doi:10.1093/brain/awq252 Brain 2010: 133; 2866–2880 | 2866

BRAIN
A JOURNAL OF NEUROLOGY

Post-surgical inflammatory neuropathy

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Post-surgical neuropathies are usually attributed to mechanical factors, such as compression, stretch, contusion or transection. The role of inflammatory mechanisms in neuropathies occurring after surgeries is poorly appreciated and not well characterized, and may provide a rationale for immunotherapy. A total of 23 selected patients with post-surgical neuropathies received nerve biopsies, of which 21 demonstrated increased inflammation. Here we report the clinical features in these 21 cases of biopsy-confirmed and 12 cases of clinically suspected post-surgical inflammatory neuropathies, in whom no trauma to the nerves was documented. All neuropathies developed within 30 days of a surgical procedure. Of 33 patients, 20 were male and the median age was 65 years (range 24–83). Surgical procedures were orthopaedic ($n = 14$), abdominal/pelvic ($n = 12$), thoracic ($n = 5$) and dental ($n = 2$). Patients developed focal ($n = 12$), multifocal ($n = 14$) or diffuse ($n = 7$) neuropathies. Focal and multifocal neuropathies typically presented with acute pain and weakness, and focal neuropathies often mimicked mechanical aetiologies. Detailed analyses, including clinical characteristics, electrophysiology, imaging and peripheral nerve pathology, were performed. Electrophysiology showed axonal damage. Magnetic resonance imaging of roots, plexuses and peripheral nerves was performed in 22 patients, and all patients had abnormally increased T_2 nerve signal, with 20 exhibiting mild ($n = 7$), moderate ($n = 12$) or severe ($n = 1$) enlargement. A total of 21 patients had abnormal nerve biopsies that showed increased epineurial perivascular lymphocytic inflammation (nine small, five moderate and seven large), with 15 diagnostic or suggestive of microvasculitis. Evidence of ischaemic nerve injury was seen in 19 biopsies. Seventeen biopsies had increased axonal degeneration suggesting active neuropathy. Seventeen biopsied patients were treated with immunotherapy. In 13 cases with longitudinal follow-up (median 9 months, range 3–71 months), the median neuropathy impairment score improved from 30 to 24 at the time of last evaluation ($P = 0.001$). In conclusion: (i) not all post-surgical neuropathies are mechanical, and inflammatory mechanisms can be causative, presenting as pain and weakness in a focal, multifocal or diffuse pattern; (ii) these inflammatory neuropathies may be recognized by their spatio-temporal separation from the site and time of surgery and by the characteristic magnetic resonance imaging features; (iii) occasionally post-surgical inflammatory and mechanical neuropathies are difficult to distinguish and nerve biopsy may be required to demonstrate an inflammatory mechanism, which in our cohort often, but not exclusively, exhibited pathological features of microvasculitis and ischaemia; and (iv) recognizing the role of inflammation in these patients' neuropathy led to rational immunotherapy, which may have resulted in the subsequent improvement of neurological symptoms and impairments.

Keywords: peripheral neuropathy; inflammation; post-surgical; autoimmunity; microvasculitis

Abbreviations: NIS = Neuropathy Impairment Score

Received June 17, 2010. Revised August 2, 2010. Accepted August 3, 2010. Advance Access publication September 15, 2010

Introduction

Peripheral nerve damage following a surgical procedure is a well-known clinical problem usually attributed to the mechanical forces of stretch, compression, contusion or transection. These neuropathies may result in prolonged patient impairments. Furthermore, they constitute a significant medico-legal problem for both anaesthesiologists and surgeons, and are a common consultation for neurologists (Cheney *et al.*, 1999). Conservative management is customarily recommended in these cases or often surgical nerve repair is attempted (Dawson and Krarup, 1989).

Occasionally, it is difficult to explain a post-surgical neuropathy by mechanical forces because it is either spatially or temporally segregated from the surgery. In these cases, inflammatory or autoimmune aetiologies need to be considered, which if proven may provide patients with opportunities for immune-based therapies. Inflammatory or immune-mediated post-surgical neuropathy is not a well-described phenomenon. Guillain–Barré syndrome has rarely been reported following surgeries (Wiederholt *et al.*, 1964; Arnason and Asbury, 1968), with endoneurial inflammatory infiltration on autopsy in some cases. Several series on idiopathic brachial plexopathy have described antecedent surgeries as possible triggers (Parsonage and Turner, 1948; Malamut *et al.*, 1994; van Alfen and van Engelen, 2006), but none of these series included pathological correlation. Furthermore, when a brachial plexopathy follows a surgery in the vicinity of the brachial plexus (e.g. cardiac surgery), it is often assumed that mechanical factors are responsible (Lederman *et al.*, 1982).

We describe the clinical, electrophysiological, imaging and pathological features in a series of patients seen at the Mayo Clinic who developed post-surgical neuropathies that were usually difficult to explain based on mechanical factors. We confirmed the inflammatory nature of the process by performing nerve biopsies in the involved segment and then treating non-improving patients with immunotherapy.

Materials and methods

Patient selection

This study was approved by the Mayo Clinic Institutional Review Board (IRB#08-006829). Patients were considered for inclusion in the study if they developed a peripheral neuropathy within 30 days of a surgical procedure and no documented nerve trauma was recognized. A total of 27 patients were identified through the routine practice in the Department of Neurology at the Mayo Clinic, Rochester (2001–10). The remainder of patients was identified retrospectively through the Mayo Electronic Record and the Peripheral Nerve Laboratory database (1999–2009). Subjects were divided into two groups that either did or did not have a nerve biopsy performed, which were termed biopsy-confirmed or clinically suspected post-surgical inflammatory neuropathy, respectively. In order to be included in the clinically suspected post-surgical inflammatory neuropathy group (no biopsy), the patients either clearly developed neuropathy outside of the immediate post-operative period or their neuropathy was spatially remote from the surgical area. In order to be included in the biopsy-confirmed post-surgical neuropathy group, a neurologist had to have suspected an inflammatory cause and a nerve biopsy showing inflammation was obtained. In the process of identifying patients for the study, only two additional patients were identified who developed post-surgical neuropathy and underwent a nerve biopsy that did not show prominent inflammation, and these two patients were not included in this study. The surgical records, including anaesthesia and blood transfusions, were reviewed by an anaesthesiologist (M.E.W.).

Scoring of neuropathy, severity and disability

Data were collected on patients via chart review, with 30 of the 33 patients having been seen personally by at least one of the authors (N.P.S., C.J.K., P.J.D. and P.J.B.D.). Neuropathy severity was quantified using the Neuropathy Impairment Score (NIS) (Dyck *et al.*, 1980), which is a linear scale of weakness, sensory loss and hyporeflexia, and is weighted heavily for weakness (Dyck *et al.*, 2005*b*). Neuropathies were categorized into focal, multifocal or diffuse patterns. Focal neuropathies involved single nerves or single limbs. Multifocal neuropathies involved multiple limbs, often sequentially. Diffuse neuropathies involved all limbs without focality by history or examination.

Ancillary testing

Patients underwent a comprehensive evaluation that included a combination of serology, CSF, neurophysiology and MRI of spinal cord and peripheral nerve. The assessment of nerve conduction studies and needle electromyography used methods standard for the electromyography laboratory at the Mayo Clinic with published references (Daube and Rubin, 2009). Standard nerve conduction studies for motor nerves are tibial, peroneal, ulnar, median, radial and musculocutaneous. Standard sensory studies are sural, superficial peroneal, medial plantar, median antidromic, ulnar antidromic, superficial radial, medial antebrachial and lateral antebrachial. Quantitative sensory testing using Computerized Assisted Sensory Examination (CASE IV) was performed (Dyck *et al.*, 1984). Autonomic testing was performed using the Mayo Clinic Autonomic Reflex Screen, which assesses cardiovagal, adrenergic and post-ganglionic sympathetic sudomotor function via the quantitative sudomotor axon reflex test; sudomotor function was further assessed in some patients via the thermoregulatory sweat test (Low, 1993). Nerve biopsy was obtained in 23 patients, 21 of whom were included in this study. The decision to proceed with nerve biopsy was based on clinical judgement and was often influenced by neuropathy severity, need for treatment guidance or imaging abnormalities. In general, distal cutaneous nerve biopsies were obtained and the nerve was processed using standard laboratory techniques for teased nerve fibres, paraffin sections, epoxy sections and immunohistochemistry preparations (Dyck *et al.*, 2005*a*). Nerve biopsies were scored by two of the authors (N.P.S. and P.J.B.D.). Mayo Clinic radiology reports were reviewed in 24 patients that received spinal cord imaging. MRI of nerve was obtained in 22 patients and was independently interpreted by two of the authors (N.P.S. and K.K.A.). Statistical analyses were performed using Excel software (Microsoft, Inc.) on parametric data sets.

