Progressive polyradiculoneuropathy in diabetes: correlation of variables and clinical outcome after immunotherapy

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Abstract

***Objective*—To quantify the progression of diabetic polyradiculoneuropathy—a condition in which immune factors have been implicated—after immunotherapy.**

***Methods*—The study evaluated 15 consecutive patients with this condition. All patients were older than 40. Four had type I diabetes and six were women. The duration of pre-existing diabetes varied from 2 to 20 years. The clinical presentation was dominated by painful progressive motor weakness, with or without exacerbation of sensory symptoms. The weakness involved all limbs, but was often asymmetric.**

***Results*—Electrophysiological testing showed a predominantly axonal polyneuropathy, with more recent denervating polyradiculopathy. Analysis of CSF showed increased protein in 14 and oligoclonal bands in five. Quantitative autonomic tests showed abnormalities in all patients. Sural nerve biopsy was performed in 14 patients; all showed fibre loss and segmental demyelination, four had occasional onion bulbs, and 10 showed various inflammatory infiltrates. After immunomodulating therapy, there was no further deterioration and clinical improvement occurred in all patients. Sweat responses, cardiovascular reflexes, and sural nerve fibre density correlated best with functional outcome. There was no significant difference between plasmapheresis and intravenous gammaglobulin.**

***Conclusion*—Immunotherapy may improve this condition, but only certain variables correlate with rapid therapeutic response.**

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Keywords: diabetes mellitus; peripheral nerve diseases; polyradiculoneuropathy; immunosuppressive treatment

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Diabetes mellitus is a leading cause of peripheral neuropathy.[1] The neuropathy can be subclinical, or may become symptomatic with variable severity. Uncommonly, it can become rapidly progressive and disabling. A recent community based study found that only 7% of all diabetic patients develop severe polyneuropathy.[2] There have been few reports of such disabling neuropathies in diabetes[3–6] Two of these studies[4 5] suggested a favourable response to immunosuppressive therapy, whereas a third one (an abstract)[6] concluded the reverse. During the past 3 or 4 years, we evaluated 15 diabetic patients with rapidly progressive polyradiculoneuropathy. We treated all patients with immunomodulating therapy and followed them up for at least 1 year. We review their clinical, electrophysiological, and pathological data.

Methods

The patients' case reports and laboratory data are summarised in tables 1–3.

PATIENT SELECTION

We studied 15 diabetic patients referred to our neuromuscular centre for progressive weakness between 1992 and 1995. The diagnosis of rapidly progressive polyradiculoneuropathy was made clinically and established electrophysiologically. All patients presented with proximal and distal weakness of their lower limbs, and distal weakness of their upper limbs. Proximal upper limb weakness was present in eight patients, and equalled proximal lower limb weakness in six patients. Two had facial weakness and two required respiratory assistance. The weakness progressed over 2 months or more in all patients by history. Electrophysiologically, the diagnosis was made when sensory nerve responses were abnormal, and needle EMG showed neurogenic changes in proximal muscles of one upper and one lower limb and their corresponding paraspinal muscles. All patients with pain also had spinal CT or MRI studies to rule out other structural radicular lesions superimposed on a diabetic polyneuropathy. Other causes of neuropathy (hereditary, nutritional, metabolic, toxic, and paraneoplastic) were excluded clinically and by appropriate laboratory tests. All subjects had detailed standard neurological and ophthalmological examinations.

