Vasculitic neuropathies

Vasculitis—inflammation of the vessel wall with vascular damage or attendant tissue injury—may be a manifestation of diverse diseases. Recent studies of classification, epidemiology, and pathogenic mechanisms of individual vasculitides provide a foundation for better understanding the broad array of clinical features encountered in patients. Intense scrutiny of the cellular components and mediators of vascular inflammation in several diseases has yielded details of spatial and temporal distribution of inflammatory molecules, some of which are the subject of new therapies. Many clinical questions remain unresolved. How do define and diagnose vasculitis continues to be debated among clinicians and pathologists. Given the pleomorphic expression of disease, what clinical features are central to a diagnosis? How do genetically determined responses of the host, duration of disease, and type of involved tissue influence the histological features? How do target therapies at inflammation without interfering with healing?

Neuropathies are a prominent feature of the systemic and secondary vasculitides. The reasons for this frequency are not immediately clear. The microvasculature of the peripheral nerve is comprised of two functionally distinct systems, an extrinsic and an intrinsic system linked by a complex anastomotic network. The rich blood supply and the capacity of nerves to function reasonably well with anaerobic metabolism normally render the nerve relatively resistant to ischaemia. However, other anatomical and physiological characteristics such as watershed areas between the distribution of major nutrient arteries and lack of autoregulation of peripheral nerve blood flow provide an explanation of the vulnerability of nerve fibres to ischaemia with certain types of vascular injury. The immediate cause of the vasculitic neuropathies is inflammation and occlusion of the vasa nervorum resulting in ischaemia of the peripheral nerve. This widespread occlusion of epineurial, or rarely perineurial and endoneurial, arterioles causes multifocal central fascicular or sector degeneration of nerve fibres.

What is the nature of the peripheral nerve vasculature that accounts for its frequent involvement in vasculitides caused by disparate immunopathogenic mechanisms? The frequency of involvement of the PNS in the systemic vasculitides despite the varying underlying pathogenic mechanism (immune complex deposition, cell mediated interactions, and antineutrophil cytoplasmic antibody (ANCA) associated neutrophilic processes) suggests a general susceptibility or reactivity to inflammatory stimuli. Further, the more frequent involvement of the PNS vasculature compared with the CNS vasculature in these disorders suggests that mechanisms present in the CNS for minimising vascular inflammation are not present in the PNS. Another largely unexplored component is the intriguing role of the autonomic nervous system in the regulation of vascular inflammation. Sympathetic innervation of the lymph nodes and spleen as well as receptors for noradrenaline (norepinephrine) on lymphocytes provides a mechanism for central autonomic modulation of systemic immune responses. Sympathetic factors within the peripheral nerve also influence local inflammation. The loss of sympathetic fibres in diabetes seems to be a proinflammatory factor in neuropathies.

Vascular inflammation spans numerous physiological and pathological processes. Accumulation of inflammatory cells in the vessel wall remains the common denominator of the vasculitides. However, the determinants of tissue damage are not always clear. Three components can be identified and targeted for therapeutic intervention: initiation of the injury, recruitment of inflammatory cells and tissue damage, and regulation of the immune response. Endothelial cells are a focus of inflammatory attack and active participants in recruitment of cells in most vascular trees. In the CNS vasculature non-endothelial cells, usually microglia, are the principle antigen presenting cells, provide co-stimulatory molecules, and contribute proinflammatory and anti-inflammatory mediators. There is no information about the antigen presenting features of endothelial cells in the PNS vasculature. Vascular-immune interactions revolve around sequential expression of a series of cell surface molecules on endothelial cells and leucocytes that provide for attachment, adhesion, and, usually, migration of leucocytes through the blood vessel walls. Expression of these molecules, selectins, integrins, and intercellular adhesion molecules (ICAMs), and their ligands provide specificity for the type of cell recruited and some correlation with the location and type of the blood vessel involved. Certain cytokines produced by activated T cells and macrophages during specific immune responses function to recruit additional cells and amplify the inflammation. The normally transient nature of vascular and perivascular inflammation correlates with the temporally limited expression of proinflammatory cytokines and adhesion molecules as well as autostimulation of anti-inflammatory molecules from the tissue parenchyma and circulation. Persistent inflammation may occur, however, with the enduring presence of an antigen, damage to the vessel wall with exposure of extracellular matrix proteins, or with immune dysregulation such as occurs in some autoimmune disease. Accompanying inflammation of the
vascular wall are several local and systemic processes that contribute to the tissue damage. The alterations in coagulation and vasomotor tone result from local damage to endothelium as well as intrinsic components of the cytokine cascade. 

