Diabetic cervical radiculoplexus neuropathy: a distinct syndrome expanding the spectrum of diabetic radiculoplexus neuropathies

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Diabetic lumbosacral radiculoplexus neuropathy is a subacute painful, asymmetrical lower limb neuropathy due to ischaemic injury and microvasculitis. The occurrence of a cervical diabetic radiculoplexus neuropathy has been postulated. Our objective was to characterize the clinical features and pathological alterations of diabetic cervical radiculoplexus neuropathy, to see if they are similar to diabetic lumbosacral radiculoplexus neuropathy and due to ischaemic injury and microvasculitis. We identified patients with diabetic cervical radiculoplexus neuropathy by review of the Mayo Clinic database from 1996 to 2008. We systematically reviewed the clinical features, laboratory studies, neurophysiological findings, neuroimaging and pathological features and compared the findings with a previously published diabetic lumbosacral radiculoplexus neuropathy cohort. Eighty-five patients (56 males, 67 with Type 2 diabetes mellitus) were identified. The median age was 62 years (range 32–83). The main presenting symptom was pain (53/85). At evaluation, weakness was the most common symptom (84/85), followed by pain (69/85) and numbness (56/85). Neuropathic deficits were moderate (median motor neuropathy impairment score 10.0 points) and improved at follow-up. Upper, middle and lower brachial plexus segments were involved equally and pan-plexopathy was not unusual (25/85). Over half of patients (44/85) had at least one additional body region affected (30 contralateral cervical, 20 lumbosacral and 16 thoracic) as is found in diabetic lumbosacral radiculoplexus neuropathy. Recurrent disease occurred in 18/85. Neurophysiology showed axonal neuropathy (80/80) with paraspinal denervation (21/65), and abnormal autonomic (23/24) and sensory testing (10/13). Cerebrospinal fluid protein was elevated (median 70 mg/dl). Magnetic resonance imaging showed brachial plexus abnormality in all (38/38). Nerve biopsies (11 upper and 11 lower limbs) showed ischaemic injury (axonal degeneration, multifocal fibre loss 15/22, focal perineurial thickening 16/22, injury neuroma 5/22) and increased inflammation (epineural perivascular inflammation 22/22, haemosiderin deposition 6/22, vessel wall inflammation 14/22 and microvasculitis 5/22). We therefore conclude that (i) diabetic cervical radiculoplexus neuropathy is a predominantly monophasic, upper limb diabetic neuropathy with pain followed by weakness and involves motor, sensory and...
autonomic fibres; (ii) the neuropathy begins focally and often evolves into a multifocal or bilateral condition; (iii) the pathology of diabetic cervical radiculoplexus neuropathy demonstrates ischaemic injury often from microvasculitis; and (iv) diabetic cervical radiculoplexus neuropathy shares many of the clinical and pathological features of diabetic lumbosacral radiculoplexus neuropathy, providing evidence that these conditions are best categorized together within the spectrum of diabetic radiculoplexus neuropathies.

**Keywords:** diabetic cervical radiculoplexus neuropathy; brachial plexus neuropathy; peripheral neuropathy; neuralgic amyotrophy; microvasculitis

**Abbreviations:** DCRPN = diabetic cervical radiculoplexus neuropathy; DLRPN = diabetic lumbosacral radiculoplexus neuropathy

### Introduction

Diabetic polyneuropathy is classified into symmetrical length-dependent and focal or multifocal varieties (Sinnreich et al., 2005; Tesfaye et al., 2010). The latter are further separated into neuropathies related to compression/entrapment and radiculoplexus neuropathies. The radiculoplexus neuropathies affect roots, plexus and individual nerves and are reported to involve cervical, thoracic or lumbosacral segments. Diabetic lumbosacral radiculoplexus neuropathy (DLRPN) is the best studied subtype. This condition begins subacutely and focally with pain, weakness and weight loss, but over time spreads to be multifocal and bilateral, leading to moderate disability (Dyck et al., 1999; Dyck and Windebank, 2002; Dyck, 2005). It has been recognized as early as the end of the 19th century (Althaus, 1885; Auche, 1890; Bruns, 1890) and described by multiple different names, including diabetic amyotrophy, Bruns–Garland syndrome, diabetic mononeuritis multiplex, diabetic polyradiculopathy, proximal diabetic neuropathy, multifocal diabetic neuropathy and the term we prefer, DLRPN.

Diabetes mellitus is widely accepted to be associated with lumbosacral radiculoplexus neuropathy but only rarely has the existence of diabetic cervical radiculoplexus neuropathies (DCRPN) been postulated. The first description of diabetic patients who developed pain followed by weakness of the upper limbs was by Althaus (1885) and Auche (1890). Bastron and Thomas (1981) considered this possibility in their study of diabetic polyradiculopathy but found no cases with cervical involvement. Pascoe et al. (1997) noted upper extremity involvement in 12 out of 44 patients (27%) who had severe DLRPN (bilateral and progressive for at least 2 months) but some of these could have been compressive mononeuropathies. In our prospective study of 33 patients with DLRPN and distal cutaneous nerve biopsy, we noted evidence of upper limb involvement in one-third of cases (n = 11) but many of these were due to median neuropathy at the wrist or ulnar neuropathy at the elbow. However, three cases (9%) had a more widespread plexopathy in keeping with DCRPN (Dyck et al., 1999). Katz et al. (2001) also asked how common brachial plexus involvement was in patients with co-existing DLRPN and found that 9 of 60 (15%) of their patient cohort had upper limb nerve involvement that most commonly involved the hands. In a study of multifocal diabetic neuropathy, Said et al. (2003) describe 3 of 22 (14%) patients with upper limb involvement. In all of these studies, the patient population had co-existing DLRPN. No one has systematically studied upper limb (cervical) radiculoplexus neuropathies in diabetes mellitus in terms of the clinical features, laboratory studies, neurophysiological findings, neuroimaging and pathological features independent of whether they have DLRPN or not.