Results

Biopsy-confirmed post-surgical inflammatory neuropathy

General characteristics

Twenty-one patients were identified with biopsy-confirmed post-surgical inflammatory neuropathy (Tables 1 and 2). The median age was 65 years (range 24–83). Eleven were female. Seven had type 2 diabetes mellitus and none had type 1 diabetes mellitus. Two had a prior history consistent with a mild length-dependent peripheral neuropathy. None had a history of an autoimmune disorder. Four had a concurrent history of cancer (colorectal adenocarcinoma, renal cell carcinoma, bladder cancer and prostate cancer). Five had a concomitant history of infection (genital herpes, diverticulitis, oral abscess, cellulitis and thoracic osteomyelitis). One had a family history of neuropathy. Six had more than one of the above putative risk factors, seven had one and eight had none. Additionally, nine were current or former smokers. In the 19 patients where it was documented, 14 reported weight loss of at least 10 pounds around the time of the development of neuropathy (median 32.5 pounds; range 10–115 pounds).

A wide spectrum of surgical procedures preceded the neuropathies (Table 2). Six surgeries were performed at the Mayo Clinic, Rochester, Minnesota, and 15 surgeries were performed elsewhere with subsequent clinical evaluation at the Mayo Clinic. Nine patients had orthopaedic procedures, eight had abdominal/pelvic procedures, two had thoracic procedures and two had dental procedures. Seventeen patients had prior surgeries without neurological complications, while four had no prior surgery. Fifteen patients undergoing thoracic, abdominal/pelvic and orthopaedic procedures received general anaesthesia consisting primarily of volatile agent (i.e. isoflurane for 13 and sevoflurane for two patients). Two patients undergoing lower extremity orthopaedic procedures received spinal blocks with the local anaesthetic bupivicaine. Two patients undergoing abdominal procedures were anaesthetized with isoflurane and received a supplemental lumbar epidural catheter for postoperative pain management with a combination of bupivicaine and fentanyl. Two patients undergoing extensive dental procedures received midazolam and fentanyl for sedation.

The median time from surgery to onset of neuropathy was two days (range 0–30 days), with 13 patients developing neuropathy within three days of surgery (Table 2). All patients reported an acute or subacute onset of symptoms. All but one patient had a monophasic illness with stabilization or recovery. A single patient (Case 12) developed multiple attacks of neuropathy following the initial post-surgical neuropathy. Pain was present in 18 patients, which was described as a combination of prickling ($n = 11$), aching ($n = 7$), cramping ($n = 5$), burning ($n = 9$), lancinating ($n = 10$) and contact allodynia ($n = 5$). Sensory loss was present in all patients. Limb weakness was present in 20 patients (two in an upper limb only, 12 in a lower limb only and six had a combination). Of the 18 patients with lower limb weakness, gait aids were required at the nadir of neurological deficit in 12 [wheelchair ($n = 3$), walker ($n = 4$), ankle-foot orthoses ($n = 5$)]. Phrenic neuropathy was seen in one patient, but no bulbar signs or symptoms were documented in any patients. Neuropathy severity was quantified using the NIS, with the median score being 38 (range 6–83.5) at the documented evaluation and presumed nadir of symptoms and signs. Neuropathies were further categorized into focal, multifocal or diffuse patterns. Focal neuropathies involved single nerves or single limbs (six patients). Multifocal neuropathies involved multiple limbs (11 patients). Diffuse neuropathies involved all limbs without focality by history or examination (four patients). The clinical neuropathy patterns were lumbosacral radiculoplexus neuropathy (10), brachial plexus neuropathy (5), sciatic mononeuropathy (5), polyradiculoneuropathy (4), and phrenic mononeuropathy (1); four patients had a combination of the patterns.

Ancillary testing

Laboratory studies were performed on all patients, which typically included a broad screen for blood count/chemistries, endocrinopathies, inflammatory/autoimmune markers, vitamin/metabolic deficiencies/toxicities and paraneoplastic processes (Table 3). With this screen nine patients were found to have abnormalities. Three patients had an elevated erythrocyte sedimentation rate (40, 36 and 53 mm/h; normal <29 mm/h), two had an elevated C-reactive protein (11 and 10.4 mg/dl; normal <8 mg/dl), three

Table 1 Comparisons of demographics and risk factors in biopsy-confirmed and clinically suspected post-surgical inflammatory neuropathy

Demographics	Biopsy-confirmed ($n = 21$)	Clinically suspected ($n = 12$)
Female, *n* (%)	11 (52%)	2 (17%)
Median age at onset, years (range)	65 (24–83)	65.5 (27–76)
History of pre-existing peripheral neuropathy, *n* (%)	2 (9.5%)	1 (8%)
History of diabetes mellitus, *n* (%)	7 (33%)	2 (17%)
History of concurrent cancer, *n* (%)	4 (19%)	3 (25%)
History of concurrent infection, *n* (%)	5 (9.5%)	2 (17%)
History of smoking, *n* (%)	9 (43%)	5 (42%)
Concomitant weight loss, *n* (%)	13/19 (74%)	5/8 (63%)
NIS score at nadir (range)	38.0 (6–83.5)	15.75 (0–31)*

*$P = 0.001$ (two-tailed Student's *t*-test); NIS = neuropathy impairment score.

Table 2 Biopsy-confirmed post-surgical inflammatory neuropathy: patient characteristics, surgery types and clinical features

Patient	Age at clinical evaluation (years)	Gender	Time from surgery to symptoms (days)	Anaesthesia type	Surgery	Clinical diagnosis	Nerve biopsied	Focal, multifocal or diffuse neuropathy	Neuropathy near site of surgery	Pain	NIS at nadir	Weight loss (pounds)	Risk factors
1	33	F	1	General	Elective abortion	Bilateral sciatic	Sural	Mu	N	Y	23	0	I
2	69	M	14	General	Right THA	Left BPN and mild LSRPN	Superficial radial	Mu	N	Y	40.5	27	DM,PN
3	49	F	<24 h	Combined	Right radical nephrectomy	Bilateral sciatic	Sural	Mu	N	Y	38.5	45	DM,Ca
4	63	M	1	Spinal	Right THA	Right lumbosacral plexopathy	Superficial peroneal	Fo	Y	Y	25	20	none
5	65	F	7	General	Splenectomy	Polyradiculoneuropathy	Sural	D	N	Y	38	ND	I
6	76	M	<24 h	General	Cervical spine decompression	Bilateral BPN	Lateral antebrachial	Mu	Y	Y	24.5	ND	none
7	75	F	3	Sedation	Root canal	Sensory polyneuropathy	Sural	D	N	Y	6	15	none
8	59	M	7	General	Ileostomy takedown	Bilateral LSRPN with mild PN	Sural	Mu	N	Y	68	35	DM,Ca
9	80	M	30	General	Bowel reanastomosis	Bilateral LSRPN	Sural	Mu	N	Y	59	40	Ca
10	64	F	1	General	Bilateral TKA	Left sciatic	Sural	Fo	Y	N	30	35	DM,FH
11	54	F	21	Sedation	Root canal	Left sciatic	Sciatic fascicular	Fo	N	N	22.25	0	I
12	78	M	21	General	CABG	[a]Left BPN, then right LSRPN, then left LSRPN	Sural	Mu	N	Y	52.25	0	Ca,I
13	68	M	21	General	Vertebral biopsy	Bilateral BPN with phrenic	Superficial radial	Mu	N	Y	60.25	70	I
14	65	M	2	General	Thoracic spine decompression	Polyradiculoneuropathy	Sural	D	N	Y	60.25	0	DM
15	24	F	1	General	Cholecystectomy	Bilateral LSRPN followed by PR	Sural	Mu	N	Y	83.5	100	none
16	54	F	30	Combined	Gastric bypass	Polyradiculoneuropathy	Sural	D	N	Y	18	115	none
17	56	M	<24 h	General	Lumbar spine fusion	Bilateral BPN, LSRPN	Sural	Mu	N	Y	59.5	30	DM
18	45	F	<24 h	Spinal	Left THA	Left LSRPN	Sural	Fo	Y	Y	9	10	none
19	74	F	<24 h	General	Right THA	Right sciatic	Superficial peroneal	Fo	Y	Y	21	0	none
20	83	F	<24 h	General	Left femur nail	Bilateral LSRPN	Sural	Mu	N	N	51	26	none
21	70	M	15	General	Circumcision	Left LSRPN	Sural	Fo	N	Y	11.5	30	DM,PN

BPN = brachial plexus neuropathy; Ca = cancer; CABG = coronary artery bypass graft; Combined = general and epidural; D = diffuse; DM = diabetes mellitus; F = female; FH = family history of neuropathy; Fo = focal; I = infection; LSRPN = lumbosacral radiculoplexus neuropathy; M = male; Mu = multifocal; N = no; ND = not documented; NIS = neuropathy impairment score; PN = peripheral neuropathy; PR = polyradiculopathy; THA = total hip arthoplasty; TKA = total knee arthroplasty; Y = yes;
a Polyphasic presentation.