Heterogeneous aetiological agents may initiate and sustain vascular inflammation. Several established and potential pathogenic mechanisms may act in concert to sustain and reinforce vessel damage. Neutrophils, in particular, and activated macrophages, both within the vessel lumen and surrounding the vessel wall, can contribute to the tissue damage. The alterations in coagulation and vasomotor tone result from local damage to endothelium as well as intrinsic components of the cytokine cascade.

Recent studies focus on T cells which, often in association with macrophages, seem to be major effector cells in many of the vasculitides. Several elegant studies in temporal arteritis (giant cell arteritis) provide insight into the pathogenesis of the vasculitides that occur in graft rejection. Other processes strongly associated with vascular injury include expression of neoantigens (usually infectious) on the endothelium and ANCA. Further, studies are beginning to explore the potential that eosinophils or mast cells have to initiate the accrual of inflammation in certain vasculitides.

Immune complexes with certain immunochaemical characteristics activate the complement cascade that induces neutrophil mediated damage to the vessel wall. The presence of granulocytes is usually associated with fibrinoid necrosis as would be expected on the basis of their release of toxic enzymes during inflammation. Necrosis in the vessel wall is a large contributor to scarring and the delayed sequelae present in vasculitides such as Wegener's granulomatosis and polyarteritis nodosa.

More recent studies focus on T cells which, often in association with macrophages, seem to be major effector cells in many of the vasculitides. Several elegant studies in temporal arteritis (giant cell arteritis) provide insight into the topography of the cells in the infiltrate. Cells in different regions of the infiltrate acquire distinct functional capabilities. CD4+ T cells in the adventitia display evidence of recent engagement with their antigen on the basis of the presence of interleukin-2 receptors and rearrangement of cytoskeleton protein talin. These cells seem to have a prominent regulatory role, secrete interferon-γ, and intermingle with macrophages producing interleukin-1β, interleukin-6, and TGF-β1. By contrast, it is the T cells in the intima-media that seem to effect damage. Further, at least four functionally distinct types of macrophages, defined by their product profile, can be identified in the lesions of vasculitis. TGFβ producing macrophages colocalise with activated CD4+ T cells and home to the adventitia; macrophages homing to the media produce metalloproteinases; and macrophages in the intima are specialised to produce inducible nitric oxide synthetase, potentially providing a compensatory vasodilatory component. Studies of the infiltrates in sural nerve and muscle biopsies have not been as revealing. Several series report a predominance of T lymphocytes and macrophages with variable granulocytes and few B cells. This supports a hypothesis that the extracellular matrix of the affected tissue itself influences the differentiation of the invading cell populations. Dendritic cells, which have a pivotal role in presenting antigen and providing accessory signals for T cell activation, appear in the incipient lesions of some patients. Investigating the expression of immunological activation markers shows a scarcity of the early marker of T cell activation IL-2R. Temporally, the pattern of adhesion molecule expression in the luminal endothelium wanes as the inflammatory lesion ages but pronounced expression appears in surrounding microvessels; this suggests that angiogenesis may contribute to persistence of the infiltrate. C4–5 membrane attack complex and immunoglobulin deposition have been identified despite the absence of histological features of leukocytoclasia. Infiltrating cells do show evidence of expression of effector molecules such as perforin, nitric oxide synthase, and matrix metalloproteinase-1 suggesting a role for these molecules in the vessel and nerve injury.

