Variable Relationship Between Peripheral Somatic and Autonomic Neuropathy in Patients with Different Syndromes of Diabetic Polyneuropathy

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SUMMARY

The relationship between abnormal peripheral nerve electrophysiology and abnormal cardiovascular autonomic function has been studied in four groups of diabetic subjects, comparable with regard to age, duration, and type of diabetes. Thirty-three had no symptoms of neuropathy, 28 had newly developed painful neuropathy, 24 had chronic painful neuropathy, and 21 had painless neuropathy with associated recurrent foot ulcers. In all three symptomatic groups, electrophysiology and autonomic function were more abnormal than in asymptomatic diabetic subjects. There was a significant overall relationship between peripheral nerve (electrophysiologic) and autonomic (cardiovascular reflex) dysfunction. However, when considered by groups, the degree of cardiovascular reflex abnormality was similar in the three symptomatic groups, whereas electrophysiology was appreciably worse in the foot ulcer group than in patients with painful neuropathy. Thus, patients with painful neuropathy had a higher ratio of autonomic (small fiber) abnormality to electrophysiologic (large fiber) abnormality. By contrast, foot ulceration was associated with the worst electrophysiologic (large fiber) abnormality. Heavier alcohol consumption and more severe retinopathy were also related to foot ulceration. In diabetic subjects with symmetrical sensory neuropathy, the relationship between large fiber and small fiber damage is not uniform. We conclude that there may be different etiologic influences on large and small fiber neuropathy in diabetic subjects and that the predominant type of fiber damage may determine the form of the presenting clinical syndrome. DIABETES 1986; 35:192–97.

Despite the long-recognized association between clinical features of peripheral somatic and autonomic neuropathy in diabetic subjects[1] and the prominence of autonomic symptoms in the various diabetic neuropathic syndromes,[2] the precise relationship between somatic and autonomic damage remains poorly understood. Although previously we reported a broad relationship between abnormalities of peripheral motor nerve electrophysiology and cardiovascular autonomic nerve function in diabetic subjects with autonomic neuropathy,[3] subsequent investigations in patients with symptoms of sensory neuropathy[4] and in diabetic subjects asymptomatic of neuropathy[5–7] have not supported the concept of an exact parallel between somatic and autonomic nerve fiber damage. In addition, some investigators have suggested that the degree of peripheral somatic neuropathy[8] or autonomic neuropathy[9,10] might determine susceptibility to neuropathic ulceration of the foot. The role of autonomic and other small fiber neuropathy in the generation of neuropathic pain is currently under discussion.[11]

We have therefore examined the relationship between peripheral somatic and autonomic neuropathy in diabetic subjects. Patients with the different syndromes of recently developed painful neuropathy, chronic painful neuropathy, and recurrent foot ulceration have been compared with diabetic subjects asymptomatic of neuropathy.

MATERIALS AND METHODS

Patients. The details of the groups of diabetic subjects studied are given in Table 1. Twenty-eight presented with neuropathic pain of <1-yr duration (new painful neuropathy, NPN), 24 had continuous or recurrent neuropathic pain for >1 yr (chronic painful neuropathy, CPN), and 21 had essentially painless neuropathy with recurrent foot ulcers (RFU). The type and subjective severity of pain at the time of study are shown in Table 2. Most of the terms are self-explanatory; "toothache" refers to the dull, deep, gnawing discomfort of the legs and feet likened by many patients to toothache. The RFU patients studied did not have serious infection at the time of study. These three groups were similar in respect of age, sex, and type of diabetes. The fourth group, 33 diabetic subjects asymptomatic of neuropathy (ASN), were selected to be comparable overall for these variables. Patients with a history of problem drinking (psychiatric or medical treatment for alcohol-related illness, alcohol-related driving convictions, etc.) or who on preliminary screening had elevated eryth-

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TABLE 1
Clinical details of patients studied

