Vasculitis confined to peripheral nerves

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Summary
The clinical, electrophysiological and pathological features and prognosis of 25 patients with vasculitis selectively affecting the peripheral nervous system were evaluated. Although most patients had a history of mononeuritis multiplex or an asymmetrical neuropathy six out of 25 had a symmetrical neuropathy, both clinically and on neurophysiological testing, by the time of presentation. There were no signs of accompanying systemic vasculitis in any of the patients and serological abnormalities were limited to an elevated erythrocyte sedimentation rate (ESR) in nine out of 21 patients and low titre anti-nuclear antibodies in four out of 20 patients. Most patients had a necrotizing vasculitis on nerve biopsy, although in some cases the diagnosis was made on the association of inflammatory cell infiltrates with extensive axonal degeneration and immune complex deposition on immunofluorescence studies. The mean time from symptom onset to diagnosis was 46 weeks. All patients were treated with corticosteroids and most with additional immunosuppressive therapy. In contrast to vasculitic neuropathy associated with systemic vasculitis the prognosis was good with 24 out of 25 survivors at a mean of 176 weeks follow-up having a mean improvement of 1.4 units on a six-point disability scale.

Keywords: vasculitis; neuropathy; treatment; prognosis

Abbreviations: CIDP = chronic inflammatory demyelinating polyneuropathy; ESR = erythrocyte sedimentation rate; IPNSV = isolated peripheral nervous system vasculitis

Introduction
Vasculitic neuropathy commonly occurs in association with systemic vasculitis, most frequently in the polyarteritis nodosa group of diseases (Moore and Cupps, 1983; Guillaumin et al., 1988) or rheumatoid vasculitis (Scott et al., 1981). Systemic vasculitis with an associated neuropathy is a devastating illness with a 5-year survival of 37% (Hawke et al., 1991; Davies, 1994). Vasculitis may also occur with lesions confined to one organ system and isolated angiitis has been reported in skin (Winkelmann and Ditto, 1964; Gilliam and Smiley, 1976; Fauci et al., 1978), brain (Fauci et al., 1978; Cohen and Hurd, 1981; Cupps et al., 1983; Moore, 1989) and the peripheral nervous system (Kernohan and Woltman, 1938; Torvik and Berntzen, 1968; Dyck et al., 1987; Hawke et al., 1991) as well as other systems (Israel et al., 1977; Bosch et al., 1992). A full description of the syndrome of peripheral neuropathy due to vasculitis without any manifestations of vasculitis in other systems was first made by Dyck et al. in 1987. They noted the lack of serological markers and of non-specific symptoms such as fever or weight loss in this group of patients, as well as the rather indolent course of the disease. Since this initial description, cases of vasculitis confined to the peripheral nervous system have become widely recognized.

The present study was undertaken to examine the clinical and pathological features of 25 patients with isolated peripheral nervous system vasculitis (IPNSV) and to determine the prognosis and response to therapy of this group based on a follow-up study of their clinical condition.

Methods
Biopsies performed in our department from 1985 to 1994 were analysed (n = 1559). Twenty-five patients were found who had evidence of a vasculitic process affecting the peripheral nervous system without any historical, clinical or serological evidence of systemic involvement by the same process. Other causes of peripheral neuropathy were excluded by history, clinical examination and appropriate laboratory investigations. The case records were reviewed and follow-up information obtained on all 25 cases was included in the final analysis. All patients except one were alive and available...
for clinical review and were seen by the authors on at least one occasion.

**Clinical data**
Clinical and electrophysiological data were obtained from the case records and then analysed. Patients were excluded if they had diabetes, connective tissue disease, malignancy, pyrexia of unknown origin, significant weight loss other than that related to muscle wasting, clinical or biochemical evidence of involvement of tissues other than peripheral nerves or biopsy proven vasculitis outside the nervous system. No *a priori* decision was made to exclude patients solely on the basis of abnormal serological tests including the presence of anti-nuclear antibodies, rheumatoid factor, anti-neutrophil cytoplasm antibodies, elevated ESR or other serological markers of connective tissue disease unless independent clinical criteria for the diagnosis of connective tissue disease were present. Each patient’s presenting neuropathy was clinically classified as mononeuritis multiplex, asymmetrical sensory and motor neuropathy or symmetrical sensory and motor neuropathy. Nerve conduction studies were performed using standard techniques and the same nomenclature was used to classify the neurophysiological data. Functional disability scores (Table 1) (Prineas, 1970) were assigned for the nadir of each patient’s illness and for their best level of performance since the initial diagnosis. These scores were assigned either on clinical review or, if retrospective, on the basis of case record review and interviews with the patients and/or their families and attending physicians. The time of diagnosis for purposes of data analysis was taken either as the time of biopsy or the time that immunomodulatory treatment was commenced, whichever came first.