Autoantibodies are not often pathogenic by themselves. However, the strong association between specific ANCA and certain types of vasculitis raise questions about potential ANCA initiated vascular damage.

Antineutrophil cytoplasmic antibodies recognise constituents of neutrophil cytoplasm including proteinase 3 (PR3), myeloperoxidase (MPO), and elastase. Translocation and release of these cytoplasmic components is part of the physiological response of neutrophils to inflammatory mediators such as TNFα. In vitro studies show that antibodies to PC3 (PC3-ANCA) bind to neutrophils and induce respiratory bursts and degranulation possibly beyond what is physiologically appropriate. PC3-ANCA also binds to endothelial cells and may increase expression of adhesion molecules. The in vivo relevance is supported by animal models of ANCA induced vasculitis and glomerulonephritis. Although MPO ANCs are less strongly associated with disease, they could mediate vascular damage in association with either H2O2 or ischaemia/ perfusion injury in one animal model.

Factors initiating the regulation of inflammation are under renewed scrutiny. Studies of genetic susceptibility and hormonal modulation of inflammation are particularly germane. Recent animal and human studies support a genetic role in certain inflammatory diseases. Genetic variations may modify components within the human inflammatory effector pathway (adhesion molecules, cytokines and their receptors) in a way that promotes vascular inflammation. Reports on hereditary α1-antitrypsin deficiency are among the new data suggesting a genetic predisposition to vasculitis. In mice that develop a spontaneous granulomatous arthritis, a hereditary defect in Fas mediated apoptosis suggests that persistent macrophages may cause damage to vessel walls. The predominant pathway of host response (cellular or humoral immune effector mechanisms) may also be under genetic control. Estrogens, which have a potentiating, or permissive role in several autoimmune diseases, increase TNFα induced adhesion molecule expression by endothelial cells. Further, estrogen has prominent effects on both vascular smooth muscle and endothelial cells. The angiogenic properties of estrogen on small vessels may contribute to the healing responses to injury in large vessels.

The clinical diagnosis of vasculitis is evolving. Numerous classification schemes based on vessel size, possible aetiology, and presumed immunopathogenic mechanism are frustrated by the enormous variability of the clinical and histopathological features of the vasculitides. The term primary vasculitis is a misnomer because all of the vasculitides are likely secondary to some form of inflammatory stimulus, usually infectious or toxic. In some cases the underlying cause either cannot be identified or has long since been cleared by the host, leaving only a chronic or recurrent inflammation centring in the vascular tissue. Vasculitides without identifiable aetiology are grouped into systemic vasculitides (so called because of their multiorgan nature) and a host of vasculitides defined by distinctive clinical features. Two new systems are the 1990 American College of Rheumatology classification criteria and the 1992 Chapel Hill consensus conference. These have recently been the subject of several epidemiological and consensus surveys to improve diagnosis but debates continue. The secondary vasculitides, defined by an identifiable, although occasionally elusive, aetiology are a large group with pleomorphic clinical features.

Because the major systemic vasculitides—polyarteritis nodosa, Wegener's granulomatosis, and Churg-Strauss syndrome—are so varied in presentation and clinical
tempo, early identification may be difficult. Several recent modifications of nomenclature are noteworthy. On the basis of affected vessel size and the presence of ANCA autoantibodies, microscopic polyarteritis is now distinguished from classic polyarteritis nodosa. In all of these diseases neuropathies are frequent, occurring in 20%-60% of patients. Neuropathies are a feature of the diagnostic criteria in both polyarteritis nodosa and Churg-Strauss syndrome. The clinical patterns of manifest neuropathy vary. Although mononeuropathy multiplex is the most distinctive pattern, symmetric polyneuropathies occur almost as often. Other neuropathies such as the occasional asymmetric polyneuropathies, brachial plexopathies, radiculopathies, and purely sensory polyneuropathies are infrequent. All together, given the rarity of the underlying diseases, an overall incidence of about 10/million, these systemic vasculitides are infrequent causes of neuropathy.