Asymmetry of weakness was defined as a difference greater than one MRC grade between one or more homologous muscle groups. The neuropathy disability score (NDS) was determined according to published references.[7 8] It is composed of three subsets: weakness (NDSW), sensory (NDSS), and reflex (NDSR). The NDSW summates motor weakness as 1 (25% deficit), 2 (50% deficit), 3 (75% deficit), or 4 (100% deficit) for each of 21 muscle groups in the head, neck, and limbs. The NDSR grades each of the major five tendon reflexes as 0 (normal), 1 (reduced), or 2 (absent). The NDSS grades the sensation over the fingers and toes as 0 (normal), 1 (reduced), or 2 (absent) for each of the four primary sen-

sory modalities. This is a standardised method with established validity in diabetic and inflammatory neuropathy.[8] The values were measured at baseline and then at 6, 12, 24, and 52 weeks (± 1 week). Given the impact of weakness on all patients, the severity of the neuropathy was rated primarily based on the weakness subset of the NDS.

LABORATORY STUDIES

These included screening studies for other causes of neuropathy including serum immunoelectrophoresis. All subjects had determinations of their haemoglobin A1C (8.40 (SD 1.15)). Renal function (blood urea nitrogen, creatinine, and 24-hour proteinuria) was also determined. All patients had creatinine values under 2.5 mg/dl and all maintained a stable renal function during the study period. All patients had CSF examination.

ELECTROPHYSIOLOGICAL STUDIES

We performed standard nerve conduction studies and EMG in all patients. All motor nerves were stimulated distally and proximally. Electrophysiological demyelination and partial motor conduction block were diagnosed based on criteria previously published.[9 10] Needle EMG evaluated distal and proximal muscles at the discretion of the electromyographer.

We also measured autonomic function in all patients. These tests included quantitative sudomotor axon responses (Q-SART), blood pressure and heart rate variation to Valsalva, deep breathing, and tilt manoeuvres.[11]

NERVE BIOPSIES

Fourteen patients had sural nerve biopsy. All nerve specimens were divided into three parts. One part was frozen in cooled isopentane in liquid nitrogen, and 8 μm thick sections stained for routine light microscopy. We stained the samples with monoclonal antibodies directed toward various inflammatory cells: CD68 recognises macrophages, CD4 and CD8 recognise their respective T lymphocytes, and CD22 recognises B cells (Dako Corporation, Carpinteria, CA, USA). The second part was embedded in plastic for semithin sections. The third portion was used for teased fibre analysis. The density of myelinated fibres was determined from 1 μm thin sections according to methods previously described.[12] Given the significant fascicular variability, the final density was that averaged from four fascicles. For teased fibre analysis, we evaluated more than 50 fibres per specimen, each containing at least four internodes, and graded their abnormalities as follows: A (normal); B (myelin wrinkling); C (segmental demyelination alone); D (segmental demyelination/ remyelination); F (segmental remyelination alone); and E (wallerian degeneration).[8]

TREATMENT PROTOCOL

Given the clinical similarity between diabetic rapidly progressive polyradiculoneuropathy and chronic inflammatory polyradiculoneuropathy, we applied similar treatment protocols. Although these treatments have not been fully evaluated in diabetic rapidly progressive polyradiculoneuropathy, we chose them based on accepted guidelines to treat chronic inflammatory polyradiculoneuropathy. All patients received immunomodulating therapy for the first 6–8 weeks. Patients 1 to 9 received three sessions of plasmapheresis weekly for one week, followed by two sessions weekly for 2 weeks and then one session weekly for 2 weeks. The total volume of exchanged plasma was 400