Episodes of brachial plexus neuropathies have been extensively studied and carry many names including idiopathic neuralgic amyotrophy, Parsonage–Turner syndrome and brachial plexus neuropathy (Parsonage and Turner, 1948; Tsairis et al., 1972; van Alfen, 2011). Patchy involvement in the upper part of the brachial plexus with suprascapular and long thoracic involvement is the most common presentation (van Alfen and van Engelen, 2006). The causes of these idiopathic forms along with rare inherited varieties are poorly understood but upper limb nerve biopsies from these cases have shown inflammatory infiltrates (Suarez et al., 1996; Klein et al., 2002).

Therefore we posed the following questions. Does DCRPN exist as a distinct disease entity? Are the clinical features including weight loss, neurophysiology and imaging features similar to DLRPN? Is the pathological cause of DCRPN ischaemic injury from microvasculitis (as in DLRPN)? And finally does DCRPN occur in association with DLRPN and diabetic thoracic radiculoneuropathies?

### Materials and methods

#### Patient selection

Patients seen at the Mayo Clinic Rochester between 1 January 1996 and 31 October 2008 with the diagnosis of cervical radiculoplexus neuropathy, brachial plexus neuropathy, brachial plexopathy, brachial plexitis, brachial neuritis, Parsonage–Turner syndrome, neuralgic amyotrophy, proximal diabetic neuropathy, anterior inter-osseus neuropathy, suprascapular neuropathy, long thoracic neuropathy or axillary neuropathy were identified through a retrospective review of their medical records. We decided not to include patients with isolated cervical radiculopathies because the differentiation between patients with an immune aetiology and those with structural degenerative disease would have been difficult. Five additional patients referred directly to one of the authors (P.J.B.D. or N.P.S.) outside of these dates were also screened. No patients in our previous DLRPN cohort were included. One patient was previously published (Staff et al., 2010). Patients with a history of diabetes mellitus or with elevated blood sugar meeting criteria for diabetes mellitus according to the American Diabetes Association (2008) were included (fasting plasma glucose > 126 mg/dl on two different days). Because of the recent
interest in neuropathies and impaired blood glucose, we also included patients meeting criteria for impaired fasting glucose (fasting plasma glucose 100–125 mg/dl on at least two different days) or impaired glucose tolerance (2-h values in oral glucose tolerance test of 140–199 mg/dl).

Three hundred and forty-five patients were initially identified and further reviewed for the following inclusion criteria: (i) history of upper extremity pain, paraesthesia or weakness; and (ii) neurological examination and/or electrophysiological abnormalities localizing the process to the cervical nerve roots, brachial plexus or upper extremity nerves. Patients with traumatic, infectious, compressive, iatrogenic, infiltrative, post-radiation or any other structural aetiology thought to be directly causative of the patient’s clinical symptoms were excluded. Patients with a diagnosis of chronic inflammatory demyelinating polyneuropathy, a known systemic vasculitis, connective tissue disease or amyloidosis were also excluded. Postoperative cases that could not be explained by intra-operative stretch or compressive injuries (there was separation in space or time of the neuropathy from the surgery) were included.

Clinical examination and follow-up

For each patient, motor and reflex neuropathy impairment scores, a linear scale of weakness and hyporeflexia (Dyck et al., 1980) were extracted for the upper and lower limbs at each encounter. A modified upper limb neuropathy impairment score was also calculated, which included shoulder elevation (trapezius), shoulder external rotation, elbow pronation, elbow supination, finger extension and flexor pollicis longus, in addition to the usual upper limb motor neuropathy impairment score. Although this modified version is not validated, it is a better representation of commonly affected muscles in DCRPN. Distribution, quality/description and severity of pain were also noted each time. Distribution and quality of sensory symptoms as well as objective evidence of sensory deficits on examination were recorded. The sensory component of the neuropathy impairment score was not included because in most cases, it does not assess the distribution of sensory loss (it only includes the end of the index finger).

Electrophysiological, imaging, quantitative sensory and autonomic testing

Nerve conduction studies and needle electromyography were performed using standard stimulation and recording techniques (Nicolet Viking IV) for the EMG laboratory at Mayo Clinic. Autonomic testing was performed using the Mayo Clinic Autonomic Reflex Screen which assesses cardiovascular, adrenergic and post-ganglionic sympathetic sudomotor function and provides a composite autonomic severity score (Low, 1993), and the Thermoregulatory Sweat Test (Fealey et al., 1989). Quantitative sensory testing using Computerized Assisted Sensory Examination (CASE IV) (Dyck et al., 1984) was performed on the affected upper extremity. MRI was reviewed by two of the authors (R.M. and K.K.A.). For the nerves that were involved radiographically, the extent of the lesion and the imaging characteristics on T₁, T₂ and post-gadolinium imaging were determined.

