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Non-diabetic lumbosacral radiculoplexus neuropathy

Natural history, outcome and comparison with the diabetic variety

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Summary

Diabetic lumbosacral radiculoplexus neuropathy (DLSRPN) (other names include diabetic amyotrophy) is well recognized, unlike the non-diabetic lumbosacral radiculoplexus neuropathy (LSRPN), which has received less attention. Our objective was to characterize the natural history and outcome of LSRPN and to assess whether it is similar to the diabetic variety in its symptoms, course, electrophysiological features, quantitative sensory and autonomic findings, and the underlying pathophysiology. We studied 57 patients with LSRPN and 33 patients with DLSRPN. We found that the age of onset, course, kind and distribution of symptoms and impairments, laboratory findings and outcomes are essentially alike. Both disorders are a lumbosacral plexus neuropathy associated with weight loss, often beginning focally or asymmetrically in the thigh or leg but usually progressing to involve the initially unaffected segment and the contralateral side. Both have prolonged morbidity due to pain, paralysis, autonomic involvement and sensory loss. In biopsied distal LSRPN nerves, we found changes similar to those found in DLSRPN—alterations typical of ischaemic injury and of microvasculitis. The long-term outcome was determined in 42 LSRPN patients: two had become diabetic, seven had relapsed and only three had recovered completely, although all had improved. We conclude that: (i) LSRPN is a subacute, asymmetrical, painful and debilitating neuropathy of the lower limbs associated with weight loss, and we think it is under-recognized; (ii) recovery from the long-term impairments of LSRPN is usually delayed and incomplete and only a small minority of patients develop diabetes mellitus; (iii) LSRPN mirrors the diabetic variety in its clinical features, course, pathological findings (ischaemic injury from microvasculitis) and long-term outcome; and (iv) LSRPN should be set apart from chronic inflammatory demyelinating polyradiculoneuropathy and from systemic necrotizing vasculitis. We infer an autoimmune basis for LSRPN and emphasize the need for controlled trials of immune-modulating therapy.

Keywords: diabetic amyotrophy; lumbosacral plexopathy; microvasculitis; necrotizing vasculitis; non-diabetic lumbosacral radiculoplexus neuropathy

Abbreviations: CASE IV = computer assisted sensory evaluation, version 4; CASS = composite autonomic severity score; DLSRPN = diabetic lumbosacral radiculoplexus neuropathy; LSRPN = lumbosacral radiculoplexus neuropathy; NIS = Neuropathy Impairment Score

Introduction

The syndrome of non-diabetic lumbosacral radiculoplexus neuropathy (LSRPN) has received little attention since its recognition in 1981 (Evans *et al*., 1981; Sander and Sharp, 1981), when two groups described a subacute painful, paralytic lower-limb neuropathy attributed to pathological involvement of the lumbosacral plexus. Evans and colleagues reported that the condition was monophasic but that morbidity was prolonged due to pain and weakness. Subsequently, individual or small groups of cases were reported emphasizing an unusual course or response to treatment (Marra, 1987; Awerbuch *et al*., 1991; Verma and Bradley, 1994; Hinchey *et al*., 1996; Triggs *et al*., 1997). Bradley and colleagues reported six cases who had elevated erythrocyte sedimentation rates, three with and three without diabetes mellitus (Bradley *et al*., 1984). They found evidence of ischaemic injury (multifocal fibre loss) and perivascular inflammatory cell

cuffing and inferred an immune mechanism. Recently, we studied biopsied distal nerves from 47 LSRPN cases (included here) and found evidence of ischaemic injury and microvasculitis (Dyck *et al*., 2000).

A similar condition described more than 100 years ago, and better recognized by most physicians, is diabetic lumbosacral radiculoplexus neuropathy (DLSRPN) (also called diabetic amyotrophy, proximal diabetic neuropathy, the Bruns–Garland syndrome, diabetic polyradiculopathy and other names). It is an asymmetrical lower-limb syndrome of pain, weakness, paraesthesia and weight loss occurring mostly in patients with mild type 2 diabetes mellitus (Bruns, 1890; Garland and Taverner, 1953; Garland, 1955, 1961; Chokroverty *et al*., 1977; Bastron and Thomas, 1981; Barohn *et al*., 1991).

On the basis of a retrospective analysis of a large cohort of patients with LSRPN, we (i) characterized the clinical, laboratory and electrophysiological features, quantitative autonomic and sensory test results and the course of the LSRPN syndrome; (ii) determined the frequency of concomitant thoracic radiculoneuropathy and cervical radiculoplexus neuropathies; (iii) related the symptomatology to the pathology; (iv) compared the characteristics of LSRPN with those of the diabetic variety (DLSRPN) to understand whether the clinical features, course and outcome are alike; and (v) provided long-term follow-up of LSRPN patients, emphasizing reoccurrence, degree of disability, outcome and the frequency of LSRPN patients eventually developing diabetes mellitus.

Methods

Patient selection

Patients with the diagnosis of proximal neuropathy, polyradiculopathy, polyradiculoneuropathy, lumbosacral plexopathy, lumbosacral plexitis, lumbosacral radiculoplexus neuropathy and femoral neuropathy seen at the Mayo Clinic between January 1, 1983 and December 31, 1998 were identified retrospectively. From their medical records, only those patients who had also undergone a distal cutaneous nerve biopsy were selected. These medical records ($n = 265$) were then reviewed to identify cases with acute or subacute LSRPN and no history of diabetes mellitus. Also included in the present cohort were 18 patients with LSRPN who were personally evaluated by the authors (10 of them were identified prospectively). Ten of these patients did not have nerve biopsies taken. The patients were selected on clinical and electromyographic grounds.