		Diabetic group			
		Asymptomatic diabetic subjects (ASN)	New painful neuropathy (NPN)	Chronic painful neuropathy (CPN)	Recurrent foot ulcers (RFU)
Number		33	28	24	21
Sex	Male	26	16	17	17
	Female	7	12	7	4
Age (yr)	Mean	50	46	53	48
	(Range)	(20–68)	(19–70)	(25–68)	(24–69)
Duration of DM	Mean	11	7	14	14
	(Range)	(0.5–31)	(0.2–32)	(0.5–31)	(2–45)
Treatment	Insulin	15	18	15	12
	OHA/diet	18	10	9	9
HbA_1 (%)	Mean	9.8	11.9	13.0	13.2
	(Range)	(5.7–13.4)	(7.2–17.9)	(8.4–19.1)	(6.8–21.1)

rocyte MCV, raised plasma gamma GT, reduced serum B_{12} or reduced plasma thyroxine, raised plasma creatinine, or impalpable pedal pulses or ankle pressure index <1[12] were not recruited. Glycemic control was assessed at the time of the study by measuring hemoglobin A_1 using the electrophoretic method (normal 5.5–7.9%).

Clinical assessment. Patients were questioned about the following symptoms of autonomic neuropathy: 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 examination of the peripheral nervous system was performed comprising assessment of light touch (cotton wool), vibration (tuning fork 128 cps), pain (pinprick), temperature (cold metal), and tendon reflexes. Abnormalities were scored as described before.[13] For each sensory modality, the score related to the anatomic level in legs and arms below which sensation was impaired: the higher the level, the higher the score (1 = toes/fingers, 2 = mid-foot/mid-hand, 3 = ankle/wrist, 4 = mid-calf/mid-forearm, etc.). Tendon reflexes were scored (0 = present, 1 = present only with reinforcement, and 2 = absent). These clinical observations are summarized in Table 3.

TABLE 2
Type and severity of neuropathic pain in patients whose clinical characteristics are given in Table 1

Pain	ASN (N = 33)	NPN (N = 27)	CPN (N = 24)	RFU (N = 21)
Type*				
Lancinating	0	23 (85%)	19 (79%)	2 (10%)
"Toothache"	0	13 (48%)	22 (92%)	2 (10%)
Burning	0	13 (48%)	17 (61%)	0
Paresthesia	0	12 (44%)	18 (75%)	0
Contact discomfort	0	10 (37%)	0‡	0
Severity†				
None	33 (100%)	0	0	18 (86%)
Mild	0	2 (7%)	11 (46%)	3 (14%)§
Moderate	0	8 (30%)	8 (33%)	0
Severe	0	12 (45%)	5 (21%)	0
Unbearable	0	5 (18%)	0	0

*See text for details.
†Rated by patients at the time of study on a five-point adjectival scale.
‡Seven CPN patients had reported contact discomfort previously.
§Only three patients in RFU had ever had neuropathic pain, which was very mild and intermittent.

Alcohol consumption. Average alcohol consumption was ascertained by direct questioning. The total number of units consumed in the previous week was recorded; one unit was defined as one-half pint of beer, one pub measure of spirit, sherry, or vermouth, one glass of wine, etc.

Retinopathy. The optic fundi were examined through dilated pupils in a dark room using direct ophthalmoscopy. Retinopathy was graded as 0 = nil, 1 = microaneurysms or dot hemorrhages only, 2 = exudates/intraretinal microvascular abnormalities, and 3 = neovascularization.

Peripheral nerve electrophysiology. Measurements were made in the left arm and leg using a DISA 1500 electromyograph, surface electrodes, and maintenance of skin temperature at 32°C with a thermostatically controlled radiant heater. Motor nerve conduction velocity was measured in the median nerve (elbow-wrist) and peroneal nerve (knee-ankle) using supramaximal stimuli. Sensory nerve conduction velocity was recorded orthodromically in the distal median nerve (index finger-wrist) and antidromically in the mid-sural nerve (calf-lateral malleolus). The stimulus was adjusted to give the largest evoked sensory action potential. Sensory action potential amplitude was assessed from a minimum of 64 averaged evoked potentials. Sensory conduction velocity was always computed from the latency to the peak of the first negative potential. In some cases, there was no evoked sensory action potential on stimulating the sural nerve (ASN = 0, NPN = 6, CPN = 3, and RFU = 16) or no evoked muscle action potential on stimulating the peroneal nerve (ASN, NPN, CPN = 0, and RFU = 6). In these cases, for further analysis, a conduction velocity was assigned that was less than the lowest recorded from nerves with evoked potentials, i.e., 20 m/s for sural sensory conduction velocity and 15 m/s for peroneal motor nerve conduction velocity.