Histological methods

All nerve biopsies were re-graded by two authors (R.M. and P.J.B.D.) using the standard techniques and normal values of our laboratory (Dyck et al., 2005). For each specimen, all available slides were reviewed and consisted of teased fibre preparations; paraffin sections [haematoxylin and eosin, Luxol fast blue/periodic acid–Schiff, Mason’s trichrome, Congo Red, methyl violet and Turnbull’s blue (iron stain)]; epoxy sections (methylene blue); and immunohistochemistry (CD45, CD68 and Dako anti-human smooth muscle actin) for almost all biopsies. Two biopsies (one from the upper and one from the lower extremity) did not include teased fibre preparations. Two other biopsies carried out at outside institutions were not available for review and not included.

Comparison with diabetic lumbosacral radiculoplexus neuropathy and statistical analyses

Descriptive summaries of DCRPN data were presented as frequencies and percentages for categorical variables and median inter-quartile ranges (IQR) and ranges for continuous variables. We compared our results to a previously published DLRPN cohort (Dyck et al., 1999). Comparisons between the DCRPN and DLRPN groups were performed using Fisher’s exact test or Wilcoxon rank sum test, as appropriate. All of the tests were two-sided and P ≤ 0.05 were considered statistically significant. Statistical analysis was performed using SAS version 9.0 (SAS, Inc.).

Results

Demographic and blood glucose characteristics

Eighty-five patients with DCRPN, 56 male and 29 female, met inclusion criteria (Table 1). The median age was 62 years (range 32–83 years). Median duration of diabetes mellitus or impaired fasting glucose was 5.5 years (range 0–42 years). Of the 75 diabetic patients, 67 had Type 2 diabetes mellitus and six had Type 1. Two had transient diabetes mellitus (gestational or steroid-induced), which later resolved but the diabetic state coincided with the development of their neurological symptoms. Ten patients had impaired fasting glucose, two of whom later developed diabetes mellitus after their episodes of DCRPN. Twenty patients were not on any medication for diabetes mellitus (two had received pancreas transplants) and the remainder used oral hypoglycaemic agents (n = 30) or insulin therapy (n = 35). Complications from chronic hyperglycaemia (12 patients with retinopathy and 17 patients with nephropathy) occurred relatively infrequently. A minority of patients (n = 18) abused tobacco. No patients had a positive family history suggestive of inherited brachial plexopathy. Compared with the patients with DLRPN, there was no significant difference in demographic and blood glucose/diabetes mellitus characteristics, although the median body mass index was significantly higher in our cohort than in DLRPN.

Neuropathy characteristics

As in DLRPN, pain was the main initial symptom (n = 53) but weakness (n = 22) and sensory complaints (n = 15) were more common as the presenting symptom in patients with DCRPN than in patients...
with DLRPN (P = 0.02) (Table 2). The disease was generally acute and tended to begin focally. Three patients presented with neuropathies outside of a limb distribution: two patients presented with shortness of breath as the predominant symptom (phrenic neuropathy), while one patient, with a past history of three episodes of facial palsy, experienced diplopia from a third nerve palsy at onset before spread of symptoms to the cervical and lumbosacral levels within a few weeks. As in DLRPN, onset was predominantly unilateral (n = 69) with subsequent spread to the contralateral side in many (n = 30), although less frequently than in our DLRPN cohort (P < 0.0001). Patients with DCRPN presented more often with an acute onset (within 24 h) than did those with DLRPN (P < 0.0001); the maximum deficit was reached in 1 week in over half of the patients with DCRPN.

At time of evaluation, weakness had become the major problem (as in DLRPN) and was present in 84 patients whereas 69 had pain and 56 had sensory deficits. On initial examination, the median motor neuropathy impairment score (10.0), the reflex neuropathy impairment score (5.0) and the modified upper limb neuropathy impairment score (12.0) indicated moderate focal motor deficits. Based on the history and clinical examination (primarily weakness), each one of the three trunks of the brachial plexus was involved to a similar extent and all three were involved in 25 patients. Thirty-seven patients were noted to have atrophy and four had fasciculations. Of the 85 patients, 46 required opioid analgesia for pain control. Different pain descriptors were used, including hurting/aching/pressure (n = 23), burning (n = 14) and shooting/lancinating (n = 19). Sixteen patients experienced allodynia and 16 patients reported no pain. Sensory symptoms consisted of both positive symptoms (tingling or paraesthesias) and negative symptoms (numbness and loss of or dead feeling) in approximately equal proportions (41 versus 35 patients, respectively). Thirteen patients complained of autonomic symptoms, mainly orthostatic dizziness and changes in sweating. Weight loss over 4.54 kg was frequent and found in 30 of 85 patients but was less common than in our DLRPN cohort (P < 0.0001).

Involvement of other regions of the Peripheral Nervous System (PNS) was common in DCRPN (as it was in DLRPN). It occurred in over half of patients with DCRPN but was somewhat less common than in the DLRPN cohort (P < 0.0001). Thirty patients experienced concomitant contralateral cervical disease, while 16 had thoracic radiculopathy, 20 DLRPN and eight other peripheral involvement [five patients with phrenic neuropathy (one of them with dysphagia), one with Horner’s syndrome, one with facial and bilateral vocal cord paresis and one with third nerve palsy]. A recurrent episode, defined by new or recurrent symptoms after initial symptoms had been stable or improved for at least 1 year, occurred in 18 patients (21%).

