Chronic and Remitting Painful Diabetic Polyneuropathy

Correlations With Clinical Features and Subsequent Changes in Neurophysiology

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Twenty-nine diabetic patients (19 men, 10 women) aged 19–71 yr with newly developed painful polyneuropathy were studied prospectively for 12–18 mo. Pain remitted completely in 16 patients within 12 mo, but continued in the other 13 patients. At presentation, no differences were found in the type or prevalence of symptoms or neurophysiological measurements (electrophysiology and cardiovascular autonomic function tests) between the patients whose pain remitted and those whose pain continued. Most electrophysiological measurements improved slightly in remitting patients but deteriorated slightly in those whose pain continued to reveal a significant difference ($P < .05$) between the groups on final review. Similarly, abnormal autonomic nerve function improved slightly when pain remitted but worsened or persisted in patients whose pain continued, again revealing a significant difference between the groups ($P < .05$) on final review. We also observed that pain remission usually occurred if the onset of symptoms shortly followed some sudden metabolic change (e.g., rapid improvement in glycemic control, ketoacidosis, anorexia nervosa) when the duration of diabetes was relatively short or when considerable weight loss preceded the onset of pain. We suggest that remitting and chronic painful diabetic polyneuropathy have distinctive clinical features at presentation and detectable neurophysiological differences during their symptomatic evolution.
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Painful diabetic polyneuropathy is a relatively common and distressing but poorly understood condition whose natural history has not been clearly established (1,2). In some patients, pain remits spontaneously (3–7), whereas others continue to have pain for many years (6,8). Differences in clinical characteristics or neurophysiological measurements among these patients might provide further insight into the cause of painful neuropathy. In addition, because the relation between the progression of neuropathic symptoms and nerve function is unknown, sequential observations of the unmodified course of diabetic neuropathy are needed to clarify both the choice of measurements and the choice of subjects for therapeutic trials.

To document the unmodified course of painful diabetic polyneuropathy from its inception, we studied 29 diabetic patients newly presenting with painful diabetic polyneuropathy. They were followed prospectively for 12–18 mo. Clinical observations were scored, and neurophysiological tests included both peripheral nerve electrophysiology (reflecting large–nerve fiber function) and cardiovascular autonomic nerve function (reflecting small–nerve fiber function).

MATERIALS AND METHODS

SUBJECTS

The 33 patients studied initially were those presenting with severe newly developed symptoms of painful polyneuropathy to a large diabetic department during 3.5 yr. They were not selected by screening but came

with spontaneous complaints of severe pain for which they were seeking relief. They all had typical neuropathic pain comprising severe discomfort described as one or more of the following: lancinating, deep toothache-like, burning, prickling (pins and needles), and contact-induced pain. Pain was invariably worst at rest, especially at night, and was relieved during but worse after exercise. Patients had no history of problem drinking or symptoms and signs suggestive of peripheral vascular disease. Erythrocyte motor nerve conduction velocity (MCV), plasma γ-glutamyl transpeptidase, serum vitamin B_{12}, and folate and plasma thyroxine were normal in all patients. Four patients were not followed up; one developed bronchial carcinoma after 1 yr, one developed rheumatoid arthritis within 6 mo, another developed peripheral vascular disease (having had normal ankle pressures at presentation) after 8 mo, and a fourth died of a myocardial infarct after 4 mo. The remaining 29 patients (16 with insulin-dependent diabetes mellitus and 13 with non-insulin-dependent diabetes mellitus; Table 1) were studied at presentation, ~6 mo later, and between 12 and 18 mo after presentation. More frequent clinic attendance and improved glycemic control were encouraged. Pain was relieved with a stepwise treatment program based on imipramine (9).

METHODS

Clinical assessment. Each patient was asked to describe the type and distribution of his/her pain in detail at every clinic visit, not just at times of neurophysiological assessment. At each visit, overall pain severity (i.e., total subjective experience of discomfort) was rated by the patient on a five-point adjectival scale: 0 = no pain, 1 = mild, 2 = moderate, 3 = severe, 4 = unbearable. Pain was classified as remitted if the patient, having stopped analgesic therapy, had been completely free of any form of neuropathic pain for at least 3 mo. In our experience and that of others (8), if remission of pain is going to occur, it is apparent within 1 yr of presentation, whereas symptoms that persist longer continue indefinitely. Baseline assessments were made before starting analgesic therapy. Possible autonomic symptoms were also noted, i.e., decreased lower-body or increased upper-body sweating, gustatory sweating, epigastric fullness, nausea, vomiting, intermittent or nocturnal diarrhea, constipation, postural dizziness, and impotence.

