Leprosy
  - Lyme disease
  - Human immunodeficiency virus/cytomegalovirus
  - Human T-lymphotropic virus-I
  - Varicella Zoster Virus
  - Septicemia
- Genetic neuropathies
  - Hereditary neuropathy with liability to pressure palsies
  - Hereditary neuralgic amyotrophy
  - Porphyria
  - Tangier disease
- Neuropathies related to malignancy
  - Direct neoplastic infiltration
  - Multifocal peripheral nervous system mass lesions
  - Lymphomatoid granulomatosis
  - Primary amyloidosis
- Other
  - Sensory perineuritis
  - Cholesterol emboli syndrome
  - Atrial myxoma
  - Intraneural hemorrhage (*e.g*., hemophilia, leukemia, idiopathic thrombocytic purpura)

Differential diagnosis

For patients with pathologic evidence of definite/probable vasculitic neuropathy, the differential diagnosis includes all conditions associated with vasculitis of the PNS, including but not limited to the primary systemic vasculitides, certain connective tissue diseases (especially rheumatoid arthritis), hepatitis B, HIV infection, hepatitis C, other causes of mixed cryoglobulinemia, sarcoidosis, cancers, and – rarely – other infections or drugs. Cancers are a sufficiently rare cause of vasculitic neuropathy to preclude the need for an extensive malignancy workup in all patients. Prior to biopsy, it is also important to consider other causes of an asymmetric/multifocal neuropathy, many of which are listed in Table IV.

Diagnosis

The first and most important diagnostic step is to identify the neuropathic profile as one suggestive of vasculitis. This mandates characterization of the neuropathy's tempo (acute, subacute, chronic), clinical course (steadily or stepwise progressive, stable, improving, relapsing), functional involvement (sensory-motor, pure sensory, pure motor), anatomic pattern (distal symmetric, distal and proximal symmetric, asymmetric, multifocal, unilateral) and inferred pathology (axonal, demyelinating). Painful, stepwise progressive, distal-predominant, asymmetric/multifocal, axonal, sensory-motor neuropathies are particularly concerning for vasculitis, even with a clinical course of several years. Conversely, pure motor or indolently progressive, sensory-predominant, distal, symmetric polyneuropathies are rarely vasculitic (47).

Electrodiagnosis

Electrodiagnostic studies in patients with NSVN almost always reveal evidence of a primary axonal, sensory-motor process (36). Thus, sensory and motor nerve conductions of involved nerves reveal low-amplitude or absent responses, normal or mildly prolonged distal latencies, normal or mildly reduced conduction velocities, and normal or mildly prolonged F-wave latencies. Although persistent, ischemia-induced, demyelinating partial motor conduction blocks are rarely seen, "pseudo"-conduction blocks occur more commonly (10-25% of patients), reflective of active axonal degeneration (24, 29). EMG reveals fibrillation potentials and motor unit potential drop-out consistent with axon loss in most clinically affected muscles.

If sufficiently extensive, most electrodiagnostic studies show evidence of a multifocal/asymmetric, distally accentuated process. That said, even the most compulsive electrodiagnostician rarely has the time and necessary patient compliance to perform multiple nerve conductions and examine a full complement of muscles in all four limbs, as would be required to diagnose "multiple mononeuropathy" by electrodiagnostic criteria alone. More

commonly, extensive but non-exhaustive testing of three or four limbs is performed, assessing for asymmetries and other non-length-dependent features that, when combined with the patient's signs and symptoms, supports a diagnosis of multifocal/asymmetric polyneuropathy.