### Laboratory testing

As in DLRPN, patients frequently displayed non-specific inflammatory, rheumatological or serological markers of a more widespread
immune response—33/69 overall with 23 having positive ESR/CRP and 10 patients having other markers of autoimmunity (anti-nuclear antibody, extractable nuclear antigen, rheumatoid factor, anti-neutrophil cytoplasmic antibodies or angiotensin converting enzyme) without abnormal C-reactive protein and erythrocyte sedimentation rate (Table 3). Seven patients also showed an increase in liver enzymes, three of whom had aspartate aminotransferase/alanine aminotransferase values >1000 mg/dl. Three other patients had very high creatine kinase enzyme levels, one of them requiring a muscle biopsy (which showed only non-diagnostic changes). Fourteen patients had anti-ganglioside antibodies measured, which were all negative and several had a negative paraneoplastic antibody panel. One patient had an IgG kappa monoclonal gammopathy of unclear significance and one other displayed positive anti-striational antibodies titre in the recovery phase that were absent in the more acute phase. None of the 15 patients tested for hereditary neuropathy with liability to pressure palsies harboured a mutation in the PMP22 gene.

CSF analysis was performed on 31 patients and usually showed elevated protein and glucose with normal cell count. Median cell count (one cell per high power field, range 0–28), glucose (92 mg/dl, range 50–207 mg/dl) and protein (70 mg/dl, range 10–207 mg/dl) values were similar to those seen in DLRPN. Of the 29 patients, four had an increased IgG synthesis rate but none had increased oligoclonal bands.

### Neurophysiology

Nerve conduction studies and needle electromyography were performed in 80/85 patients and were consistent with a...
predominantly axonal process (Table 3). In several cases, the EMG confirmed a peripheral localization which was only partially suspected. Compound muscle action potential and sensory nerve action potentials were generally reduced, but less frequently than in the DLRPN cohort (**P** = 0.0005 and **P** = 0.01, respectively). This finding can most probably be explained partially by the pattern of involvement as nerve conduction studies do not assess upper plexus lesions well. In addition, cases of isolated phrenic, anterior inter-osseus, long thoracic, suprascapular or axillary neuropathies often fail to reveal any abnormalities on standard nerve conduction studies alone. Conduction velocities and distal latencies were generally only minimally abnormal. Demyelinating features were rarely noted (10/80 patients) and consisted most commonly of conduction blocks (6/10 patients), two of which could be explained by superimposed compressive neuropathies. Needle examination revealed frequent fibrillation potentials in almost all patients (75/80) with decreased recruitment of large amplitude, long duration polyphasic motor unit potentials.

### Table 3 Investigations in DCRPN and DLRPN

<table>
<thead>
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<th>DLSRPN</th>
<th><strong>P</strong></th>
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<td>(0–1)</td>
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<td>Median total CASS score (IQR) [range]</td>
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<td>Muscle atrophy or increased T2 signal</td>
<td>21</td>
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**ESR** = erythrocyte sedimentation rate; **CRP** = C-reactive protein; **CMAP** = compound muscle action potential; **SNAP** = sensory nerve action potential; **ANA** = antinuclear antibodies; **ACE** = angiotensin converting enzyme. **RF** = rheumatoid factor antibodies; **ANCA**; anti-neutrophilic cytoplasmic antibodies; **ENA** = anti-extractable nuclear antigen antibodies.

**VDT** = vibration detection threshold; **CDT** = cooling detection threshold; **HP5a** = Heat–Pain 5 threshold: abnormality is <5th or >95th percentile.

*Wilcoxon rank sum test for continuous data and Fisher’s exact test for dichotomous data. Significance **P** ≤ 0.05.
Cervical paraspinal abnormalities occurred relatively frequently [about one-third of patients (21/65)] but were less common than lumbosacral paraspinal abnormalities in DLRPN ($P < 0.0001$). Electrophysiological abnormalities were often more widespread than clinical deficits but the pattern of involvement was similar. All three levels of the brachial plexus were involved to a similar extent on electrophysiological testing. The upper plexus was involved in 45/80 patients, the middle plexus in 39/80 and the lower plexus in 46/80. Pan-plexus electrophysiological involvement (all three levels simultaneously) occurred in 24/80 (30%). Of the 80 patients, 37 had electrophysiological involvement outside the brachial plexus per se, either affecting isolated peripheral nerves alone ($n = 10$, two phrenic, three long thoracic, one axillary, two suprascapular and two anterior inter-osseus nerves), or specific peripheral nerves focally superimposed upon a more diffuse involvement ($n = 11$) or other nerve regions (i.e. contralateral cervical, thoracic roots or lumbosacral plexus).

Quantitative sensory testing for vibration, cooling and heat-pain detection thresholds was performed on 13 patients on their affected upper limb and confirmed the presence of sensory deficits in 10 of the patients. Large (vibration) and small (cooling) myelinated fibres and unmyelinated fibres (heat-pain) were all commonly affected. These results show that sensory nerves are involved in DCRPN and are similar to the sensory abnormalities of DLRPN.

Although autonomic complaints were uncommon, when tested formally with an autonomic reflex screen, 23 of 24 patients showed autonomic abnormalities. All three modalities (post-ganglionic sudomotor, cardiovagal and cardioadrenergic) were affected. The median composite autonomic severity score was 3.5 (range 1–9) which showed a moderate autonomic neuropathy overall. The findings are similar to those found in the DLRPN cohorts but are less severe ($P = 0.007$). Similarly, the Thermoregulatory Sweat Test showed changes in 11 of 13 tested patients, five of which were in a segmental upper limb pattern.