A standard-scored clinical examination of the peripheral nervous system was conducted as described previously (10). Retinopathy was graded as 0 = nil, 1 = microaneurysms or dot hemorrhages only, 2 = exudates/cotton wool spots/intraretinal microvascular abnormalities, 3 = neovascularization. Weight was recorded as body mass index (BMI) = weight in kg/(height in meters)^2; normal range 20–25 kg/m^2, and was documented from hospital records except in six subjects in whom symptoms started immediately after diagnosis of diabetes. Undocumented recall of prediabetic weight had to be used in these six subjects. Anorexia nervosa was diagnosed according to criteria described previously (11). Glycemic control was assessed by hemoglobin A_1 (HbA_1) measurement with an electrophoretic technique (normal range 5.5–8.0%).

Peripheral nerve electrophysiology. Measurements were made in the left arm and leg with surface electrodes at a constant skin temperature of 32°C. All measurements were made by the same observer (R.J.Y.) with a single DISA 1500 electromyograph as described previously (10). MCV and the amplitude of the evoked muscle action potential (EMAP) were measured in the median and peroneal nerves. Sensory nerve conduction

TABLE 1
Clinical characteristics of patients at presentation with painful diabetic polyneuropathy

Clinical characteristics at presentation	Outcome of pain		
	Remitting	Continuing	Significance of difference
Gender (M/F)	11/5	8/5	NS
Age (yr)*	42 (19–71)	50 (22–68)	NS
Treatment			NS
Insulin	9	7	
Oral hypoglycemic agent/diet	7	6	
Diabetes duration (yr)*	3.9 (0.2–14)	11.0 (0.1–33)	$P < .01$
Recent events			$P < .001$
Diagnosis of diabetes†	9	2	
Ketoacidosis†	2	0	
Rapid improvement in control†	2	0	
Anorexia nervosa‡	3	0	

*Mean (range).
†Occurred within 3 mo before onset of pain.
‡Established disorder; all 3 were at the nadir of weight loss.

velocity (SCV) and the amplitude of the evoked compound sensory action potential (SPA) were recorded orthodromically in the distal median and antidromically in the sural nerves.

Cardiovascular autonomic function tests. Five tests were used as described previously (12). These were heart rate responses to the Valsalva maneuver (Valsalva ratio), standing up (30:15 ratio) and deep breathing (max-min heart rate), fall in systolic blood pressure on standing (post blood pressure), and the rise in diastolic blood pressure during sustained handgrip (grip). Tricyclic drugs and phenothiazines might have affected the blood pressure–dependent autonomic tests. However, at baseline, no patients were taking these drugs; at 6 mo they were used by 88% of group R (remitting pain) and 62% of group C (continuing pain); at final assessment none of group R and 31% of group C patients were taking these drugs. We do not think that our conclusions have been modified appreciably by drug effects.

Statistics. Statistical analysis was done by the BMDP statistical software package (University of California, Los Angeles, 1983). The Mann-Whitney *U* test was used for between-group comparisons, and Student's paired *t* test was used for within-group comparisons at different times. Patients were grouped solely on the basis of their final symptoms.

RESULTS

CLINICAL OBSERVATIONS

Pain. Within 12 mo pain remitted completely (i.e., pain score of 0 on no medication for >3 mo) in 16 patients (group R) but was still continuous or intermittent in 13 (group C; mean pain score of 1.6, range 1–4). Group R patients rated their initial pain as more severe (mean pain score of 3.2, range 2–4) than group C patients (mean pain score of 2.4, range 1–4), although all were spontaneously seeking treatment for their pain. Recalled duration of pain before presentation was shorter in group R (7 wk, range 2–32 wk) than in group C (23 wk, range 6–40 wk) ($P < .01$). Thus, onset was more acute in group R and more insidious in group C. Pain was always present in the feet but frequently spread to involve the entire leg. In 7 patients (4 from group R, 3 from group C) the pain became more generalized, involving the trunk and arms. At least two or more of the six characteristic types of discomfort were usually described. Lancinating pains were the most common in both groups (81% group C, 85% group R). Burning sensations were more frequent in group R (69%) than in group C (23%) ($P < .05$). Toothache-like discomfort, paresthesia, contact discomfort, and numbness occurred equally in both groups.