Table 3 Biopsy-confirmed post-surgical inflammatory neuropathy: ancillary studies

Patient	Surgery	Clinical diagnosis	Laboratory studies	QST	Electrophysiology				MRI		
					CMAP	SNAP	EMG	QSART	↑T_2	Enlarged nerves	Gadolinium-enhanced
1	Elective abortion	Bilateral sciatic	CSF protein	V, C	↓	↓	Fb, NMU	ND	Y	Mod	N
2	Right THA	Left BPN and mild LSRPN	CRP, AchR, CSF protein	C, HP	↓	↓	Fb, NMU	NL	Y	Mild	N
3	Right radical nephrectomy	Bilateral sciatic	ESR	TP, V, C, HP	↓	↓	Fb, NMU	↓	Y	Mod	N
4	Right THA	Right lumbosacral plexopathy	CSF protein	C, HP	↓	↓	Fb, NMU	↓	Y	Mod	N
5	Splenectomy	Polyradiculoneuropathy	CSF protein	V, C, HP	↓	↓	Fb, NMU	NL	Y	Mod	N
6	Cervical spine decompression	Bilateral BPN	NL	ND	NL	↓	Fb, NMU	ND	Y	Mild	N
7	Root canal	Sensory polyneuropathy	NL	ND	↓	↓	Fb, NMU	ND	ND	ND	ND
8	Ileostomy takedown	Bilateral LSRPN with mild PN	CSF protein	V, C, HP	↓	↓	Fb, NMU	↓	Y	Mod	N
9	Bowel reanastomosis	Bilateral LSRPN	ESR, p-ANCA, CSF protein	ND	↓	↓	Fb, NMU	ND	Y	Mild	N
10	Bilateral TKA	Left sciatic	p-ANCA, CSF protein, CSF WBCs	V, C, HP	↓	↓	Fb, NMU	↓	Y	Mild	N
11	Root canal	Left sciatic	CSF protein	V, C, HA	NL	NL	NMU	ND	Y	Severe	Y
12	CABG	[a]Left BPN, then right LSRPN, then left LSRPN	ESR, RF, CSF protein	TP, V, C, HP	↓	↓	Fb, NMU	↓	Y	Mod	N
13	Vertebral biopsy	Bilateral BPN with phrenic	Cu, CSF protein	V, C	↓	↓	Fb, NMU	NL	ND	ND	ND
14	Thoracic spine decompression	Polyradiculoneuropathy	NL	C	↓	↓	Fb, NMU	↓	ND	ND	ND
15	Cholecystectomy	Bilateral LSRPN followed by PR	NL	ND	↓	↓	Fb, NMU	ND	Y	Mod	N
16	Gastric bypass	Polyradiculoneuropathy	NL	V	NL	↓	Fb, NMU	NL	ND	ND	ND
17	Lumbar spine fusion	Bilateral BPN, LSRPN	CSF protein	TP, V, C, HP	↓	↓	Fb, NMU	↓	Y	Mod	N
18	Left THA	Left LSRPN	NL	ND	NL	↓	Fb, NMU	ND	Y	Mild	N
19	Right THA	Right sciatic	CSF protein	TP, V, HP	↓	↓	Fb, NMU	ND	Y	Mod	N
20	Left femur nail	Bilateral LSRPN	RF	ND	↓	↓	Fb, NMU	ND	Y	Mod	N
21	Circumcision	Left LSRPN	CRP	ND	↓	↓	Fb, NMU	ND	Y	Mild	N

AChR = neuromuscular acetylcholine receptor antibody; BPN = brachial plexus neuropathy; C = increased cooling threshold; CABG = coronary artery bypass graft; CMAP = compound muscle action potential; CRP = C-reactive protein; Cu = copper; EMG = electromyography; ESR = erythrocyte sedimentation rate; Fb = fibrillation potentials; HA = hyperalgesia; HP = increased heat-pain threshold; LSRPN = lumbosacral radiculoplexus neuropathy; Mod = moderate; N = no; ND = not documented; NL = normal; NMU = neurogenic motor unit potentials; p-ANCA = perinuclear-staining antineutrophil cytoplasmic antibodies; PR = polyradiculopathy; QSART = quantitative sudomotor axon reflex test; QST = quantitative sensory testing; RF = rheumatoid factor; SNAP = sensory nerve action potential; THA = total hip arthroplasty; TKA = total knee arthroplasty; TP = increased touch-pressure threshold; V = increased vibration threshold; WBCs = white blood cells; Y = yes; Downward arrow indicates reduced or absent; upward arrow indicates increased.

had elevated rheumatoid factor (16, 48 and 88 IU/ml; normal <15 IU/ml), one patient had elevated acetylcholine receptor binding antibodies (0.04 nmol/l; normal <0.02 nmol/l), one had a low serum copper level (0.64 μg/ml; normal 0.75–1.45 μg/ml) and two exhibited positive perinuclear-staining antineutrophil cytoplasmic antibodies. Three patients had multiple abnormalities of the above-mentioned tests. All elevated C-reactive protein and erythrocyte sedimentation rate results were drawn at least 2 months after surgery. Data on CSF were obtained in 18 patients. Median CSF protein was 60 mg/dl (range 23–115 mg/dl), with 12 having an elevated protein by laboratory standards. One patient had a pleocytosis (29 cells/μl). Immunoglobulin-G index and oligoclonal bands were screened in 14 patients, all of which were within normal ranges.

Nerve conduction and electromyography were performed in all patients (Table 3). In affected limbs, there were reduced compound muscle action potentials in 17 patients and reduced or absent sensory nerve action potentials in 20 patients. Electrophysiological correlates of demyelination were not prominent on any of the nerve conduction studies. Fibrillation potentials and long duration motor unit potentials in the affected nerve segment were observed in all but one patient (Case 11) who had electrodiagnostic study within one week of symptom onset (before changes are expected to occur in denervated muscles). Autonomic reflex screen with quantitative sudomotor axon reflex test of affected limbs was performed in 11 patients, with reduced or absent quantitative sudomotor axon reflex test responses in seven patients. Thermoregulatory sweat testing was performed in five patients, with abnormal sweat responses in the distribution of signs and symptoms in four patients. Quantitative sensory testing was performed in affected limbs in 14 patients, all of which showed some abnormality, with a combination of sensory deficits in touch-pressure ($n = 4$), vibration ($n = 11$), cooling ($n = 12$) and heat-pain ($n = 9$) modalities with hyperalgesia in one.

MRI of the roots, plexuses and peripheral nerves were performed in 17 patients (Table 3) and of the spinal cord in 19 patients (seven cervical, six thoracic and 17 lumbosacral). There was no spinal cord signal abnormality in any of the studies. Conversely, all patients had abnormal magnetic resonance signal in the roots, plexuses or peripheral nerves in the distribution of their clinical neuropathies. There was increased T_2 signal in all studies (Fig. 1), with mild nerve enlargement in six, moderate enlargement in 10 and severe enlargement in one. In the 12 cases where gadolinium contrast was administered, only one nerve exhibited minimal enhancement, which was also the case that demonstrated severe enlargement (Case 11; Fig. 1D). Case 11 had clinical, imaging and pathological features unlike any of the other cases. This patient developed a focal sciatic neuropathy in the setting of dental procedure and had both imaging and biopsy findings that were suggestive of a focal inflammatory demyelinating neuropathy (20% segmental demyelination on teased fibres).

