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Painless Diabetic Motor Neuropathy: A Variant of DLRPN?

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Keywords

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Introduction

Many varieties of neuropathy occur with diabetes mellitus (DM) from different underlying mechanisms, the most common being a symmetrical, length-dependent, sensorimotor polyneuropathy (DSPN). A less frequent diabetic neuropathy which can cause severe morbidity, diabetic lumbosacral radiculoplexus neuropathy (DLRPN), is a painful, rapidly evolving, asymmetric, lower-limb, paralytic neuropathy associated with weight loss¹. The name DLRPN emphasizes the association of this syndrome with DM and its sites of involvement (roots, plexus and nerves).

The natural history and underlying mechanisms of DLRPN have been debated with various names reflecting different views that include: diabetic myelopathy², diabetic amyotrophy³, Bruns-Garland syndrome⁴, diabetic mononeuritis multiplex⁵, proximal diabetic neuropathy⁶, diabetic lumbosacral plexopathy⁷, diabetic polyradiculopathy⁸ and multifocal diabetic neuropathy⁹. Regardless, in most discussions of DLRPN, pain is usually present.

In early clinical descriptions of DLRPN, Chokroverty and colleagues state that this syndrome can be symmetrical, slowly progressive and occasional painless¹⁰. They and others suggest that the pathological basis of DLRPN is probably metabolic derangement^{10–13}. Others note that the disease is usually asymmetrical and painful, presenting as a “mononeuritis multiplex” due to ischemic injury⁵. Asbury incorporates both concepts proposing that the acute and asymmetrical cases are due to ischemic injury whereas the slower, more symmetrical cases result from metabolic derangement and that “proximal

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(motor) diabetic neuropathy” encompasses a spectrum of disorders⁶. Additional authors note that cases of purely proximal diabetic motor neuropathies exist, but are poorly defined¹⁴.

Recent studies report ischemic injury from microvasculitis as the pathophysiological basis of typical, painful, DLPRN^{15–19}. In contrast, diabetic patients with lower limb motor syndromes without pain have received little attention. Amato and Barohn highlight that motor polyradiculoneuropathies without pain do occur in DM²⁰. Although they consider this painless syndrome could be a type of DLPRN, they question whether such cases are chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) occurring in diabetic patients, an association also suggested by others^{21–24}. Their discussion rekindles interest into how to best classify diabetic patients with a motor predominant painless neuropathy. However, there has been no systematic evaluation of the clinical, electrophysiological, and pathological features of this painless syndrome.

Here, we study a cohort of diabetic patients with a lower limb and motor predominant neuropathy without pain and compare this group to a cohort of previously studied DLPRN patients¹. In order to formally answer if painless diabetic motor neuropathy is a variant of DLPRN, diabetic CIDP, or another entity, we ask 1) What are the clinical features of this painless syndrome? 2) What are the laboratory and electrophysiological findings? 3) What are the pathological features? As we believe the classification should be primarily based on the underlying disease mechanism, we place the most emphasis on pathological findings in this group compared to nerve biopsies from DLPRN, DSPN and CIDP.