Patient characteristics. At presentation there were no differences in sex, age, or diabetic treatment between the two groups (Table 1). We noted that within 3 mo before onset of pain, all group R patients had experienced clinical events likely to cause acute metabolic disturbance, including diagnosis of diabetes, ketoacidosis, rapid improvement in glycemic control due to change in diabetic management, and anorexia nervosa. By contrast, in group C, only two patients had recently diagnosed diabetes, and metabolic control was stable in the others. Associated proximal motor neuropathy with wasting and grade 3 to grade 4/5 weakness was present in six patients, three from group R, three from group C; wasting and weakness improved during the following 12 mo in these six patients. Weakness grading scale used was as follows: *0*) no muscle twitch, *1*) muscle twitch but no movement, *2*) movement but could not overcome gravity, *3*) difficulty overcoming gravity, *4*) difficulty overcoming active resistance, *5*) normal.

Weight loss. All 11 patients with recently diagnosed

TABLE 2
Body mass index (BMI) and glycosylated hemoglobin (HbA_1) at presentation, 6 mo, and 12–18 mo in 29 diabetic patients newly presenting with painful polyneuropathy

		Time						
Variable	Outcome	Presentation	*P*	6 mo	*P*	12–18 mo	*P*	Within-group changes from presentation (*P*)
BMI (kg/m²)	Remitting	20.8 ± 0.7 (15.6–24.9)	<.01	22.0 ± 0.8 (16.3–28.1)	<.05	23.8 ± 0.6 (20.6–28.6)	NS	<.001
	Continuing	24.9 ± 1.1 (18.7–32.1)		25.5 ± 1.3 (19.6–32.1)		26.2 ± 1.1 (19.3–32.7)		<.05
HbA_1(%)	Remitting	10.4 ± 0.8 (7.2–17.7)	<.05	10.1 ± 0.6 (7.6–14.8)	<.05	12.1 ± 1.1 (7.9–18.4)	NS	<.05
	Continuing	13.3 ± 0.9 (8.0–19.9)		12.2 ± 0.9 (7.6–18.0)		12.6 ± 0.9 (8.0–17.8)		NS

For grading system see text. Normal BMI range 19–14 kg/m² for females, 20–25 kg/m² for males.
Normal HbA_1 range 5.5–8%. Other ranges shown in parentheses. NS, not significant.

diabetes reported substantial weight loss before diagnosis and either gained no weight or lost more weight between starting diabetic treatment and developing neuropathic pain. Similarly, all those with established diabetes had documented weight loss before developing pain. In group R, estimated weight loss before presentation was not significantly more than in group C (change in BMI: group R, -3.3 kg/m^2, range -1.0 to -8.3; group C, -2.5 kg/m^2, range -0.5 to -7), but the weight at presentation was lower in group R, and the subsequent weight gain was greater compared with group C (Table 2).

Retinopathy. Retinopathy was commonly undetectable (17 of 29 patients, 59%) at presentation. During follow-up, similar and significant ($P < .05$) increases in the frequency and severity of retinopathy occurred in both groups (group R, mean score 0.9 ± 0.4 initial, 2.1 ± 0.4 final; group C, mean score 1.1 ± 0.4 initial, 2.0 ± 0.4 final). Nevertheless, after 18 mo, five (31%) patients in group R and two (15%) in group C still had no retinopathy.