Systemic vasculitis may develop in association with a connective tissue disease. Rheumatoid arthritis, the most common connective tissue disease, affects 1% of the population. Systemic rheumatoid vasculitis, histologically indistinguishable from polyarteritis nodosa, occurs in 5%-15% of cases of rheumatoid arthritis. Of these, 40-50% of patients will develop a clinically apparent vasculitic neuropathy. Thus, rheumatoid arthritis is a more frequent cause of vasculitic neuropathy than polyarteritis nodosa, Wegener's granulomatosis, or Churg-Strauss syndrome. In distinction to the vasculitic neuropathy appearing in 1%-10% of patients with rheumatoid arthritis, a sensorimotor neuropathy, most likely related to compression/trauma, is present in 75% of patients with rheumatoid arthritis. Consequently, neuropathies associated with rheumatoid arthritis are notable both for their frequency and the need to determine the underlying mechanism for appropriate treatment.

In systemic lupus erythematosus, systemic vascular injury is frequent and develops from three, often coexisting, processes: atherosclerosis, thrombosis, and inflammation. However, neurological abnormalities often develop due to processes independent of vascular abnormalities. Although peripheral neuropathies, particularly polyneuropathies, occur in 6%-21% of patients, a vasculitis is present histologically in just a small portion of these. More often, sural nerve biopsies show non-specific inflammation including perivascular mononuclear infiltration and intimal thickening. In Sjogren's syndrome, peripheral neuropathies are also prominent. Noteworthy are the sensory ganglionitis, autonomic neuropathy, and polyneuropathy. Of the neuropathies reported present in 5%-30% of patients with defined Sjogren's syndrome, a definable vascular mechanism appears in only a few patients.

Vasculitis secondary to a defined infection or toxin is clearly the most often encountered vasculitis and an important etiology in peripheral nerve vasculitis. Infections of all classes of agents can cause inflammation of arterial and venous blood vessels affecting any organ. The link between infection and systemic vasculitis comes from the prevalence of hepatitis B surface antigen and antihepatitis B virus antibodies in polyarteritis nodosa and hepatitis C infections and mixed cryoglobulinaemia related vasculitis.

Neuropathies also occur in Lyme disease and HIV infections; among the reported mechanisms is a vasculitis. The appearance of a CD8 T cell mediated vasculitis in patients with HIV with low peripheral blood CD4 T cell counts is striking. Toxins as a cause of vasculitis are increasingly established. Mercurochloride induces vasculitis in rats and amphetamines are prominent in both human and animal disease. Even medications such as propylthiouracil and hydralazine are related to the onset of vasculitis. More recently, biological modifiers, particularly interferons, are strongly associated with autoimmune disorders although the occurrence of vasculitis is not easily defined.

Finally, there are the issues of diagnosis. The diagnosis of vasculitis is fundamentally an invasive process. Identification of inflammatory cells that diminish the delivery of blood to tissue is a critical feature. Further, the numerous causes that may result in vasculitis can often be distinguished only at the cellular level. Histological studies characterising lesions on the basis of the infiltrating cells may provide information on both the mechanisms inducing inflammation and predict the sequelae of the lesions.

The search for a non-invasive marker for vasculitis remains disappointing. For most of the vasculitides, blood studies reveal evidence of some non-specific systemic inflammation such as raised sedimentation rate, C reactive protein, and low level ANA; alternatively, the blood studies may be entirely normal. There is no serological test that confirms or excludes a vasculitis. Subsets of the vasculitides are associated with specific autoantibody profiles. In Wegener's granulomatosis and microscopic polyarteritis nodosa, ANCs may be a useful diagnostic marker but they have not helped define patients presenting with peripheral neuropathies; nor do they help identify patients who are in relapse. Other antibodies such as SSA, SSB, and anti-Sm, are useful adjuncts to identifying an underlying diagnoses of Sjogren's syndrome and systemic lupus erythematosus but are not diagnostic for any particular disease.