MATERIAL AND METHODS

Patient selection

After IRB approval, we reviewed medical records of patients seen at Mayo Clinic Rochester in Neurology between January 1, 1985 and December 31, 2005 with coded diagnoses of polyradiculopathy, polyradiculoneuropathy, lumbosacral plexopathy, lumbosacral radiculoplexus neuropathy, proximal diabetic neuropathy, diabetic amyotrophy, or diabetic mononeuritis multiplex from whom a distal cutaneous nerve biopsy was obtained. Neuropathic impairment was quantitated using the Neuropathy Impairment Score (NIS), a global score of weakness, reflex and sensory loss²⁵. 470 patients were identified who were further reviewed for the following clinical and electrophysiological features: 1) documented absence of neurogenic pain or use of analgesic drugs for the disease, 2) weakness in one or both lower limbs, 3) presence of sensory symptoms or signs, 4) nerve conduction studies (NCS) or needle electromyography (EMG) abnormalities involving at least two peripheral nerves from at least two nerve root levels (a lumbosacral plexopathy). Patients were selected irrespective of whether the NCS showed axonal or demyelinating features. Patients could have upper limb or thoracic involvement but the prominent abnormalities were of lower limbs. All patients had DM (two fasting plasma glucose values ≥ 126 mg/dL) or a prior diagnosis of DM. In all but seven patients, information regarding weight change in relation to the onset of their neuropathic symptoms was documented. Patients who had structural lesions on imaging, other clear causes of neuropathy, or central nervous system disease that interfered with neuropathy evaluation were excluded. Between January 1, 2006 and March 31, 2009 we prospectively identified four additional patients who fulfilled our clinical criteria. We compared the pathological findings in this painless cohort to biopsies from 33 previously reported DLPRN patients¹, 21 previously reported DSPN patients¹, and 25 CIDP patients who met both our²⁶ and the AAN AIDS Task Force clinical and electrophysiological criteria for CIDP²⁷.

Electrophysiologic, quantitative sensory and autonomic testing

All patients underwent NCS and EMG testing using laboratory normal values. Nine patients had quantitative sensation testing performed using CASE IV28–31 and quantitative autonomic testing, a measure of postganglionic sudomotor, adrenergic, and cardiovascular function³².

Histologic methods

All distal cutaneous nerve biopsies were re-graded by two authors (PJBD, MGS). On all nerve specimens teased fiber preparations; paraffin sections stained with hematoxylin and eosin (H&E); Luxol Fast Blue/Periodic-Acid-Schiff (LFB/PAS), Mason's trichrome, Congo-red, methyl violet and Turnbull blue (iron stain); epoxy sections stained with methylene blue; and paraffin sections immunostained with CD45, CD68, and Dako anti-human smooth muscle actin (smactin) were reviewed.

Statistics

Descriptive statistics were used to compare attributes between groups. For continuous measurements results were expressed as medians/ranges using Wilcoxon rank sum tests. For dichotomous variables Fisher's exact test was used.

RESULTS

Demographic and laboratory characteristics

We identified 23 patients who fulfilled our criteria for painless diabetic motor predominant neuropathy. 12 were men and 11 women, with a median age of 62.2 years (range 36 to 78) with DM for a median duration of 5.4 years (range 0 to 23). In seven patients, DM was identified at presentation of neurological illness. All patients except one had type 2 DM; eight were insulin requiring and the rest used oral hypoglycemic medication; all had good glucose control. Chronic diabetic complications (retinopathy, nephropathy) were identified in four patients. Weight loss (≥ 10 pounds) was similar in severity and frequency between the painless diabetic cohort [13 of 16 (81%)] and the DLRPN cohort [28 of 33 (84%)], however body mass index was significantly higher in the painless group (Table 1). CSF testing performed in 16 patients demonstrated elevated protein with normal cell count. Laboratory results suggestive of an inflammatory process (rheumatoid factor, antinuclear antibodies, erythrocyte sedimentation rate, etc.) were present in a minority of patients. When compared to the DLRPN cohort, the painless group was not significantly different with regards to gender, age, type of DM, glycemic control or associated DM complications (Table 1).

Neuropathy Characteristics

The most common clinical pattern seen in this painless cohort was a motor predominant neuropathy developing over weeks to months with bilateral foot drop that progressed to involve proximal lower limb muscles with lesser upper limb involvement (Table 2). The impairment was severe, with all patients experiencing weakness and half of the patients being wheelchair-bound at presentation. 22 of 23 patients had sensory symptoms, 15 with numbness and seven having prickling paresthesias involving the distal lower limb. Nine patients had symptoms of autonomic dysfunction: orthostatic hypotension (2), urinary dysfunction (1), constipation (3), gastroparesis (2), impotence (5) and sweat dysfunction (1). Two-thirds of the patients had bilateral onset of symptoms and almost all had bilateral involvement by the time of evaluation (Table 2).

