Nerve Function and Metabolic Control in Teenage Diabetics

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SUMMARY

Peripheral somatic and autonomic nerve function have been studied in 79 teenage (16–19 yr) diabetics and 20 age- and sex-matched normal controls. Almost three-quarters of the diabetics (72%) had abnormal peripheral somatic nerve function tests, and one-third (31%) had abnormal cardiac parasympathetic tests. Both motor and sensory peripheral somatic nerve abnormalities were related to poor prevailing glycemic control (HbA_1) and duration of diabetes. Thus, the 27 patients with three or more (maximum six) peripheral nerve abnormalities had significantly higher HbA_1 levels ($P < 0.001$) and longer duration of diabetes ($P < 0.01$) than the 22 with no abnormalities. Individual peripheral somatic nerve tests almost invariably correlated only with HbA_1 (median motor, $P < 0.05$; peroneal motor, $P < 0.001$; sural sensory, $P < 0.001$) or duration of diabetes (median sensory, $P < 0.001$). Sensory potential amplitude, as well as conduction velocity, was frequently reduced, implying axonal involvement. These findings suggest that abnormal peripheral and autonomic nerve function are common in young insulin-dependent diabetics and that poor metabolic control is a major determinant of the damage. DIABETES 32:142–147, February 1983.

The role of hyperglycemia in the pathogenesis of diabetic neuropathy remains uncertain.[1,2] In non-insulin-dependent diabetics motor nerve conduction abnormalities have been related to the degree of hyperglycemia at diagnosis[3] and to the effect of starting treatment.[4,5] In insulin-dependent diabetics improvements in motor nerve conduction have been shown after commencement of insulin therapy[6,7] or, in patients established on insulin, after 6 wk of improved glycemic control.[8] However, with regard to symptoms and morbidity, it is not the motor but rather the sensory somatic and autonomic components of diabetic neuropathy that are the preeminent problems;[9] indeed, electrophysiologically, the abnormalities of sensory nerve conduction are the most consistent subclinical alteration.[10] Despite this, there have been no detailed studies that have examined the relationships between sensory or autonomic nerve function and metabolic control in diabetics.

Since both age and duration of diabetes affect nerve electrophysiology,[11] we have investigated metabolic control, peripheral somatic motor and sensory nerve function, and autonomic nerve function in a group of teenage insulin-dependent diabetic patients of similar age in whom the onset and duration of diabetes were accurately known.

SUBJECTS

In Scotland, young insulin-dependent diabetics invariably attend a hospital diabetic clinic. All 91 insulin-dependent diabetic patients in the age group 16–19 yr, who were registered at the Diabetic Department of the Royal Infirmary, Edinburgh at the time of recruitment, were asked to participate in this study. Seventy-nine agreed to take part, and the 12 who did not were similar in respect of sex, duration of diabetes, clinic blood glucose results, and number of previous episodes of diabetic ketoacidosis or severe hypoglycemia. Of the 79 studied, 42 were female and 37 were male. The sex distribution throughout the range of durations of diabetes (6 mo–17 yr; median, 5 yr) was approximately equal. Twenty healthy normal volunteers (10 schoolboys and 10 female student nurses) of the same age (16–19 yr) acted as control subjects. Each subject attended on one occasion when the clinical examination and peripheral and autonomic nerve tests were performed and venous blood was withdrawn.

METHODS

Glycemic control. Plasma glucose was measured by a glucose-oxidase technique. Total glycosylated hemoglobin (HbA_1) was measured by an electrophoretic method[12] from

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nondialyzed blood. The range of HbA_1 for normal subjects in this laboratory is 5.5–7.9%.[12] Coefficient of variation for measurements within assays was 2.7% and between assays was 6.5%.

Clinical examination. A standard direct inquiry was made for symptoms of somatic and autonomic neuropathy. Clinical examination of light touch, pin-prick, vibration, deep pain and joint position sensation, motor power, tendon reflexes, and direct funduscopy was carried out by a single observer (R.J.Y.).