Nerve pathology

Nerve biopsies were performed in all 21 patients (Figs 2–4), at a median of 12 weeks from the onset of symptoms (range

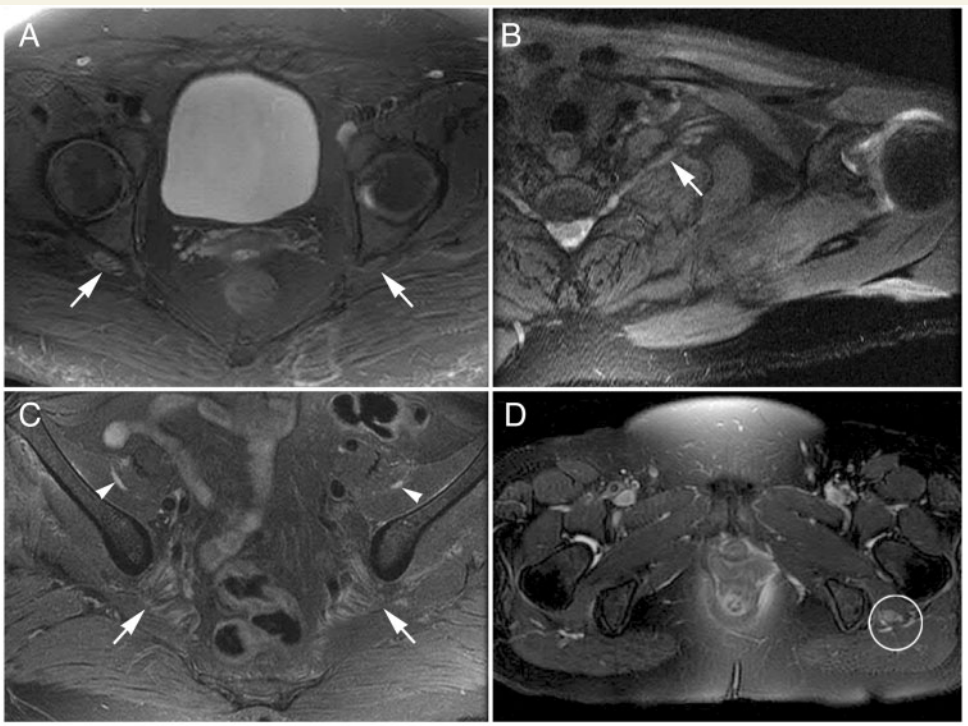

Figure 1 MRI characteristics of post-surgical inflammatory neuropathy. (**A**) T_2 hyperintensity and mild enlargement of bilateral sciatic nerves, right more than left (arrows) (Case 3); (**B**) T_2 hyperintensity and mild enlargement of left C8 root and lower trunk (arrow) (Case 2); (**C**) T_2 hyperintensity and moderate enlargement of the bilateral femoral nerves (arrowheads) and mild enlargement of the sciatic nerves (arrows) (Case 21); (**D**) T_2 hyperintensity and severe enlargement of left sciatic nerve (circled) (Case 11).

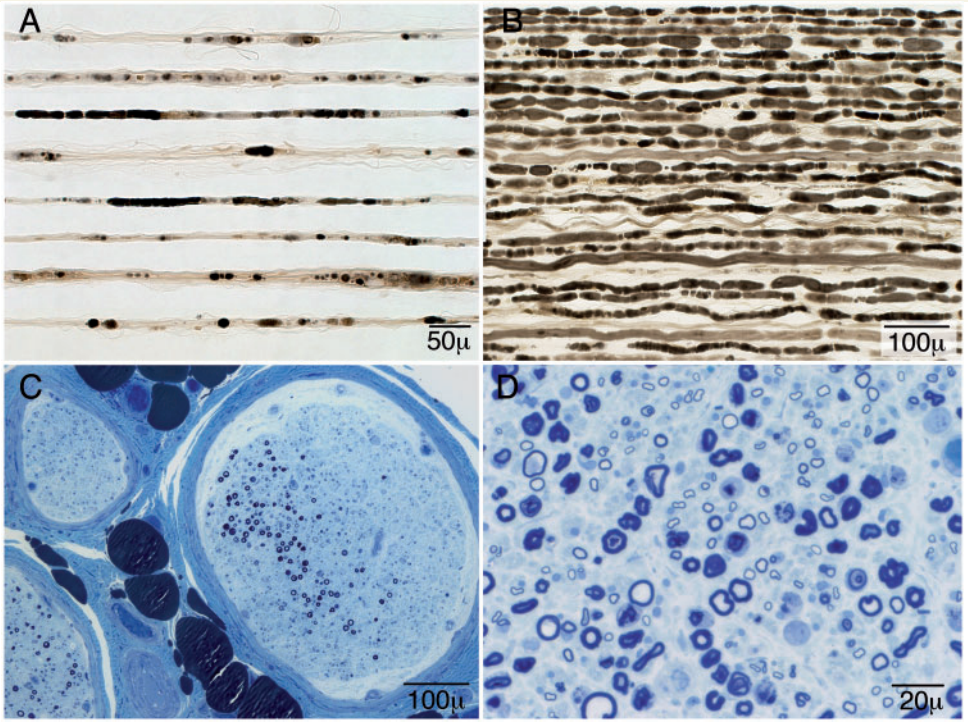

Figure 2 Axonal degeneration and focal fibre loss in post-surgical inflammatory neuropathy. (**A**) Teased fibre preparation showing multiple strands with fulminant late axonal degeneration (Case 3). (**B**) Teased fibre preparation showing multiple closely aligned strands of fulminant early axonal degeneration (Case 1). (**C**) Low power methylene blue epoxy section of nerve illustrating multifocal fibre loss (Case 2). (**D**) High power methylene blue epoxy sections showing prominent axonal degeneration of large myelinated fibres (Case 1).

2–100 weeks). Twenty were superficial sensory nerves (15 sural, 2 superficial peroneal, 2 superficial radial and 1 lateral antebrachial) and one was a targeted fascicular sciatic biopsy. Teased fibre preparation ($n = 20$) revealed abnormal degrees of axonal degeneration (≥5%) in 16 patients, segmental demyelination (≥4%) in seven and increased numbers of empty strands (≥20 strands) in 13 (Table 4). In 18 biopsies there were pathological correlates of ischaemic nerve injury, with 11 biopsies revealing focal fibre loss, 13 biopsies with neovascularization, 15 biopsies with perineurial thickening ($n = 12$) or degeneration ($n = 10$) and one biopsy with injury neuroma (Table 4). Eleven biopsies demonstrated hemosiderin deposition. Nine biopsies revealed small (10–49 cells), five revealed moderate (50–99 cells) and seven revealed large (≥100 cells) epineurial perivascular inflammatory cell collections. The collections were epineurial perivascular in all 21 patients, with 12 of these biopsies also demonstrating small collections of endoneurial perivascular inflammation. With immunostaining, the perivascular inflammatory collections were predominantly positive for CD-45 (lymphocyte-predominant), with occasional CD-68 (macrophage) positive cells intermixed. In biopsies with fulminant active axonal degeneration there was also diffuse endoneurial CD-68 staining consistent with the scavenging role of macrophages in this process. Features of nerve microvasculitis were seen in 15 biopsies, which were either suggestive (7 vessel wall inflammation) or diagnostic (8 vessel wall inflammation and destruction). Biopsies diagnostic of microvasculitis were observed in focal (5/6) and multifocal (3/11) neuropathies, but not in the diffuse (0/4) post-surgical neuropathies.

Treatment and follow-up

Seventeen patients received immunomodulatory therapy following nerve biopsy results. Fifteen received intravenous methylprednisolone (typical course of 12 weekly doses of 1 g methylprednisolone), one received oral steroids and one received intravenous immunoglobulin.

Longitudinal follow-up was obtained in 14 patients (median 10.5 months, range 3–71 months). Thirteen of these patients had sufficient follow-up documentation for an NIS, which showed significant improvement from the initial evaluation to last follow-up (30 versus 24, $P = 0.001$, paired Student's *t*-test; Fig. 5). Two of these patients (Cases 11 and 19) did not receive immunomodulatory therapy but also demonstrated significant improvement. Of the 14 patients with follow-up, 12 had initially reported pain that was subsequently improved in 11 (one without immunotherapy).

Clinically suspected post-surgical inflammatory neuropathy

Twelve additional patients were identified who developed a neuropathy within 1 month of a surgical procedure and did not have a nerve biopsy but were suspected to have an inflammatory