Table 1 Clinical features of patients

No	*Sex*	*Age (y)*	*DM type/ duration (y)/ HbA1C (%)*	*Pain*	*Sensory Sx/ duration (months)*	*Motor Sx/ duration (months)*	*Trunk/vertex sensory loss*	*Autonomic Sx*	*Hypertension/ kidney/retina*	*Weight loss (kg)*	*CSF Protein (mg/dl)*
1	F	42	I/20/8.5	No	LE/24	LE>UE/12 asymmetric	No/No	CV, GI, P	Yes/Yes/Yes	5	84
2	M	52	II/14/8.7	No	LE>UE/6	LE>UE/3 asymmteric	Yes/No		No/No/Yes	10	170
3	M	53	I/16/7.3	LB	UE>LE/24	LE>UE/4 asymmetric	Yes/Yes	CV, GI, P, S	Yes /Yes/Yes	14	76
4	M	59	II/10/8.7	No	LE+UE/12	LE+UE+R/2 symmetric	Yes/Yes	CV, GI, P, S	Yes/Yes/No	10	42
5	F	60	I/5/7.5	LB	UE>LE/6	LE>UE/3 asymmetric	No/No	CV	Yes/Yes/Yes	9	56
6	M	60	II/10/8.3	LB	LE/4	LE>UE/6 symmetric	No/No	GI	No/No/No	10	135
7	F	66	II/2/8.9	LE	LE/5	LE/4 asymmetric	No/No	CV, P	No/No/No	25	71
8	F	71	II/18/9.8	LB, LE	LE/12	LE>UE/2 symmetric	Yes/Yes		No/No/No	5	90
9	M	71	II/10/7.9	LE	LE/12	LE+UE+R/5 asymmetric	Yes/No	CV, S	Yes/No/No	14	125
10	M	49	II/4/7.0	LB, LE	LE/24	LE+UE+F/18 symmetric	Yes/No	CV, GI, P, S	No/Yes/No	19	176
11	F	42	I/36/10.4	LB	LE/12	LE+UE+F/7 symmetric	Yes/Yes	CV, GI, P	No/Yes/Yes	9	128
12	M	66	II/5/8.3	LB	LE/6	LE>UE/4 symmetric	Yes/No	CV, GI	No/No/No	12	53
13	F	72	II/4/8.1	LB, UE	LE+UE/9	LE+UE/4 asymmetric	Yes/No		No/No/No	13	73
14	M	66	II/4/8.7	LB, LE	LE/5	LE>UE/5 asymmetric	Yes/No	CV, GI, S	No/Yes/No	10	150
15	M	68	II/10/8.6	LB, LE	LE/4	LE>UE/3 symmetric	No/No	CV, S	Yes/No/No	9	140

Sx=Symptoms and signs; LE/UE=lower/upper extremities; F=face; R=respiratory; LB=low back; CV=cardiovascular; P=pupils; GI=gastrointestinal; S=abnormal sweating

*Table 2 Motor nerve conduction studies**

Patient	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*
Median M:															
D/P (Amp/mV)	0.8/0.6	3.2/2.4		6.2/5.6	7.0/6.0	6.1/5.7	7.0/7.0	2.0/1.5	7.0/6.0	4.2/3.4		5.1/5.0	6.0/5.0	2.7/1.4	4.0/3.6
DL (ms)	8.0	7.1		7.0	5.5	6.7	4.2	4.9	4.7	4.2		3.8	4.5	3.4	4.6
CV (m/s)	24	31		39	41	44	45	35	42	38		47	50	49	50
F (ms)	NR	51		44	39	41	29	NR	34	35		35	32	30	32
Ulnar M:															
D/P (Amp/mV)	0.7/0.5	2.0/1.6	4.0/3.0	2.0/1.4	4.0/3.0		10/9.7	1.0/0.9	6.0/5.0	0.8/0.6	1.0/0.9	5.2/4.3	3.5/3.1	5.0/4.0	4.5/4.0
DL (ms)	4.6	5.4	3.9	4.2	4.5		3.0	3.8	4.3	4.3	6.3	3.8	4.3	3.3	3.8
CV (m/s)	36	36	48	41	35		48	30	40	38	20	46	37	50	46
F (ms)	NR	46	36	50	40		31	NR	37	36	NR	39	38	31	33
Peroneal M†:															
D/P (Amp/mV)	1.0/0.8	NR	0.4/0.3	1.4/1.1	NR	1.4/0.6	0.4/0.4	NR	0.5/0.4	0.3/0.2	0.3/0.2	NR	1.3/0.9	1.9/1.4	1.5/1.2
DL (ms)	5.5		12.1	6.5		7.1	6.7		3.5	4.3	7.5		6.2	4.4	5.3
CV (m/s)	38		37	43		32	42		36	36	31		36	35	41
F (ms)	NR		NR	NR		70	NR			NR			50	62	56
Tibial M:															
D/P (Amp/mV)	NR		0.6/0.4	NR	NR	5.0/3.5	1.9/0.8	0.8/0.6	NR	0.6/0.5	NR	2.0/1.5	1.1/0.9	4.1/3.3	2.6/2.0
DL (ms)			5.1			6.5	6.2	6.3		4.7		5.9	5.3	5.3	5.0
CV (m/s)			35			31	30	31		28		34	44	39	44
F (ms)			NR			72	62	NR		63		70	32	59	52