Cardiovascular autonomic function tests. Five tests were used as described before.[14] These were the heart rate responses to the Valsalva maneuver (Valsalva ratio), standing up (30:15 ratio) and deep breathing (maximum-minimum heart rate); the fall in systolic blood pressure on standing (postural blood pressure); and the rise in diastolic blood pressure during sustained handgrip (grip).

TABLE 3
Clinical examination: means and ranges for scored clinical peripheral nerve examination and number of autonomic symptoms

	Asymptomatic diabetic subjects (ASN) N = 33	New painful neuropathy (NPN) N = 28	Chronic painful neuropathy (CPN) N = 24	Recurrent foot ulcers (RFU) N = 21
Sensory score	0.7	5.2	6.0	9.5
Pinprick + cold metal	(0–4)	(0–16)	(2–17)	(9–16)
Sensory score	2.0	6.0	5.6	8.1
Cotton wool + vibration	(0–7.5)	(0–15)	(3–12)	(4.5–16)
Reflex score	0.7	4.3	3.4	7.7
	(0–4)	(0–13)	(0–10)	(0–18)
Autonomic symptoms	0.2	1.6	1.8	2.1
(number)	(0–1)	(0–4)	(0–4)	(1–5)

Derivation of combined variables. Although the tests have been considered individually, we also compared overall electrophysiologic and autonomic abnormalities. The electrophysiologic and autonomic nerve function results were first reduced to a single expression for each patient as follows: standardized variables were calculated for each electrophysiologic and autonomic observation by subtracting the result from the mean for nondiabetic controls and dividing by the standard deviation for controls.

Our own laboratory normal ranges, shown in Table 4, were used for normal means and standard deviations. Each standardized variable was then an expression of the number of standard deviations from the mean of nondiabetic subjects. For each patient, the sum of the six standardized electrophysiologic variables gave a single, combined electrophysiologic variable (CEV). A single, combined autonomic variable (CAV) was calculated in the same way from the sum of the five standardized cardiovascular autonomic function test variables.

Statistical analysis. Analyses were computed using the statistical software package BMDP (University of California, 1983). Comparisons between groups were made using Student's *t*-test after an analysis of variance had established overall differences. The relationships between variables were

TABLE 4
Grouped results of peripheral nerve electrophysiology and cardiovascular autonomic function tests