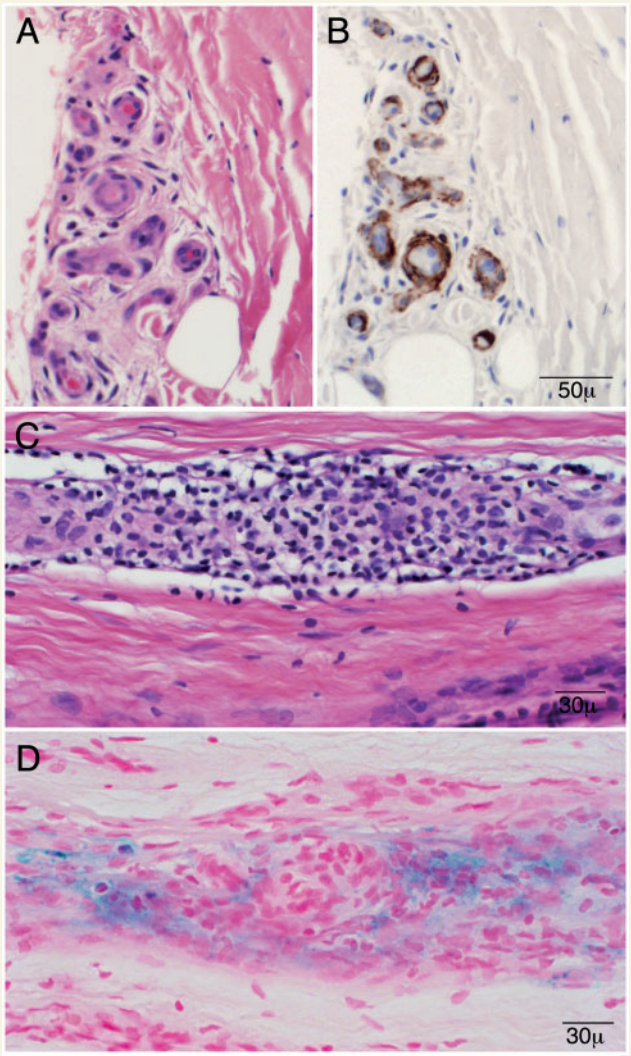

Figure 3 Neovascularization, inflammation and hemosiderin deposition in post-surgical inflammatory neuropathy. (**A** and **B**; Case 3) Serial high power paraffin cross-sections stained with haematoxylin and eosin (**A**) and smooth muscle actin immunostaining (**B**) showing neovascularization. (**C** and **D**; Case 4) High power haematoxylin and eosin stained (**C**) and corresponding Turnbull blue stained (**D**) longitudinal paraffin sections showing inflammation and long-standing bleeding (hemosiderin deposition = blue discoloration) in the vessel wall. These findings taken together are diagnostic of microvasculitis.

neuropathy on clinical grounds (Tables 1 and 5). The neuropathy either developed >24 h after surgery or was spatially segregated from the surgical site. These patients also presented in a focal ($n = 6$), multifocal ($n = 4$) or diffuse ($n = 2$) fashion characterized by weakness ($n = 10$), pain ($n = 9$) and sensory loss ($n = 11$). Details of clinical presentation and ancillary testing in these patients are provided in Table 5. As a group the clinically suspected post-surgical inflammatory neuropathy patients had less severe neuropathy than the biopsy-confirmed patients (NIS median 15.75 versus 38.25, $P = 0.001$, two-tailed Student's *t*-test) (which was often the reason that a biopsy was deferred). Additionally, 6 of 12 patients had isolated upper limb signs and symptoms, similar to idiopathic brachial plexus neuropathies, which is a well-documented post-surgical phenomenon (Parsonage and Turner, 1948; Malamut *et al.*, 1994; van Alfen and van Engelen, 2006).

Representative cases

Case 4 (focal): right lumbosacral plexopathy following right total hip arthroplasty

A 63-year-old male without significant past medical history reported a 6-year history of right hip and groin pain that was aggravated by exercise and alleviated by rest. Hip radiographs demonstrated degenerative changes in the right hip, and he subsequently underwent a right total hip arthroplasty with a general anaesthetic consisting primarily of isoflurane.

On waking from surgery, he did not notice any neuropathic pain, numbness or weakness. The next morning he had severe shooting, burning, aching pain in his entire right leg. It was also noted at that time that he was unable to dorsiflex or plantarflex his right foot, with additional mild proximal right lower extremity weakness.

In the intervening month prior to our evaluation, his weakness remained stable and he required either a walker or wheelchair for ambulation. His pain symptoms had somewhat improved, but he still complained of numbness and tingling in his foot and the lateral aspect of his lower leg with associated allodynia.

Neurological examination of the right lower extremity revealed severe weakness of peroneal- greater than tibial-innervated muscles, and mild weakness of hip flexors and extensors, knee abductors, flexors and extensors. Sensory exam revealed sensory loss (touch, vibration, proprioception, cooling, heat-pain and pinprick) in the right lower extremity below the knee. Deep tendon reflexes were reduced at the right knee and absent at the right ankle. Plantar responses were flexor.

A broad serological survey was negative or normal. CSF evaluation showed a mildly elevated protein (66 mg/dl; normal 15–45 mg/dl) with a normal glucose (53 mg/dl) and cell count (white blood cells 1 cell/μl, red blood cells 0 cell/μl). Nerve conduction studies showed reduced right tibial and absent peroneal compound muscle action potentials with absent sural and superficial peroneal sensory nerve action potentials. There were dense fibrillation potentials and no activation in peroneal division sciatic nerve-innervated muscles, dense fibrillations with poor activation in tibial-innervated muscles, and mild fibrillation potentials without motor unit changes in femoral and obturator-innervated muscles. Paraspinal muscles showed occasional fibrillation potentials. MRI of the lumbosacral plexus demonstrated T_2 hyperintensity and moderate enlargement of the right sciatic nerve. There was no contrast enhancement.

A right superficial peroneal biopsy showed a severe neuropathic process, which was characterized by multifocal myelinated fibre loss and axonal degeneration (88% axonal degeneration on teased fibres). There was neovascularization, perineurial thickening and hemosiderin deposition (Fig. 3D). There were large epineurial perivascular inflammatory collections, some of which involved and

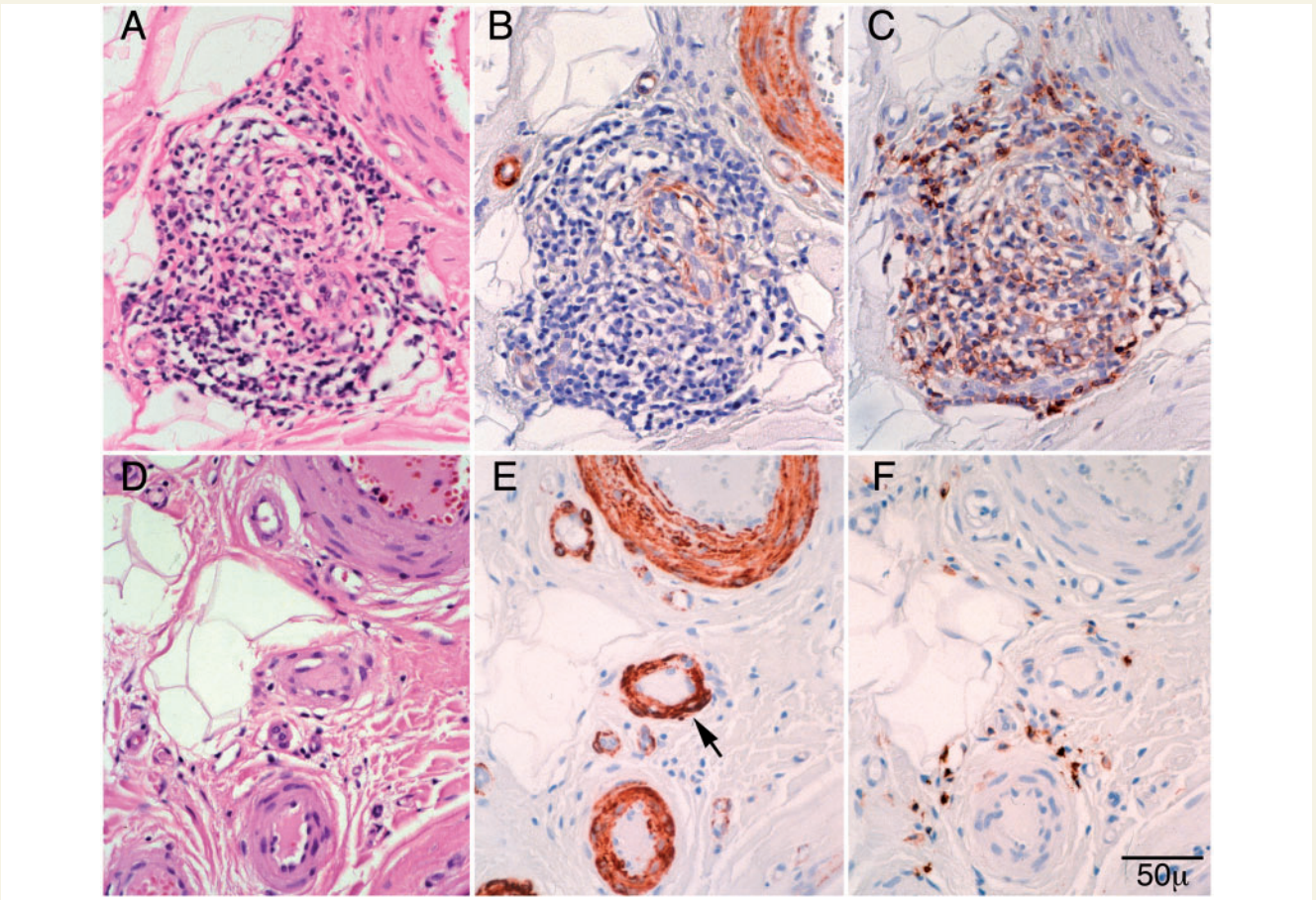

Figure 4 Evidence for focal nature of epineurial microvasculitis in post-surgical inflammatory neuropathy. Serial paraffin sections from a region of microvasculitis: top row is proximal portion of epineurial microvessel and bottom row is distal portion of same vessel (arrow denotes vessel involved with microvasculitis in upper panel). Note the separation and destruction of the vessel wall by inflammation in the top row. There is no intact lumen remaining. (**A** and **D**) Haematoxylin and eosin; (**B** and **E**) smooth muscle actin immunostaining; (**C** and **F**) CD-45 (leukocyte common antigen) immunostaining (Case 2).

disrupted the vessel walls (Fig. 3C), and a diagnosis of microvasculitis was given.