*Underlined values indicate electrophysiological demyelination.
†Recorded from the extensor digitorum brevis or anterior tibialis.
D/P=Distal/proximal; NR=no response

ml/kg divided as above. Patients 10 to 15 received two courses of 2 g/kg intravenous gammaglobulin (IVIg) 4 weeks apart. These treatment schedules are considered equivalent in efficacy when administered in immune therapies.[13] Patients whose nerve biopsies showed dense periarterial inflammatory cells on routine non-immunological stains (patients 2, 9, and 15) received oral corticosteroids for 3 months (60 mg prednisone daily for 2 weeks and tapered by 10 mg every 2 weeks). All these patients required the administration of insulin during corticosteroid therapy.

The clinical and laboratory data were evaluated statistically. The relation between clinical improvement and various factors was investigated with correlation analysis. The clinical statistical significance was determined as $p<0.01$.

Results

The patients' clinical presentations, results of the neurological examination, and CSF analysis are summarised in table 1. The sensory nerve conduction studies showed absent or markedly reduced amplitudes for all sural and ulnar nerves; the median and radial sensory nerves were similarly abnormal in all patients but two (7 and 8) who had low normal amplitudes. The results of the motor nerve conduction studies are listed in table 2. The autonomic function tests showed absent or reduced Q-SART responses distally, abnormal Valsalva ratio, and abnormal heart rate variation to deep breathing in all patients. Only six patients (1, 3, 4, 5, 11, and 15) had significant orthostatic hypotension (systolic blood pressure fall ⩾30 mm). The nerve biopsy findings are summarised in table 3.

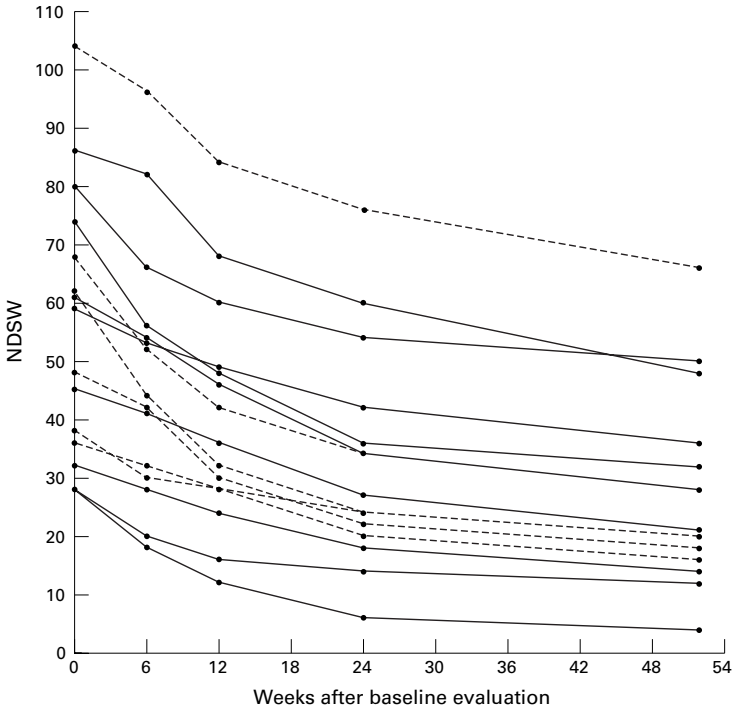
During the period of observation, all 15 patients improved, and we did not encounter clinical deterioration in any patient over 1 year (figure). Experience with large series of patients with diabetic neuropathy[7 8] showed that an NDSW change of 5 points or more is clinically meaningful. We found that the mean change in absolute NDSW scores was significant and exceeded this value at all points of evaluation in this group of patients. The improvement in NDSW averaged 9.0 (SD 5.1) points at week 6, and 29.1 (SD 9.3) points by week 52. When we considered the percentage of total change versus time, 55.5 (SD 12.1)% of the improvement occurred in the first 12 weeks, and 80 (SD 7.2)% occurred in the first 24 weeks of observation. There were no significant differences between the immunomodulating modalities (plasmapheresis *v* IVIg).