Neurological examination showed a largely symmetrical polyradicular pattern with distal lower limb segments being most affected in contrast to DLRPN patients in whom the proximal lower limb is the most severely affected. However, proximal segments were involved to the same degree as DLRPN (Table 1) which is evidence against this painless syndrome simply being a length-dependent process. There was prominent upper limb involvement in 17/23 painless patients that was of a greater severity (higher upper limb NIS) than in DLRPN patients resulting in a significantly higher median NIS in the painless group (Table 1). These findings taken together suggest that the deficits are more severe, more often bilateral at onset and overall more widespread in the painless diabetic motor syndrome as compared to DLRPN.

Physiological Testing

NCS demonstrated reduced/absent upper and lower limb sensory nerve and compound muscle action potential amplitudes without temporal dispersion or conduction block with mild slowing of conduction velocities and mild prolongation of distal and F-wave latencies (Table 3). Needle examination demonstrated patchy but widespread involvement of multiple lumbosacral myotomes with denervation and chronic motor unit potential changes. Lumbosacral paraspinal fibrillation potentials were seen in 14 of the 19 patients tested. Of the nine patients who had quantitative sensory and autonomic studies performed, all sensory studies were abnormal and all but one autonomic studies were abnormal. Generalized autonomic dysfunction was seen in four of the five patients tested who were clinically symptomatic. Four patients showed impairment in postganglionic sudomotor function, with abnormal adrenergic responses in one, and cardiovagal impairment in another (Table 4). When compared to DLRPN, there were no significant differences in NCS, quantitative sensory or autonomic testing. Needle examination showed more involvement of the L5, S1 myotomes in the painless group as compared to DLRPN which showed greater L2,3,4 involvement. Both cohorts had clear paraspinal denervation supporting proximal axonal pathology.

Pathological findings

Nerve biopsies showed evidence of ischemic injury and microvasculitis (Table 4). Overall, the density of myelinated nerve fibers was reduced in all but one biopsy, and was severe in eight. Evidence for nerve ischemia included: 1) focal or multifocal fiber loss (figure 1A, 1B); 2) focal perineurial degeneration or thickening (figure 2A); 3) epineurial neovascularization (figure 2A); 4) abortive regeneration of nerve fibers beyond the original perineurium forming microfasciculi (injury neuroma) (figures 1C, 2B); 5) regenerating clusters in 16 nerves (few in 11 and frequent in five). Onion-bulbs were seen frequently in one biopsy (figure 1D), occasionally in another, and were absent in all other biopsies.

Perivascular and vascular inflammation of small arterioles, venules and capillaries without involvement of larger vessels was encountered in all nerves, mostly affecting epineurial vessels, but occasionally affecting the perineurial and endoneurial vessels. The inflammatory infiltrates typically consisted of small collections of mononuclear lymphocytes (Table 5). All inflammatory collections reacted to CD45 (leukocyte) and to a lesser extent CD68 (macrophage). Inflammatory cells were within the vessel wall in 15/23 nerve biopsies, suggesting microvasculitis. Destruction of vessel wall elements with separation of the smooth muscle layers of the tunica media by leukocytes (features diagnostic of microvasculitis) were found in three nerves (Fig 2, C–H). Evidence of previous bleeding was noted in 11/23 nerves, frequently in the perineurium, often adjacent to microvessels. Teased fibers demonstrated increased frequency of axonal degeneration in 16 nerves (mild or moderate in 15 and severe in one) and an increased number of empty nerve strands (Table 5). A low rate of segmental demyelination that tended to be clustered along

the length of individual myelinated nerve fibers was also seen. The painless diabetic motor neuropathy nerves were indistinguishable from painful DLRPN nerves demonstrating ischemic injury and microvasculitis. As compared to the painless cohort, both CIDP and DSPN nerve biopsies showed significantly less multifocal fiber loss, neovascularization, perineurial thickening, injury neuroma, axonal degeneration, hemosiderin, and vessel wall inflammation. Neither cohort was suggestive of microvasculitis. DSPN but not CIDP nerves showed significantly less inflammation overall and CIDP biopsies exhibited significantly more segmental demyelination and onion-bulbs compared to all groups (Table 5).