Cases selected for inclusion had subacute (usually a definite onset on a given day with progression of symptoms over days, weeks or months) onset of pain, weakness or paraesthesia of one or both lower limbs and electromyographic characteristics which localized the disease process to the lumbosacral roots, plexus and nerves. For inclusion, there had to be electromyographic abnormality in muscles innervated by at least two peripheral nerves and at least two nerve roots. Paraspinal denervation could be present or not present. Excluded were patients who met the above criteria but who had structural lesions explaining the symptoms or deficits. Also excluded were patients with diabetes mellitus (fasting blood sugar in the diabetic range ($\geqslant$126 mg/dl; American Diabetes Association criteria), chronic inflammatory demyelinating polyneuropathy, systemic vasculitis or connective tissue diseases, Lyme disease, sarcoidosis, a history of radiation exposure or other diagnoses which could explain the neurological deficit. The most common diagnoses excluded were: (i) DLSRPN ($n = 55$); (ii) chronic inflammatory demyelinating polyneuropathy ($n = 39$); (iii) predominantly motor, axonal polyradiculopathy of unknown causes ($n = 26$); (iv) monoclonal gammopathy of undetermined significance neuropathy ($n = 24$); (v) systemic vasculitic neuropathy ($n = 11$); (vi) lymphoma ($n = 8$); (vii) other immune neuropathy ($n = 7$); (viii) motor neurone disease ($n = 7$); (ix) POEMS syndrome (a condition characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) ($n = 6$); (x) a structural cause ($n = 6$); and (xi) radiation plexopathy ($n = 6$). Patients were selected irrespective of whether the clinical involvement was localized to the buttock, hip, thigh or leg. Patients were not excluded if they also developed upper extremity neuropathic symptoms or signs, provided that the LSRPN appeared to be a separate and more problematic disorder.

We compared our LSRPN cohort with a cohort of DLSRPN patients who were identified prospectively and reported previously (Dyck *et al*., 1999).

Neuropathic evaluations

All patients had been evaluated by a Mayo Clinic neurologist. The characteristics and distribution of the neuropathy were quantitated using the Neuropathy Impairment Score (NIS) (Dyck *et al*., 1980), which provides a single score of neuropathic impairment summarizing muscle weakness, decrease of muscle stretch reflexes and decreased sensation, based on a standard group of tests and continuous grading of abnormality, correcting scores for age, sex, anthropomorphic features and physical fitness.

Laboratory methods

Fasting blood glucose levels were known for all patients and glycated haemoglobin levels were known for many. Many patients also had had tests which further characterized their disorder and could exclude other causes of neuropathy (sedimentation rate, rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibody, extractable nuclear antigen, HIV, etc.). Most had CSF evaluations performed. All but three had imaging of the lumbosacral spine with MRI or CT myelography.

Electrophysiological methods

All patients had characterizing nerve conduction and needle electromyography examinations. Nerves and muscles were selected for study according to symptoms and findings.

Quantitative autonomic and sensory testing methods

Quantitative autonomic testing was performed using an autonomic reflex screen (Low, 1993), which measures post-ganglionic sudomotor, adrenergic and cardiovagal function. Quantitative sensory testing was performed by computer-assisted sensation evaluation, system IV (CASE IV) (Dyck *et al*., 1978, 1993*b*) for the dorsal foot, lateral leg or anterior thigh, and values were expressed as percentiles of normal deviates, taking into account age, height and applicable anthropomorphic characteristics (Dyck *et al*., 1995).

Recent follow-up telephone survey

We recently (May 2000) interviewed all available patients by telephone and completed a questionnaire about pain, weakness, sensory loss and present disability. We also asked about recurrent neurological disease and whether the patients had developed diabetes mellitus since their last evaluation by us.

Analysis

Descriptive statistics were used to express results and to compare attributes between groups. For continuous measurements, we expressed results as medians and ranges and compared groups using the Wilcoxon rank sum test. For dichotomous variables, we used Fisher's exact test.

Results

Clinical and laboratory studies

Of 57 LSRPN patients identified, 29 were men and 28 were women. Their median age was nearly 70 years (Table 1). None of our patients had diabetes mellitus. As expected, the median glucose and glycated haemoglobin concentrations of the LSRPN group were significantly lower than those of the DLSRPN group (Table 1). Weight loss ($\geqslant$10 pounds) was recorded in 42 of 57 patients but was less than that experienced by the DLSRPN cohort (Table 1). In general, the weight loss occurred in the early stages of the neurological syndrome when the symptoms were worsening.

Typically, the CSF had an increased protein content and a normal number of nucleated cells (Table 1). The CSF protein and glucose levels were both significantly lower in the LSRPN than in the DLSRPN cohort. Most patients had normal erythrocyte sedimentation rates, although five patients had mildly to moderately increased sedimentation rates ($>$40 mm/h); the median sedimentation rate was a little higher in the LSRPN than in the DLSRPN cohort (Table 1). Some patients also had elevated concentrations of rheumatoid factor and had antinuclear antibodies (Table 1). Imaging of the lumbosacral spine with MRI or CT myelograms failed to show structural lesions that could explain the neurological deficits. Many patients also had lumbosacral plexus MRI scans, which were normal. Ten patients had undergone lumbar laminectomy for presumed lumbosacral radiculopathy from herniated disk. None of these patients improved with surgery and all continued to deteriorate postoperatively, with development of symptoms and findings beyond one nerve root distribution.