Recent studies attempting to identify factors that might indicate relapses of vasculitis have focused on circulating adhesion molecules and endothelial factors. Endothelial cells as well as T lymphocytes and macrophages release soluble forms of adhesion molecules on cytokine stimulation; they are considered a consequence of endothelial cell activation in response to inflammatory stimuli. Increased ICAM and VCAM do not reflect endothelial activation or injury specifically.

The recent advances in understanding cellular interactions and their control mechanisms in vasculitis promises refinement in therapy. The mysteries of the clinical manifestations of vascular inflammation remain unresolved.

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RESPONSIVENESS OF OUTCOME MEASURES IN ROCKETED CONTROLLED TRAIL IN NEUROLOGY

The choice of the most appropriate primary and secondary outcome measures is often the most complex issue in the design of a randomised controlled clinical trial. It has implications for the cost of the trial, the sample size, the burden that the trial will place on patients and clinicians taking part, and the likelihood that the result of the trial will influence clinical practice. As illustrated by Freeman et al. in the previous issue of this Journal (February pp 150–6), whichever outcome is chosen is important that it has been properly validated in a representative sample of patients with the disease under study. They assessed whether the short form 36 (SF-36), the most often used generic measure of health status, has the properties necessary to detect clinically significant change in the type of patients included in treatment trials in multiple sclerosis. They found that it was clinically appropriate, had acceptable convergent validity and discriminant construct validity, and had good internal reliability. However, they report important floor and ceiling effects in certain domains of the measure, and a lack of responsiveness to purported clinical improvements after hospital admission for rehabilitation in a group of relatively severely disabled patients. This last finding may have been due to floor effects in severely disabled patients, and may not be applicable to more typical trial patients, but it would nevertheless be unwise to rely solely on the SF-36 to measure the effectiveness of disease modifying treatment in multiple sclerosis.

What should be done when a clinical outcome measure seems to lack responsiveness to useful clinical improvement in the disease of interest? Firstly, it is important to resist the temptation to revert to a surrogate outcome measure that reflects progression of the pathology of the disease rather than the clinical burden. Surrogate outcomes can be very sensitive measures of the biological effects of treatments, but very poor indices of the clinical effect. For example, Campath-1 almost completely halts the formation of new lesions on MRI brain imaging in multiple sclerosis, but it has no significant effect on clinical progression of the disease. Randomized use of antiarrhythmic drugs after myocardial infarction substantially reduces the incidence of ventricular ectopics on 24 hour ECG monitoring, but dramatically increases mortality, and sodium fluoride produces significant increases in bone density in women with osteoporosis, but it dramatically increases the risk of major fractures. In each of these

274 Moore

Corticobasal degeneration

Corticobasal ganglionic degeneration (CBGD) or corticobasal degeneration (CBD) is a pathological diagnosis in search of a nosological niche. It was originally described as corticodentatonigral degeneration by Rebeiz et al., who recognised its relation to Pick's disease because of the focal cortical atrophy and the ballooned neurons (Pick cells). The clinical syndrome was first characterised by a combination of unilateral extrapyramidal signs and prominent apraxia, usually diagnosed in movement disorder clinics. “Alien hand,” vertical gaze palsy, and reflex myoclonus are frequent but non-obligatory signs. Both the clinical syndrome and the pathology were considered unique and well matched initially, but soon several descriptions of CBD pathology were considered unique and frequent but non-obligatory signs. Both the clinical syndrome and the pathology were considered unique and well matched initially, but soon several descriptions of CBD pathology appeared, the clinical presentation of which was behavioural or aphasic, similar to the study of Mathuranath et al. (this issue, pp 304–312).

The reverse also became evident. There have been several well described cases of the clinical corticobasal degeneration syndrome (CBDs) where the pathology turned out to be Pick's disease, or “dementia lacking distinctive histology”, or the “motor neuron type of frontotemporal dementia.” It also seems that the clinical syndrome of unilateral extrapyramidal symptoms, apraxia, and alien hand is more often accompanied by frontotemporal disinhibition dementia (FTD) and progressive aphasia (PA) than was previously thought.