Treatment and Course

16/23 patients returned for follow-up at our institution, 13 of whom were treated with various immunotherapies; intermittent intravenous immunoglobulin (6), intermittent plasma exchange (3), and pulse intravenous methylprednisolone (4). 11/13 patients had detailed examinations at follow-up with overall significant improvement in NIS scores (Figure 3). Mean pre-treatment NIS score was 65.5 (range 16.5 to 131) and mean post-treatment 40.8 (range 11 to 74.5) (p value 0.018). Overall, symptoms and findings improved with time and the disease course seemed to be monophasic.

DISCUSSION

There has been debate as to what is the cause of painless, motor and lower limb predominant neuropathy in diabetic patients. One possibility is that these cases represent one end of the spectrum of DLRPN. On the other hand, the symmetrical and painless characteristics of this motor predominant neuropathy may suggest that it is “diabetic CIDP”^{22–24, 33}. We recently studied the epidemiology of CIDP asking whether CIDP occurs more commonly in DM and found no association²⁶. However, we acknowledge that if “diabetic CIDP” exists, it may manifest as this painless diabetic motor predominant neuropathy.

We found that the clinical features of painless diabetic motor neuropathy were slightly different than those of typical DLRPN. The painless syndrome tends to begin insidiously (none had acute onset) and progresses at a slower pace. Compared to DLRPN, many more had bilateral onset, whereas DLRPN commonly begins asymmetrically and unilateral. Overall, the clinical course was more severe and widespread than DLRPN as evidenced by more severe distal segment impairment (worse NIS leg and EMG changes in L5/S1 segments) and more frequent and severe upper limb involvement. However, most clinical characteristics were quite similar between these two conditions. Both are motor and lower limb predominant neuropathic syndromes with autonomic and sensory involvement of large and small fibers. Both are frequently associated with substantial weight loss. Additionally, the NCS/EMG findings demonstrate axonal (as opposed to demyelinating) radiculoplexus neuropathies with widespread but patchy changes and prominent denervation involving lumbosacral greater than thoracic or cervical segments in both conditions.

There were some features of the painless motor predominant diabetic neuropathy that resemble typical CIDP, such as the generalized symmetrical proximal and distal involvement, the slow course and the absence of pain. Elevated CSF protein is typical of all three groups, so is not useful in distinguishing painless patients from CIDP or DLRPN. The pattern of sensory involvement seen in the painless cohort was pan-modal (both large and small fiber), whereas CIDP is large fiber predominant^{34, 35}. The prominent and severe autonomic involvement in the painless syndrome would be atypical for CIDP³⁶. Although our patients had mild slowing of conduction velocities, they did not meet AAN CIDP electrophysiological criteria²⁷ nor our criteria for CIDP²⁶. As a result, we do not think that this painless diabetic motor neuropathy clinically or physiologically is correctly categorized as “diabetic CIDP.”

From the outset, we felt that the best way to classify the painless lower-limb motor predominant neuropathy would be by the pathophysiological disease mechanism. Proximal fascicular biopsies from mixed motor and sensory nerves would have been ideal but were not done. Given the retrospective nature of this study and the fact that patients had sensory involvement, we felt that distal sensory nerve biopsies were appropriate and would be informative. We found very consistent findings on the nerve biopsies demonstrative of ischemic injury from microvasculitis that was indistinguishable from typical DLRPN. Although segmental demyelination was observed on teased nerve fiber preparations, the rates were low and tended to be grouped demyelination, supporting secondary segmental demyelination from axonal atrophy³⁷. Grouped demyelination was also seen in painful DLRPN associated with ischemic injury¹⁸. Only one biopsy raised the possibility of inflammatory demyelination with frequent onion-bulbs, but in this case the electrophysiology was axonal. In contrast, biopsies from CIDP patients did not show evidence of ischemic injury, hemosiderin-laden macrophages or vessel wall inflammation (microvasculitis). The rates of segmental demyelination and onion-bulbs were much higher and axonal degeneration much lower in CIDP than in the painless cohort. This data is strong evidence that the pathology of CIDP and painless, diabetic motor neuropathy are distinct and that they are not the same disease.