We investigated the relation between clinical improvement (measured as percentage NDSW change from baseline) and various factors with correlation analysis. The clinical presentation

Table 3 Nerve biopsy findings

No	*Density of MF*	*Endoneurial oedema*	*Onion bulbs*	*Inflammatory cells*	*Blood vessels*	*Segmental demyelination*	*Segmental remyelination*	*Axonal degeneration*
1	435	Present	Absent	Absent	Thick BM	11	9	12
2	1850	Present	Present	CD68, CD22, CD4, CD8	Thick	18	12	15
3	830	Present	Absent	Absent	Thick	15	10	18
4	780	Present	Present	CD68	Thick	17	10	27
5	285	Absent	Absent	CD68	Calcium	24	17	18
6	2530	Absent	Absent	CD68	Thick	32	15	13
7	960	Present	Absent	CD68, CD4, CD8	Thick	18	6	16
8	575	Absent	Present	CD68	Thick	22	12	14
9	715	Present	Absent	CD68, CD22, CD4, CD8	Thick	14	15	16
10	1220	Present	Present	CD68	Thick	18	10	12
12	605	Present	Absent	Absent	Thick	15	10	18
13	1810	Present	Absent	Absent	Thick	12	15	18
14	1314	Absent	Absent	CD68	Thick	14	8	12
15	1922	Present	Absent	CD68, CD22, CD4, CD8	Occluded	21	7	19

MF=Myelinated fibres; n >7000/mm^2



Neuropathy disability score: weakness subset (NDSW) for 15 diabetic patients with rapidly progressive polyradiculoneuropathy treated with immunomodulating therapy. Solid lines represent patients receiving plasmapheresis, dashed lines represent patients receiving intravenous gammaglobulin.

alone did not predict therapeutic response. Although the patient with the highest haemoglobin A1C value had the highest baseline NDSW, we did not find a significant correlation between A1C values and NDSW, change in NDSW, or percentage change in NDSW. Three measures correlated with the percentage change in NDSW at 12 weeks, which was the first evaluation after the completion of immunomodulating therapy. The six patients with density of myelinated fibres in the sural nerve greater than 1000 improved by 41.7 (SD 10.5)% at 12 weeks, whereas the other eight patients improved by 23.2 (SD 5.3)% (p=0.006). The seven patients with CSF protein concentrations greater than 100 mg/dl improved by 37.8 (SD 13.8)%, whereas the other eight patients improved by 24.4 (SD 5.3)% (p=0.044). The five patients with heart rate change to deep breathing greater than 7 bpm improved by 41.8% (SD 13.0%), whereas the other 10 patients improved by 25.1% (SD 6.7%) (p=0.042).