Characteristics of the neuropathy

The characteristic symptoms were asymmetrical lower limb pain (57 of 57 patients), weakness and atrophy (57 of 57) and paraesthesia (49 of 57). The different types of pain included aching, hurting, stabbing, electrical shock-like and burning. A troubling pain was excessive tenderness to touch (allodynia), recorded in 24 of 57 patients. Pain was the first and most severe symptom at onset in almost all patients. However, this pattern changed, and by the time of tertiary evaluation at the Mayo Clinic weakness had become the most severe symptom (Table 2). The symptoms usually began on a known date and progressed over days, weeks or months. In general, the condition had been present for months by the time of evaluation at our institution (Table 1). All but one patient required some type of aid in ambulation at the time of evaluation because the weakness was so severe (Table 2). In addition to motor and sensory symptoms, about one-half of the patients (28 of 57) had one or more autonomic symptoms. These included orthostatic hypotension ($n = 4$), urinary dysfunction ($n = 11$), change in sexual function ($n = 11$), diarrhoea and/or constipation ($n = 13$), or a change in sweating ($n = 3$).

The disorder usually began focally in proximal or in distal lower limb segments, but then progressed to involve other segments not involved initially. The most severe initial symptoms began in the hip or thigh somewhat more often than in the leg or foot (Table 2). The disorder began unilaterally in almost all cases (50 of 57) and asymmetrically in all cases. It also began focally in most cases, initially involving only the foot or leg in 17 of 57, only the hip or thigh in 25 of 57 and only the buttock or back in three of 57 cases. In 12 of 57 it began in a more widespread fashion, involving combinations of different segments. However, as the disorder progressed almost all patients developed more widespread involvement, with both the leg and the thigh involved in 52 of 57 cases and bilateral symptoms and findings in 51 of 57 cases. Consequently, by the time of our evaluation the condition appeared much more widespread and symmetrical than when it began. In a minority of cases, symptoms remained confined to the leg (three of 57) or thigh (two of 57).

The pattern of neuropathy was essentially the same in the

Table 1 *Clinical and laboratory characteristics of LSRPN patients compared with DLSRPN patients*

	LSRPN patients				DLSRPN patients				*P**
	n	Median	Range	SD	*n*	Median	Range	SD	
Continuous measures									
Age (years)	57	69.4	27.8–86.5	12.3	33	65.4	35.8–75.9	10.4	0.03
Duration of neuropathy at evaluation (months)	57	7.0	0.5–60.0	12.4	33	6.7	1.4–42.0	8.9	n.s.
Onset to bilateral (months)	45	3.0	0.0–72.0	11.6	32	3.0	0.0–60.0	10.6	n.s.
Fasting plasma glucose (mg/dl)	57	96.0	69.0–124.0	11.5	30	144.5	75.0–225.0	44.3	0.0001
Glycated haemoglobin (%)	34	5.5	4.3–7.1	0.7	30	7.5	5.1–12.9	2.0	0.0001
Body mass index (kg/m^2)	50	25.1	17.8–35.4	4.6	29	25.7	17.8–36.7	4.9	n.s.
Weight change (lb)†	57	−15.0	−90.0–0.0	19.6	33	−30.0	−120.0–0.0	32.6	0.002
Creatinine (mg/dl)	53	1.0	0.6–1.9	0.2	30	0.9	0.7–3.4	0.5	n.s.
CSF glucose (mg/dl)	49	63.0	48.0–88.0	9.3	26	85.0	56.0–130.0	19.4	0.0001
CSF protein (mg/dl)	50	66.5	18.0–283.0	56.9	26	89.5	44.0–214.0	35.3	0.009
CSF cells (cells/μl)	48	1.0	0.0–12.0	2.2	26	1.0	1.0–11.5	2.1	n.s.
Erythrocyte sedimentation rate (mm/h)	56	13.5	0.0–62.0	14.4	31	6.0	0.0–60.5	14.6	0.02
NIS									
Total	57	36.5	6.0–106.3	21.2	33	43.0	7.0–87.0	18.6	n.s.
Lower limb	57	33.5	6.0–77.0	17.0	33	37.0	7.0–62.0	14.4	n.s.
Hip and thigh	57	13.0	0.0–31.0	7.5	33	14.5	0.5–29.0	8.1	n.s.
Leg	57	22.0	0.0–49.0	12.0	33	22.5	4.0–40.0	9.6	n.s.
Dichotomous measures		Yes	No			Yes	No		
Sex, male	57	29	28		33	20	13		n.s.
Rheumatoid factor-positive	40	6	34		27	2	25		n.s.
ANA-positive	50	8	42		32	7	25		n.s.

LSRPN = lumbosacral radiculoplexus neuropathy; DLSRPN = diabetic lumbosacral radiculoplexus neuropathy; SD = standard deviation. n.s. = not significant ($P > 0.05$); NIS = Neuropathy Impairment Score. *Wilcoxon rank sum test for continuous data and Fisher's exact test for dichotomous data; †weight change is from onset to evaluation.

LSRPN and the DLSRPN groups. Pain was the most severe symptom initially in both groups, but weakness became the more disabling symptom later. Both conditions began focally and unilaterally, but they both evolved into generalized and bilateral lower-limb neuropathies. About half of the patients in both groups had autonomic symptoms. The median NIS of the LSRPN and DLSRPN groups were also very similar (Table 1) and not significantly different. Both conditions were associated with elevated CSF protein levels and substantial weight loss (Table 1).