Peripheral somatic nerve tests. Nerve conduction studies were performed by the same observer with a DISA electromyograph, using surface electrodes. Both motor and sensory stimuli were supramaximal, and local skin temperature was maintained at 32–34°C throughout. The left arm and left leg were used in each case. Motor nerve conduction velocity (MNCV) was measured in the median nerve (elbow-wrist) and peroneal nerve (knee-ankle). Sensory nerve conduction velocity (SNCV) (latency measured to the first negative peak of the compound action potential) and sensory potential amplitude (SPA) were recorded orthodromically in the terminal segment of the median nerve (1st digit-wrist) and antidromically in the proximal segment of the sural nerve (deep to gastrocnemius-lateral malleolus). For sensory measurements, at least 64 potentials were averaged. Complete nerve conduction studies were obtained on all subjects, except in six diabetics where the recordings of sural sensory measurements were technically unsatisfactory. The measurements for control subjects were repeated on 2 different days and the coefficients of variation of individual measurements were: median MNCV, 4.9%; peroneal MNCV, 2.6%; median SNCV, 3.7%; median SPA, 6.5%; and sural SPA, 4.4%. MNCV and SNCV were defined as abnormal in the diabetics if they

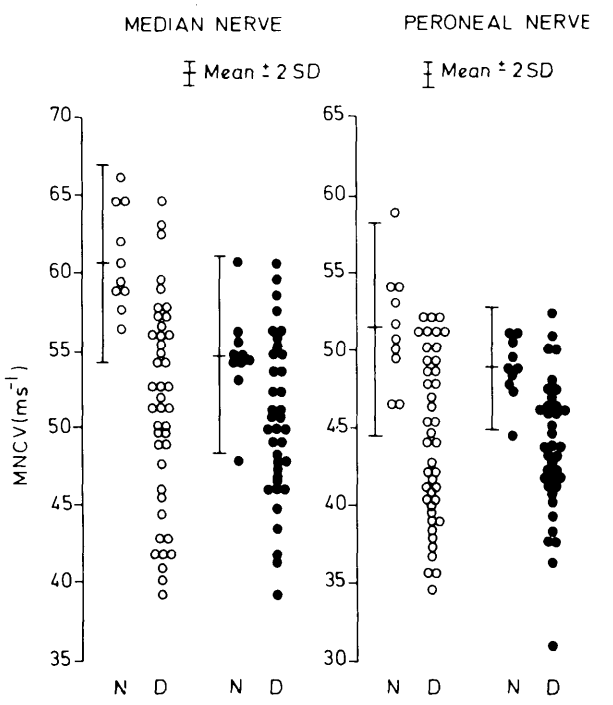

FIGURE 1. Individual motor nerve conduction velocity (MNCV) results for normals (N) and diabetics (D) (female, ○; male, ●). Group means ± 2 SD are shown for normals.

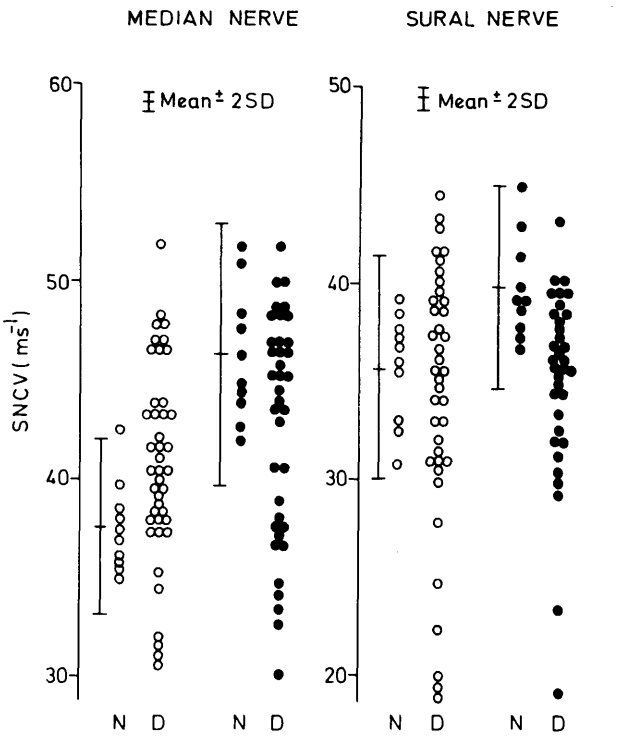

FIGURE 2. Individual sensory nerve conduction velocity (SNCV) results for normals (N) and diabetics (D) (female, ○; male, ●). Group means ± 2 SD are shown for normals.

were more than two standard deviations below the mean for the normal controls (Figures 1 and 2). Because of skewed distributions for the results of SPA in the normal subjects, these measurements were defined as abnormal if they were below the lower limit of the normal control range (Figure 3). Scattergrams of the peripheral nerve test results in the normal and diabetic subjects are shown in Figures 1–3, and the mean results are shown in Table 1. In the normal subjects there were significant differences between the mean values for the males and females of median MNCV ($P < 0.01$), median SNCV ($P < 0.001$), sural SNCV ($P < 0.01$), and median SPA ($P < 0.001$), but not of peroneal MNCV or sural SPA. There were no sex differences observed in the diabetics.