Laboratory

The laboratory evaluation of a patient with suspected vasculitic neuropathy is designed to assess for (1) non-neurologic organ dysfunction; (2) measures of systemic inflammation; and (3) specific causes of a multifocal neuropathy or vasculitis. With the aforementioned differential diagnosis in mind, potentially useful laboratory tests include CBC, eosinophil count, metabolic panel, urinalysis, two-hour glucose tolerance test, ESR, C-reactive protein, ANA, ENA, rheumatoid factor, C3, C4, ANCAs, serum protein electrophoresis, ACE, cryoglobulins, hepatitis B surface antigen, hepatitis C antibodies, Lyme antibodies, HIV antibodies, and HTLV-I antibodies. Malignancy screening should be performed if indicated by other clinical features, laboratory findings, or risk factors. No paraneoplastic antibodies are specifically associated with cancer-related vasculitic neuropathy (55).

Pooling data from all published series and case reports, ESR is elevated in 50% of patients with NSVN, typically to a mild degree. The incidence of other laboratory abnormalities is ANA 25%, anemia 25%, leukocytosis 15%, rheumatoid factor 10%, decreased complement 5%, CSF pleocytosis 5%, elevated CSF protein 30%, and CSF oligoclonal bands 10%. Mean CSF protein ranges from 44 to 56 mg/dL. ANCAs are distinctly uncommon in NSVN, occurring in 3% (3/90) of reported patients (37, 38, 56, 57). Three studies compared laboratory findings in patients with NSVN to those in patients with SVN. In the OSU study, elevated ESR, leukocytosis, and rheumatoid factors occurred with increased frequency in SVN than NSVN, but not ANA, anemia, decreased complement, CSF pleocytosis, or increased CSF protein (52). In Japan, elevated CRP, elevated ESR, rheumatoid factors, leukocytosis, and ANCAs were more prevalent in MPA-associated neuropathy than NSVN, whereas ANA, DNA antibodies, RNP antibodies, SSA/SSB antibodies, and elevated CSF protein were not (31). In the United Kingdom, anemia, elevated ESR, and ANCAs were associated with SVN but not ANA, rheumatoid factors, elevated CSF protein, or CSF pleocytosis (37). Therefore, the best laboratory predictors of an underlying systemic vasculitis in a patient with vasculitic neuropathy are elevated CRP, elevated ESR, ANCAs, and perhaps rheumatoid factors.

Pathology

In the absence of a specific laboratory marker or clinical profile, nerve or nerve/muscle biopsy is required in all patients with suspected NSVN to confirm, corroborate, or refute the clinical diagnosis. The most commonly biopsied nerves are the sural and superficial peroneal. A peroneus brevis muscle biopsy is always obtained concomitant with a superficial peroneal nerve biopsy (52). Sural nerve biopsies are also sometimes combined with muscle biopsies (e.g., gastrocnemius, quadriceps, or anterior tibialis) (37, 58, 59). For patients in whom the sural or superficial peroneal nerves are not involved by clinical or electrodiagnostic criteria, the superficial radial, lateral antebrachial cutaneous, intermediate femoral cutaneous, and saphenous nerves can be biopsied.

Diagnosis of pathologically *definite* vasculitic neuropathy requires nerve biopsy evidence of inflammation within the vessel wall *and* signs of vascular damage such as fibrinoid necrosis, endothelial disruption or degeneration, fragmentation/loss of the internal elastic lamina, degeneration of vascular smooth muscle cells, hemorrhage, or acute thrombosis (60, 61). Some neuromuscular pathologists diagnose definite but inactive vasculitis in biopsies revealing perivascular inflammation and markers of more chronic vascular injury such as hyperplasia/fibrosis of the vessel wall or chronic thrombosis with recanalization (26, 59).

What are the usual nerve biopsy findings in patients with pathologically definite NSVN? With one exception (62), all pathologic studies of NSVN and SVN have revealed changes indicative of a primary axonal process. Axons are more vulnerable to ischemia than Schwann cells, perineurial cells, and fibroblasts (28). Affected fascicles are characterized by decreased myelinated nerve fiber density, conspicuous Wallerian degeneration, regenerating axonal clusters, and infrequent secondary demyelination/remyelination (31, 63). Axon loss tends to be centrofascicular in distribution in proximal watershed areas (*e.g.*, sciatic nerve bifurcation in distal thigh) but becomes multifocal in distal parts of the nerve due to intermingling of descending fibers (28, 63, 64).