The patient was treated for 3 days with high-dose intravenous methylprednisolone (1 g) followed by weekly doses (1 g) for a total of 12 weeks. In follow-up, after the course of intravenous steroids, his pain and weakness were improved. He reported rare lancinating pains and he was walking independently with use of an ankle-foot orthosis device. His NIS at last follow-up (15 months after initial evaluation) improved from 25 to 14.5.

Case 3 (multifocal): bilateral sciatic neuropathies following radical nephrectomy

A 49-year-old female with a medical history of type 2 diabetes mellitus (diagnosed 4 years earlier), hypertension and restless legs syndrome was found to have a renal cell carcinoma on a computed tomography of the abdomen. She underwent radical right nephrectomy with a general anaesthetic consisting primarily of the volatile agent isoflurane. She also had a lumbar epidural catheter placed for infusion of bupivicaine and fentanyl to provide intraoperative and postoperative analgesia. Approximately three days postoperatively, the patient noticed altered sensation and weakness in her lower limbs. She described severely painful 'pins and needles' sensations in her legs bilaterally up to approximately the knee. There was bilateral severe leg weakness, worse in the right leg compared with the left. This combination of pain and weakness initially caused her to be wheelchair bound.

Over the ensuing months, she received opioid and anticonvulsant therapy for pain relief, and the painful paraesthesias somewhat improved. She also had mild improvement in the left-sided weakness, but not on the right. Due to the improvement in pain, she was able to transition from a wheelchair to a cane; however, she did not feel that her function had improved significantly since the onset of her symptoms.

At the time of our evaluation of her case (2.5 months after surgery), she reported painful prickling paraesthesias in her left foot and her right heel. There was also a 'thick feeling' of the skin of her right lateral leg. She reported bilateral leg weakness, much worse in her right leg, with a flail right foot. Neurological examination was notable for moderate weakness in bilateral hamstrings, with severe weakness in the right greater than left

Table 4 Nerve biopsy results in biopsy-confirmed post-surgical inflammatory neuropathy

Patient	Focal, multifocal or diffuse neuropathy	Time from symptoms to biopsy (weeks)	Nerve biopsied	Teased fibres						Inflammation				Ischaemic injury				
				Normal: A, B (%)	Demyelination: C, D (%)	Axonal: E, H (%)	Remyelination: F, G (%)	Classifiable: (number)	Empty Strands: (number)	Perivascular Inflammation (small, moderate, large)[a]	CD-45 positive collections	Hemosiderin deposition	Microvasculitis (diagnostic, suggestive or none)	Focal fibre loss	Neovascularization	Perineurial thickening	Perineurial degeneration	Injury neuroma
1	Mu	2	Sural	26	0	70	3	121	2	Moderate	+		Suggestive					
2	Mu	24	Superficial radial	59	11	21	9	91	19	Large	+	+	Diagnostic	+	+	+		
3	Mu	12	Sural	8	0	92	0	77	29	Large	+	+	Diagnostic	+	+	+	+	
4	Fo	6	Superficial peroneal	12	0	88	0	68	26	Large	+	+	Diagnostic	+	+		+	
5	D	100	Sural	72	2	3	23	96	9	Small	+		Suggestive					
6	Mu	7	Lateral antebrachial	85	2	0	14	117	8	Small	+		None			+		
7	D	9	Sural	6	79	13	2	84	23	Small	+		None	+	+	+	+	
8	Mu	20	Sural	58	7	26	9	43	58	Small	+		Suggestive	+	+	+	+	
9	Mu	8	Sural	68	4	19	9	68	37	Small	+		Suggestive	+				
10	Fo	36	Sural	4	0	96	0	24	79	Large	+	+	Diagnostic		+	+		
11	Fo	2	Sciatic fascicular	77	20	1.5	1.5	90	12	Small	+		None		+	+		
12	Mu	36	Sural	83	1	5	11	80	27	Small	+		None		+	+	+	
13	Mu	28	Superficial radial	9	0	91	0	77	34	Large	+	+	Suggestive	+				
14	D	23	Sural	90	2	2	6	87	20	Moderate	+		Suggestive		+		+	
15	Mu	2	Sural	22	0	78	0	99	3	Small	+	+	None					
16	D	16	Sural	ND	ND	ND	ND	0	ND	Small	+	+	None	+		+		
17	Mu	24	Sural	60	19	14	8	74	32	Moderate	+	+	Suggestive	+	+	+	+	
18	Fo	7	Sural	73	0	23	4	92	14	Moderate	+		Diagnostic	+	+	+	+	
19	Fo	10	Superficial peroneal	5	0	95	0	77	35	Large	+	+	Diagnostic				+	
20	Mu	9	Sural	57	1	34	7	86	21	Moderate	+	+	Diagnostic		+			
21	Fo	22	Sural	54	5	32	9	69	30	Large	+	+	Diagnostic	+	+	+	+	+
TOTALS: Median (Range)	F: 6 M: 11 D: 4	12 (2–100)		57.5 (4–90)	1.5 (0–79)	24.5 (0–96)	5 (0–23)	83 (0–121)	24.5 (2–79)	Small: 9 Moderate: 5 Large: 7	21	11	Diagnostic: 8 Suggestive: 7 None: 6	11	13	12	10	1

D = diffuse; Fo = focal; Mu = multifocal; ND = not done; + = present.

a Perivascular inflammatory collections: small = 10–49 cells, moderate = 50–99 cells, large = ≥100 cells. Categories A through G refer to specific teased fiber classifications as described in Reference (Dyck *et al*., 2005*a*).

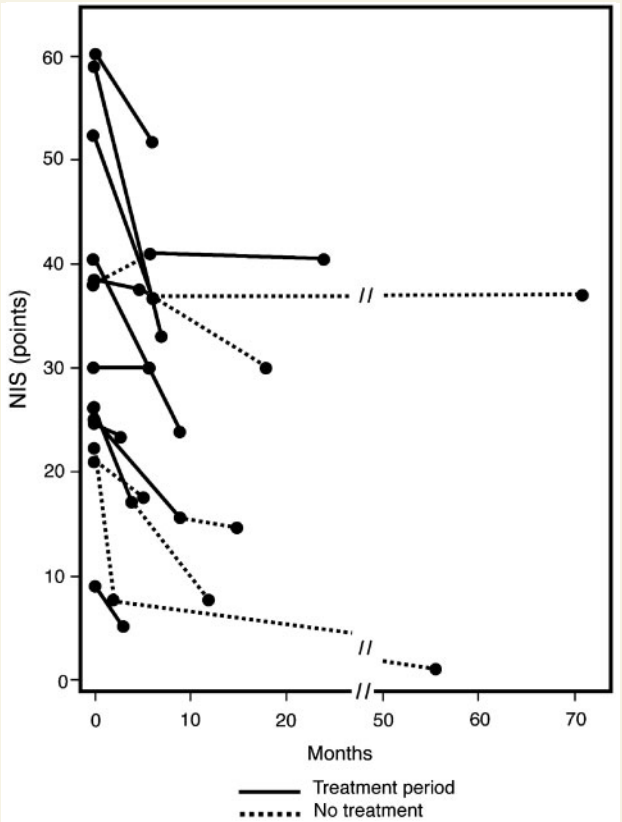

Figure 5 Longitudinal follow-up of post-surgical inflammatory neuropathy. NIS improves over time (paired Student's *t*-test, $P = 0.001$). Solid lines denote treatment period and dashed lines are during times of no treatment. Every patient showed improvement or stabilization.

peroneal- and tibial-innervated muscles. There was loss of sensation (touch, vibration, proprioception, cooling, heat-pain and pinprick) over the lateral part of her right leg and over the dorsum of the foot. Reflexes were absent at the knees and ankles and the plantar responses were flexor.