The nine patients who met any of these three criteria improved by 34.8 (SD 13.4)% at 12 weeks, whereas the other six patients improved by 24.4 (SD 6.2)% (p=0.067). Four patients met all three criteria and improved by 46.7 (SD 8.1)% at 12 weeks, whereas the other 11 patients improved by 24.8 (SD 6.4)% (p=0.006). Five patients met two of the three criteria, including the four patients who met all three criteria, and one with density of myelinated fibres>1000 and CSF protein>100 mg/dl. These five patients improved by 44.8 (SD 8.1)% at 12 weeks, whereas the other 10 patients improved by 23.5 (SD 5.1)% (p=0.002).

Discussion

The results of this study suggest that (1) certain diabetic patients with rapidly progressive polyradiculoneuropathy do respond rapidly to immunotherapy; (2) all patients improve without relapses for at least 1 year.

The therapeutic response in our diabetic patients was variable. There was definite improvement in the weakness subset of the neuropathy disability score in all patients. Only those with dense perivascular inflammatory infiltrates on routine stains were treated with prednisone and similar results were seen. All treated patients reported dramatic subjective improvement, in particular rapid resolution of their pain.

Our patients presented with accelerated proximal and distal weakness, hypoflexia or areflexia, and predominantly distal sensory loss. Several also had truncal and trigeminal sensory involvement consistent with a centripetal pattern of neuropathy.[14] This deterioration occurred despite the lack of recent modification in their diabetic treatment and stable renal function. Twelve patients presented with clinically overt autonomic abnormalities that coincided with the exacerbation of their motor and sensory deficits. When evaluated by objective autonomic quantitative testing, all patients had significant abnormalities.

Several authors reported rapid deterioration in diabetic neuropathy. In a first series published in the form of an abstract,[6] the authors suggested that these patients with rapidly progressive weakness may have concomitant chronic inflammatory demyelinating polyneuropathy and diabetes mellitus. Paradoxically, they found that patients overall did not respond to immunosuppressive therapy. Said *et al*[3] described a rapidly progressive sensorimotor polyneuropathy in type I diabetes. The nerve biopsies showed excessive regeneration, and the authors suggested a metabolic abnormality. In their second study, Said *et al*[4] described their findings in proximal asymmetric diabetic polyneuropathy. Inflammatory or vasculitic changes were present in several biopsies, and three patients responded to steroid treatment. Another series published in the form of an abstract[15] reported 10 insulin dependent patients with rapid or slowly progressive weakness who variably responded to immunomodulating therapy; most were men and some had monoclonal proteins. Krendel *et al*[5] described 24 cases of diabetic neuropathy that responded to immunosuppressive treatment. They divided their patients into two groups: "an axonal form" in which the presentation was similar to that of patients with diabetic proximal neuropathy; and a "demyelinating form" in which the course and biopsy findings were similar to chronic inflammatory demyelinating polyneuropathy. Analysis of their electrophysiological data showed no difference between the groups.[16] Several of their treated patients did not have CSF analysis or sural nerve evaluation, and no specified criteria were used to determine the implementation of immunosuppressive treatment. More recently, Stewart *et al*[17] reported on seven

diabetic patients with progressive and predominantly motor polyneuropathy who responded to immunomodulating therapy. Their patients met the electrophysiological criteria for chronic inflammatory demyelinating polyneuropathy and are therefore instances of chronic inflammatory demyelinating polyneuropathy in diabetes. In reviewing chronic inflammatory demyelinating polyneuropathy series, several authors found occasional cases associated with diabetes[18 19] and thought that they represented a mere coincidence.

Our patients presented in a manner similar to patients with chronic inflammatory demyelinating polyneuropathy. However, we think that there are several important differences.