**Nerve biopsy and histology**
Sural nerve biopsy was performed in all cases. The whole sural nerve was taken at the level of the lateral malleolus under local anaesthesia. The nerve was divided into three to five sections, each ~1 cm in length. One piece was fixed in picric acid, embedded in paraffin and sectioned transversely and longitudinally in 5 μm sections which were then stained with haematoxylin and eosin. Another piece was stained for 24 h in 1% osmium tetroxide, macerated in glycerol and then teased apart under a dissecting microscope to separate individual nerve fibres. One piece was fixed in cold 3% glutaraldehyde in 0.1% cacodylate buffer for 3 h followed by 2% osmium tetroxide for 1 h. This tissue was then dehydrated in graded concentrations of ethanol, embedded in Spurr’s resin and cut transversely in 0.5–1.0 μm sections that were stained with toluidine blue. Another portion of the nerve was frozen in liquid nitrogen and from this portion of the nerve 5 μm cryostat sections were cut for immunohistochemical staining.

**Classification of nerve pathology**
The nerve pathology in cases where vasculitis was a diagnostic consideration on clinical or pathological grounds was characterized as showing definite, probable or possible vasculitic change. All cases included in the final analysis had definite or probable changes of vasculitis. ‘Definite’ vasculitis (Fig. 1C) was diagnosed if the endoneural or epineural vessels showed evidence of vessel wall infarction in association with perivascular or transmural infiltration by inflammatory cells, whether these were monocytes or polymorphonuclear leucocytes. Vessel wall infarction was diagnosed if there was evidence of destruction and disorganization of the muscularis by fibrinoid necrosis, disruption of the endothelium, thrombosis of the lumen or haemorrhage into the wall of the vessel. Definite vasculitis was also considered to be present if perivascular inflammatory infiltrates were associated with evidence of previous vessel wall infarction as indicated by fibrous obliteration with or without recanalization, disruption of the internal elastic lamina or haemosiderin within the vessel wall (old haemorrhage) (Hawke et al., 1991). ‘Probable’ vasculitis was diagnosed if medium-sized vessels (>120 μm) were surrounded by inflammatory cell cuffs and this finding was in association with prominent acute axonal degeneration or evidence of focal nerve damage with aberrant regenerating nerve cell clusters. Probable vasculitis was also considered to be present if either small vessel cuffing was associated with segmental nerve infarction (Fig. 1A and B) on the toluidine blue sections or >40% of fibres in the teased nerve preparation were undergoing acute axonal degeneration.

**Statistical analysis**
The disability scores were examined with standard measures of variance and central tendency. The disability score for each patient at the nadir of their illness was compared with that at their zenith after therapy was commenced with a distribution free Mann–Whitney test (Minitab). The actual and expected survival of the group was analysed. Actual survival was calculated using a Kaplan–Meier survival plot (Cox, 1984) and the relative survival calculated using life table methods based on age and sex data from Australian mortality tables (Australian Life Tables 1980–1982).

**Results**
The results are summarized in Tables 1 and 2. Of the 1559 biopsies a pathological diagnosis of vasculitis was made in 101, of which 76 were graded as definite and 25 as probable according to the criteria above. On analysis of the clinical data there were 25 patients identified with vasculitis which was confined to peripheral nerves. The pathology in the nerve biopsies showed definite vasculitis in 19 of the cases and probable vasculitis in the remaining six according to the criteria defined above. The epineurial vessels were the
Isolated peripheral nerve vasculitis

Table 1 Clinical features of patients with IPNSV

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Mean 60 176 46 3.25 2
Median 64 145 26