Autonomic nerve tests. Five simple cardiovascular autonomic reflex tests were performed on each subject. The heart rate changes during the Valsalva maneuver (Valsalva ratio), deep breathing (max–min heart rate), and on standing up (30:15 ratio) reflect parasympathetic damage, while the blood pressure responses to standing up and sustained handgrip detect sympathetic damage. These tests have previously been described in detail.[13–15] One diabetic subject was found to have asymptomatic supraventricular tachycardia due to cardiomyopathy; therefore, his autonomic function tests were excluded. Eight tests in six other diabetics were also technically unsatisfactory and have also been excluded. The age group under study is appreciably younger than we have previously reported and some of the normal ranges are slightly different from those we have defined before. The parasympathetic test results in the normal subjects are shown in Figure 4. For the sympathetic tests a rise in diastolic blood pressure of 10 mm Hg or less during sustained handgrip was, as before, defined as abnormal (normals, 38 ± 13 (SD)

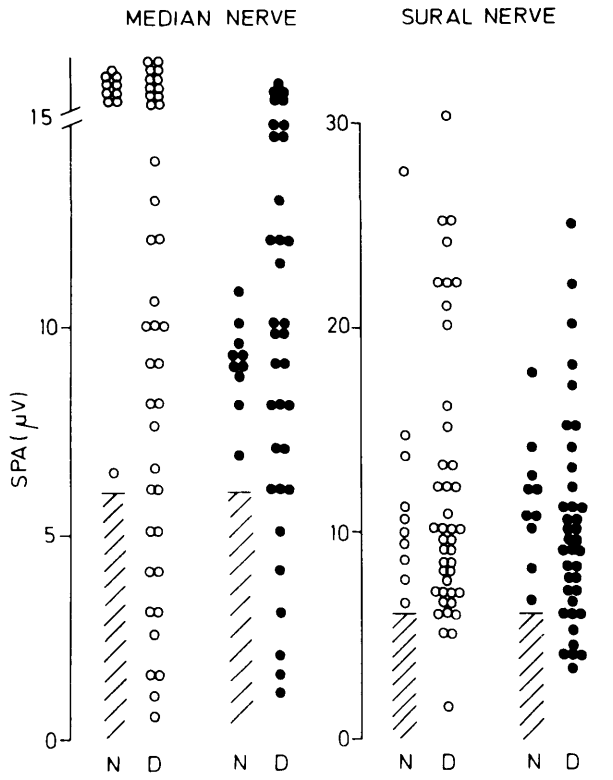

FIGURE 3. Individual sensory potential amplitude (SPA) results for normals (N) and diabetics (D) (female, ○; male, ●). Hatched area represents defined abnormal range.

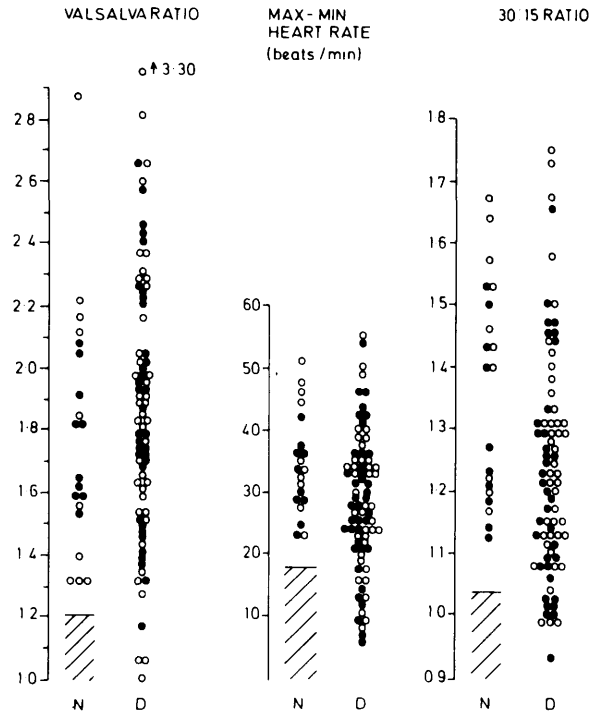

FIGURE 4. Individual Valsalva ratio, maximum–minimum heart rate, and 30:15 ratio results for normals (N) and diabetics (D) (female, ○; male, ●). Group means are shown for normals. Hatched area represents defined abnormal range.

mm Hg; range, 23–64), while a fall in systolic blood pressure on standing of more than 14 mm Hg was considered abnormal (normals, 1 ± 6 mm Hg; range, +10 to −10).

