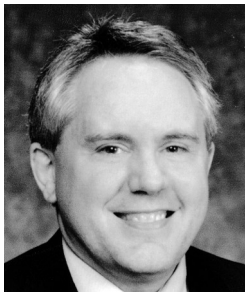
Editorial

Localized Vasculitis and the Peripheral Nervous System



Vasculitides are diseases in which blood vessel walls are infiltrated and destroyed by inflammatory cells, with secondary ischemic damage in affected tissues. Many classifications of vasculitis have been proposed through the years based on etiology, pathologic characteristics, sizes of involved vessels, and clinical attributes. Two schemes in popular use are those published by the American College of Rheumatology and Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis[1,2]. Excepting cutaneous leukocytoclastic angiitis, vasculitides in these classifications are systemic disorders affecting more than one organ. However, vasculitides localized to a single organ or site have been reported for almost all tissues[3]. They are usually categorized by vessel size and histology, e.g., isolated forms of polyarteritis nodosa (PAN), giant cell arteritis, or small-vessel vasculitis. Some localized vasculitides are *formes frustes* of systemic vasculitides, but others are truly self-limited, pathogenically distinct processes.

Systemic vasculitides involving small- to medium-size arteries commonly produce neuropathies[4]. However, in some patients, vasculitis remains restricted to the peripheral nervous system (PNS) despite longterm followup[5]. Hence, analogous to localized vasculitides affecting other tissues, there is an isolated form of PNS vasculitis, termed nonsystemic vasculitic neuropathy (NSVN)[5]. Many patients with NSVN have been reported, albeit with few dedicated series (Table 1)[5-11]. The cohort reported by Kararizou and colleagues in this issue of *The Journal* is thus a welcome addition[12]. Although no epidemiologic studies have appeared, NSVN is the most commonly reported form of PNS vasculitis, accounting for more than 25% of patients in large series[4].

NSVN can develop at any age (mean age at diagnosis 59 years)[11]. Women appear to be preferentially affected. Weight loss occurs in 40% of patients and fever in 15%. Some weight loss is due to pain-related anorexia and depression. NSVN produces 3 patterns of clinical involvement: multiple mononeuropathy (multifocal neuropathy); "overlapping" multiple mononeuropathy or asymmetric polyneuropathy; and distal symmetric polyneuropathy (DSPN). In a cohort reported by Collins, *et al*, where all patients were examined by the authors, and scrupulous attention paid to sensory, motor, and reflex asymmetries, 85% of patients had asymmetric polyneuropathies, 13% multifocal neuropathies, and 2% DSPN[10]. However, data from other reports yield a much different distribution: 45% multifocal neuropathy, 30% asymmetric polyneuropathy, and 25% DSPN[11]. In the study by Kararizou and colleagues, 41% had symmetric polyneuropathies, but "mild" asymmetries were discounted, an explanatory variable probably shared by many other vasculitic neuropathy series with a significant proportion of DSPN. When patients are carefully examined, almost all vasculitic neuropathies exhibit at least mildly asymmetric clinical features[10,13,14].

Diagnosis of NSVN hinges on laboratory studies, electrodiagnostic testing, and nerve or nerve/muscle biopsy, but the important first step is to recognize the clinical profile as one potentially compatible with PNS vasculitis. NSVN is easily identified in patients developing pain, weakness, and numbness in the distribution of one peripheral nerve, followed by similar attacks involving other nerves. However, such classical presentations are exceptional. More commonly, NSVN is a stepwise progressive, painful, distal-predominant, asymmetric, sensorimotor polyneuropathy. In most patients, diagnosis is delayed for several months. In the 3 series with such data, median duration of neuropathy symptoms prior to biopsy ranged from 5 to 7.5 months[8-10]. In contrast, patients collected by Kararizou and colleagues were symptomatic for a median of 60 months. This stark departure from precedent goes unexplained. Until confirmed by other studies, it would be premature to consider a diagnosis of NSVN in most patients with an indolent DSPN for many years.

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Table 1. Nonsystemic vasculitic neuropathy cohorts (modified from Reference 11).