Measurement [normal value]	Asymptomatic diabetic subjects (ASN) N = 33	New painful neuropathy (NPN) N = 27	Chronic painful neuropathy (CPN) N = 24	Recurrent foot ulcers (RFU) N = 21	Significance					
					ASN vs. NPN	ASN vs. CPN	ASN vs. RFU	NPN vs. CPN	NPN vs. RFU	CPN vs. RFU
Median motor conduction velocity [54.2 ± 5.0 m/s]	50.9 ± 4.0 (44.6–62.5)	44.1 ± 4.5 (33.0–51.4)	44.6 ± 4.1 (36.0–53.5)	40.6 ± 5.6 (26.1–48.0)	‡	‡	‡	NS	*	*
Peroneal motor conduction velocity [46.1 ± 4.1 m/s]	42.7 ± 4.5 (33.0–52.6)	34.1 ± 5.8 (17.4–46.7)	32.7 ± 4.8 (18.7–35.8)	25.1 ± 8.7 (15.0–41.2)	‡	‡	‡	NS	‡	‡
Median sensory conduction velocity [42.4 ± 4.2 m/s]	36.4 ± 4.5 (23.6–42.2)	34.2 ± 5.4 (20.0–43.6)	33.4 ± 5.2 (20.6–41.4)	29.4 ± 5.3 (20.0–38.9)	NS	NS	‡	NS	†	*
Sural sensory conduction velocity [33.7 ± 3.3 m/s]	28.2 ± 4.8 (20.3–39.5)	25.3 ± 4.1 (20.0–33.3)	23.9 ± 3.4 (20.0–30.1)	21.1 ± 2.3 (20.0–26.8)	*	‡	‡	NS	†	NS
Median sensory potential amplitude [10.0 ± 1.5 μV]	8.4 ± 3.5 (2.5–15.1)	5.0 ± 3.6 (1–17.4)	3.6 ± 2.3 (0.5–10)	1.9 ± 1.7 (0.1–5.0)	†	‡	‡	NS	‡	†
Sural sensory potential amplitude [5.8 ± 1.7 μV]	7.4 ± 6.4 (1–25)	2.9 ± 2.3 (0–7.9)	2.4 ± 3.7 (0–6.9)	0.7 ± 0.5 (0–1.3)	†	‡	‡	NS	‡	‡
Valsalva ratio [1.75 ± 0.39]	1.25 ± 0.14 (1.04–1.67)	1.13 ± 0.15 (1.0–1.53)	1.11 ± 0.11 (1.0–1.37)	1.09 ± 0.11 (0.99–1.39)	†	†	‡	NS	NS	NS
30:15 ratio [1.29 ± 0.17]	1.05 ± 0.07 (0.96–1.30)	1.02 ± 0.07 (0.96–1.25)	1.01 ± 0.03 (0.97–1.14)	1.01 ± 0.03 (0.96–1.07)	NS	*	†	NS	NS	NS
Max-min HR [31 ± 9 beats/min]	17.6 ± 8.3 (4–36)	11.1 ± 8.6 (0–32)	10.4 ± 9.5 (0–31)	5.9 ± 5.2 (0–24)	*	†	‡	NS	NS	NS
Post BP [−1 ± 8 mm Hg]	10.1 ± 9.8 (0–36)	21.5 ± 14.9 (0–64)	26.5 ± 26.9 (0–106)	26.1 ± 15.5 (0–54)	*	*	†	NS	NS	NS
Grip [30 ± 10 mm Hg]	28.9 ± 9.0 (10–56)	18.9 ± 9.3 (5–41)	19.4 ± 10.0 (5–43)	20.7 ± 11.1 (3–43)	†	†	*	NS	NS	NS

Normal values (mean ± SD) for nondiabetic subjects of comparable age range are shown in the left-hand column. Group means ± SD and ranges are shown for each clinical category.
The significance of differences for all group comparisons is shown on the right (*$P < 0.01$, †$P < 0.001$, and ‡$P < 0.0001$).

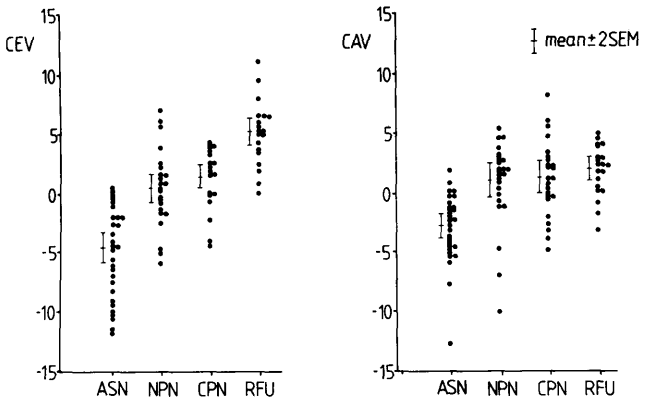

FIGURE 1. Comparison of combined electrophysiologic variables (CEV) and combined autonomic variables (CAV) in the four groups of diabetic subjects studied: ASN, diabetic subjects asymptomatic of neuropathy; NPN, new painful neuropathy; CPN, chronic painful neuropathy; and RFU, recurrent foot ulcers.

studied using linear regression analysis. Partial correlation analysis was used to study the relationship between peripheral nerve electrophysiology and autonomic nerve function, free from the confounding effects of age, duration of diabetes, and prevailing glycemic control.