Other sites of neurological involvement

Neurological involvement of the upper limb was common (26 of 57 patients), but in all cases the upper limb involvement was much milder than the lower limb involvement. Most of these cases were mononeuropathies (mostly ulnar neuropathy at the elbow and less often median neuropathy at the wrist) or cervical radiculopathies. Although they were common, it was unclear whether these mononeuropathies were due to the same pathophysiology as the lower limb disorder. Many of them were probably compression neuropathies. However, some patients (six of 57) had symptoms and deficits affecting multiple upper limb nerves, which appeared to be similar to the lower limb disease (e.g. a cervical radiculoplexus neuropathy). Also, nine of 57 patients had thoracic radiculopathies with bands of abdominal or chest pain sometimes associated with an out-pouching of the abdominal wall. The upper limb mononeuropathies, cervical radiculoplexus neuropathies and thoracic radiculopathies were seen at similar frequencies in the LSRPN and DLSRPN groups.

Electrophysiological results

There were marked reductions of the compound muscle and sensory nerve action potentials with only mild slowing of nerve conduction velocities (Table 3). Four patients showed focal conduction blocks of the ulnar nerve across the elbow, and a fifth had slowing of conduction through this segment. These ulnar neuropathies were felt to be due to compression, related to immobility and prolonged times in a chair or bed. Needle electromyography showed frequent fibrillation potentials, decreased recruitment of motor unit potentials and long-duration, high-amplitude, sometimes polyphasic motor unit potentials in muscles innervated by multiple lumbosacral roots and peripheral nerves in a patchy, asymmetrical fashion. Muscles from L2–4, L5S1 and lumbosacral paraspinal levels were involved (Table 3). Sometimes there were electrophysiological abnormalities in segments that did not seem to be affected clinically. The findings were similar in the LSRPN and DLSRPN groups (Table 3). The conduction velocities were significantly lower, the distal latencies were significantly longer and the paraspinal muscles showed significantly more fibrillation potentials in the DLSRPN than in the LSRPN group.

Table 2 *Severity of symptoms, anatomical location and use of ambulating aids in LSRPN and DLSRPN (numbers of patients)*

Evaluation	Most severe symptom					Most involved anatomical site					Aids in ambulation			
	Pain	Prickling or numbness	Weakness	None	*P**	Foot or leg	Hip or thigh	Buttock or back	None	*P**	Wheelchair	Walker, cane or brace	None	*P**
LSRPN														
Onset ($n = 57$)	49	1	7	0		21	33	3	0					
					<0.0001					n.s.				
Mayo Clinic evaluation ($n = 57$)	10	0	47	0		27	30	0	0		28	28	1	
					0.03					0.0001				<0.0001
Telephone follow-up ($n = 42$)	12	1	26	3		32	7	0	3		5	21	16	
DLSPRN														
Onset ($n = 33$)	27	0	6	0		12	18	3	0					
					<0.001					n.s.				
Mayo Clinic evaluation ($n = 33$)	13	0	20	0		14	19	0	0		16	14	3	
					0.05					<0.001				<0.001
Telephone follow-up ($n = 31$)	6	2	21	2		24	5	0	2		3	16	12	
LSPRN versus DLSPRN														
Onset					n.s.					n.s.				
Mayo Clinic evaluation					0.03					n.s.				n.s.
Telephone follow-up					n.s.					n.s.				n.s.

LSPRN = lumbosacral radiculoplexus neuropathy; DLSPRN = diabetic lumbosacral radiculoplexus neuropathy; n.s. = not significant ($P > 0.05$). *Fisher's exact test.

Table 3 *Nerve conduction, electromyographic and quantitative autonomic testing in LSRPN patients compared with DLSRPN patients at the Mayo Clinic evaluation*

Variable	LSRPN			DLSRPN			*P**
	n	Median	Range	*n*	Median	Range	
Nerve conduction studies[†]							
Sural							
SNAP (μV)	65	2.0	0.0–18.0	37	0.0	0.0–7.0	0.0001
CV (m/s)	22	42.0	36.0–54.0	4	39.5	35.0–41.0	n.s.
DL (ms)	43	4.0	3.3–5.1	6	4.4	4.0–4.8	n.s.
Peroneal							
CMAP (mV)	80	0.5	0.0–8.3	38	0.2	0.0–7.5	n.s.
CV (m/s)	56	40.0	23.0–52.0	27	36.0	24.0–46.0	0.0009
DL (ms)	57	4.7	3.1–7.9	27	5.6	4.0–14.1	0.0001
Tibial							
CMAP (mV)	72	1.4	0.0–14.0	31	0.7	0.0–11.4	n.s.
CV (m/s)	60	41.0	33.0–53.0	25	36.0	20.0–48.0	0.0003
DL (ms)	60	4.7	3.3–7.5	25	5.2	3.8–10.8	0.003
Needle electromyography[†,‡]							
L2, 3, 4 muscles							
Fibrillation potentials	88	1.0	0.0–3.0	44	1.0	0.0–3.0	n.s.
Long MUPs	87	1.0	0.0–3.0	39	1.0	0.0–3.0	n.s.
L5, S1 muscles							
Fibrillation potentials	101	1.0	0.0–3.0	56	1.4	0.0–2.8	n.s.
Long MUPs	97	1.0	0.0–3.0	55	1.1	0.0–2.0	n.s.
LS paraspinal muscles							
Fibrillation potentials	64	0.7	0.0–3.0	35	1.5	0.0–3.0	0.004
Long MUPs	28	0.0	0.0–3.0	18	1.0	0.0–2.0	n.s.
Autonomic reflex screen (CASS score)							
Sudomotor index	12	2.0	0.0–3.0	14	2.5	1.0–3.0	n.s.
Adrenergic index	12	2.0	0.0–4.0	14	2.5	0.0–4.0	n.s.
Cardiovascular index	12	1.0	0.0–2.0	13	2.0	0.0–3.0	0.009
Total CASS	12	5.0	0.0–8.0	14	7.0	2.0–10.0	n.s.