### Imaging

Thirty-eight patients had neuroimaging of the affected brachial plexus. All had 1.5 ($n = 30$) or 3.0 ($n = 7$) T MRI except for one patient with a pacemaker who had a high resolution CT scan with 3D reconstruction (Table 3). Among those 38, seven had bilateral studies, two had extension of the MRI into the forearm and one patient had a follow-up study 6 months after onset, for a total of 47 MRI studies and one CT scan. All studies were reviewed by the same peripheral nerve radiologist (K.K.M.). Of the 48 examinations, 47 were abnormal and 38 of 38 patients examined had abnormal peripheral nerve imaging. The only normal study was the MRI of a patient who complained of bilateral shoulder pain and had imaging of both brachial plexuses, but where only unilateral findings were noted on neurological examination and on imaging. The most frequent abnormality was increased $T_2$ signal in the nerves (45/47), varying from very mild–to-moderate in severity. In all affected cases, the brachial plexus trunks and cords were abnormal, even when the lesion localized to a single nerve on neurological examination or EMG (i.e. isolated long thoracic neuropathy or axillary neuropathy). Nerve roots or individual nerves were also commonly affected but less frequently (31/44 and 33/46, respectively) than the brachial plexus itself. Diffuse nerve hypertrophy (32/48) or contrast enhancement (3/16) were also noted, as were changes in muscle signal (21/46). The muscle changes showed oedema (increased $T_2$ signal) in a subacute setting, or fatty atrophy (increased $T_1$ signal) in a chronic setting, and thus were helpful in confirming the time course. Variable degrees of axillary, mediastinal or suprascapular lymph node abnormalities (enlargement, increased number) were seen in a minority of patients (6/46). In general, except for the changes in muscles that could be localized with precision, the abnormalities noted in the nerves were diffuse; only two studies showed focal nerve enlargement and four localized increased $T_2$ signal to specific cords or nerves.

### Motor deficits and follow-up

Of the 85 patients, 42 were seen at least once in follow-up (at a median of 68 days after first evaluation; range 8–3021 days), and 22 were seen at least twice in follow-up (last follow-up at a median of 335 days after first evaluation; range 48–2213 days) (Table 4). Neuropathy impairment scores were available for 40 of the 42 patients. Although the median motor neuropathy impairment score minimally worsened from first evaluation to first follow-up for these 40 patients, overall most patients demonstrated improvement at first follow-up, with 24/40 improving (median improvement of nine points), 6/40 remaining stable and 10/40 worsening on the neuropathy impairment score (median worsening of two points only). All other neuropathy impairment score subscores improved or remained stable at each follow-up. In addition to these objective outcomes, 32/42 patients felt subjectively improved at first follow-up.

### Pathological findings

Biopsies were available on 22 patients with DCRPN, 11 of an upper extremity nerve and 11 of a lower extremity nerve (Table 5). All patients with lower extremity biopsies had concomitant DLRPN. In the upper limb, biopsies were taken from the superficial radial nerve ($n = 8$), the lateral antebrachial cutaneous nerve ($n = 1$), the ulnar motor branch to the flexor carpi ulnaris ($n = 1$) and the proximal posterior cord of the brachial plexus ($n = 1$). In the lower limb, biopsies were taken from the sural nerve ($n = 9$), the superficial peroneal nerve ($n = 1$) and the intermediate femoral cutaneous nerve ($n = 1$).

Teased fibre preparations confirmed a fulminant neuropathic process in all the nerve biopsies from patients with DCRPN (Table 5 and Fig. 3A). A median of 22% axonal degeneration (range 0–97%) was noted. A low rate of segmental demyelination (2%) was observed, which was often grouped on the same nerve fibre, suggesting demyelination secondary to axonal atrophy (Dyck, 2005). An increased number of empty strands were also seen. In paraffin and epoxy preparations, evidence of ischaemic injury was present with multifocal fibre loss (15/22 biopsies; Fig. 3B and D), focal perineurial thickening (16/22) and perineurial degeneration (9/22), microvessel neovascularization (14/22) and injury neuroma (5/22). Perivascular inflammation was noted in all
cases, consisting of individual cells (n = 1) or small (n = 10), moderate (n = 8) or large (n = 3) collections of inflammatory cells (Figs 2 and 4). The collections were mainly surrounding and involving small epineurial vessels. Inflammation involving the vessel wall was noted in 14/22 biopsies (Figs 2C, I and 4E) (raising the possibility of microvasculitis) and five of them were diagnostic of microvasculitis. Smooth muscle actin immunostaining highlighted the focal vessel wall destruction (Fig. 2B) and infiltration of wall leaflets by inflammatory cells (Fig. 2H). Large-vessel vasculitis was seen in only one case which had concomitant microvasculitis (see illustrative case later and Fig. 4). All inflammatory infiltrates reacted to common leukocyte antigen (anti-CD45) on immunohistochemistry (Figs 2C, I, 4C and E). Haemosiderin deposition, usually in the perineurium, a sign of previous bleeding, was noted in 6/22 of the biopsies (Fig. 3C).

When comparing the upper limb to the lower limb biopsies in patients with DCRPN, notable differences could be seen. On teased nerve fibres, the upper limb biopsies contained more axonal degeneration than the lower limb biopsies and fewer empty nerve strands. All cases diagnostic of microvasculitis were from upper limb nerves. These results suggest that the more active inflammatory neuropathic process in patients with DCRPN occurred in upper limb nerves.

When comparing the 11 upper limb DCRPN nerves to the previously published 33 lower limb DLRPN nerves, the pathological abnormalities were very similar and suggested ischaemic injury and microvasculitis. Consequently, rates of ischaemic injury (multifocal fibre loss, perineurial thickening, neovascularization and injury neuroma) and of inflammatory lesions (perivascular inflammatory collections, inflammation involving vessel walls and haemosiderin-laden macrophages) were similar between DCRPN and DLRPN biopsies. In contrast, perineurial degeneration and changes diagnostic of microvasculitis were seen significantly more frequently in DCRPN nerves than in nerves of patients with DLRPN (P = 0.05 and P = 0.007, respectively) (Table 5).