RESULTS

Electrophysiology and autonomic results—group comparisons (Table 4). The control diabetic group, asymptomatic of neuropathy (ASN), had abnormal electrophysiologic and autonomic function tests when compared with our nondiabetic normal ranges. However, significantly greater abnormalities of both electrophysiology and cardiovascular autonomic function were found in all three neuropathic groups. In addition, diabetic subjects with painless neuropathy and recurrent foot ulceration (RFU) exhibited worse electrophysiologic abnormalities than either of the painful neuropathy groups (NPN and CPN). Electrophysiologic abnormalities occurred in all six tests, but sensory potential amplitudes showed more profound abnormalities and greater group differences than did either motor or sensory nerve conduction velocity measurements. This was true whether the comparison was between the control (ASN) and all three neuropathic groups or between diabetic subjects with painful neuropathy (NPN and CPN) and those with painless neuropathy and foot ulceration (RFU). In contrast, there were no differences in autonomic abnormalities between the three neuropathic groups. However, all neuropathic groups (NPN, CPN, and RFU) were more abnormal than the control, asymptomatic diabetic subjects (ASN) in respect of autonomic nerve function.

Combined variables—group differences (Figure 1). Combined electrophysiologic (CEV) and combined autonomic (CAV) variables were calculated as described above and the scatter of individual results with confidence limits for means is shown for each patient group in Figure 1. This illustrates again that the foot ulcer (RFU) group had much worse electrophysiology (CEV) than either of the painful neuropathy groups (NPN and CPN), whereas there were no differences in cardiovascular autonomic nerve function (CAV). Both electrophysiology (CEV) and autonomic function (CAV) were much worse in the two groups with painful neuropathy (NPN and CPN) than in the diabetic controls (ASN).

Other influences on nerve function. Because such factors as age, duration of diabetes, and prevailing glycemic control can influence neurophysiologic measurements, we were concerned to ensure that they were not responsible for any of the apparently different relationships between peripheral somatic and autonomic neuropathy in the clinically defined subgroups. Considered individually, age was related to CAV ($r = 0.21$, $P < 0.05$), duration of diabetes to CEV ($r = 0.26$, $P < 0.01$), and degree of hyperglycemia (HbA_1) to both (CEV, $r = 0.40$, $P < 0.001$; CAV, $r = 0.18$, $P < 0.05$). However, when statistical allowance was made for these potentially confounding associations, the relationships described above and illustrated in Figure 1 were unaltered. Thus, electrophysiologic but not autonomic abnormalities remained greater in the foot ulcer group (RFU) than in those with painful neuropathy (NPN and CPN). Conversely, the amount of autonomic abnormality for a comparable degree of electrophysiologic abnormality was greater in the painful neuropathy groups.

Relationship between peripheral somatic and autonomic nerve function. The relationships between electrophysiology (CEV) and autonomic function (CAV) were examined further by regression analysis after allowing for the effects of age, duration of diabetes, and glycemic control. There was an overall relationship between CEV and CAV when all the diabetic subjects were considered together ($r = 0.41$, $P < 0.001$). In addition, when the subgroups (ASN, NPN, CPN, and RFU) were considered separately, there was no significant difference between the slopes of the regression lines. However, when CEV was the dependent variable (y), but not when CAV was the dependent variable, there were significant differences in intercepts ($P < 0.001$). Thus, the CEV intercept of RFU was greater than for NPN or CPN, which in turn were greater than for ASN. This confirms that although CEV and CAV are related, the deductions from Figure 1 regarding the relative proportions of the two abnormalities in the different subgroups are still valid.