One may ask whether a concurrent or prominent DSPN is causing the sensory symptoms and the pathological findings with the proximal weakness resulting from a separate process. While we acknowledge that a minor component of painless motor predominant neuropathy may be due to DSPN, we contend that DSPN is unlikely a major player. Previous work has shown a strong correlation between the development of diabetic neuropathy, retinopathy and nephropathy after many years of hyperglycemic exposure³⁸. Only 4/23 of our patients had chronic hyperglycemic complications. The median duration of DM in our patients was 5.4 years compared to 12.0 years in a community diabetic cohort. Furthermore, the widespread sensory and autonomic findings in our painless patients and in DLRPN have also been reported in non-diabetic LRPN patients³⁹ supporting that these abnormalities are not primarily due to the diabetic state. Most significantly, when we compared the biopsies of our painless patients to those with DSPN there was significantly more ischemic injury, inflammation and microvasculitis (Table 5). Therefore, we judge that the clinical, electrophysiological and pathological findings in these painless patients are not due to metabolic complications from DSPN.

Given the retrospective nature of our study, the treatment response data of painless diabetic motor neuropathy patients needs to be interpreted with caution. The observation that almost all of those whom received immunotherapy had some improvement, and that the degree of improvement was significant, (as judged by NIS) supports an autoimmune pathogenesis. Three non-treated patients spontaneously improved as well. Overall, this data supports an inflammatory neuropathy that is likely treatment responsive and probably monophasic, as after the treatment course, the patients did not worsen or relapse. This clinical picture is more in keeping with a self-limited process such as DLRPN as opposed to the usual progressive course of CIDP.

Consequently, we conclude that the painless, lower-limb, motor predominant neuropathy seen in diabetic patients is “painless DLRPN” and represents a variant of DLRPN and not diabetic CIDP or a separate entity. Painless DLRPN patients may be more akin to those described by Chokroverty with a symmetrical, slowly progressive disease course¹². The lack of pain may in fact be a partial explanation for the more insidious, slower course as these patients are unable to precisely date the onset of symptoms. As proposed by Asbury, we demonstrate that DLRPN is a spectrum of disorders exhibiting a range of clinical presentations. However, we do not find that some forms of DLRPN are due to metabolic

factors whereas other forms are due to ischemic injury. Here, we provide evidence that ischemic injury from altered immunity and microvasculitis is the pathophysiological mechanism accounting for both painful and painless DLRPN.

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Figure 1.

Figure 2.

[illegible]

Figure 3.

Table 1
Clinical and Laboratory Characteristics in Painless Diabetic Motor Neuropathy and Painful DLRPN