	Dyck, 1987[5], n = 20	Said, 1988[6,7], n = 32	Davies, 1996[8], n = 25	Collins, 2003[10], n = 48	Kararizou, 2005[12] n = 22
Age, yrs (mean ± SD)	62.4 ± 12.3	61 ± 14	61.9 ± 13.2	61.8 ± 14.5	54.1 ± 14.5
Gender ratio (women:men)	13:7	18:14	13:12	30:18	10:12
Constitutional symptoms exclusionary	No	No	Yes	No	No
Selected for absence of systemic spread during followup	Yes	No	Yes	No	No followup
Diabetics excluded	Yes	?	Yes	Yes	Yes
Median duration of symptoms before diagnosis, mo	?	?	6	5	60
Median duration of followup after diagnosis	?	5 years	145 weeks	63 months	No followup
Pain (% of patients)	?	19/32 (75)	?	46/48 (98)	19/22 (86)
Asymmetric findings (% of patients)	16/20 (80)	24/32 (75)	17/25 (68)	47/48* (98)	13/22** (59)
ESR elevation (% of patients)	10/19 (53)	19/32 (59)	10/16 (63)	31/48 (65)	4/22 (18)
Spread of vasculitis to other ogans (% of patients)	0	11/32 (34)	0	3/48 (6)	No followup
Relapse rate (% of total patients)	?	7/32 (31)	9/25 (36)	18/48 (38)	No followup
Overall mortality (% of patients)	3/20 (15)	10/32 (31)	1/25 (4)	10/48 (21)	No followup
5 year survival, %	?	85	?	87	No followup

* Mild asymmetries not discounted. ** Mild asymmetries discounted. ESR: erythrocyte sedimentation rate; SD: standard deviation.

Peripheral nerves have a highly anastomosed vascular supply that protects them from focal ischemia and a large safety margin in resting blood flow relative to metabolic/oxygen needs of the nerve, making them highly resistant to regional ischemia[15]. In vasculitis, axonal degeneration ensues only after extensive occlusion of epineurial vessels. Epineurial arterioles 20–300 µm in diameter are preferentially affected in most vasculitic neuropathies. As confirmed by Kararizou, *et al*, NSVN tends to involve smaller vessels (< 100 µm) within this range[5].

Nerve damage in NSVN is predominantly axonal, characterized by decreased density of myelinated nerve fibers and increased wallerian degeneration. Segmental demyelination/remyelination is also increased but tends to cluster on individual teased fibers and consecutive internodes, consistent with secondary demyelination induced by primary axonal degeneration[6]. Three patients reported by Kararizou, *et al* had pathologic evidence of demyelination, but the authors did not specify whether the demyelination was clustered or random. Nerve fiber loss is usually asymmetric within and between fascicles. In completely ischemic nerves, all cellular elements degenerate, but true infarction (coagulative necrosis) does not occur. Cellular infiltrates in NSVN predominate in the epineurium and comprise CD4+ and CD8+ T cells and macrophages. B cells are uncommon and natural killer cells, neutrophils, and eosinophils rare[16].

Clinically suspected NSVN requires confirmation by nerve biopsy. The sural nerve is most commonly biopsied, but combined nerve/muscle procedures are a diagnostic alternative[6]. Pathologically definite vasculitis requires vascular inflammation and signs of vascular destruction such as fibrinoid necrosis. Perivascular/transmural inflammation alone is nonspecific. "Probable" or "healed" vasculitis may be defined in specimens lacking definite vasculitis[4,17]. Pathologic alterations suggestive of vasculitis include vascular thickening, luminal obliteration, thrombosis, neovascularization, hemosiderin deposits, vascular immune deposits, asymmetric nerve fiber loss, prominent wallerian degeneration, focal perineurial damage, and myofiber necrosis. Muscle biopsies in patients with isolated PNS vasculitis often demonstrate inflammation and myopathic changes. The reported incidence of muscle vasculitis ranges from 16% to 81%[6,10]. The true diagnostic sensitivity of sural nerve and nerve/muscle biopsies for definite vasculitis in NSVN is unknown, but estimated sensitivity is 50–60%[11].