LSRPN = lumbosacral radiculoplexus neuropathy; DLSRPN = diabetic lumbosacral radiculoplexus neuropathy; SNAP = sensory nerve action potential; CV = conduction velocity; DL = distal latency; CMAP = compound muscle action potential; MUP = motor unit potential; n.s. = not significant ($P > 0.05$); CASS = composite autonomic severity score. *Wilcoxon rank sum test; [†]patients were counted twice if both sides were sampled; [‡]values listed are median per level on one side and are recorded as 0 = normal, 0.5 = ±; 1 = +; 2 = ++; 3 = +++ and 4 = ++++. Absent responses are not included.

Quantitative autonomic testing

Twelve patients had quantitative autonomic tests. The composite autonomic severity score (CASS) was normal (score 0) in one, mildly abnormal (score 1–3) in one, moderately abnormal (score 4–6) in six and severely abnormal (score 7–10) in four patients. The median CASS score of 5.0 (Table 3) showed moderate autonomic dysfunction overall, whereas the median sudomotor, adrenergic and cardiovascular indices were all abnormal, demonstrating that the autonomic dysfunction was generalized and not just of lower extremity autonomic fibres. When compared with the DLSRPN patients, the only significant difference seen was a worse cardiovascular index for diabetic patients (Table 3). The total CASS scores were not significantly different and the LSRPN and DLSRPN groups both suffered from a generalized autonomic dysfunction.

Quantitative sensory testing

Twenty-four patients had quantitative sensory testing for vibration, cooling and heat-pain sensation thresholds performed at different anatomical sites of the lower extremity using CASE IV. Results are expressed as low (hyperaesthesia or hyperalgesia, ⩽5th percentile), normal (6th to 94th percentile) or high (hypoaesthesia or hypoalgesia, ⩾95th percentile) thresholds (Table 4). Hypoalgesia was found in 10 of 37 heat-pain tests, whereas hyperalgesia was found in five of 37 heat-pain tests. For vibration, 16 of 33 tests had raised thresholds and none had lowered thresholds, and for cooling, 18 of 40 tests had raised thresholds and one had a lowered threshold. These results show that there was unequivocal sensory abnormality at different anatomical sites of all sensory modalities. When compared with quantitative sensory testing of DLSRPN patients, there were no significant differences seen (Table 4).

Pathological alterations

The pathological abnormalities in distal cutaneous nerve biopsy have been presented in detail elsewhere (Dyck *et al*., 2000). These studies showed evidence of nerve ischaemia:

Table 4 *Number of non-diabetic (LSRPN) and diabetic (DLSRPN) quantitative sensation tests having defined levels of abnormality using CASE IV at the time of tertiary Mayo Clinic evaluation*

Evaluation	LSRPN (tests); no. of patients = 24				DLSRPN (tests); no. of patients = 17				$P^{\dagger}$
	Total tests	Hyperaesthetic (⩽5th*)	Normal (6th–94th*)	Hypoaesthetic (⩾95th*)	Total tests	Hyperaesthetic (⩽5th*)	Normal (6th–94th*)	Hypoaesthetic (⩾95th*)	
Vibration									
Foot	24	0	10	14	17	0	4	13	
Leg	3	0	3	0	8	0	3	5	
Thigh	6	0	4	2	2	0	1	1	
Total	33	0	17	16	27	0	8	19	n.s.
Cooling									
Foot	24	0	13	11	17	0	8	9	
Leg	9	1	3	5	3	0	0	3	
Thigh	7	0	5	2	2	0	1	1	
Total	40	1	21	18	22	0	9	13	n.s.
Heat-pain 5									
Foot	19	2	10	7	17	2	9	6	
Leg	11	2	6	3	6	1	2	3	
Thigh	7	1	6	0	3	0	2	1	
Total	37	5	22	10	26	3	13	10	n.s.

LSRPN = lumbosacral radiculoplexus neuropathy; DLSRPN = diabetic lumbosacral radiculoplexus neuropathy; CASE IV = computer-assisted sensory examination system IV; n.s. = not significant ($P > 0.05$). *Percentiles; †Fisher's exact test

(i) focal or multifocal fibre degeneration or loss in 31 of 47 nerves; (ii) focal degeneration or scarring of the perineurium in 33 of 47 nerves; (iii) epineurial neovascularization in 21 of 47 nerves; (iii) abortive regeneration of nerve fibres within or beyond the original perineurium forming microfasciculi (injury neuroma) in 16 of 47 nerves; and (v) changes in myelinated fibres typical of ischaemic injury (enlarged dark axons with light cores). We attributed these ischaemic changes to microvasculitis. Epineurial perivascular inflammatory collections were seen in all nerves, and there were features suggestive of microvasculitis with inflammatory cells separating microvessel wall elements in half (24 of 47) of the nerves. Fibrinoid degeneration (typical of large-vessel vasculitis) was seen rarely, but when smooth muscle actin immunohistochemistry was performed fragmentation and destruction of the smooth muscle components of the vessel wall by mononuclear cells, diagnostic of a microvasculitis, was common (Fig. 1). Analysis of graded conditions of teased fibres confirmed the impression that fibre loss and axonal degeneration were the main fibre abnormality in LSRPN. There was an abnormal frequency of empty nerve strands (median 25.5, range 1–89), axonal degeneration (median 17.2%, range 0–100%) and segmental demyelination (median 2.6%, range 0–13%) when compared with age-matched control nerves. When compared with the DLSRPN cohort, the pathological findings were essentially the same. The only difference was significantly more empty nerve strands in the DLSRPN cohort.