	Painless Syndrome				Painful DLRPN				<i>p</i> [*]
	N	Median	Range	SD	N	Median	Range	SD	
Clinical									
Age, yr	23	62.2	36.3 – 78.4	11.1	33	65.4	35.8 – 75.9	10.4	NS
Body mass index, kg/m ²	23	29.1	18.0 – 44.5	7.4	29	25.7	17.8 – 36.7	4.9	0.01
Weight change, lb	16	–30.0	–100.0 – 0.0	29.7	33	–30.0	–120.0 – 0.0	32.6	NS
Duration of neuropathy at evaluation, mo	23	11.0	2.0 – 108.0	25.0	33	6.7	1.4 – 42.0	8.9	NS
Time to bilateral, mo	21	0.0	0.0 – 36.0	7.9	32	3.0	0.0 – 60.0	10.6	0.001
Time to maximum disability, mo	23	10.0	3.0 – 108.0	23.3	31	5.0	0.3 – 20.0	4.7	0.005
NIS Total	23	70.3	11.0 – 124.0	26.6	33	43.0	7.0 – 87.0	18.6	<0.0001
NIS Upper limb	23	13.0	0.0 – 56.3	20.4	33	4.0	0.0 – 25.5	8.7	0.005
NIS Lower limb	23	50.0	8.0 – 70.0	13.4	33	37.0	7.0 – 62.0	14.4	0.001
NIS Hip and thigh	23	18.0	0.0 – 31.0	8.5	33	14.5	0.5 – 29.0	8.1	NS
NIS Leg	23	34.0	8.0 – 46.0	8.4	33	22.5	4.0 – 40.0	9.6	0.001
Laboratory									
Fasting plasma glucose, mg/dL	23	150.0	84.0 – 293.0	57.6	30	144.5	75.0 – 225.0	44.3	NS
Glycated hemoglobin, %	22	7.1	4.8 – 14.8	2.5	30	7.5	5.1 – 12.9	2.0	NS
Creatinine, mg/dL	21	0.9	0.4 – 7.4	1.5	30	0.9	0.7 – 3.4	0.5	NS
Cerebrospinal fluid glucose, mg/dL	23	88.0	45.0 – 156.0	28.3	26	85.0	56.0 – 130.0	19.4	NS
Cerebrospinal fluid protein, mg/dL	23	89.0	30.0 – 211.0	44.3	26	89.5	44.0 – 214.0	35.3	NS
Cerebrospinal fluid cells, cells/μL	23	2.0	1.0 – 17.0	3.4	26	1.0	1.0 – 11.5	2.1	0.02
Erythrocyte sedimentation rate, mm/h	19	17.0	0.0 – 53.0	13.8	31	6.0	0.0 – 60.5	14.6	0.02
N	N	Yes	No		N	Yes	No		<i>p</i>
Clinical									
Gender, male	23	12	11		33	20	13		NS
Diabetes, type 2	23	22	1		33	32	1		NS
Insulin use	23	8	15		31	13	18		NS
Retinopathy	17	4	13		17	4 [†]	13		NS

	Painless Syndrome			Painful DLRPN			* <i>p</i>
	N	Median	Range	N	Median	Range	
Nephropathy	23	3	20	33	2	31	NS
Cardiovascular disease	22	7	15	33	3	30	NS
Laboratory							
Rheumatoid factor, reactive	11	2	9	25	1	24	NS
ANA, positive	18	4	14	32	7	25	NS

DLRPN = diabetic lumbosacral radiculoplexus neuropathy; SD=standard deviation; NS = not significant ($p > 0.05$); NIS = Neuropathy Impairment Score.

* Wilcoxon rank sum test for continuous data and Fisher's exact test for dichotomous data.

† Nonproliferative retinopathy.

Table 2

Neuropathy Characteristics in Painless Diabetic Motor Neuropathy and Painful DLRPN

	Painless Syndrome	Painful DLRPN	<i>p</i> [*]
	N = 23	N = 33	
Onset			
Acute	0	10	0.002
Subacute	21	23	
Chronic	2	0	
Onset Pattern			
Bilateral	15	4	0.0001
Unilateral	8	28	
Progression			
Rapid (< 6 wks)	0	1	0.02
Intermediate (6 – 26 wks)	8	21	
Slow (> 26 wks)	15	9	
Course			
Monophasic	22	25	NS
Polyphasic	1	8	
Most involved site			
Distal (foot or leg)	13	14	<0.001
Proximal (hip or thigh)	4	19	
Equal (distal and proximal)	6	0	
Buttock or Back	0	0	
Aids in ambulation			
Wheelchair	11	16	NS
Walker, Cane or Brace	11	14	
None	0	3	
Unknown	1	0	

DLRPN = diabetic lumbosacral radiculoplexus neuropathy; NS = not significant ($p > 0.05$).

* Fisher's exact test.