Cellular infiltrates in NSVN are perivascular and predominate in the epineurium (24, 31, 65, 66). They are composed primarily of T cells and macrophages, with T cells generally outnumbering macrophages by a factor of 2 to 3 (31, 67, 68). B cells are uncommon (2-3% of inflammatory cells) (31,67), and NK cells and polymorphonuclear leukocytes rare (67, 68). Epineurial T cells are almost always $CD4^+$ or $CD8^+$, but $CD4^+/CD8^+$ ratios vary from study to study (29). Only 1% of T cells express the γδ T-cell receptor (65).

The vasculitic lesions themselves are almost always located in the epineurium, with infrequent perineurial and rare endoneurial involvement (24, 26, 31, 32). Some investigators classify NSVN as a microvasculitis that preferentially involves epineurial microvessels (venules, capillaries, and small arterioles with few layers of smooth muscle and no internal elastic lamina)(32,69). "Small arterioles" are variably defined as having diameters less than 40 μm or 70μm (69-71). Larger arterioles have diameters up to 100 μm. Arterial vessels with diameters greater than 100 μm are conventionally referred to as small arteries (72). All endoneurial and perineurial vessels are microscopic (<40μm), whereas most epineurial vessels are larger in size (50-300μm) (28). Therefore, PNS microvasculitis should predominate in the endoneurium, but endoneurial vasculitis is rare (24, 52, 54, 73). In the only quantitative studies,

diameters of involved epineurial vessels in NSVN were 88±31 μm and 98±87μm, confirming that NSVN has a predilection for smaller epineurial vessels but not in the defined ranges for microvasculitis (30, 31).

Another unsettled question concerns the pathologic definition of microvasculitis. Some groups require only transmural infiltration of microvessels by mononuclear inflammatory cells without associated vascular damage (32, 70, 71, 74) under the theory that small vessels do not readily undergo fibrinoid necrosis (69). However, necrosis of endoneurial microvessels does occur (73, 75, 76), and affected microvessels in the kidneys and lungs in patients with AAV are frequently necrotic (77, 78). Moreover, a pathologic finding of PNS microvasculitis without vascular damage *might* be a nonspecific finding, occurring with undetermined frequency in such disorders as chronic inflammatory demyelinating polyradiculoneuropathy, paraneoplastic sensory neuronopathy, motor neuron disease, Buerger disease, cholesterol emboli syndrome, and local trauma (60, 70, 71, 74). For these reasons, until better evidence becomes available, the diagnosis of microvasculitis should be reserved for cases with vascular damage. To enhance the identification of microvascular injury, Dyck and colleagues immunostain their biopsies with antibodies against anti-human smooth-muscle actin, assessing for fragmentation, loss, or destruction of vascular smooth muscle cells (79).

To increase the sensitivity of nerve or nerve/muscle biopsy for vasculitis, most workers describe pathologic changes "suggestive" or "suspicious" for "probable" vasculitic neuropathy in specimens lacking diagnostic findings (26, 32, 52, 59, 60, 80). Pathologic criteria for probable vasculitis are nonuniform, but most require perivascular or vascular inflammation and one or more alterations supportive of active or healed vasculitis, including Wallerian degeneration, asymmetric fiber loss, thickening of vessel walls, luminal narrowing or obliteration, thrombosis with recanalization, epineurial neovascularization, hemosiderin deposits, focal perineurial degeneration or thickening, injury neuroma, endoneurial purpura, enlarged axons filled with organelles, and epineurial vascular deposits of immunoglobulin or complement (32, 52, 59, 60, 63, 79, 81-83). In one cohort survey of patients undergoing superficial peroneal nerve/peroneus brevis muscle biopsy for possible vasculitic neuropathy, pathologic findings significantly associated with definite vasculitis were Wallerian degeneration, predominantly axonal pathology, asymmetric nerve fiber loss, and myofiber necrosis/regeneration (52).