Neurological assessment. At presentation, sensory scores were worse in group C: vibration 1.1 ± 0.5 in group R vs. 3.5 ± 0.8 in group C, $P < .01$; pinprick 1.2 ± 0.5 in group R vs. 3.6 ± 0.9 in group C, $P < .05$; temperature 1.8 ± 0.5 in group R vs. 3.8 ± 0.7 in group C, $P < .05$. Vibration and pinprick did not change during the follow-up period. In group R deterioration occurred in touch (1.7 ± 0.5 initial, 3.7 ± 0.4 final; $P < .01$) and temperature perception (1.8 ± 0.5 initial, 3.6 ± 0.5 final; $P < .05$) during follow-up but no changes were found in group C. Tendon reflexes were similar at presentation (17.4 ± 0.8 in group R vs. 16.9 ± 1.1 in group C, not significant) but had deteriorated in group C by final review (17.9 ± 0.6 in group R vs. 15.2 ± 0.8 in group C, $P < .01$).

Each patient had at least one autonomic symptom initially (mean 1.6 ± 0.3 in group R, 1.6 ± 0.3 in group C). Mean number of symptoms increased slightly in both groups during the first 6 mo but then improved in group R while remaining increased in group C (1.6 ± 0.3 initial, 2.8 ± 0.6 final; $P < .05$). Six months after presentation, sweating abnormalities were most common (11 of 16 patients in group R, 10 of 13 patients in group C), then gastrointestinal symptoms (7 of 16 patients in group R, 6 of 13 in group C) and postural hypotension (3 of 16 in group R, 6 of 13 in group C). Over half the men were initially impotent (7 of 11 in group R, 5 of 8 in group C); resolution of impotence occurred in 4 patients of group R, but the number with impotence increased to 6 of 8 in group C.

NEUROPHYSIOLOGICAL OBSERVATIONS

Electrophysiology. Mean values for motor and sensory electrophysiology were below the normal range throughout (Table 3). At presentation, MCV in both peroneal and median nerves was equally abnormal in both groups. Subsequently, MCV tended to improve in group R but deteriorate in group C so that significant ($P < .05$) differences between the groups emerged by 12–18 mo.

TABLE 3
Peripheral nerve electrophysiology at presentation, 6 mo, and 12–18 mo in 29 diabetic patients newly presenting with painful polyneuropathy

		Time						
Test	Outcome	Presentation	*P*	6 mo	*P*	12–18 mo	*P*	Within-group changes from presentation (*P*)
Peroneal EMAP (mV)	Remitting	2.2 ± 0.5	NS	2.0 ± 0.3	NS	2.9 ± 0.5	<.05	<.05
(5.6 ± 3.2)	Continuing	2.5 ± 0.7		2.2 ± 0.6		2.0 ± 0.8		NS
Peroneal MCV (m/s)	Remitting	34.7 ± 1.2	NS	34.8 ± 1.2	NS	35.6 ± 1.2	<.05	NS
(46.1 ± 4.1)	Continuing	33.8 ± 2.0		31.1 ± 2.7		30.3 ± 2.6		NS
Median EMAP (mV)	Remitting	11.2 ± 0.9	<.05	11.9 ± 0.9	<.05	10.8 ± 0.8	<.05	NS
(11.8 ± 3.6)	Continuing	8.0 ± 1.4		8.2 ± 1.3		7.9 ± 1.2		NS
Median MCV (m/s)	Remitting	43.7 ± 1.1	NS	46.7 ± 0.9	<.05	46.7 ± 1.2	<.05	<.05
(54.2 ± 5)	Continuing	44.5 ± 1.3		43.9 ± 1.2		42.9 ± 1.2		NS
Sural SPA (μV)	Remitting	2.8 ± 0.6	NS	3.1 ± 1.1	NS	2.0 ± 0.7	NS	NS
(5.8 ± 6)	Continuing	2.5 ± 0.7		1.3 ± 0.6		1.0 ± 0.4		NS
Sural SCV (m/s)	Remitting	25.8 ± 1.4	NS	21.7 ± 1.8	NS	23.3 ± 1.9	NS	NS
(33.7 ± 3.3)	Continuing	24.1 ± 2.0		20.5 ± 1.9		19.7 ± 1.9		NS
Median SPA (μV)	Remitting	5.8 ± 1.0	NS	6.9 ± 1.3	<.05	6.4 ± 1.0	<.05	NS
(10.0 ± 1.5)	Continuing	4.5 ± 0.9		3.7 ± 1.1		3.1 ± 0.6		<.05
Median SCV (m/s)	Remitting	35.6 ± 1.3	NS	36.7 ± 1.1	<.05	39.3 ± 1.3	<.05	<.05
(42.2 ± 4.2)	Continuing	34.9 ± 1.5		32.4 ± 1.9		35.4 ± 1.7		NS

EMAP, amplitude of evoked muscle action potential; MCV, motor nerve conduction velocity; SPA, amplitude of compound sensory action potential; SCV, sensory nerve conduction velocity; NS, not significant. Reference range for each measurement is shown in first column.