Table 4 Follow-up of motor neuropathy impairment scores in DCRPN and DLRPN

<table>
<thead>
<tr>
<th>Site</th>
<th>At first evaluation</th>
<th>At first follow-up</th>
<th>At last follow-up</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCRPN n = 40</td>
<td>10 (4–14) [0–45]</td>
<td>11.8 (2.5–23) [0–45]</td>
<td>15 (7–23) [0–30.25]</td>
<td>0.25</td>
</tr>
<tr>
<td>Modified upper limbs</td>
<td>12.5 (8–18.5) [0–24]</td>
<td>15.5 (10.5–18.5) [0–37.5]</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Upper limbs</td>
<td>6 (1.8–12.8) [0–36]</td>
<td>10 (2–18.5) [0–64]</td>
<td>15 (4.5–22.3) [0–27.5]</td>
<td>0.51</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>0 (0–3) [0–10.5]</td>
<td>0 (0–3) [0–30.5]</td>
<td>15 (7–23) [0–30.25]</td>
<td>0.05</td>
</tr>
<tr>
<td>Total</td>
<td>10 (4–14) [0–45]</td>
<td>11.8 (2.5–23) [0–45]</td>
<td>15 (7–23) [0–30.25]</td>
<td>0.25</td>
</tr>
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</table>

Table 4 Follow-up of motor neuropathy impairment scores in DCRPN and DLRPN

Treatment

Thirty-two of our patients received some form of immunotherapy, which was variable but included oral or intravenous steroids, intravenous immunoglobulin or plasmapheresis. Two of our patients with DCRPN were part of a randomized controlled trial of their co-existing DLRPN and received infusions of 1 g of intravenous methylprednisolone given intermittently over 12 weeks (two other patients with DCRPN were also part of that trial but received placebo). Sixteen patients felt some improvement with the immunotherapy, mainly in the pain; six felt the treatment did not help and the outcome was unclear in eight patients. Two patients had to have their treatment stopped because of side-effects (visual blurring and hyperglycaemia). Treated patients were usually much more severely affected than untreated patients (motor neuropathy impairment score of 18.5 versus 8, P = 0.0005) but improved to a greater degree, so that by last follow-up their deficit was the same as untreated patients (motor neuropathy impairment score of 7.88 versus 7.75, P = 0.57).
Subgroup analysis

We looked at the subgroup of patients with impaired fasting glucose or transient diabetes mellitus as well as at the subgroup of patients with DCRPN, without associated DLRPN, diabetic thoracic radiculoneuropathies or cranial neuropathy (referred to here as ‘isolated DCRPN’).

The 12 patients with impaired fasting glucose or transient diabetes mellitus presented with similar symptoms to the patients with diabetes mellitus Type 2 but had somewhat less neurological impairment (motor neuropathy impairment score of 4.0) and less frequent weight loss (8.3%). However, they had a comparable frequency of involvement of other body nerve regions than the initially affected upper limb (41%).

Of the 57 patients with isolated DCRPN (no cranial, thoracic or lumbosacral involvement), six had diabetes mellitus Type 1, 41 had diabetes mellitus Type 2 and 10 had impaired fasting glucose or transient diabetes mellitus. Median glycated haemoglobin was 8.5% compared with 7.5% for our whole cohort. Presenting symptoms of the neuropathy and the pain characteristics were similar. At first evaluation, their median motor neuropathy impairment score was lower (7.5 versus 10.0), whereas upper limb neuropathy impairment score (7.5 versus 9.0) and modified upper limb neuropathy impairment score (10.5 versus 12.0) were similar. Overall, the isolated DCRPN group did not seem meaningfully different from the whole DCRPN group.

Illustrative case

A 62-year-old female with recent diagnosis of Type 2 diabetes mellitus and initiation of oral hypoglycaemic agents underwent right total knee arthroplasty. Ten days after her surgery, she developed pain and paraesthesias in her shoulders and arms, followed a few weeks later by severe right-hand numbness with allodynia and progressive wrist drop, which evolved over the ensuing month to severe weakness throughout the right upper extremity. Left-hand weakness and paraesthesias, as well as mild bilateral lower extremity numbness were also noted along with a 9.1 Kg weight loss.

At the time of our evaluation (3 months after surgery), neurological examination demonstrated moderate-to-severe weakness in the right upper extremity except for trace weakness in deltoid and...
external rotators, moderate weakness of the left hand (predominantly in median-innervated muscles) and mild weakness in the right quadriceps. There was loss of sensation (all modalities) in bilateral lower trunk and right radial nerve distributions with asymmetrically reduced reflexes in the upper extremities.

Inflammatory and vasculitic markers, paraneoplastic panel and hepatitis screen were negative. CSF analysis was normal. EMG confirmed an active neurogenic process in bilateral brachial plexuses, including cervical paraspinal denervation. MRI of the right brachial plexus showed mild-to-moderate diffuse hyperintensity of the whole brachial plexus, particularly infra-clavicularly and into the terminal branches of the upper arm, without gadolinium enhancement.