The true sensitivity of nerve biopsy for vasculitic neuropathy is unknowable due to the lack of a reliable reference standard short of autopsy. However, in patients with non-diagnostic biopsies, clinically probable vasculitic neuropathy can be diagnosed by recourse to clinical and pathologic criteria (52). The sensitivity of a definite biopsy for vasculitis is then estimated as [(number of definite cases) ÷ (number of definite cases plus number of probable cases)] x100%. Utilizing this error-prone method, a superficial peroneal or sural nerve biopsy finding of definite vasculitis is about 50% sensitive for NSVN (Table V).

In the Vital *et al*. series, the fraction of NSVN patients with "probable" vasculitis (including those in their microvasculitis cohort) was 21/35, contrasting with only 4/26 for MPA-associated vasculitic neuropathy (*i.e*., 4 probable, 22 definite), a significant difference (32). A similar over-representation of patients with "probable" NSVN was reported by Dyck *et al*. (15/20 NSVN *vs*. 19/45 SVN) and Bennett *et al*. (13/22 NSVN *vs*. 9/31 SVN) (24, 37). These observations suggest that vascular pathology in NSVN is milder and less necrotizing than in SVN, consistent with the recent pathologic study comparing other forms of localized vasculitis with systemic PAN (17).

The yield of muscle biopsy for vasculitis in NSVN is highly variable, ranging from 16-100%, with a mean of ~50%(25, 32, 37, 51, 84-86). Recent studies suggest that adjacent skin is also subclinically involved in NSVN. In one report, a non-lesional skin biopsy of the distal leg in a patient with NSVN revealed leukocytoclastic vasculitis (46). In another report, distal leg skin biopsies in three patients demonstrated perivascular T cells and macrophages in dermal vessels (43). As a further indication of NSVN's propensity to involve skin, 3/48 NSVN patients in the OSU cohort developed cutaneous vasculitis during long-term follow-up, and in the Vital series, 5/119 patients had isolated nerve/skin vasculitis (32, 51). By analogy, the dermatology literature is replete with reports of cutaneous polyarteritis nodosa (cPAN) accompanied by neuropathy (see below). Hence, NSVN can be associated with regional involvement of both muscles and skin.

Clinical variants

In addition to the "classic" form of NSVN detailed above, several syndromes may represent clinical variants. The first is vasculitis restricted to

Table V. Estimated sensitivity of nerve biopsy for nonsystemic vasculitic neuropathy.

Nerve Biopsied	Reference	Definite biopsies	Probable/Possible biopsies	Estimated sensitivity of definite biopsy
Superficial peroneal	Abgrall (85)	2	1	2/3 (67%)
	Collins (51)	11	8	11/19 (58%)
	Vital (32)	14	21	14/35 (40%)
	Total	*27*	*30*	*27/57 (47%)*
Sural	Dyck (24)	5	15	5/20 (25%)
	Davies (26)	19	6	19/25 (76%)
	Garces-Sanchez (50)	6	2	6/8 (75%)
	Collins (51)	14	16	14/30 (47%)
	Sugiura (31)	11	12	11/23 (48%)
	Mathew (34)	7	4	7/11 (64%)
	Bennett (37)	8	14	8/22 (36%)
	Total	*70*	*69*	*70/139 (50%)*

nerves and skin (87). The best characterized entity in this group is cPAN (9, 88, 89). Cutaneous PAN affects small-to-medium-sized arteries in the deep dermis and panniculus, which undergo fibrinoid necrosis typical of PAN. The characteristic skin lesions are recurrent, painful nodules in the lower legs that often ulcerate. Other skin manifestations include livedo racemosa, gangrene, urticaria, and bullae. The course of the disease is prolonged but benign, featuring multiple episodes of reactivation and resolution. Although other organs are not involved, there is commonly an associated multifocal or distal symmetric neuropathy in the lower limbs, mimicking the distribution of the skin lesions. Pooling data from many reports, 40-45% of patients have neuropathic signs and symptoms (9, 88-94), and 50% have EMG evidence of neuropathy (9, 89, 91, 93). Five patients underwent muscle biopsies in one series, all of which revealed necrotizing vasculitis (88). Thus, this is a localized, PAN-type vasculitis predilected for skin, arteries, and muscles in the lower limbs.