Retinopathy and alcohol—group comparisons (Table 5). We have considered two other factors, grade of retinopathy as a measure of microangiopathy and alcohol consumption, which might influence the type of neuropathy or susceptibility to foot ulceration. The smoking habits of all four groups were comparable. Retinopathy was worse overall and admitted alcohol consumption slightly greater in the diabetic subjects with recurrent foot ulcers (RFU) than in the other neuropathy groups (NPN and CPN) or in diabetic subjects asymptomatic of neuropathy (ASN). Regression analysis was used to investigate whether the severity of retinopathy or level of alcohol consumption was related to abnormal electrophysiology (CEV) or abnormal autonomic function (CAV). All patients were considered together. There were significant associations (CEV versus grade of retinopathy, $r = 0.23$, $P < 0.02$; CAV versus grade of retinopathy, $r = 0.29$, $P < 0.003$; CEV versus alcohol consumption, $r = 0.32$, $P < 0.001$; and CAV versus alcohol consumption, $r = 0.25$, $P < 0.01$), but the analysis did not indicate that CEV or CAV was particularly related to either retinopathy or alcohol consumption.

TABLE 5
Grade of retinopathy and admitted alcohol consumption

			Asymptomatic diabetic subjects (ASN) N = 33	New painful neuropathy (NPN) N = 27	Chronic painful neuropathy (CPN) N = 24	Recurrent foot ulcers (RFU) N = 21	Significance					
							NPN vs. ASN	CPN vs. ASN	CPN vs. NPN	RFU vs. ASN	RFU vs. NPN	RFU vs. CPN
Retinopathy	Grade 0		23	15	7	7						
	Grade 1		5	5	10	6						
	Grade 2		4	3	3	2						
	Grade 3		1	5	4	10						
	Mean grade for group		0.5	1.3	1.2	1.9	NS	*	NS	*	*	*
Alcohol	Units/wk	Mean	7.7	10.9	8.3	17.7	*	NS	NS	*	*	*
		Range	(0–20)	(0–20)	(0–20)	(0–30)						
Smokers	Number (%)		13 (39%)	13 (48%)	12 (50%)	9 (43%)	NS	NS	NS	NS	NS	NS

Significance of differences for all group comparisons is shown on the right (*$P < 0.01$).

DISCUSSION

This study shows that although there is a relationship between peripheral somatic neuropathy and autonomic neuropathy in diabetes, the relationship is not uniform. In particular, there were consistent differences between patients with painful neuropathy and those with painless neuropathy and foot ulceration. All diabetic subjects with symptomatic neuropathy had similar degrees of autonomic neuropathy, but peripheral somatic neuropathy was markedly worse in those with foot ulcers (RFU) than in those with painful neuropathy (NPN and CPN).

This variation in the relative amounts of electrophysiologic and autonomic abnormality in the different peripheral neuropathy syndromes has not been identified before. Several studies have demonstrated some relationship between peripheral somatic and autonomic neuropathy in diabetic subjects. Martin[1] assessed clinical sudomotor and vasomotor function in 20 patients with symptoms of peripheral neuropathy; Bishnu and Berenyi[15] used the Valsalva maneuver as the only measure of autonomic function in 31 patients with clinical peripheral neuropathy; we previously measured motor nerve conduction velocity in 32 patients with symptomatic autonomic neuropathy;[3] Canal et al.[5] studied 105 insulin-dependent diabetic patients, 37% of whom were said to have symptoms of peripheral neuropathy, but the type was not stratified; Tackmann et al.[4] studied 30 patients, all but 3 of whom had symptoms of peripheral neuropathy; Sundkvist[6] examined 52 long-term diabetic subjects asymptomatic of neuropathy; and we[7] have also studied 79 young, insulin-dependent diabetic subjects asymptomatic of neuropathy. In all these reports, the relationship between peripheral somatic and autonomic nerve abnormalities was positive but weak, so that continuing doubts exist as to whether large myelinated (peripheral somatic) and small unmyelinated (autonomic) nerve fibers are damaged in parallel by diabetes. Our present results demonstrate that the category of peripheral neuropathy as well as age, duration of diabetes, and prevailing glycemic control need to be considered when interpreting such data. When these factors are taken into account, although a broad overall relationship between large myelinated and small autonomic fiber dysfunction is confirmed, supporting the concept of some common pathogenic factors, there are also striking differences between the different neuropathic groups, favoring additional, selective etiologic influences.