Recent telephone survey

Forty-two of 57 patients were contacted in the recent follow-up telephone survey. Of the 15 patients who were not contacted, eight were deceased and the rest were lost to follow-up.

The median follow-up time was 35.5 months (range 5.0–198.5 months). Only three patients reported that they had recovered completely; nine others reported they had almost recovered. The remaining 30 patients reported they were left with bothersome symptoms and impairments. Nonetheless, real improvement had occurred in all patients. At the time of the earlier Mayo Clinic evaluation of these 42 patients, 25 used a wheelchair, five used a walker, 11 used a cane or leg brace and one walked independently. At the time of the later telephone follow-up only five used a wheelchair, nine used a walker, 12 used a cane or leg brace and 16 walked independently.

Weakness remained the most disabling long-term problem in 26 patients and 38 patients continued to report some weakness. Although some still had severe proximal weakness necessitating a wheelchair, most of the ongoing weakness involved distal segments, foot drop being the most common problem. Pain was the most disabling long-term problem in 12 patients and 23 patients still had some degree of pain. Most of this pain also involved distal segments, allodynia being an ongoing problem for eight patients. Numbness was the most significant problem for one patient. The persistent symptoms were confined to distal segments (legs and feet) in 25 of the 39 non-recovered patients.

Seven of the 42 patients contacted had recurrent episodes of the lumbosacral plexopathy with pain and weakness on the same or opposite side at a later time. Two of the 42 patients later developed diabetes mellitus (one 5 years and the other 7 years after neuropathy evaluation at the Mayo Clinic).

At the telephone follow-up (median 25.9 months, range 4.5–46.5 months), the long-term prognosis of DLSRPN

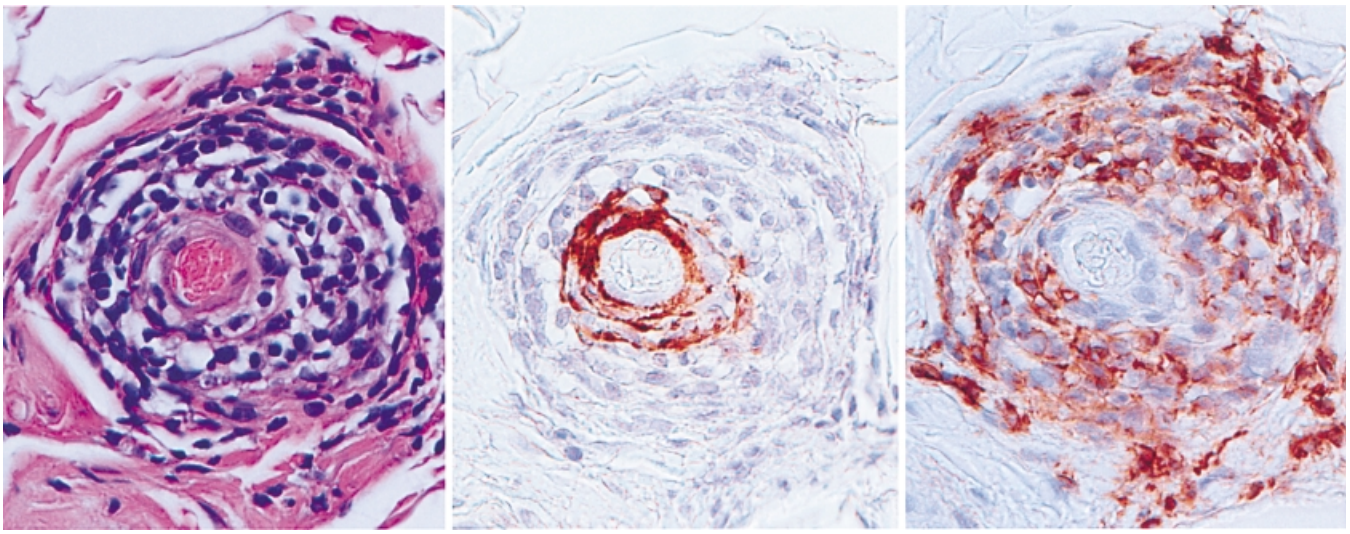

Fig. 1 Serial paraffin sections of an epineurial blood vessel showing microvasculitis in the sural nerve of a patient with non-diabetic lumbosacral radiculoplexus neuropathy. The section on the left is stained with haematoxylin and eosin, the section in the middle is reacted with anti-human smooth muscle actin (Dako, Carpenteria, Calif., USA), and the section on the right is reacted for leucocytes (CD45). The smooth muscle fibres of the tunica media (middle panel) are separated by mononuclear cells. Muscle fibres are fragmented and decreased in amount. The changes are those of focal microvasculitis. All three figures were photographed at magnification ~×500.

patients was similar to the prognosis of LSRPN patients. Only two of the 31 DLSRPN patients who were contacted reported they had returned to normal health. Most still had troublesome degrees of pain and weakness. Nevertheless, real improvement had occurred and many fewer patients relied on the use of a wheelchair or another aid in walking than had done so at evaluation (Table 2).