Table 3

Electromyography in Painless Diabetic Motor Neuropathy and Painful DLRPN

Nerve Conduction Studies ^{**}		Painless Syndrome			Painful DLRPN		
Nerve	Attribute	N	Median	Range	N	Median	Range
Sural	SNAP, μ V	23	0.0	0.0 – 7.0	37	0.0	0.0 – 7.0
	CV, m/s	3	41.0	36.0 – 48.0	4	39.5	35.0 – 41.0
	DL, ms	5	4.8	4.1 – 4.9	6	4.4	4.0 – 4.8
Peroneal	CMAP, mV	20	0.1	0.0 – 2.1	38	0.2	0.0 – 7.5
	CV, m/s	10	35.0	23.0 – 42.0	27	36.0	24.0 – 46.0
	DL, ms	10	5.8	4.7 – 15.5	27	5.6	4.0 – 14.1
Tibial	CMAP, mV	22	0.7	0.0 – 5.5	31	0.7	0.0 – 11.4
	CV, m/s	14	34.5	20.0 – 43.0	25	36.0	20.0 – 48.0
	DL, ms	14	5.7	4.6 – 9.4	25	5.2	3.8 – 10.8
Ulnar	CMAP, mV	23	4.8	0.7 – 9.5	33	6.8	0.0 – 16.1
	CV, m/s	23	47.0	24.0 – 61.0	29	48.0	35.0 – 57.0
	DL, ms	23	3.3	2.5 – 9.9	29	3.2	2.2 – 5.2
Median	SNAP, μ V	23	6.0	0.0 – 20.0	31	7.0	0.0 – 49.0
	CV, m/s	11	50.0	43.0 – 57.0	23	52.0	45.0 – 61.0
	DL, ms	15	4.0	3.1 – 5.8	26	3.9	2.5 – 5.4
Needle Studies [†]							
Attribute	N	Median	Range	N	Median	Range	p^*
L2,3,4 muscles							
Fibrillation potentials	44	1.0	0 – 3	24	1.0	0 – 3	NS
Long MUPs	39	1.0	0 – 3	22	2.0	1 – 3	0.0002
L5,S1 muscles							
Fibrillation potentials	56	1.4	0 – 2.8	32	1.4	0 – 2.5	NS
Long MUPs	55	1.1	0 – 2	28	1.5	0 – 3	0.04
Paraspinal muscles							

Nerve Conduction Studies^{***}

		Painless Syndrome			Painful DLRPN			<i>p</i> [*]
Nerve	Attribute	N	Median	Range	N	Median	Range	
Fibrillation potentials		35	1.5	0 – 3	22	1.0	0 – 2	NS
	Long MUPs	18	1.0	0 – 2	10	1.0	0 – 1	NS

DLRPN = diabetic lumbosacral radiculoplexus neuropathy; NS = not significant ($p > 0.05$); SNAP = sensory nerve action potential; CV = conduction velocity; DL = distal latency; CMAP = compound muscle action potential; MUPs = motor unit potentials

^{*} Wilcoxon rank sum test for continuous data and Fisher's exact test for dichotomous data.

^{***} 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.

Table 4

Quantitative Sensory and Autonomic Testing in Painless Diabetic Motor Neuropathy and Painful DLRPN

Painless Syndrome					Painful DLRPN			
Quantitative Sensory Testing								
Modality	Site	N	Normal	Abnormal	N	Normal	Abnormal	<i>p</i> [*]
VDT	Foot	9	1	8	17	4	13	NS
	Leg	2	1	1	8	3	5	NS
	Thigh	1	0	1	2	1	1	NS
	Any site	9	1	8	17	4	13	NS
CDT	Foot	8	3	5	17	8	9	NS
	Leg	1	1	0	3	0	3	NS
	Thigh	1	1	0	2	1	1	NS
	Any site	8	3	5	17	8	9	NS
HP5 †	Foot	8	2	6	17	9	8	NS
	Leg	2	0	2	6	2	4	NS
	Thigh	1	0	1	3	2	1	NS
	Any site	8	2	6	17	9	8	NS
Autonomic reflex screen (CASS score)								
Component		N	Median	Range	N	Median	Range	<i>p</i> [*]
Sudomotor Index		9	2.0	0.0 – 3.0	14	2.5	1.0 – 3.0	NS
Adrenergic Index		9	2.0	0.0 – 4.0	14	2.5	0.0 – 4.0	NS
Cardiovagal Index		9	2.0	0.0 – 3.0	13	2.0	0.0 – 3.0	NS
Total CASS		9	6.0	0.0 – 10.0	14	7.0	2.0 – 10.0	NS