Extensive serological evaluations were notable only for a mild elevation in erythrocyte sedimentation rate (40 mm/h). Spinal fluid revealed a normal glucose (107 mg/dl), protein (37 mg/dl), cell count (white blood cells 1 cell/μl, red blood cells 0 cell/μl), cytology, oligoclonal bands, immunoglobulin-G index, bacterial cultures and West Nile Virus serology. Nerve conduction studies were normal in the upper extremities (median sensory and ulnar motor), whereas there was no measurable right tibial and peroneal compound muscle or sural sensory nerve action potential. The left peroneal compound muscle action potential was reduced in amplitude with normal conduction velocity, distal latency and F-wave. Needle examination revealed prominent fibrillation potentials and neurogenic motor unit potentials in a pattern consistent with a right sciatic neuropathy. MRI of the lumbar spine revealed facet joint arthropathy at L3–5 interspaces but was otherwise normal. MRI of the lumbosacral plexus showed prominence of both sciatic nerves, greater on the right, without abnormal enhancement, which was thought to represent a nonspecific inflammatory process (Fig. 1A).

A right sural nerve biopsy revealed evidence for an ongoing inflammatory neuropathic process (Figs 2A, 3A and B). There was a severely decreased density of myelinated fibres with actively degenerating profiles, multifocality, perineurial thickening and neovascularization. Teased fibre preparation showed a markedly increased rate of axonal degeneration (92%) and an increased number of empty strands. Multiple small, moderate and large collections of mononuclear inflammatory cells around epineurial vessels were seen. The inflammation was disrupting the walls of small epineurial vessels with associated hemosiderin-laden macrophages and was diagnostic of microvasculitis.

The diagnosis of inflammatory mononeuropathies secondary to microvasculitis was made. The patient was treated for 3 days with high-dose intravenous methylprednisolone (1 g), followed by weekly doses (1 g) for a total of 12 weeks. In follow-up, after the course of intravenous steroids, the patient reported resolution of pain and was able to discontinue opioid medications (she remained on anticonvulsant therapy). Her weakness was mildly improved initially after treatment, but the patient reported a marked increased mobility, which was felt to be due to the combined effects of improved pain and weakness. Her NIS at last follow-up (30 months after initial evaluation) improved from 38.5 to 30.

Case 7 (diffuse): sensory-predominant polyneuropathy following root canal

A 75-year-old female with a history of hypertension underwent a root canal under conscious sedation. Three days later she developed numbness in the right hand and forearm, followed by similar symptoms in the left hand the next day. By the next week she noted bilateral foot numbness and pain had developed in the arms and feet. The pain was characterized as having a burning and shooting quality, with sensitivity to light touch. She lost 15 pounds in weight concurrent with the sensory disturbance. She had no weakness.

Neurological examination demonstrated sensory loss to vibration with preservation of touch, proprioception, cooling, heat-pain and pinprick modalities. Contact allodynia to light touch and hyperalgesia to pinprick were documented in the hands and feet. Deep tendon reflexes were reduced at the ankles. Strength was normal.

A broad serological survey was negative or normal. CSF evaluation showed a normal protein (31 mg/dl), glucose (57 mg/dl) and cell count (white blood cells 1 cell/μl, red blood cells 0 cell/μl). Nerve conduction studies demonstrated absent median and ulnar sensory nerve action potentials. The sural sensory nerve action potential was normal (7 μV). There was reduced amplitude left median, ulnar, peroneal and tibial compound muscle action potentials, with mildly prolonged distal latencies in all but the peroneal nerve. The conduction velocities were relatively preserved. The median and ulnar F-waves were within estimate, while the tibial F-wave was absent. Needle electromyography demonstrated reduced recruitment of long duration motor unit potentials in distal leg muscles. The study was interpreted as a mixed axonal and demyelinating sensorimotor peripheral neuropathy.

A whole left sural nerve biopsy was performed, which on teased fibre preparation exhibited segmental demyelination (79%) and axonal degeneration (13%). There was mild focal fibre loss,

Table 5 Clinically suspected post-surgical inflammatory neuropathy: patient characteristics, surgery types, clinical features and ancillary studies

Patient	Age at clinical evaluation (years)	Gender	Time from surgery to symptoms (days)	Surgery	Clinical diagnosis	Focal, multifocal or diffuse neuropathy	Neuropathy near site of surgery	Pain	NIS at nadir	Weight loss (pounds)	Risk factors	Lab studies	QST	Electrophysiology				MRI		
														CMAP	SNAP	EMG	QSART	↑ T_2	Enlarged nerves	Gadolinium-enhanced
22	68	M	4	Lumbar CSF leak repair	Left > right LSRPN	Mu	N	Y	21.5	25	DM	NL	ND	↓	↓	Fb, NMU	ND	Y	Mod	Y
23	52	M	21	Cervical spine fusion	Right BPN	Fo	Y	N	0	0	none	NL	ND	NL	↓	Fb, NMU	NL	Y	N	N
24	43	M	7	Aortic valve replacement	Length-dependent peripheral neuropathy	D	N	Y	2	0	none	ANA, CSF protein	ND	↓	↓	Fb, NMU	ND	ND	ND	ND
25	27	M	<24 h/17	Cholecystectomy	Left (<24 h) then right (17 days) BPN	Mu	N	Y	26.75	ND	I	NL	ND	↓	↓	Fb, NMU	ND	Y	Mild	N
26	60	F	21	Appendectomy	Autonomic neuropathy	D	N	Y	0	ND	none	NL	ND	NL	NL	NL	↓	ND	ND	ND
27	71	M	22	Aortic valve replacement	Bilateral LSRPN and left facial	Mu	N	Y	26.5	20	none	NL	HA	↓	NL	Fb, NMU	↓	ND	ND	ND
28	67	M	1	Radical prostatectomy	Right Lumbosacral plexopathy	Fo	N	Y	17.5	18	Ca	ACE, CSF protein	TP	↓	↓	Fb, NMU	ND	Y	N	N
29	64	M	<24 h	Right nephrectomy	Right BPN	Fo	N	Y	2	25	Ca	CSF protein	C	↓	↓	Fb, NMU	ND	Y	Mod	N
30	68	M	<24 h	Bowel reanastomosis	Right ulnar	Fo	N	Y	1	16	DM, PN	NL	ND	↓	↓	Fb, NMU	ND	ND	ND	ND
31	67	M	<24 h	CABG	Right sciatic	Fo	N	ND	31	ND	I	Cryo	ND	↓	↓	Fb, NMU	ND	ND	ND	ND
32	76	M	<24 h	Right femur nailing	Right BPN	Fo	N	Y	21	ND	Ca	NL	ND	↓	↓	Fb, NMU	ND	ND	ND	ND
33	44	F	9	Right brachial plexus schwannoma resection	Left phrenic and right median	Mu	N	Y	14	0	none	NL	ND	NL	↓	Fb, NMU	ND	ND	ND	ND

ACE = angiotensin converting enzyme; ANA = antinuclear antibodies; BPN = brachial plexus neuropathy; C = increased cooling threshold; Ca = cancer; CABG = coronary artery bypass graft; CMAP = compound muscle action potential; Cryo = cryoglobulinaemia; D = diffuse; DM = diabetes mellitus; F = female; Fb = fibrillation potentials; Fo = focal; HA = hyperalgesia; I = infection; LSRPN = lumbosacral radiculoplexus neuropathy; M = male; Mod = moderate; Mu = multifocal; N = no; NIS = neuropathy impairment score; NMU = neurogenic motor unit potentials; ND = not documented; NL = normal; PN = peripheral neuropathy; QSART = quantitative sudomotor axon reflex test; QST = quantitative sensation testing; SNAP = sensory nerve action potential; TP = increased touch-pressure threshold; WBCs = white blood cells; Y = yes; downward arrow indicates reduced or absent; upward arrow indicates increase.

regenerating clusters and perineurial degeneration. Scattered small collections of lymphocytes were observed around epineurial and perineurial venules and microvessels, without vessel disruption.

A diagnosis of a sensory inflammatory demyelinating polyneuropathy was made and the patient received a 7-month tapering course of prednisone. Gabapentin was initiated for pain control. On last clinical follow-up, 22 months after neuropathy onset, the patient was improved and left with mild residual neuropathic symptoms.

Discussion

We have described the demographics, clinical features, electrophysiology, imaging and pathology in a series of patients with post-surgical inflammatory neuropathy. In our cohort, post-surgical inflammatory neuropathy presented in either a focal, multifocal or diffuse fashion. Clues to the inflammatory aetiology of the neuropathy were sometimes available in the spatiotemporal segregation of the neuropathy from the surgery. Focally increased T_2 signal and enlargement within nerve segments on MRI sometimes provided another clue to the inflammatory aetiology. In other cases, inflammatory neuropathies were identified on biopsy in patients who otherwise appeared to have a mechanically induced neuropathy. Ancillary testing did not usually provide evidence for a systemic inflammatory/immune process; however, these tests were helpful in ruling out other causes of neuropathy. In the end, nerve biopsy was often utilized to confirm the diagnosis of inflammatory neuropathy and direct treatment for the patients, most of whom received immunosuppressant medications. All patients reported some degree of improvement following treatment, although the two patients followed up that were not treated also showed improvement, which in these patients probably reflects a monophasic process. In general, pain improved more rapidly than weakness and all but one patient had some residual weakness at the last follow-up. Given the retrospective nature of the study, it is not possible to make strong claims regarding the efficacy of treatment in this entity.