Therapeutic treatment trial

We treated 10 personally evaluated patients with corticosteroids, usually with infusions (1 g/week) of intravenous methylprednisolone for 8–16 weeks. All 10 patients improved, sometimes dramatically, during the treatment period, and eight of the 10 judged their improvement as marked. The results are presented in detail elsewhere (Dyck and Dyck, 2000).

Discussion

Already there is some information on the clinical features, natural history and outcome of non-diabetic LSRPN (Evans *et al*., 1981; Sander and Sharp, 1981). However, knowledge about the condition is limited because of the small numbers of patients, lack of prolonged follow-up, lack of sensory or autonomic test evaluations and the relatively recent recognition of LSRPN as a separate condition. Here we address questions about the characteristics of the syndrome, disease associations, natural history and outcome on the basis of a study of a larger cohort than previously studied and in comparison with a cohort of patients with the diabetic variety of the condition. The previous largest study was of 10 patients (Evans *et al*., 1981). Like Evans and colleagues, we chose to include only cases with electromyographic abnormalities in muscles innervated by at least two different peripheral nerves, arising from at least two different nerve roots. However, unlike them, we also chose to include cases with radicular involvement (paraspinal denervation) because we do not think there are fundamental pathophysiological differences between cases with and without paraspinal denervation. We chose to call this disorder non-diabetic lumbosacral radiculoplexus neuropathy because the anatomical distribution of clinical and electrophysiological deficits and the pathological evidence of lesions in distal cutaneous nerves implies that this disorder is a multifocal disease affecting roots, lumbar and lumbosacral plexus, and proximal to distal levels of nerve. Without the benefit of the detailed evaluation done here (nerve conduction and electromyography, quantitative sensation and autonomic testing, and biopsied nerve), some of these cases could have been identified as having a more restricted neuropathy, i.e. a mononeuropathy (such as a femoral neuropathy), or a motor polyradiculopathy.

Although weakness is the most disabling symptom in most patients, LSRPN is not just a motor neuropathy. From our detailed studies, we infer that motor, sensory (all classes) and autonomic (several classes) fibres are all typically affected. Elsewhere, we show evidence in the 47 of these patients who underwent nerve biopsy that ischaemic damage due to microvasculitis is the putative cause of the disorder (Dyck *et al*., 2000). Although a concomitant cervical radiculoplexus neuropathy or thoracic radiculoneuropathy also occurred near the time of onset of the LSRPN in a small percentage of cases, we think these associated disorders are too infrequent

to be identified as a characteristic component of the syndrome.

The features of the syndrome undoubtedly have implications for understanding its underlying pathophysiological mechanism. The middle to old age at onset is perhaps in keeping with a vasculitic process, as necrotizing vasculitis occurs more frequently in older age groups. The subacute onset of unilateral or asymmetrical involvement of the thigh or leg, then involvement of the segment not initially affected, and then involvement of the contralateral limb in almost all cases is not easily explained; however, a process like ischaemic injury from vasculitis, with progressively more vessels involved over time, might explain this course. We note that pathological vasculitic lesions are known to be much more widespread than is indicated by their expression in clinical deficits. Also, the pan-modality fibre loss found in histological sections and inferred from other studies, including the involvement of motor, sensory (all classes) and autonomic (several classes) fibres, would fit well with ischaemic injury. Conceivably, the small size and the anatomical location of the vessels involved (most prominently in the lumbosacral plexus) or their pathological derangement (occlusion, transudation of plasma constituents or other mechanisms) may cause a more generalized asymmetrical process rather than the discrete multiple mononeuropathy typical of large-arteriole necrotizing vasculitis. The microvasculitis of LSRPN may be a variety of non-systemic vasculitis restricted to the neuromuscular system. Pain in this disorder needs to be explained. Transection of nociception fibres and the secondary neurobiological events underlying sustained pain probably explain the severe morbidity from pain these patients have. This degree of pain is not characteristic of inflammatory–demyelinating neuropathies but is characteristic of necrotizing vasculitic lesions. The prolonged course of the disorder and the incomplete recovery observed is perhaps also in keeping with a smouldering vasculitic process, although axonal degeneration from ischaemic injury with only partial reinnervation is perhaps more likely. The elevated sedimentation rate, antinuclear antibody titre and presence of rheumatoid factor in a small number of cases and the substantial weight loss in most cases is in keeping with a vasculitic process. The elevated CSF protein concentration is an indication that the pathological process extends, in most cases, to the level of the roots and explains the observed paraspinal denervation.

What is the explanation for the concomitant thoracic radiculoneuropathy or cervical radiculoplexus neuropathy? These were common enough that a chance association can be dismissed. Also, these neuropathies occurred during the same period that the LSRPN developed. One possibility is that a low-grade microvasculitis affects roots, plexus and nerves at multiple cervical, thoracic and lumbosacral levels. Only if it reaches a certain severity does it become expressed. It is unclear why nerves at lumbosacral levels are particularly vulnerable. In favour of the idea of more generalized vasculitic involvement is the demonstrated pan-autonomic dysfunction, which is not readily explained by a process confined to lower extremity nerves (i.e. cardiovagal abnormalities cannot be attributed to lesions of lower limb nerves). Assuming that the basis for the cervical radiculoplexus neuropathies and the thoracic radiculopathies is a microvasculitis, it may be that upper limb and thoracic nerve microvessels are sometimes also affected but are less involved than are lumbosacral segments and only rarely does this involvement become clinically apparent.