Clinically, the proximal weakness was often asymmetric, and had a predilection for the L2-L4 myotomes in most patients. Nociceptive sensory loss often equalled or exceeded that of proprioceptive loss, and was present over the trunk in several patients. Radicular pain was pronounced and early. Weight loss was constant and rather marked. The autonomic abnormalities became prominent at the time of presentation. This association was found by others[3 4] and is rare in chronic inflammatory demyelinating polyneuropathy.[20] Previous authors suggested an immunological basis for diabetic autonomic neuropathy.[21–23] We found that the results of the autonomic tests predicted improvement at all points of study more reliably than nerve conduction studies. Several of these features suggest that patients with diabetes and rapidly progressive popyneuropathy may be more extended forms of Bruns-Garland disease rather than chronic inflammatory demyelinating polyneuropathy. All our patients improved, and none worsened after the discontinuation of immunotherapy, a course that would not be expected in chronic inflammatory demyelinating polyneuropathy.[2]

Electrophysiologically, the nerve conduction and electromyographic studies were more often axonal, with signs of electrophysiological demyelination only in occasional nerve segments. Unlike other authors,[17] we found electrophysiological conduction block without temporal dispersion in one patient only (case 14), an incidence similar to that found by another group when randomly screening diabetic patients.[24] The proximal drop in the motor response amplitudes in patients 6 and 7 was associated with excessive temporal dispersion and could have been partly due to the axonal process. None of our patients fulfilled the ad hoc criteria[10] for pure demyelinating polyneuropathy.

Pathologically, when compared with large series of patients with chronic inflammatory demyelinating polyneuropathy,[18] the diabetic nerves of our patients had a similar incidence of axonal degeneration and demyelination, and whereas there were greater abnormalities involving the blood vessels, we concur with Stewart *et al*[17] that these were not significantly distinctive. On immune staining, perivascular inflammatory infiltrates were present in 10 of 14 nerves. In agreement with another study,[4] we did not find polymorphonuclear cells amidst the infiltrates. Unlike vasculitis, we did not find vascular wall necrosis. Our immunohistochemical staining disclosed a predominance of macrophage mediated demyelination indicating the activity of the neuropathy. The lymphocytic inflammatory infiltrates consisted predominantly of T cells, both helper and suppressor, a finding noted by others.[25] We encountered dense B lymphocytic infiltrates in three of 14 biopsies, an incidence similar to that found in two other series.[17 26] Although relatively uncommon, the B cells are present only in diabetic nerves and are not seen in chronic inflammatory demyelinating polyneuropathy.[27 28] Finally, one nerve showed perineurial calcifications indicative of the chronicity of the neuropathy.[29]

On analysis of various confounding factors, the presence of significant autonomic dysfunction (heart rate change to breathing <7 bpm; Q-SART over distal leg <0.2 μl/cm^2), and appreciable axonal loss (fibre density <1000/mm^2) on sural nerve biopsies were independent poor prognostic factors. On the other hand, the presence of raised CSF protein (>100 mg/dl) and preserved ulnar motor conduction velocities (>38 m/s) were good prognostic markers and predicted good and rapid therapeutic response. The presence of onion bulbs and of inflammatory infiltrates correlated with improvement of the absolute NDSW at weeks 6 and 12 respectively, but this effect was not found when NDSW% change was considered.

Our preliminary results provide quantitative data about diabetes and PRN, and justify a prospective randomised study to determine whether immunotherapy can be beneficial in these instances. Although the tighter diabetic control during the study may have contributed to the clinical benefit, the improvement did not correlate with pretreatment diabetic control values. Also long term follow up is necessary to adequately evaluate the effect of immunosuppressive therapy.[30] The issue of whether diabetes predisposes the peripheral nerve to immune attacks by exposing one or more antigens to the immune system is an intriguing one[31–33] but this could not be addressed by our study. Even in patients most responsive to immunomodulating therapy, we were unable to detect circulatory antibodies described in other immune neuropathies.[34] This suggests that other endogenous and yet undetermined factors play an important part in the genesis of diabetes and rapidly progressive polyradiculoneuropathy. As the natural history of diabetic rapidly progressive polyradiculoneuropathy is uncertain, and because some patients will improve without immunomodulating therapy, our results are only suggestive of benefit with immunotherapy.

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