Analysis. Standard statistical tests were used throughout. Results in the text are expressed as mean ± standard deviation.

RESULTS

Glycemic control. In the 79 diabetics the mean random plasma glucose at the time of the test was 12.2 ± 6.8 mmol/L (range, 3.4–30.0). No patient was ketonuric. Mean HbA_1 was 11.8 ± 3.0% (range, 6.1–21). There was a significant correlation between plasma glucose and HbA_1 ($r = 0.43$, $P < 0.001$), but there was no relationship between either plasma glucose or HbA_1 and duration of diabetes.

TABLE 1
Mean electrophysiologic measurements

	Normal		Diabetic	
Measurement	Male	Female	Male	Female
Median MNCV (± SD) ms^{-1}	54.6 ± 3.2	60.6 ± 3.7	50.1 ± 5.2	50.9 ± 7.2
Median SNCV (± SD) ms^{-1}	46.2 ± 3.4	37.5 ± 2.3	42.3 ± 5.7	40.0 ± 5.1
Median SPA (± SD) μV	9.0 ± 1.2	16.4 ± 4.1	9.8 ± 5.1	10.0 ± 4.8
Peroneal MNCV (± SD) ms^{-1}	48.8 ± 2.0	51.5 ± 3.5	43.6 ± 4.4	44.3 ± 5.5
Sural SNCV (± SD) ms^{-1}	39.8 ± 2.6	35.7 ± 2.7	35.7 ± 4.0	35.3 ± 6.2
Sural SPA (± SD) μV	11.4 ± 3.1	11.9 ± 6.1	10.3 ± 5.7	12.9 ± 9.7

Clinical features. No patients had symptoms of somatic or autonomic neuropathy and only three had minimally abnormal clinical findings; one had diminished pin-prick sensation to the level of the ankles and two had diminished ankle jerks. All three of these patients had at least four abnormal peripheral somatic electrophysiologic nerve tests (maximum six).

Peripheral somatic nerve tests. Twenty-two patients (28%) had uniformly normal peripheral somatic nerve tests, 15 (19%) had motor abnormalities alone, 9 (11%) had sensory abnormalities alone, and 33 (42%) had combined motor and sensory abnormalities. The individual results are shown in Figures 1–3.

It was systematically investigated whether any relationship existed between each of the six peripheral somatic nerve tests and the remaining five. Significant correlations were found for peroneal MNCV with median MNCV ($P < 0.001$), sural SNCV ($P < 0.001$), and log sural SPA ($P < 0.001$); median MNCV with median SNCV ($P < 0.001$) and log median SPA ($P < 0.05$); sural SNCV with median SNCV ($P < 0.01$); and log sural SPA with log median SPA ($P < 0.001$). Since there was a clear interrelationship between the various tests, in keeping with the known uniform involvement of the peripheral nerves in diabetic polyneuropathy, it was considered justifiable to amalgamate the motor and sensory results as shown in Figure 5. Patients were divided arbitrarily into three groups: those with no abnormalities (22), those with one or two abnormalities (30), and those with three or more abnormalities (27); the maximum possible number of abnormalities was six. There were significant differences between the groups