A second variant is diabetic lumbosacral radiculoplexus neuropathy. Patients with diabetes mellitus are not immune to developing a NSVN-like, multifocal, distally accentuated vasculitic neuropathy (76). They may even be so predisposed, but the relative risk of vasculitic neuropathy in diabetics compared to non-diabetics has never been investigated. A clinically distinct vasculitic syndrome occurs in 1% of diabetics (especially older men with type 2 diabetes) and goes by such names as diabetic amyotrophy, diabetic lumbosacral radiculoplexus neuropathy, Bruns-Garland syndrome, and proximal diabetic neuropathy (80, 95-102). Most patients first develop acute pain in their hip/thigh or, less commonly, lower leg or entire lower limb. Weakness ensues days-to-weeks after the onset of pain. Early on, proximal lower limb muscles are more commonly affected than distal muscles, but weakness routinely spreads to other segments of the same limb, involving more than one myotome and peripheral nerve. Pain and weakness usually begin unilaterally and spread contralaterally in 80-90%. Most patients lose weight. Upper limb involvement occurs in ~10%. Laboratory workup is notable only mildly elevated ESR in ~20% and elevated CSF protein in 85% (mean 90 mg/dL). The condition is self-limited. Symptoms worsen over a period of one week to three years (median four months) and then slowly improve over one-to-42 months (median 15 months). Most patients are left with some residual weakness, especially distally. There is a 10-15% relapse rate. Nerve biopsies reveal T-cell predominant perivascular/vascular inflammation involving epineurial and, to a lesser extent, endoneurial microvessels, accompanied changes suggestive of vasculitis, including asymmetric fiber loss, neovascularization, hemosiderin, focal perineural thickening, injury neuroma, and complement deposition in vessel walls, but *necrotizing* vasculitis is rarely seen (80, 99, 102-104). These findings support the hypothesis that diabetic amyotrophy is a PNS microvasculitis and thus a variant of NSVN, characterized by predominant microvascular involvement, severe pain, weight loss, primary lower limb involvement, and self-limited course.

An analogous syndrome is "non-diabetic lumbosacral radiculoplexus neuropathy," which must be distinguished from the rarely reported *acute,* painful, idiopathic, monophasic lumbosacral plexopathy syndrome that occurs as a regionally displaced variant of the more prevalent neuralgic amyotrophy involving the brachial plexus (105-107). Unlike this entity, non-diabetic lumbosacral radiculoplexus is a *progressive* condition. The only cohort (n=57) was assembled by investigators at the Mayo Clinic (79, 108), but additional patients matching this profile have been reported (109-112). In the Mayo Clinic cohort, median age of onset was 69.5 years (range 27-86). There was no gender preference. All patients experienced severe, acute pain and developed weakness after an unspecified delay. Pain/weakness typically progressed over days-to-months (median duration of symptoms prior to diagnosis 7.0 months), commenced in the proximal or distal lower limb, and then spread to adjacent segments (proximal-predominant 36; distal-predominant 21). They were initially unilateral in 50/57 but became bilateral in 51/57. Weight loss occurred in 74% and sensory symptoms in 86%. 10% had an associated cervical radiculoplexus neuropathy. Mean CSF protein was 66.5 mg/dL. ESR was above 40 mm/hour in 9%. Electrodiagnostic studies showed evidence of an axonal lumbosacral polyradiculoneuropathy, with maximal involvement of the L5-S1 myotome. Nerve biopsies revealed perivascular lymphocytic infiltrates in the epineurium and, to a lesser extent, perineurium and endoneurium, with predominant microvessel involvement. Microvasculitis (with vessel damage) occurred in 15%, but fibrinoid necrosis was rare. Additional features suspicious for vasculitis were seen in up to 70% of biopsies. Thus, the findings were suggestive of a largely non-necrotizing microvasculitis. After a median of 35.5 months, all patients had improved, but 90% were still weak, 55% still had pain, and 17% had relapsed. This entity appears to be another variant of NSVN, defined by more prevalent weight loss, proximal lower limb weakness, and microvascular involvement.