In contrast to LSRPN, much more has been written about the diabetic variety of lumbosacral plexopathy (DLSRPN). The diabetic variety is known to begin focally with pain as the worst initial symptom, but over time the condition becomes more generalized and bilateral, weakness becoming the most problematic symptom (Barohn *et al*., 1991; Dyck *et al*., 1999). Although the weakness may be the most disabling symptom, quantitative sensory and autonomic testing has shown that all populations of sensory and autonomic fibres are involved (Dyck *et al*., 1999). The mechanisms underlying DLSRPN have been the subject of debate. Some have argued that metabolic factors and hyperglycaemia are the primary mechanisms (Chokroverty *et al*., 1977; Chokroverty, 1982), whereas others have argued that ischaemic damage predominates (Raff *et al*., 1968; Raff and Asbury, 1968; Barohn *et al*., 1991). Recently, some authors have written that immune mechanisms, including necrotizing vasculitis, may be involved (Said *et al*., 1994; Llewelyn *et al*., 1998; Kelkar *et al*., 2000). We found compelling evidence, from a study of a large, prospectively chosen DLSRPN cohort, that ischaemic damage due to microvasculitis is the basis of the disorder (Dyck *et al*., 1999).

We found a striking similarity in the symptoms, neurological findings, course, outcome, electrophysiological features and pathological alterations in our cohorts of LSRPN and DLSRPN. For example, in both disorders the thigh was the initial symptom site slightly more frequently than leg, but the symptoms spread to involve other segments and to become bilateral. For both disorders, pain was the predominant initial symptom; however, by the time of tertiary evaluation weakness was the greatest problem. The CSF protein was elevated and substantial weight loss occurred in both conditions. The kind and severity of neuropathic symptoms and neuropathic impairments were essentially alike, and the NIS of the groups were not significantly different. Also, the motor, sensory and autonomic classes of fibres were unequivocally involved in both conditions. Similarly, the pathological findings from distal cutaneous nerve biopsies were essentially the same in the LSRPN and the DLSRPN groups (Dyck *et al*., 2000). In both conditions, the primary pathological process appears to be ischaemic injury from microvasculitis.

This study may be used to shed light on the basis for weight loss and increased CSF protein in DLSRPN. Most early investigators attributed these alterations to poor metabolic control of diabetes mellitus. The fact that weight loss and an elevated CSF protein concentration also occur in

non-diabetic patients (LSRPN) suggests a cause other than poor glycaemic control. As weight loss occurred in both DLSRPN and LSRPN, microvasculitis may be a more likely explanation.

Some statistically significant differences were found between the two cohorts, but their magnitude was small. The nerve conduction and electromyographic abnormalities, the amount of weight loss, the elevated CSF protein, the cardiovascular index and the increased number of empty nerve strands were significantly more abnormal in the DLSRPN cohort. The most likely explanation for these slightly worse features in DLSRPN is the co-existence of mild diabetic polyneuropathy in some DLSRPN patients, although selection of more severe cases in the DLSRPN group remains a possibility.

We emphasize that both conditions cause prolonged and severe morbidity and disability and that recovery is usually incomplete. At tertiary evaluation, approximately one-half of patients in both cohorts were wheelchair-bound and most were still on continuous pain medication. However, unequivocal improvement occurred in almost all cases and few patients remained wheelchair-dependent by the time of our recent telephone interview. Complete recovery was rare. Most patients were left with distal sensory loss, weakness or pain. The probable reason a distal segment recovers less well is that reinnervation occurs later and less effectively in distal segments.

Although most patients have long-term deficits, LSRPN appears to be a monophasic illness. However, in a minority of cases (~17%) the neuropathy recurred in the same or opposite lower limb.

The question might be raised whether patients with LSRPN have mild diabetes mellitus that simply has not been detected. This seems unlikely as only two of 42 LSRPN patients had developed diabetes mellitus after years of follow-up. Consequently, chronic hyperglycaemia is probably not involved in the pathogenesis of LSRPN. Because of the evidence that LSRPN and DLSRPN are so similar, it also seems unlikely that chronic hyperglycaemia is a primary cause of DLSRPN.

Although chronic hyperglycaemia is probably not the direct cause of DLSRPN, it may be a risk factor. Further studies of the incidence of lumbosacral plexus neuropathies among diabetic and non-diabetic populations might help to clarify whether chronic hyperglycaemia is a risk factor for the diabetic variety. The only information available on the frequency of DLSRPN comes from the Rochester Diabetic Neuropathy Study, in which ~1% of community diabetic patients had DLSRPN (Dyck *et al*., 1993*a*), but the frequency has not yet been estimated for the non-diabetic control population.

In summary, we have found that diabetic and non-diabetic lumbosacral plexus neuropathies are similar in most respects and may in fact be the same condition, but it remains to be determined whether diabetes mellitus is a significant risk factor for DLSRPN. We believe that both conditions are due to a microvasculitis and that results of open therapeutic trials are sufficiently promising to provide a rationale for double-blind placebo-controlled trials of immune-modulating therapies. We think that LSRPN remains an under-recognized condition as it is quite common in our referral practice and has often gone unrecognized or has been treated inappropriately—10 patients of the present cohort were unnecessarily operated on for disc disease. Because of its severity and chronicity and because it is potentially treatable, the condition deserves more attention than it has received. We suggest that LSRPN should be set apart from chronic inflammatory demyelinating polyneuropathy on the one hand and from systemic necrotizing vasculitis causing a multiple mononeuropathy on the other hand, because of differences in natural history, underlying pathology and putative treatments.

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