TABLE 4
Cardiovascular autonomic function tests at presentation, 6 mo, and 12–18 mo in 29 diabetic patients newly presenting with painful polyneuropathy

Test	Outcome	Time: Presentation	P	6 mo	P	12–18 mo	P	Within-group changes from presentation (P)
Max-min Heart rate (beats/min) (31 ± 9)	Remitting	11.5 ± 1.5	NS	11.3 ± 1.8	NS	12.9 ± 2.3	<.05	<.05
	Continuing	11.3 ± 3.0		7.5 ± 2.0		8.0 ± 2.2		NS
Lying/standing 30:15 ratio (1.29 ± 0.17)	Remitting	1.00 ± 0.01	NS	1.03 ± 0.02	NS	1.12 ± 0.003	<.05	<.01
	Continuing	1.06 ± 0.04		1.01 ± 0.01		1.05 ± 0.03		NS
Valsalva ratio (1.75 ± 0.39)	Remitting	1.30 ± 0.08	NS	1.36 ± 0.07	<.05	1.46 ± 0.09	<.05	NS
	Continuing	1.44 ± 0.12		1.17 ± 0.07		1.36 ± 0.13		NS
Postural blood pressure (mmHg) (−1 ± 8)	Remitting	−25 ± 4	NS	−24 ± 4	<.01	−15 ± 3	<.05	NS
	Continuing	−19 ± 5		−43 ± 7		−32 ± 6		NS
Grip (mmHg) (3 ± 10)	Remitting	18 ± 2	NS	17 ± 2	NS	18 ± 2	NS	NS
	Continuing	20 ± 3		14 ± 3		19 ± 3		NS

Reference range for each measurement is shown in first column. NS, not significant.

A similar pattern was seen for peroneal EMAP, whereas median EMAP was lower in group C than in group R throughout. In the sensory nerves, findings were different in the arm and leg. In the leg, sural SCV and SPA did not differ between the two groups and tended to deteriorate, although nonsignificantly, in both groups over the observation period. In the median nerve there were no differences between the groups at presentation in SCV or SPA, but during follow-up, median SCV improved in group R ($P < .05$) and median SPA deteriorated in group C ($P < .05$) so that significant differences between the groups emerged ($P < .05$) for the motor measurements.

Autonomic function tests. At presentation, mean values for all cardiovascular tests except grip were appreciably below mean control values and there were no differences between the groups (Table 4). During follow-up the values in group R improved (max-min heart rate $P < .05$, 30:15 ratio, $P < .01$); Valsalva ratio, postural blood pressure not significant) but values in group C either deteriorated very slightly or remained unchanged. By final assessment, significant ($P < .05$) group differences had become apparent for max-min heart rate, 30:15 ratio, Valsalva ratio, and postural blood pressure.

GLYCEMIC CONTROL

Initial hyperglycemia was significantly less in group R than in group C, but glycemic control in group R deteriorated ($P < .05$) during follow-up, whereas no appreciable changes were seen in group C (Table 2). The range of glycemic control in both groups was wide and did not correlate with pain severity. No relationship was found between changes in nerve function tests with time and HbA_1 levels.

DISCUSSION

No relation between symptomatic recovery in painful diabetic neuropathy and measurements of nerve functions has been established previously. In our patients with newly presenting painful polyneuropathy, remission or continuation of neuropathic discomfort occurred in almost equal numbers. The two resulting groups were similar in age, sex, and type of diabetic treatment. Although electrophysiological and autonomic measurements were indistinguishable at baseline, statistically significant differences in neurophysiology emerged during follow-up; improvement, or at least arrest of deterioration, was found in the remitting group, in contrast to further deterioration in the group with continuing pain.