Natural history

The natural history of *untreated* NSVN is largely unknown because nearly all reported patients have been treated with immunosuppressive agents, with rare exceptions (22, 27, 34, 40, 113-115). Based on these exceptional cases and reported patients' clinical courses prior to treatment, we know that NSVN can: (1) Slowly progress for up to 40 years; (2) Slowly progress for several years and then stabilize or subacutely accelerate; (3) Follow a monophasic course with complete or near-complete recovery for up to three years; (4) Progress in a fulminant, Guillain-Barré syndrome-like fashion, producing severe quadriparesis over weeks-to-months; and (5) Spontaneously relapse and remit, with inter-attack intervals ranging up to five years or even "decades" (116). The relative frequency and severity of these various natural evolutions are unknown.

Pathogenesis

The preponderance of data supports the hypothesis that NSVN and, for that matter, almost all SVNs are autoimmune disorders primarily mediated by cellular cytotoxicity. A cell-mediated pathogenesis is supported by multiple lines of evidence. First, all pathologic studies demonstrate a marked predominance of T cells and macrophages in epineurial infiltrates in sural nerve biopsies of patients with NSVN (31,67,68,117). Second, many of the T cells are activated and express markers characteristic of cytotoxic T lymphocytes (61, 68, 118). Third, markers of antigen presenting cells are upregulated in the epineurium and, to a lesser extent, endoneurium. Specifically, mannose receptors are massively expressed on epineurial perivascular cells (probably activated macrophages) (119); MHC class II molecules – which present peptide antigens to $CD4^+$ T cells – are inconsistently upregulated on epineurial T cells, macrophages, Schwann cells, endothelial cells, and perineurial cells (67, 117, 120, 121); and CD1a/CD1b molecules are expressed on some Schwann cells and epineurial macrophages (119, 122). Unlike MHC II, CD1 molecules present lipid antigens to CD1-restricted T cells. Fourth, co-stimulatory molecule CD86, which interacts with CD28 on naïve and resting T cells, is upregulated on endothelial cells in NSVN (122). Fifth, co-stimulatory molecule ICOS (inducible costimulator) is significantly upregulated on epineurial T cells in patients with various vasculitic neuropathies (123). ICOS is expressed preferentially by activated, memory $CD4^+$ and $CD8^+$ cells, modulating their effector function. There is a corresponding upregulation of ICOS-ligand (ICOS-L) on macrophages in areas where ICOS-expressing T cells are found, implying that macrophages act as antigen presenting cells to re-stimulate memory T cells and sustain the effector phase of the chronic immune response. Sixth, CD58 – an adhesion/co-stimulatory molecule interacting with CD2 on T cells – is upregulated on Schwann cells and endothelial cells (122). Seventh, in a DNA microarray analysis of three patients with vasculitic neuropathy, many of the upregulated immune genes were indicative of T cell and/or macrophage activation (124). These observations support a pathogenic model wherein disease-specific, autoreactive T cells are recruited to the PNS and activated by self-glycolipid antigens presented by macrophages and Schwann cells abetted by requisite stimulatory/co-stimulatory molecules, then maturing into cytotoxic T lymphocytes that damage target cells in epineurial vessels, with periodic re-stimulation of effector T cells by ICOS-L-expressing macrophages in the epineurium.

