Nerve vasculitis: The importance of vessel size categorization in nerve biopsy

From "Distinctive clinical features in biopsy-proven nerve large-arteriole vasculitis and microvasculitis"

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Systemic and non-systemic vasculitic neuropathies are described by nerve biopsy showing evidence of either large-arteriole vasculitis or microvasculitis. No studies have asked whether there are different clinical features between pathologically confirmed large-arteriole vasculitis and microvasculitis. This study was conducted to investigate if vasculitis involving vasa nervorum of different sizes (<75 µm classified as microvasculitis and ≥75 µm classified as large arteriole vasculitis) results in different clinical manifestations, including associated systemic autoimmune diseases and laboratory findings. Data were retrospectively collected from patients evaluated at Mayo Clinic from 2001-2020 with pathologically confirmed nerve vasculitis comparing these two groups. 278 patients met the inclusion criteria of having robust clinical information, being evaluated by a Mayo Clinic neurologist, and having definite or highly suggestive vasculitis on nerve biopsy vasculitis, of which 125 cases were nerve large-arteriole vasculitis and 153 cases were nerve microvasculitis. The sural nerve was the most frequently sampled, followed by the superficial peroneal nerve, with a few cases involving proximal fascicular nerve biopsies.

Major findings include nerve large-arteriole vasculitis exhibiting a more acute onset (50.4 vs 26.8%, p=0.0001) being more readily diagnosed due to the clearer or more acute onset (4.3 vs 10.5 months, p<0.0001), a shorter time to plateau (3.5 vs 8.9 months, p<0.0001), and a clinical pattern of neuropathy more often presenting as distal asymmetric polyneuropathy (48.0 vs 19.6%, p<0.0001) compared to nerve microvasculitis. On the other hand, nerve microvasculitis predominantly presented as radiculoplexus neuropathy or polyradiculoneuropathy, indicating greater nerve root involvement with more proximal limb abnormalities such as shoulder or hip weakness, as can also be seen by electrophysiologic findings. Autonomic symptoms, such as bowel or bladder dysfunction, orthostatic symptoms, and erectile dysfunction were more common in nerve microvasculitis (24.2 vs 7.2%, p=0.0002). The composite autonomic scoring scale, which reflects worse autonomic function at higher values, was also higher in nerve microvasculitis group (3.7 vs 2.2, p=0.002) (Table 1).

Both nerve large-arteriole vasculitis and nerve microvasculitis span the disease spectrum of systemic and non-systemic vasculitis, but with different prevalence. Nerve large-arteriole vasculitis was more commonly in systemic vasculitis (77%), while nerve microvasculitis occurred less frequently in systemic vasculitis (29%). Many systemic vasculitis diseases were ANCA-associated vasculitis (40% of nerve large-arteriole vasculitis), especially microscopic polyangiitis (23.2% of nerve large-arteriole vasculitis), followed by rheumatoid arthritis (12.8% of nerve large-arteriole vasculitis). On the other hand, nerve microvasculitis comprised 71% of non-systemic vasculitis cases, while nerve large-arteriole vasculitis accounted for 23%. Many of non-systemic vasculitis cases were due to diabetic or non-diabetic radiculoplexus neuropathy (30.8% of nerve microvasculitis) and 94% of these diabetic or non-diabetic radiculoplexus neuropathies pathologically had nerve microvasculitis. Given that nerve large-arteriole vasculitis was more strongly associated with systemic vasculitis, it made sense that nerve large-arteriole vasculitis demonstrated a higher prevalence of systemic symptoms compared to microvasculitis including constitutional symptoms (60.8 vs 47.1%, p=0.02), asthma (8.8 vs 0.7%, p=0.0009), sinusitis (11.2 vs 0%, p<0.0001), pulmonary infiltrates (9.6 vs 2%, p=0.005), glomerulonephritis (8.0 vs 0%, p=0.0004), rash (25.6 vs 13.1%, p=0.008), and arthritis (10.4 vs 3.9%, p=0.03). Similarly, laboratory findings in large-arteriole vasculitis showed more frequent abnormalities, including anemia (12.1 vs 13.1 g/dL, p<0.0001), leukocytosis (10.5 vs 7.0 x 10^9/L, p<0.0001), eosinophilia (19 vs 6%, p=0.001), higher platelet count (344.6 vs 261.2x 10^9/L, p<0.0001), and elevated inflammatory markers such as C-reactive protein (43.3 vs 8.2 mg/L, p=0.0001) and erythrocyte sedimentation rate (39.3 vs 19.6 mm/hr, p<0.0001), reflecting more systemic involvement compared to nerve microvasculitis. In contrast, microvasculitis was more associated with having diabetes mellitus than was nerve large arteriole vasculitis (24.8% vs 13.6%, p=0.02) (Table 1).

Commentary: This study underscores the distinct clinical features of nerve large-arteriole vasculitis and nerve microvasculitis, shedding light on their pathophysiology: that is nerve microvasculitis is associated with greater proximal nerve and root involvement manifesting as proximal weakness and sensory disturbance, while nerve

Table 1: Key distinguishing clinical features between nerve biopsy-proven large-arteriole vasculitis and nerve microvasculitis

Features	Nerve large-arteriole vasculitis (*n*=125)	Nerve microvasculitis (*n*=153)	*p*-value
Systemic vasculitis - ANCA-associated	77% 40%	29% 5%	<0.0001
Constitutional symptoms	61%	47%	0.02
Non-systemic vasculitis - diabetic or non-diabetic radiculoplexus neuropathy	23% 2.4%	71% 31%	<0.0001
Underlying diabetes mellitus	14%	25%	0.02
Disease course - acute - chronic	 50% 34%	 27% 58%	0.0001
Pattern of neuropathies - Distal asymmetric polyneuropathies - Radiculoplexus neuropathy	 48% 10%	 20% 32%	<0.0001
Proximal lower limb involvement	26%	51%	<0.0001
Autonomic symptoms	7%	24%	0.0002
Composite autonomic scoring scale	2.2 ± 1.5	3.7 ± 2.2	0.002

ANCA = anti-neutrophil cytoplasm antibodies

large-arteriole vasculitis typically shows watershed infarction (occurring at mid-thigh and mid-arm levels), thus manifesting as primarily distal asymmetrical neuropathies. However, these processes represent a continuum of anatomical involvement rather than entirely distinct entities. With the unclear pathomechanism, different antigens might speculatively contribute to this variation or variations in vascular shear flow could play a role. Additionally, this study confirms the association between nerve large-arteriole vasculitis and connective tissue disorders and more systemic vasculitis whereas microvasculitis is more associated with diabetes mellitus. We plan to further publish findings on clinical outcomes and pathological distinctions between the two conditions.

References:

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