Greene et al. (13) and Boulton et al. (8) recorded some sequential electrophysiological but not autonomic measurements in painful diabetic neuropathy. In those studies the patients had exclusively (8) or predominantly (13) long-standing pain, in contrast to our patients with newly presenting pain. This may account for the lack of observed change in their studies, which amounted to only a very small deterioration in MCV over 4 yr (8). The retrospective study by Archer et al. (14) of patients with newly presenting painful neuropathy, most of whom remitted, did not include any sequential electrophysiology, but small improvements of heart rate variation were reported in a few patients, consistent with our observations in the remitting group.

Nerve function abnormalities are common in diabetic patients with no symptoms of neuropathy and may not always reflect structural pathology (10,15,16). However, both electrophysiology and autonomic function are appreciably worse in patients with symptomatic

neuropathy (10); structural alterations involving both large and small fibers have been demonstrated in such patients (17–20), and a recent study suggested that most of the electrophysiological abnormality in symptomatic neuropathy is due to structural changes (21). Thus, in our patients whose symptoms remitted, the electrophysiological changes may represent initial large nerve fiber degeneration followed by subsequent regeneration. It is not known whether a similar relationship exists between cardiovascular autonomic nerve function tests and pathological changes in peripheral small fibers, although there is increasing evidence that abnormal cardiovascular tests are correlated with peripheral sympathetic dysfunction and may therefore be a marker for generalized small fiber pathology (22,23). Our results do show, however, that abnormal autonomic function tests in diabetic patients, hitherto thought capable only of deterioration, can improve.

The cause of neuropathic pain is unknown. Glucose has been shown to have an effect on pain generation and electrophysiology (24,25). However, in our patients, pain severity was inversely related to blood glucose at presentation, rapid improvement of glycemic control commonly precipitated painful neuropathy, and glycemic control deteriorated in the remitting group. Relative levels of glycemia are therefore unlikely to be responsible for the observed differences in symptoms or neurophysiology. It has been suggested that pain generation might be caused by nerve fiber regeneration or degeneration, alterations in the proportion of large and small nerve fibers involved, or a change in the nature of the pathology (26). With the exception of sural nerve electrophysiology and sustained handgrip, differences between the remitting and chronic patients emerged for all electrophysiological and autonomic tests. This is consistent with axonal regeneration causing remission and degeneration causing pain. Because pain was either exclusive to or worst in the legs, the lack of difference in sural nerve measurements may seem surprising. Possibly, sural nerve damage at the stage observed was so severe it obscured differences. The symptomatic associations with other electrophysiological tests clearly does not exclude large–nerve fiber involvement. Small-fiber damage is considered to be an invariable feature of painful neuropathy (26), spontaneous discharges from C-fibers occur in experimental diabetes (27), and the autonomic nervous system has been implicated in pain generation (28,29). Autonomic changes found by us are certainly consistent with a role for small-fiber degeneration and regeneration in the evolution of painful neuropathy.

In addition to finding these neurophysiological distinctions, we have made four observations that may be relevant to understanding the difference between remitting and chronic painful diabetic polyneuropathy. *1*) Remission of pain was associated with the occurrence of events likely to cause a sudden disturbance to the metabolic milieu, whereas patients with continuing pain had chronic unvarying poor glycemic control. *2*) Duration of diabetes was shorter in the remitting group than in the chronic group. *3*) Clinically ascertained sensory loss was less in the remitting group. *4*) Although preceding weight loss was common to all patients as has been noted before (3,14,30), it was most pronounced in the remitting group. Conceivably, a nutritional influence may be superimposed on the effect of diabetes in these patients. This idea is supported by experiments showing that vitamin-substituted protein-calorie malnutrition in nondiabetic animals causes axonal degeneration (31), and that nondiabetic anorexia nervosa patients exhibit neuropathy (32). It is not surprising that sudden metabolic disturbance, short duration of diabetes, less severe sensory loss, and more readily reversible nutritional influences should be associated with spontaneous recovery of neuropathy. Nevertheless, it is of interest that neurophysiologically these patients were similar at presentation to those with chronic painful neuropathy. This emphasizes the complexity of factors that determine nerve function and that should be considered when planning clinical trials in neuropathy.

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