In addition to mononuclear cells, epineurial vessel walls often contain deposits of immunoglobulin and complement in sural nerve biopsies from patients with NSVN. Combining data from four studies, epineurial vascular deposits of IgM are present in 47% of biopsies, IgG in 46%, C3 in 72%, and any immunoglobulin or C3 in 87% (26, 30, 67, 84). Epineurial vascular deposits of complement terminal membrane attack complex (MAC) are found in ~80% of patients with NSVN and SVN (67). Thus, immune complex deposition or *in situ* formation might represent another mechanism of vascular damage in NSVN, but immune deposits are found only in heavily infiltrated vessels (30,67), raising concern for nonspecific accumulation in damaged vessels and complement activation by necrosis. The rarity of B cells and polymorphonuclear leukocytes also argues against immune complex deposition as a primary mechanism. The near-complete absence of circulating ANCAs in patients with NSVN suggests that ANCAs are not pivotal to the pathogenesis of NSVN (56).

Many other inflammatory mediators are upregulated in sural nerve specimens from patients with vasculitic neuropathy (systemic and nonsystemic), including pro-inflammatory cytokines (66, 125-127), cytokines implicated in type 1 (Th1) helper T-cell responses (128), chemokines and chemokine receptors involved in T cell and macrophage migration (128), IL-6 (mixed results) (66, 125, 128-130), Th2 cytokines (mixed results) (125, 128), allograft inflammatory factor-1 (131), nitric oxide (68, 127), COX-2 (68, 132), matrix metalloproteinase (MMP)-1 (68, 127), MMP-2 and MMP-9 (86, 127, 133, 134), receptor for advanced glycation end-products (130), nuclear factor κβ (126, 130, 135), various cellular adhesion molecules (122, 126, 136), various oxidative and hypoxic stress-induced proteins (35, 127, 130), and components of the plasminogen activator system (127).

Treatment

Treatment recommendations for primary systemic vasculitides are grounded on comparisons with natural history controls; retrospective cohort surveys; randomized, controlled, open trials; and a few randomized, controlled, blinded trials (137-139). Over the past 15 years, treatment has evolved from the "standard" Fauci protocol of continuous oral cyclophosphamide (CYC) and high-dose prednisone to a more individualized, less toxic approach tailored to the patient's age, extent and severity of disease, and risk factors. Although "standard" combination therapy was highly effective in inducing remission in WG, it converted the disease into a chronic, relapsing disorder associated with significant disease-and treatment-related morbidity (140). Current treatment strategies seek to minimize exposure to CYC by use of non-CYC-based maintenance regimens or by replacement of CYC in the induction phase for patients with non-severe disease.

Concerning NSVN, no randomized controlled trials of therapy have appeared. In fact, there is no controlled data whatsoever on treatment of this condition, apart from one class III retrospective cohort survey reported by investigators at OSU (51). This study analyzed treatment responses and long-term outcomes (median follow-up 63 months) in 48 patients with NSVN. Twenty-eight were initially treated with corticosteroids alone, and 20 received combination therapy (CYC in 18). Combination therapy was significantly more effective than corticosteroid monotherapy in inducing sustained remission (95% *vs.* 61%) and improving disability (85% *vs.* 57%), with additional trends towards reduced relapse rate (29% *vs.* 59%), chronic pain (44% *vs.* 71%), and

Table VI. Neurologic outcomes in survivors of nonsystemic and systemic vasculitic neuropathies.

"Final" disability	NSVN (26, 51)	SVN (52, 54, 154, 155)
No or essentially no symptoms	17%	8%
Mild symptoms, no restrictions	43%	32%
Mildly to moderately impaired; ambulatory without assistance	21%	34%
Ambulatory with assistance, dependent in some ADLs	16%	21%
Non-ambulatory	3%	5%

ADLs: activities of daily living; NSVN: nonsystemic vasculitic neuropathy; SVN: systemic vasculitis-associated neuropathies.

5-year mortality. No patient treated with CYC for greater than six months relapsed, whereas patients treated with CYC for one-to-six months had a 54% relapse rate, but CYC was discontinued in 40% because of adverse effects.