A right superficial radial nerve biopsy revealed evidence of both nerve large vessel vasculitis and of microvasculitis (Fig. 4). Teased fibre preparation showed increased axonal degeneration (98%) and empty nerve strands. There was a severely decreased density of myelinated fibres with actively degenerating profiles. There was inflammation involving a large nerve arteriole with evidence of fibrinoid necrosis. A large inflammatory collection disrupted the walls of a small epineurial vessel, which was diagnostic of microvasculitis.

The diagnosis of a post-surgical diabetic cervical radiculoplexus neuropathy secondary to vasculitis was made. The patient was treated with weekly intravenous methylprednisolone for 12 weeks and reported marked improvement of pain with minimal improvement in weakness immediately after treatment. Eight months later, her weakness was meaningfully better with an improved neuropathy impairment score from 35 to 23 points and reinnervation on EMG.

**Discussion**

We reviewed the clinical, laboratory, neurophysiological, imaging and pathological features of 85 patients presenting with an upper extremity syndrome of pain, weakness or sensory symptoms of peripheral origin in the context of diabetes mellitus, that we termed DCRPN. We have shown that DCRPN is an acute upper limb neuropathy presenting with pain, followed by prominent weakness, which begins focally but often spreads to involve the contralateral limb, thoracic and lumbosacral segments. It is usually monophasic with improvement and has at least a 21% recurrence rate. Our evaluation suggests an axonal sensorimotor inflammatory upper limb neuropathy with nerve pathology demonstrating ischaemic injury often due to nerve microvasculitis.

We noted many similarities between our patients with an upper limb painful diabetic neuropathy and our previously published cohort of diabetic patients with subacute painful lower limb neuropathy (DLRPN). No significant differences were seen in demographic variables (middle age to older onset with slight male predominance) and characteristics of their diabetes (Type 2 diabetes mellitus predominance with good glycaemic control, short duration of diabetes mellitus, on both oral hypoglycaemic and insulin with a low rate of microvascular complications). DCRPN and DLRPN shared a similar clinical presentation of acute to subacute focal onset of pain, subsequent development of disabling...
weakness and spread to unaffected segments and other body regions. The CSF protein was elevated in both, suggesting that the pathological process extended to the root level. Paraspinal muscle involvement on EMG was further evidence of root involvement in both DCRPN and DLRPN. As in DLRPN, the nerve conduction studies/EMG and quantitative sensory and autonomic testing confirmed patchy but widespread involvement of motor, sensory and autonomic nerves of all fibre classes (large and small myelinated

**Figure 2** Evidence for focal nature of microvasculitis in DCRPN. Serial paraffin sections (A–F) showing microvasculitis (*top row*) with vessel wall destruction and muscle fragmentation (B) but no inflammation on a distal section of the same epineurial blood vessel (*middle row*). Another epineurial blood vessel from a different patient showing also microvasculitis (G–I). Note the separation and destruction of the vessel wall by inflammation in both vessels. (A, D and G) Haematoxylin and eosin; (B, E and H) smooth muscle actin immunostaining; (C, F and I) CD-45 (leukocyte common antigen) immunostaining.
and unmyelinated) resulting from a non-length-dependent neuropathic axonal injury. Mild differences were found which may be due to the DCRPN cohort being more mildly affected than DLRPN. Our inclusion criteria may have partially explained this difference as in our DLRPN cohort we insisted that two nerves from two different nerve root distributions were involved whereas in DCRPN we allowed upper limb mononeuropathies. We believed that it was best to include diabetic mononeuropathies because non-diabetic neuralgic amyotrophy is recognized to sometimes present as mononeuropathies. Both syndromes started unilaterally and both frequently progressed to bilateral disease. Overall, patients with DCRPN eventually developed less contralateral involvement than patients with DLRPN did, but they commonly had widespread involvement of other regions. The neuropathy in DCRPN presented more acutely and, while still causing significant morbidity, also improved more quickly than in DLRPN (on first follow-up, the neuropathy impairment score generally improved in DCRPN but not in DLRPN; Said et al., 1994; Llewelyn et al., 1998; Dyck et al., 1999, 2000; Kelkar et al., 2000). This finding of similar pathology between the upper and lower limb forms supports a common disease mechanism between DLRPN and DCRPN.

In addition to these many similarities, the frequent co-occurrence of thoracic (DTRPN) and lumbosacral (DLRPN) involvement in our patients with DCRPN, as well as the frequent co-occurrence of DCRPN in patients presenting as DLRPN (Dyck et al., 1999; Katz et al., 2001) strongly argue in favour of a common underlying mechanism and for classifying these disorders together as diabetic radiculoplexus neuropathies. Analysis of our isolated DCRPN cohort showed that they were similar in terms of their glucose characteristics and neuropathy presentation and deficits to the patients with DCRPN with more widespread involvement (co-existing cranial, thoracic and lumbosacral disease), confirming that DCRPN should be viewed as part of the diabetic radiculoplexus neuropathy spectrum. Furthermore, of the 20 patients with both DCRPN and DLRPN, 15 of them predominantly involved the upper limb providing evidence that DCRPN should
Figure 4. Evidence of concomitant necrotizing vasculitis and microvasculitis involving medium- and small-vessels in DCRPN from the illustrative case (see text). Longitudinal section showing fibrinoid necrosis (arrows A and B) and necrotizing vasculitis of a medium vessel (A, B and C) and microvasculitis (lower right vessel in A, D and E) in the same nerve field (illustrative case). (A and D) Haematoxylin and eosin; (B) Masson trichrome; (C and E) CD-45 (leukocyte common antigen) immunostaining.
Patients were seen by a Mayo clinic neurologist \((n = 84)\) or physiatrist \((n = 1)\), and 53/85 were seen by a neuromuscular specialist. Another limitation is that Mayo clinic is a quaternary centre, which makes a referral bias towards more complicated cases likely. Nonetheless, 14/85 patients were from Olmsted County (the local community), suggesting that this disorder is not very rare.