Age = age (in years) at diagnosis; F/U = weeks of follow-up since diagnosis; M/R = (M)onophasic or (R)elapsing course;
Delay = delay (in weeks) between onset and diagnosis; Pattern: clin. = clinical pattern of neuropathy, NCS = nerve conduction studies
(MM = mononeuritis multiplex, As = asymmetrical sensory and motor neuropathy, S = symmetrical sensory and motor neuropathy);
Therapy: S = corticosteroids (<0.5 mg kg⁻¹ day⁻¹), S(Hi) = high dose corticosteroids (>0.5 mg kg⁻¹ day⁻¹), Aza = azathioprine
(100–150 mg day⁻¹), Cyclo = cyclophosphamide; Path. = pathological diagnosis (Pr = probable vasculitis, D = definite asclculitis); DS:
N = disability score at the nadir of the illness, Z = best disability score achieved after starting treatment. 'Deceased at time of follow-up.'

predominant site of involvement. Immunofluorescence studies were done in 24 of the patients and were positive in 22, with
demonstrated immune complex deposition in vessel walls, as
indicated by the presence of immunoglobulin plus complement and or fibrinogen (Table 2). Two of these
patients have been previously reported (Hawke et al., 1991).
Serological investigations were largely negative; of 20
patients in whom anti-nuclear antibodies were sought only
four were positive and most of these in low titre (<1/180).
Rheumatoid factor was assayed in 18 cases and was negative
in 16. The two positive cases were both present in low titre
(<1/16). A significant number of patients had an elevated
ESR. Of 16 cases where the ESR was measured seven had
rates >40 mm h⁻¹ and an additional three had rates between
20 and 40 mm h⁻¹. One patient had a peripheral eosinophilia
on blood film examination. Men and women were equally
affected. The mean age of onset of symptoms was 60 years
and all patients were of European ancestry.

At follow-up all patients except one were alive which is
not significantly different from life table predictions. A total
of 20 of 23 patients assessed according to the disability scale
were ambulant and self-caring without walking aids. The
interval to diagnosis after the onset of symptoms was long
with a median time of 6 months before biopsy. The majority
of cases appeared to have a monophasic course but 32% had
had at least one relapse at follow up and this proportion might
be expected to grow with longer observation. The patients
nadir of disability during the first attack of neuropathy had
a mean of 3.3 on the disability scale and the subsequent
mean disability following institution of therapy reached a
zenith of 1.9 on the same scale (Table 1 and Fig. 2). This is
significant at a level of 0.0025 (Mann-Whitney test).

Almost half the patients had a history of clinical
mononeuritis multiplex but six had an asymmetrical sensory
and motor neuropathy and eight had a clinically symmetrical
neuropathy at the time they were first examined. Nerve
conduction studies prior to treatment were available in 24
patients. As these studies were done in a number of centres
they are not directly comparable for statistical purposes.
Nevertheless 10 studies showed electrophysiological
mononeuritis multiplex and five studies showed asymmetry
without frank mononeuritis. Of the nine studies that showed
Isolated peripheral nerve vasculitis

Fig. 1 (A) Transverse section of sural nerve in IPNSV showing evidence of segmental nerve infarction. At this level one fascicle (a) shows a mild reduction of myelinated fibres, whereas in other fascicles (b and c) no fibres remain and the endoneurium shows homogenous hyaline change consistent with infarction. Bar = 50 μm. (B) At a level 1 cm proximal to A all fascicles contain myelinated fibres. Nerve fibre regeneration at this level is shown by the presence of numerous cluster formations (arrows) and the presence of epineurial myelinated fibres (arrow heads) following the epineurial blood vessels. Bar = 100 μm. (C) Transverse section of sural nerve from a patient with IPNSV. The arteriole in the centre of the picture is surrounded by inflammatory cells, the vessel wall is necrotic and the lumen is occluded by debris. Magnification, ×66.

a symmetrical polyneuritis, three patients had had clinical mononeuritis multiplex and one had had an asymmetric neuropathy. These findings are presumably due to delay between the clinical examination and the neurophysiological testing as an increasing burden of vasculitic damage in nerve trunks tends to cause a neuropathy to evolve towards a symmetrical picture.