Furthermore, if one follows up cases of FTD or primary PA, one eventually may encounter the development of typical CBDs, further underlying the relation of these syndromes clinically and pathologically. Mathuranath et al are doing a service to the neurological community by emphasising the overlap of these conditions by their illustrative cases and thoughtful review of the literature. This clinical and pathological overlap led us to the concept of Pick complex, as Pick’s disease is somewhat arbitrarily restricted to the specific pathology of Pick bodies by many neuropathologists. This concept received a substantial confirmation by the discovery of autosomal dominant families of FTD and parkinsonism linked to chromosome 17q and the numerous underlying tau mutations. Some of these families have a behaviour disorder resembling FTD, progressive language loss (PA), and parkinsonism (CBDS) represented in a single pedigree and the pathology ranges from CBD-like “Pick variants” to progressive supranuclear palsy within the same mutation.

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EDITORIAL COMMENTARY

Pattern of dopaminergic loss in the striatum of humans with parkinsonism induced by MPTP

The small group of drug addicts in the United States who unwittingly injected a bad batch of synthetic narcotic around 1982 had no idea that some of their number would develop a Parkinson’s disease–like illness within weeks. It transpired that the chemist who had made the offending drug had unwittingly synthesised 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which proved to be a potent and specific nigral toxin. A postmortem examination of one such affected patient showed prominent cell loss in the substantia nigra with a single eosinophilic inclusion similar to a Lewy body.

Not surprisingly, this discovery gave an enormous boost to the environmental theories of Parkinson’s disease aetiology. But still, years later, we are no closer to identifying a unifying environmental toxin, and advances in our understanding of the genetics of familial parkinsonism have clearly demonstrated that environmental factors alone cannot be the answer. Nevertheless, observations of the manner in which MPTP is toxic has been a stimulus to research into mitochondrial function in Parkinson’s disease and the MPTP model (using rodent or primate species) has become a standard and powerful tool in the laboratory investigation of parkinsonism. But what of the few patients affected by MPTP who were in the neurological headlines all those years ago? The answer is that they have been diligently followed up, both clinically and using functional imaging. This has not always been easy, due to the lifestyle chosen by some of the subjects.

The report by Calne et al of low 18F-fluorodopa uptake in subjects who had been exposed to MPTP but were clinically well, demonstrated the potential of 18F-fluorodopa positron emission tomography (PET) scanning as a marker of subclinical dopaminergic cell loss. Some others who escaped parkinsonism in the aftermath of their exposure have gone on to develop clinical parkinsonism years later. A few incapacitated patients underwent fetal cell implantation and their outcome data have been published. In this issue, pp313–316, Snow et al report 18F-fluorodopa PET data from nine subjects who were exposed to MPTP about 10 years earlier, eight of whom developed mild parkinsonism. Idiopathic Parkinson’s disease affects the ventrolateral tier of nigral neurons first, and this leads in turn to focal loss of the posterior putamen 18F-fluorodopa signal, followed by involvement of the anterior putamen and caudate as the disease progresses to involve other nigral areas. In the patients with MPTP exposure, however, Snow et al reported a decrement of tracer uptake throughout the caudate and putamen. They also found less asymmetry of uptake than in patients with idiopathic Parkinson’s disease. This difference in striatal 18F-fluorodopa uptake between patients with MPTP parkinsonism and idiopathic Parkinson’s disease is a further indicator that these two conditions are not quite the same and the authors conclude that idiopathic Parkinson’s disease is not caused by transient exposure to MPTP. A complicating factor which Snow et al consider in their manuscript is the known variability in the pattern of striatal involvement in MPTP animal models according to the dosing schedule used. Two of the subjects of Snow et al reported exposure to MPTP over 3 to 4 months, whereas others had shorter exposure.

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