Some authors have suggested that brachial plexopathies in diabetic patients is merely a chance occurrence (Wilbourn, 1999). While we agree that this may be true in some cases, and that to answer this question definitively, large epidemiological studies would need to be done, we strongly believe that the frequent co-occurrence of different forms of diabetic radiculoplexus neuropathies together with associated weight loss is compelling evidence for a common pathological mechanism and an association with diabetes mellitus. Therefore, we conclude that DCRPN is likely to be a distinct disease entity that is part of the spectrum of diabetic radiculoplexus neuropathies.

We speculate that diabetes mellitus is one of perhaps several risk factors that predisposes patients to altered immunity leading to an auto-immune attack on the nerve small blood vessels. Other possible risk factors include starting treatment for hyperglycaemia, immunization, infectious illness or having a surgical procedure performed. It is noteworthy that 20 of the 85 patients were diagnosed with diabetes mellitus within a year of their developing DCRPN and most of these had concomitant initiation of insulin or oral hypoglycaemic treatment, which could have acted as a trigger to this immune deregulation (Gibbons and Freeman, 2010). The various positive inflammatory and rheumatological markers are also consistent with an alteration in the immune system. The majority of patients \((49/85)\) reported a potential immune trigger \((10 \text{ post-viral/systemic illness, 3 post-vaccination, 26 post-surgical procedures and 9 after minor trauma or heavy exercise})\) to the DCRPN episode. The frequent preceding surgeries before the development of DCRPN suggest that a surgical procedure may constitute an important risk factor/trigger in addition to diabetes mellitus itself in leading to an inflammatory plexus neuropathy. This position is supported by the observation that one-third of patients with post-surgical inflammatory neuropathy previously described were also diabetic (Staff \textit{et al.}, 2010). The possible improvement with immunotherapy would also suggest a role of altered immunity and implies that early treatment may be beneficial. While further randomized controlled trials would be needed, the pathological alterations of microvasculitis may favour using high-dose steroids at the onset of pain and weakness, over other immune treatments \(\text{such as intravenous immunoglobulin)}\) (Gorson, 2006).

Previous studies (Parsonage and Turner, 1948; Tsairis \textit{et al.}, 1972; England and Summer, 1987) have examined an upper limb immune-mediated plexus neuropathy in non-diabetic patients, with the largest one \((\text{van Alfen and van Engelen, 2006})\) investigating 246 Dutch patients with detailed description of their clinical presentation and evolution. Our patients are generally distinct from patients with idiopathic and hereditary neuralgic amyotrophy by their autonomic features, more frequent weight loss, common bilateral upper limb and lower trunk involvements, and co-occurring thoracic and lumbosacral radiculoplexus neuropathies. Specifically, compared to the van Alfen and van Engelen, 2006 series, our patients had more involvement outside of the brachial plexus \(38\% \text{ versus } 17\%\) and had more involvement of the lower trunk of the brachial plexus \(58\% \text{ versus } 4\%\). More patients experienced weight loss in our group \(35\% \text{ versus } 20\%\) and almost all had evidence of autonomic dysfunction. The degree of autonomic involvement was more than would be expected from the degree of glucose dysregulation and is typical of other diabetic radiculoplexus neuropathies (Dyck \textit{et al.}, 1999). In the van Alfen series, diabetes mellitus was not felt to be more represented in those with idiopathic or inherited brachial plexus neuropathies compared to the general population, but of their six patients with diabetes mellitus, four had recurrent attacks.

As in DLRPN, the findings on clinical examination were more focal than those on neurophysiology and nerve imaging, which tended to be much more widespread. The imaging findings are particularly important. Few MRI descriptions of inflammatory neuropathies exist as most MRI series of non-traumatic brachial plexopathies \((\text{Wittenberg and Adkins, 2000; Mullins \textit{et al.}, 2007})\) have a limited number of inflammatory cases. When reviewed by a peripheral nerve radiologist, abnormalities were noted in all patients with DCRPN in our study \((38/38)\). While MRI has been traditionally performed to rule out neoplastic or other compressive lesions, these findings reinforce its role as a potential diagnostic confirmatory test in inflammatory disease. We have found increased \(T_2\) signal to be the most sensitive abnormality, being present in 45 of 47 MRIs. Although less frequent, changes in muscle signal were also important as they helped discriminate between an acute or subacute denervating process \((\text{increased} \ T_2 \text{ signal secondary to oedema})\) versus a more chronic process \((\text{increased} \ T_1 \text{ signal secondary to fatty atrophy})\).

Herein, we describe diabetic patients with acute to subacute painful and paralytic upper limb neuropathies in terms of clinical, laboratory and pathological features and conclude that they have DCRPN. We have shown that our DCRPN cohort shares many of the same features as a DLRPN cohort and that both are due to ischaemic injury, frequently from microvasculitis. We have found that the upper limb, lower limb and truncal syndromes often occur together. Therefore, we propose that DCRPN, diabetic thoracic radiculoneuropathies and DLRPN are part of a more diffuse spectrum disorder of diabetic radiculoplexus neuropathies. Their common co-occurrence along with their association with diabetes mellitus would suggest that diabetes is a strong risk factor in their pathogenesis. Identification of DCRPN expands the PNS complications of diabetes mellitus.

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