There are no other controlled trials with which to compare these results, but they are congruent with data reported in one other NSVN series, wherein disability scores improved in 10/11 (91%) patients administered combination therapy (corticosteroids plus CYC, azathioprine, or methotrexate) versus 6/11 (55%) treated with corticosteroids alone (26). Recently, Mathew *et al*. reported treatment responses in 10 patients with NSVN followed for greater than one year (34). Seven received prednisolone alone, two CYC and prednisolone, and one no treatment. All 10 improved and achieved a "good" outcome, but 2/7 in the prednisolone group relapsed versus 0/2 in the CYC group. This limited data suggests that patients with progressive NSVN should be treated with prednisone and CYC, probably in accord with protocols established for the primary systemic vasculitides, whereby CYC is replaced with a less toxic maintenance drug after three-to-six months, assuming the neuropathy has remitted (progression of neuropathic deficits arrested and early signs of improvement). Patients with stable-to-improving symptoms might be observed, given NSVN's potential to spontaneously remit. Responses to IVIg and plasma exchange have been reported in individual patients (43, 44).

Outcome

Although no direct comparisons have been performed, NSVN appears to have a better prognosis than the SVNs. Mortality rates for NSVN were 4% and 15% in two cohorts selected for absence of spread to non-neurologic tissues during follow-up (24, 26) and 21% and 31% in two cohorts not excluding such patients (51, 141). Five-year survival in the latter two studies was 85% and 87%. By comparison, 5-year survival in modern systemic vasculitis cohorts averages ~75% (142-147). An unexpected finding in the OSU NSVN cohort was the high relapse rate. 46% of patients relapsed following a sustained treatment response (51). Relapse was defined as new signs or symptoms of weakness, sensory loss, or neuropathic pain (*not* nonspecific symptoms such as malaise and fever) (34). Relapses occurred 6-47 months after onset of treatment (median 15 months) and ranged in number from one-to-four. Ten relapsing patients had discontinued therapy, but eight were still taking prednisone. No patient relapsed on CYC. All relapses but one responded to re-treatment with corticosteroids, CYC, and/or IVIg. Combining data from all NSVN series and case reports with 12 months or more of follow-up, the relapse rate per treated patient is 32% (29, 34, 38, 44).

Data from Japan suggests that NSVN is a less severe neuropathy than those encountered in MPA and CSS (31, 53). Indeed, the final outcome in long-term survivors is reasonably good, with 60% of patients having no or mild symptoms and no significant functional limitations, but 60% report some degree of chronic pain (26, 51). No study has compared final disability in patients with NSVN and SVN, but data compiled from several series (Table VI) reveals marginally improved outcome in NSVN.

Conclusion

Despite an ever increasing number of clinical and pathogenic studies on NSVN, the disease is still poorly understood, vaguely defined, and perhaps under-recognized. It is a pleomorphic condition that shares pathologic features with the primary systemic necrotizing vasculitides but is milder in severity, more restricted in anatomic distribution, and possibly more likely to involve microvessels. Although NSVN is sometimes truly confined to the PNS, the same clinical picture occurs with subclinical involvement of adjacent tissues such as skin and muscles, suggesting that the triggering antigen may not be neural-specific.

Many important nosologic, pathogenic, diagnostic, and therapeutic questions remain unanswered. At the most fundamental level, what is the primary cause? Does NSVN share pathogenic mechanisms with such systemic vasculitides as MPA and PAN? Is it truly a cell-mediated process, or do the observed mononuclear cell infiltrates have a non-specific bystander or regulatory function (65, 118)? Are diabetic/non-diabetic radiculoplexus neuropathy variants of NSVN or distinct diseases? Is NSVN pathogenically related to cPAN and localized skin/muscle vasculitis? What is the natural history of the disease? What are the best clinical predictors of systemic spread? What is the optimal treatment regimen? How should clinically suspected patients with non-diagnostic nerve biopsies be managed? Of note, a Guideline Group has been commissioned by the Peripheral Nerve Society to address some of these questions, but prospective, multi-center collaborations will be needed to significantly advance our knowledge of the condition.

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