Our study substantially increases the number of reported cases of post-surgical inflammatory neuropathy, which to our knowledge had previously been limited to Guillain-Barré syndrome (Wiederholt *et al.*, 1964; Arnason and Asbury, 1968) or idiopathic brachial plexitis (Parsonage and Turner, 1948; Malamut *et al.*, 1994; van Alfen and van Engelen, 2006). Conversely, the literature is replete with studies on the general topic of post-surgical neuropathies. These post-surgical neuropathies are typically attributed to mechanical factors (stretch, compression, transection, contusion, suture), neurotoxicities from anaesthesia or ischaemia. Putative risk factors have also been ascribed for post-surgical neuropathies including surgical positioning, age, gender, body mass index, hospital length-of-stay, diabetes mellitus, tobacco use and vascular disease (Barner *et al.*, 2002, 2003).

It is unclear what the incidence of post-surgical inflammatory neuropathy is, but there are widely variable data on the overall incidence of post-surgical neuropathy, with the variability often related to the study population. In a large tertiary academic centre, Welch *et al.* (2009) found that centre's overall frequency of perioperative (within 48 h) peripheral nerve injuries over a 10-year period to be 0.03%. This frequency is significantly lower than other large all-inclusive studies that reported incidences of 0.11% (Blitt *et al.*, 1995) and 0.14% (Parks, 1973). While the frequency of all perioperative neuropathies may have decreased over time, it is just as likely that these differences are associated with the use of diverse definitions for peripheral nerve injuries and variability in identification of cases using retrospective record reviews. The frequency of post-surgical neuropathies is often higher when investigated in specific surgical scenarios, ranging from 0.7 to 5.5% (Weber *et al.*, 1976; Lederman *et al.*, 1982; Warner *et al.*, 2000; Cardosi *et al.*, 2002). For example, lower extremity neuropathies after procedures performed on patients in lithotomy positions are far more frequent than those same neuropathies in patients undergoing abdominal procedures while positioned supine (Warner *et al.*, 2000). Although ulnar neuropathies following surgery are considered common, a large retrospective epidemiological study demonstrated a frequency of only 0.036% in patients undergoing non-cardiac procedures (Warner *et al.*, 1994). A prospective study of ulnar neuropathy in 1502 surgical patients subsequently found a frequency of 0.5% (Warner *et al.*, 1999). What proportion of these neuropathies is inflammatory in nature is unclear given the lack of biopsy material in any of these incidence studies.

At our tertiary referral centre, it is our impression that post-surgical inflammatory neuropathy is relatively common. Although a coincidental (and not causal) association of inflammatory neuropathy and surgery is possible, we feel this is unlikely based on our experience in this study and clinical practice. Our search strategy for identifying patients was not exhaustive and we readily found 33 patients that had features consistent with a post-surgical inflammatory neuropathy. Furthermore, in our search for these cases we found only two patients suspected of having post-surgical inflammatory neuropathy whose nerve biopsy did not reveal inflammation (not included in the study). Based on the ease of identifying patients (30 of 33 cases were personally seen by one of the authors) and the fact that several biopsy-confirmed post-surgical neuropathy cases appeared otherwise mechanical in nature, we suspect that post-surgical inflammatory neuropathies are a larger problem than we are reporting. The main difficulty is that the only way to identify a post-surgical inflammatory neuropathy with certainty at this time is by doing a nerve biopsy. We suspect that the vast majority of patients with post-surgical inflammatory neuropathy are assumed to have a mechanical cause and so nerve biopsy is rarely considered. For this reason, even if most post-surgical neuropathies are mechanical, the incidence of inflammatory causes is vastly under-appreciated.

Although mechanical forces are the probable cause of the majority of surgery-related neuropathies, the development of inflammatory infiltration into nerve discovered in our cases is not expected in a purely mechanical insult. Active axonal degeneration, as seen in 16 of our biopsies, may result in endoneurial macrophage (CD-68 positive cells) infiltration but does not cause significant lymphocyte-mediated (CD-45 positive cells) inflammation, as is also seen in our cohort. What stimulates the lymphocytic inflammatory attack on nerve in the post-surgical period is far

from clear. In all likelihood, there is a complex interplay of inflammatory stress responses from surgery, genetic predisposition (Klein *et al.*, 2002), subclinical pre-existing inflammation or neuropathy and possibly even mechanical forces, which all combine to trigger the inflammatory neuropathy. This issue is of particular interest in the patients (18/33) that developed a neuropathy within three days of the surgery before a primary learned immune response would be expected to develop.

It is possible that the surgical process, transfusions and/or anaesthetics may also be contributing to post-surgical inflammatory neuropathies. Fifteen of the biopsied patients received general anaesthesia, two received spinal blocks, two received a combination of general anaesthetics and epidural analgesia, and two were sedated. Seven patients received transfusion of blood products. Stress related to surgical procedures and the perioperative period has been well documented in many types of procedures to reduce immune function and to be associated with increased generalized inflammatory responses (Brown *et al.*, 1989). Inhalation anaesthetics have been associated with immunosuppression lasting for weeks after surgical procedures (Hunter, 1999; Myles *et al.*, 2004). Transfusion of blood products, especially those containing white blood cells, can cause immunosuppression and promote inflammatory responses (Brand, 2002; Vamvakas, 2004). Overall, patients undergoing surgery and anaesthesia, especially those with major procedures and concomitant transfusions, have a high potential to be immunocompromised postoperatively and to have an increased frequency of inflammatory responses.

Other possible risk factors associated with post-surgical inflammatory neuropathies in our study included diabetes mellitus (9/33) cancer (7/33), infection (7/33) and a history of smoking (14/33). In our limited retrospective series, the effects of risk factors cannot be ascertained but raise areas for future study.

The clinical presentation and pathology of our patients were heterogeneous, with focal, multifocal and diffuse patterns being found. Given this heterogeneity, it is not clear to the authors whether the post-surgical inflammatory neuropathies represent one entity or more than one. Nonetheless, the fact that the majority (15/21) of biopsies were suggestive or diagnostic of nerve microvasculitis and ischaemic nerve injury does suggest that there is one predominant pathology. These ischaemic and microvasculitic pathological findings were more represented in the patients with either focal or multifocal neuropathy presentations (none of the four with symmetrical polyradiculoneuropathy were diagnostic of microvasculitis). Interestingly, many of these patients had clinical (subacute onset of pain and weakness with weight loss) and pathological features (ischaemic nerve injury and microvasculitis) similar to both the diabetic and non-diabetic lumbosacral radiculoplexus neuropathies (Dyck *et al.*, 2000, 2001), and may represent a form of this entity that is provoked by surgical stress. In the other cases with diffuse post-surgical inflammatory polyradiculoneuropathies (none of which appear to be classic Guillain-Barré syndrome), it is possible that there are inflammatory mechanisms other than microvasculitis involved.

Of particular interest are five cases (Cases 4, 10, 18, 19 and 20) that developed biopsy-confirmed post-surgical inflammatory neuropathies in the same lower limb of an orthopaedic surgical procedure. All of these cases were diagnostic of nerve microvasculitis on nerve biopsy of distal cutaneous nerves remote from the orthopaedic surgical site. In the past, these post-surgical neuropathies have been understandably assumed to be mechanical, given the strong physical forces used in many orthopaedic procedures, and previous electromyography studies have shown presence of both clinical and subclinical neuropathies following hip arthroplasty (Weber *et al.*, 1976). Our data provide strong evidence that in some cases of lower limb neuropathies following orthopaedic procedures, an inflammatory component is prominent, if not causative.

In conclusion, it is important for physicians to recognize that not all neuropathies that occur in the post-surgical setting are due to compression, transection or stretch. If a neuropathy occurs after a delay or in a territory remote from the surgical site, an inflammatory-immune mechanism should be considered, and if possible, a nerve biopsy for confirmation should be performed to ensure that the best treatment is given. At this point, however, it is less clear how extensive a neurological evaluation (i.e. nerve biopsy) is appropriate in patients that develop neuropathies in the same limb that the surgery was performed on. Our data suggest that inflammation may be an important mechanism of nerve injury in these cases, but who should receive immunotherapy and how many patients need nerve biopsy are provocative ideas that warrant future study.

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