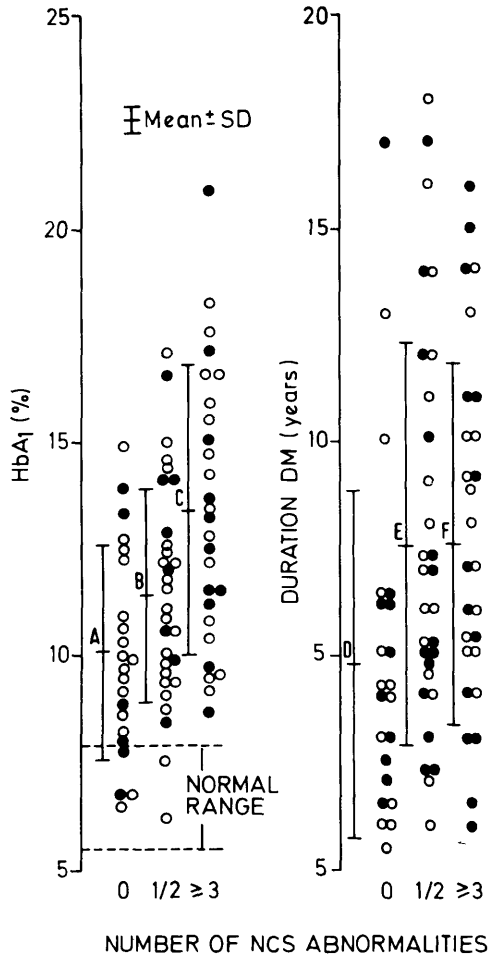

FIGURE 5. HbA_1 and duration of diabetes in teenage diabetics with 0 (N = 22), 1 or 2 (N = 30), 3 or more (N = 27) peripheral somatic nerve (NCS) abnormalities (female, ○; male, ●). Means (A–F) ± SD are shown for each group. Differences between means were analyzed by Student's *t* test: CvsA ($P < 0.001$); CvsB ($P < 0.02$); BvsA (NS); EvsD ($P < 0.05$); FvsD ($P < 0.05$); FvsE (NS).

for both HbA_1 and duration of diabetes as shown in Figure 5, but not for plasma glucose.

Table 2 shows the relationships between the individual peripheral somatic nerve test results and both HbA_1 and duration of diabetes. MNCV correlated significantly with HbA_1, in both the arm and the leg, whereas the sensory measurements (SNCV, SPA) correlated significantly with HbA_1 only in the leg. By contrast, duration of diabetes was correlated with motor and sensory measurements only in the arm and not in the leg. Plasma glucose correlated significantly only with peroneal MNCV ($r = 0.38$, $P < 0.001$).

Autonomic nerve function tests. Abnormal parasympathetic tests were found in 24 diabetics (31%). Figure 4 details the individual results. In 19 diabetics only one parasympathetic test was abnormal, in 4 patients two were abnormal, and 1 patient had three abnormal tests. Two patients, one male and one female, also had abnormal postural blood pressure responses (−20 mm Hg and −24 mm Hg, respectively). The male patient had two abnormal parasympathetic tests and in the female all three parasympathetic tests were abnormal. No patients had abnormal handgrip responses. In those patients with abnormal autonomic tests, the mean duration of diabetes (7.7 ± 0.9 yr) and HbA_1 (12.6 ± 0.6%) was greater than in those with normal tests (6.6 ± 0.6 yr, 11.4 ± 0.4%) but neither of these differences was statistically significant.

Other complications. Thirty-two patients had previously documented ketoacidosis; 25 had had a maximum of three episodes, while the other 7 had had more than three episodes. Retinal microaneurysms were noted in six patients, but no other features of diabetic retinopathy were seen. No significant relationship was found between previous ketoacidosis or retinopathy and either peripheral somatic or autonomic nerve abnormalities.

DISCUSSION

We have found that the majority (72%) of our young diabetics had at least one abnormal electrophysiologic test. Studies of peripheral somatic nerve function have been reported in diabetic children and adolescents before,[16–19] but the results are difficult to compare with ours because, with the exception of the study by Gamstorp et al.,[18] wide age ranges were included, local skin temperature was not controlled, either motor or sensory conduction alone was measured, and the analyses did not take into account variations in normal values throughout childhood and adolescence.[20] This may account for the lower frequency of electrophysiologic abnormalities reported by these authors (9%, Eeg-Olofsen et al.;[17] 32%, Lawrence et al.;[16] 50%, Ludvigsson et al.[19]). In the study by Gamstorp et al.,[18] 21 (51%) of 37 children aged 12–16 yr had at least one electrophysiologic abnormality, and abnormal nerve conduction was more common with long duration of diabetes. Given that 81% of their patients had duration of diabetes of less than 5 yr, as compared with just

TABLE 2
Correlation of individual peripheral somatic nerve tests with HbA_1 and duration of diabetes

		HbA_1		Duration of diabetes	
Limb	Peripheral nerve test	Correlation coefficient	Significance	Correlation coefficient	Significance
Arm	Median MNCV	0.35	$P < 0.005$	0.28	$P < 0.02$
	Median SNCV	0.09	NS*	0.23	$P < 0.05$
	Log median SPA	0.16	NS	0.36	$P < 0.001$
Leg	Peroneal MNCV	0.40	$P < 0.001$	0.11	NS
	Sural SNCV	0.30	$P < 0.01$	0.12	NS
	Log sural SPA	0.39	$P < 0.001$	0.10	NS

*NS is not significant.