Reduced conduction velocity is found in many diabetic subjects without symptoms of neuropathy, may be partly reversible,[16] and does not necessarily imply structural neuronal abnormality. Evoked sensory action potential amplitudes reflect the number of functioning large sensory fibers and reduction implies definite structural neuronal loss.[17] The difference in sensory potential amplitude between patients with recurrent foot ulcers and those with painful neuropathy was greater than for motor or sensory conduction velocity. Therefore, severe loss of large sensory nerve fibers is closely related to the development of diabetic foot ulceration. In both hereditary[18] and nondiabetic-acquired[19] neuropathies associated with acrodystrophy, loss of large myelinated afferent fibers from the skin is also the most salient feature. As yet it is unclear how severe axonal loss leads to ulceration.

In contrast to the electrophysiologic findings, autonomic symptoms and abnormal autonomic nerve function were similar in all three neuropathic groups. It has been proposed that small unmyelinated fiber sympathetic neuropathy may have a cardinal role in the pathogenesis of foot ulcers.[20] Our results do not support this hypothesis and, indeed, previous evidence for a relatively greater degree of autonomic neuropathy in diabetic patients prone to ulceration is inconsistent.[9,10,21] Thus, although autonomic neuropathy, both visceral and peripheral, is a usual accompaniment of foot ulceration in diabetic subjects, it is unlikely to be of prime pathogenic importance because many other diabetic subjects with symptomatic peripheral neuropathy have equivalent autonomic damage but do not develop foot ulcers. This deduction might be criticized in that we have compared peripheral, somatic nerve function with more proximal, visceral cardiovascular autonomic nerve function. No reliable test of peripheral autonomic nerve function exists, but the available evidence suggests that peripheral sudomotor function in the lower limbs and cardiovascular reflex tests do correlate quite well.[4,10,22] Cardiovascular reflex tests have been shown to correlate with all symptoms of autonomic neuropathy,[23] so it is unlikely that the conclusions would have been different if distal autonomic function had been measured.

When compared with the foot ulcer group, those with painful neuropathy had appreciably less large fiber damage as revealed by electrophysiology but equivalent small fiber neuropathy as shown in cardiovascular autonomic reflex tests, i.e., a higher ratio of small fiber to large fiber damage. The pathogenesis of pain in peripheral neuropathy is still obscure and many mechanisms have been proposed.[24] Our observations are consistent with the morphometric findings of Behse et al.,[25] which showed involvement of both large and small fibers, and also with the disproportionate involvement of unmyelinated and small myelinated fibers seen in sural nerve biopsies from a few patients with painful diabetic neuropathy.[26,27]

Retinopathy was most severe in the diabetic subjects with recurrent foot ulceration. A "foot-eye" syndrome[28] has been recognized before. Neural microangiopathy may contribute to the pathogenesis of neuropathy,[29,30] but our results do not show an especially close relationship between retinopathy and abnormal electrophysiology suggestive of microangiopathic nerve damage favoring large fiber axonal loss. Alternatively, microangiopathy may also occur in the feet causing local ischemia that contributes to ulceration. Foot ulceration was also associated with heavier alcohol consumption. Alcoholic neuropathy is predominantly a large fiber axonopathy.[31] It is tempting to speculate that alcohol and diabetes have a synergistic effect on nerves, but the lack of a close overall relationship between alcohol consumption and abnormal electrophysiology makes this doubtful. Because retinopathy may also be partly related to alcohol consumption,[32] a triangular relationship between neuropathy, microangiopathy, and alcohol consumption could account for the observed statistical associations.

In conclusion, we present evidence that the relative involvement of large and small fibers in the polyneuropathies of diabetes mellitus is not uniform, although there is a general association between the large and small nerve fiber damage. Since this finding correlates with some of the clinical manifestations of diabetic neuropathy, further understanding of the mechanisms of large and small fiber damage should lead to better symptomatic and preventive strategies.

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