Which patients should be biopsied? Kararizou and coworkers conclude that biopsies should be "routinely performed" in all patients with unexplained polyneuropathies, "when noninvasive methods have been ineffective." This recommendation is certain to provoke controversy. The approach of most neuromuscular clinicians is more selective, considering the low yield of nerve biopsies in patients with indolent DSPN and potential side effects of the procedure: permanent sensory loss in 100%; chronic pain in up to 76% (mean 28% in published studies); and wound infections in 7%[10,18-20]. Nerve biopsy is more likely to yield vasculitis in patients with asymmetries, significant motor involvement, prominent pain, acutely relapsing courses, progressive deficits over several months, or laboratory markers of systemic inflammation.

Many activated cytotoxic T lymphocytes (CTL) are found in the epineurium of patients with NSVN, implicating T cell-mediated cytotoxicity in the pathogenesis of this disorder[11,21]. In this model, disease-specific, autoreactive T cells are recruited to the PNS and activated by self-glycolipid antigens presented by endothelial or Schwann cells and

various costimulatory molecules, maturing into CTL that damage target cells in epineurial vessels, abetted by toxic oxygen free radicals, nitric oxide, cytotoxic cytokines, prostaglandins, and matrix metalloproteinases released by activated T cells and macrophages[11]. In agreement with previous reports, Kararizou, *et al* found immunoglobulin deposits in epineurial vessel walls in 18/22 of their patients and C3 deposits in 17/22, but consistent with the only other study to address this issue[16], deposits were restricted to intensely inflamed vessels and thus were potentially nonspecific (related to breakdown of the blood-nerve barrier). The paucity of B cells and polymorphonuclear leukocytes in nerve biopsies of NSVN patients offers further evidence against immune complex disease.

The natural history of NSVN is unknown. In the absence of randomized controlled trials, treatment of NSVN depends on anecdotal experience and extrapolation from systemic vasculitis trials. The "standard" immunosuppressive regimen for most systemic necrotizing vasculitides involves a combination of corticosteroids and cyclophosphamide, a protocol developed for Wegener's granulomatosis[22] and since proven more effective than corticosteroid monotherapy in patients with PAN and antineutrophil cytoplasmic autoantibody-associated vasculitis with adverse prognostic factors[23]. Patients reported by Kararizou, *et al* were all initially treated with prednisone alone, the consensus approach to NSVN[24]. However, analysis of therapeutic responses in one 48-patient NSVN cohort showed that combination therapy was more effective than corticosteroid monotherapy in inducing remission and improving disability, with trends toward reduced relapse rate, chronic pain, and mortality[10]. These results are congruent with published experience in NSVN (68% of patients improved with corticosteroid monotherapy vs 86% with cyclophosphamide or combination therapy)[11].

NSVN has low risk for systemic dissemination, provided no symptoms, signs, or serologic features of systemic vasculitis are identified and immunosuppressive therapy is implemented[10]. However, outcome is not "good" for all patients. Disease or treatment-related mortality in 2 cohorts was 10% and 13%[7,10]. Up to 46% of patients relapse after a sustained treatment response[10]. In longterm survivors, neurologic outcome is favorable, but only 15% are asymptomatic, 15–20% remain dependent, and 60% have chronic pain[8,10].

In some patients, NSVN may be a limited form of systemic vasculitis whose non-PNS manifestations are aborted by treatment[6]. In support of this hypothesis, many clinical and laboratory features of NSVN overlap with those of the systemic vasculitides[10], and nerve biopsy findings are indistinguishable[16]. Further, many NSVN patients have inflammatory or ischemic changes in muscle. On the other hand, some untreated patients with NSVN have PNS-restricted symptoms for years to decades[5,10,12,25]. As PNS tissue is highly resistant to focal ischemia, long-standing NSVN cannot be ascribed to increased PNS vulnerability to a systemic process. Instead, there must be some PNS-specific antigen perpetuating the vasculitis that beckons identification.

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