42% in our study, the prevalences of peripheral somatic nerve abnormalities are probably comparable.

Autonomic nerve abnormalities have not previously been investigated in a large group of teenage diabetics, perhaps because they have usually been equated with symptomatic autonomic neuropathy, which is considered a late complication of diabetes.[15] Nevertheless, this study demonstrates that cardiac parasympathetic reflex abnormalities are not uncommon in young insulin-dependent diabetics.

We have shown that disturbances of motor and sensory peripheral somatic nerve function in young type I diabetics are related to both the prevailing glycemic control, as assessed by HbA_1, and the duration of diabetes. In established older diabetics, motor conduction abnormalities have previously been found to correlate with the duration of diabetes.[11] Motor conduction abnormalities at diagnosis have also been shown to improve after starting diabetic treatment,[3,4,7] and the magnitude of such an improvement in non-insulin-dependent diabetics has been related to the degree of improvement in glycemic control as assessed by HbA_1.[5] However, nerve function in diabetics established on treatment has not previously been related to the prevailing level of metabolic control. This is important because it is quite possible that the reversible abnormalities of motor nerve conduction present at diagnosis reflect a temporary metabolic upset of peripheral nerve function that is distinct from the lesion responsible for clinically relevant neuropathy. Furthermore, these earlier studies have shown changes or relationships only for motor nerve conduction whereas our study demonstrates that sensory nerve abnormalities are also related to glycemic control and duration of diabetes. A suggested explanation for the previous difficulty in establishing a link between abnormal nerve function and poor metabolic control in established diabetics is that until recently there was no reliable measure of longer-term glycemic control; the absence of correlations between blood glucose and nerve conduction in the present study exemplifies this. The autonomic abnormalities were not clearly related to metabolic control and duration of diabetes, possibly because of the relatively small number of abnormalities, but trends are apparent for both.

Although the motor and sensory peripheral nerve measurements are interrelated and the total number of peripheral somatic nerve abnormalities detected in this study has been shown to be related both to HbA_1 and duration of diabetes, the predominant influence on the individual sensory nerves in the arms and legs appears to be different. Thus, we have found a relationship between sensory potential amplitude and metabolic control, but not duration of diabetes, for the proximal segment of the sural nerve, and the reverse for the distal segment of the median nerve. It is recognized that the clinically obvious distal to proximal gradient of abnormality in diabetic sensory somatic neuropathy[9] is also apparent *pathologically*[21] and *electrophysiologically*.[22] It may be, therefore, that the distal abnormalities we have demonstrated in the median nerve are permanent, related predominantly to duration of diabetes, and represent an integrated response to repeated metabolic insults over the years, whereas the more proximal lesions of the sural nerve, although electrophysiologically similar, may still be reversible, and hence correlated with the prevailing HbA_1. This interpretation of our findings is consistent with a metabolic etiology for peripheral sensory nerve damage in human diabetes in which there is a distal to proximal gradient of abnormality, the severity of which, at any point in the nerve, corresponds to the net combined effects of metabolic control and duration of diabetes.

Sensory potential amplitude is proportional to the number of intact large myelinated (> 7 μm in diameter) conducting fibers,[23] whereas motor and sensory conduction velocity measurements reflect predominantly Schwann cell damage.[24] It has been shown, however, by counting motor unit numbers[25] that MNCV can also be related to axonal dysfunction. Therefore, our results imply that there is extensive axonal as well as Schwann cell malfunction in young diabetic patients who are free of clinically detectable neuropathy. This supports collateral evidence from animal models of diabetes that the axon is involved early in the development of diabetic peripheral nerve damage.[1,26]

In experimental diabetes, electrophysiologic abnormalities are often present without morphologic changes[27] but, given the former, the latter will ultimately occur.[28] In humans, relationships between clinical and electrophysiologic abnormalities are uncertain. Similarly, whether cardiac parasympathetic abnormalities without symptoms will prove an accurate predictor of later symptomatic autonomic neuropathy with its poor prognosis[29] is unknown at present. Further prospective studies are required to resolve these important points.

We present evidence for widespread damage, which relates to metabolic control, to the peripheral somatic and autonomic nerves in the majority of teenage diabetics. If these abnormalities are found to progress in parallel with poor metabolic control and to presage clinically apparent damage, then the implications for possible prevention of the neuropathic complications of diabetes will be clear.

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