DLRPN = diabetic lumbosacral radiculoplexus neuropathy; NS = not significant ($p > 0.05$); VDT = vibration detection threshold; CDT = cooling detection threshold; HP5 = Heat-Pain 5 threshold

^{*} Wilcoxon rank sum test for continuous data and Fisher's exact test for dichotomous data.

[†] For HP5, abnormality is $\leq$ 5th percentile or $\geq$ 95th percentile.

Table 5

Pathologic Findings of Biopsy in Painless Diabetic Motor Neuropathy, Painful DLRPN, CIDP and Diabetic Polyneuropathy

	Painless Syndrome		Painful DLRPN		CIDP		DSPN	
	N = 23		N = 33	<i>p</i> *	N = 25	<i>p</i> *	N = 21	<i>p</i> *
Paraffin and Epoxy Sections								
Endoneurial and Perineurial Abnormality								
Fiber degeneration or loss	22		25	NS	15	0.005	15	0.04
Multifocal fiber degeneration or loss	11		19	NS	2	0.003	2	0.01
Focal perineurial degeneration	3		6	NS	0	NS	0	NS
Focal perineurial thickening	18		24	NS	2	<0.0001	2	<0.0001
Injury neuroma [‡]	11		12	NS	0	<0.0001	0	0.0002
Onion Bulbs	2		1	NS	14	0.02	2	NS
Interstitial Abnormality								
Perivascular inflammation	23		33	NS	25	NS	6	<0.0001
Individual cells (< 10 cells)	2		0		3		5	
Small collections (11–50 cells)	16		21		20		1	
Moderate collections (51–100 cells)	3		7		1		0	
Large collections (> 100 cells)	2		5		1		0	
Inflammation of vessel wall	15		15	NS	2	<0.0001	0	<0.0001
Diagnostic of microvasculitis	3		2	NS	0	NS	0	NS
Hemosiderin in macrophages	11		19	NS	3	0.009	0	0.0002
Neovascularization	17		21	NS	3	<0.0001	1	<0.0001
Teased Fiber Conditions [§]								
	Median	Range	Median	Range	Median	Range	Median	Range
Normal: A, B (%)	52.2	13 – 100	45.7	0 – 92	60	4 – 91	77.6	62 – 92
Demyelination: C, D (%)	3.9	0 – 33	2.6	0 – 25	23.1	6 – 58	1.6	0 – 12
Remyelination: F, G (%)	15.7	0 – 48	11.9	0 – 33	11.5	0 – 32	12.0	2 – 22
Axonal: E, H (%)	12.5	0 – 67	30.9	0 – 100	3.1	0 – 59	3.3	0 – 23
Classifiable (no.)	54.0	6 – 174	63.0	7 – 127	78	27 – 100	75	21 – 203
Empty (no.)	43.0	7 – 99	42.5	5 – 93	32	4 – 27	27	1 – 70

DLRPN = diabetic lumbosacral radiculoplexus neuropathy; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; DSPN = diabetic polyneuropathy; NS = not significant ($p > 0.05$).

* Wilcoxon rank sum test for continuous data and Fisher's exact test for dichotomous data.

[†] Healthy control age (median 61.5 years) and gender (9M 5F) not significantly different than painless LE syndrome.

[‡] Injury neuroma = abortive regenerative activity outside of the original perineurium.

[§] Teased fiber types: A = normal, B = myelin wrinkling, C = demyelination, D = demyelination and remyelination, E = axonal degeneration, F = remyelination, G = myelin reduplication, H = regeneration after axonal degeneration, empty = unclassifiable strands without myelinated fibers.