All patients were treated with immunosuppressing agents. Corticosteroids were used in all cases, eight in relatively low dose (<0.5 mg kg\(^{-1}\) day\(^{-1}\) and the rest high dose (>0.5 mg kg\(^{-1}\) day\(^{-1}\)). Of the patients treated with high dose steroids 12 had an additional agent. The commonest supplementary agents were Azathioprine and cyclophosphamide (six cases each). A single patient was given methotrexate.

Discussion.
The most striking clinical difference between IPNSV and generalized vasculitis with peripheral nerve involvement is the prognosis (Fig. 3). The vast majority of patients with IPNSV survive and, with treatment, show improvement in their disability. This reflects the finding in studies of generalized vasculitis with peripheral nerve involvement that the poor prognosis in these conditions was not generally attributable to the nerve involvement per se with most deaths being due to failure of other organ systems (Hawke et al., 1991). It has been suggested (Said et al., 1988; Kissel and Mendell., 1994) that IPNSV, rather than being an organ-specific vasculitis, is a mild form of systemic vasculitis where nerves are most affected because their long course makes them especially vulnerable to small areas of ischaemia. This seems unlikely from a number of points of view. The good prognosis of IPNSV does not relate to a less severe neuropathy than that seen in systemic vasculitis as many of our patients had a very severe neuropathy, while many patients with severe systemic vasculitis may have relatively mild neuropathy or none at all (Cohen and Hurd, 1981; Said et al., 1988; Hawke et al., 1991). It is also not always true that small infarcts in other organs are likely to remain asymptomatic; quite small volumes of tissue infarction in liver, kidney or muscle may produce marked changes in the serum levels of liver enzymes or creatine phosphokinase and very small infarcts in brain...
The clinical picture in patients with IPNSV is dominated by their neuropathy and even if there is sub-clinical involvement of other tissues this does not appear to have either symptomatic or prognostic relevance. Where the initial sections in a nerve biopsy from a case with suspected vasculitis are not diagnostic it is often helpful to cut further sections from the biopsy tissue as the process is often patchy and deeper blocks may well be diagnostic.

One of the interesting characteristics of IPNSV is the marked recovery in function seen in individual nerves that appear devastated at the height of the illness. This is somewhat surprising in a condition where the presumptive pathology for nerve injury is axonal degeneration due to ischaemic infarction. Some of this recovery may be due to ischaemic injury that has stopped short of nerve fibre infarction. The occasional occurrence of distinct conduction block in some patients with vasculitis suggests that nerve ischaemia from vasculitis can produce demyelination or functional disruption of conduction without necessarily resulting in axonal infarction (Ropert and Metral, 1990). There are clinical and experimental models that provide support for this concept of sub-infarctive ischaemic damage (Nukada and Dyck, 1987; Nukada, 1990; Homberg et al., 1992). Even in patients where peripheral nerves have been severely damaged by vasculitis, as evidenced by complete clinical paralysis and minute or absent distal compound muscle action potentials accompanied by profuse denervation potentials, the degree of long-term recovery can be surprisingly good. This may be because the underlying anatomy of the nerve sheath is preserved, permitting axonal regrowth down the original pathways. The relative resistance of fibroblasts to ischaemia probably contributes to this.

The pathophysiology of vasculitis remains uncertain in most cases but there is a considerable body of evidence, particularly from animal studies in serum sickness, to suggest that the pathological changes commonly result from the deposition of immune complexes in blood vessel walls. This evidence has been reinforced by the finding of immunoglobulin and complement deposited in blood vessel walls in...
neuropathies associated with systemic vasculitis (Kissel et al., 1989; Hawke et al., 1991; Kissel and Mendell, 1992) and by the demonstration of hepatitis B antigen in immune complexes in some cases of polyarteritis nodosa. Other more recent evidence has been presented that supports a role for cell-mediated mechanisms. The finding that CD8 T cells and macrophages predominate in the vessel lesions of vasculitic neuropathy (Kissel et al., 1989) suggests that a cytotoxic T cell-mediated process causes vascular damage. Similar findings have been reported in vasculitis confined to muscle and nerve (Panegyres et al., 1990, 1992). It is of interest that epineurial rather than endoneurial vessels are affected in IPNSV. The former do not have a blood nerve barrier function in that they lack tight junctions between endothelial cells and show a low rate of endocytosis. This suggests that some circulating factor, such as antibody or complement directed against a neural antigen, may accumulate around epineurial cells and evoke an immune response. In support of this is the fact that 87% of patients had evidence of immune complex deposition as shown by the presence of immunoglobulin, complement or both in vessel walls. This contrasts with the absence of any such deposition in both normal nerves and even nerves affected by other autoimmune inflammatory processes, such as chronic inflammatory demyelinating polyneuropathy (McCombe et al., 1987). There seems little doubt that a significant proportion of patients with vasculitic neuropathy pursue a relapsing and remitting course. The time course of this can be quite indolent. Several patients in this series who had made a good recovery from their initial illness had a relapse months to years after their immunosuppression had been completely withdrawn. The best characterized immune-mediated relapsing and remitting peripheral neuropathy is chronic inflammatory demyelinating peripheral neuropathy (CIDP). The relationship of IPNSV to CIDP is unclear but several parallels can be drawn. In both cases an immune reaction to a presumptive peripheral nerve antigen results in local inflammation and tissue destruction. While no definite antigen has been isolated in either disease it seems likely that CIDP represents a response to a myelin antigen. Similarly in IPNSV, no candidate epitopes have been described but presumably the responsible antigen or neuritogen is confined to blood vessels in peripheral nerves, and most likely is expressed on endothelial cells. It is possible that an antigen derived from peripheral nerve cells, either Schwann cells or neurons, may be serendipitously found in low concentrations on endothelial cells of adjacent epineurial vessels and initiate an immune response that is directed at the endothelial cells rather than the primary antigen source. Be that as it may, both CIDP and IPNSV appear to respond to immunosuppression and to have a favourable long-term prognosis when appropriately treated. The immunosuppressive therapy used in these patients varied widely because they were treated by different practitioners. Nevertheless some themes of treatment emerge.

All patients were treated with corticosteroids, although the dosage varied widely. Patients with more severe neuropathies tended to be given larger doses of steroids and most treating physicians added a second ‘steroid sparing’ agent to the regimen of those on large doses. In most cases the agent used was azathioprine, although one patient received methotrexate. The most severe cases were treated with cyclophosphamide, an alkylating agent, to induce rapid and profound immunosupression. In general this was given as high-dose intravenous pulse therapy at the time treatment was commenced but two patients received chronic low-dose oral cyclophosphamide.

Nerve biopsy is critical to the diagnosis of IPNSV. Without a nerve biopsy vasculitis cannot be reliably separated from other rapidly progressive neuropathies because many cases of IPNSV will appear symmetrical both clinically and neurophysiologically by the time they present to a neurologist. Because only nerve tissue is involved and accompanying serological abnormalities are sporadic and non-specific, biopsy of nerve tissue itself is the appropriate diagnostic procedure. The pathological criteria for diagnosis of IPNSV must include vessel wall infarction for the diagnosis to be considered definite. This stipulation is, however, too stringent for clinical utility. From a practical point of view any nerve with prominent inflammatory cell infiltrates accompanied by devastating acute axonal death on teased nerve fibre preparation (>40% of fibres undergoing axonal degeneration) should be regarded as probable vasculitis particularly if supported by finding immunoglobulin, complement and/or fibrinogen in the vessel walls. Such a finding should prompt treatment with immunosuppressive therapy. If prominent acute axonal degeneration is seen without mononuclear cuffs around vessels then further sections should be cut through the paraffin blocks of nerve tissue. In several of our cases with definite vasculitis the initial paraffin sections were normal but diagnostic lesions were found when further sections were examined.

Isolated vasculitis affecting peripheral nerves produces a small percentage of all disabling neuropathies. It can have an indolent presentation and may not be recognizable as mononeuritis multiplex by the time a patient presents. It can only be diagnosed with certainty on nerve biopsy and a firm diagnosis provides the basis for therapy that is likely to provide a clear benefit to the patient. It should be considered in any patient who presents with a progressive sensory and motor neuropathy where a definite cause cannot be established.

References


Winkelmann RK, Ditto WB. Cutaneous and visceral syndromes of necrotizing or 'allergic' angiitis: a study of 38 cases. Medicine (Baltimore) 1964; 43: 59–89.

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