Early Involvement of the Spinal Cord in Diabetic Peripheral Neuropathy

DINESH SELVARAJAH, MRCP[1]
IAIN D. WILKINSON, PHD[2]
CELIA J. EMERY, PHD[1]
NIGEL D. HARRIS, PHD[3]
PAMELA J. SHAW, PHD[4]
DANIEL R. WITTE, PHD[5]
PAUL D. GRIFFITHS, PHD[2]
SOLOMON TESFAYE, MD[1]

OBJECTIVE — The pathogenesis of diabetic peripheral neuropathy (DPN) is poorly understood. We have recently reported a significant reduction in spinal cord cross-sectional area at the stage of clinically detectable DPN. In this study, we investigated whether spinal cord atrophy occurs in early (subclinical) DPN.

RESEARCH DESIGN AND METHODS — Eighty-one male type 1 diabetic subjects, 24 nondiabetic control subjects, and 8 subjects with hereditary sensory motor neuropathy (HSMN) type 1A underwent detailed clinical and neurophysiological assessments. Diabetic subjects were subsequently divided into three groups based on neuropathy severity (19 with no DPN, 23 with subclinical DPN, and 39 with clinically detectable DPN). All subjects underwent magnetic resonance imaging of the cervical spine and cord area measurements at disc level C2/C3.

RESULTS — Mean corrected spinal cord area index (SCAI) (corrected for age, height, and weight) was 67.5 mm [95% CI 64.1–70.9] in diabetic subjects without DPN. Those with subclinical (62.4 mm [59.5–65.3]) and clinically detectable DPN (57.2 mm [54.9–59.6]) had lower mean SCAIs compared with subjects with no DPN ($P = 0.03$ and $P < 0.001$, respectively). No significant difference was found between diabetic subjects without DPN and nondiabetic control subjects (69.2 mm [66.3–72.0], $P = 0.47$). Mean SCAIs in subjects with HSMN type 1A (71.07 mm [65.3–76.9]) were not significantly different from those for nondiabetic control subjects and diabetic subjects without DPN. Among diabetic subjects, SCAI was significantly related to sural sensory conduction velocities and the Neuropathy Composite and Symptom Scores.

CONCLUSIONS — Spinal cord involvement occurs early in DPN. There is also a significant relation between reduction in SCAI and neurophysiological assessments of DPN.

Diabetes Care **29:2664–2669, 2006**

Diabetic peripheral neuropathy (DPN) is one of the most common forms of neuropathy in the western world (1). Although metabolic and vascular (2) mechanisms have been proposed, a complete understanding of the pathogenesis of DPN remains elusive (3,4).

Research into DPN has focused mainly on the peripheral nervous system with central nervous system involvement being relatively overlooked. However, involvement of the spinal cord has been reported in postmortem studies, which demonstrated axonal loss, gliosis, and demyelination within the spinal cord (5–9). In many of these studies, patients with DPN were not examined specifically, and it is therefore not possible to conclude whether these changes were due to neuropathy or diabetes per se. Knowledge of the full extent of nervous system involvement is crucial for a greater understanding of the pathogenesis of DPN.

In a recent pilot study, we demonstrated a significant reduction in cross-sectional area of the cervical spine using magnetic resonance imaging (MRI) in subjects with advanced DPN compared with nondiabetic control subjects (10). However, the relevance of these findings to the pathogenesis of DPN is dependent on whether spinal cord shrinkage occurs early. The present study was adequately powered to examine spinal cord involvement in patients with early (subclinical) DPN.

RESEARCH DESIGN AND METHODS

— Type 1 male diabetic subjects from the Royal Hallamshire Hospital Diabetes Register were screened for the study between October 2001 and January 2004. To be eligible, participants had to meet the following inclusion criteria: type 1 diabetes diagnosed for >5 years and age between 18 and 65 years. We excluded patients for the following reasons: clinical evidence of disease in the central nervous system (e.g., cerebrovascular disease), significant back problems (either known degenerative back disease or symptoms that have occurred on a regular basis or have required consultation for investigation and treatment), a history of spinal trauma, nondiabetic neuropathies, a history of alcohol consumption of >20 units/week (1 unit is equivalent to 1 glass of wine or 1 measure of spirits), painful neuropathy (as patients may have acute reversible painful neuropathic syndromes without functional nerve abnormalities), diabetic neuropathies other than DPN (e.g., mononeuropathies or proximal motor neuropathies), or claustrophobia or other factors that precluded MRI. We also recruited age- and sex-matched nondiabetic control subjects and subjects with hereditary sensory motor neuropathy (HSMN) type 1A (Charcot-Marie-Tooth 1A). Subjects with HSMN type 1A were identified from a specialist neurology clinic where the diagnosis was confirmed by identification of mutations/duplications on PMP-22. Subjects from the same proband were excluded to avoid selection bias. All subjects gave written

From the [1]Diabetes Research Unit, Royal Hallamshire Hospital, Sheffield, U.K.; the [2]Academic Unit of Radiology, University of Sheffield, Sheffield, U.K.; the [3]School of Health, University of Bath, Bath, U.K.; the [4]Academic Unit of Neurology, University of Sheffield, Sheffield, U.K.; and the [5]Department of Epidemiology and Public Health, Royal Free and University College London Medical School, London, U.K.

Address correspondence and reprint requests to Dr. Solomon Tesfaye, Diabetes Research Unit, Royal Hallamshire Hospital, Sheffield S10 2JF, U.K. E-mail: solomon.tesfaye@sth.nhs.uk.

Received for publication 25 March 2006 and accepted in revised form 18 August 2006.

Abbreviations: DPN, diabetic peripheral neuropathy; HSMN, hereditary sensory motor neuropathy; MRI, magnetic resonance imaging; NCS, Neuropathy Composite Score; NSS, Neuropathy Symptom Score; SCAI, spinal cord area index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0650

informed consent before participation in the study, which had prior approval by the South Sheffield Regional Ethics Committee.

Diabetic peripheral neuropathy assessments

Neuropathic symptoms were documented by completion of a standard questionnaire (Neuropathy Symptom Score [NSS]). Then the outcome of a detailed neurological examination was graded by defined criteria according to the standard Neuropathy Impairment Score questionnaire (11).

All subjects underwent *1*) vibration and cooling detection thresholds acquired from the dorsal aspect of the right foot using the Computer Assisted Sensory Evaluation IV (W.R. Electronics, Stillwater, MN) system employing standard techniques (12,13); *2*) cardiac autonomic function tests performed with a computer-assisted technique (14); and 3) nerve conduction studies performed at a stable skin temperature of 31°C and a room temperature of 24°C using a Medelec electrophysiological system (Synergy Oxford Instruments, Oxford, U.K.). The following nerve attributes were measured: *1*) sural sensory nerve action potentials and conduction velocities and *2*) common peroneal and tibial motor nerve distal latency, compound muscle action potential, and conduction velocity. On the basis of these clinical and neurophysiological assessments, diabetic subjects were divided into three groups: *1*) no DPN, consisting of asymptomatic subjects with normal clinical and neurophysiological assessments, *2*) subclinical DPN, consisting of asymptomatic subjects with normal clinical and at least two abnormalities on neurophysiological assessments; and *3*) clinically detectable DPN, comprising subjects with both clinical and neurophysiological abnormalities.

In addition, a Neuropathy Composite Score (NCS) derived from the assessments described above (Neuropathy Impairment Score of the Lower Limbs plus seven tests of nerve function) was calculated (15,16). A full description of the method of calculation has been described elsewhere (15,16). This scoring system takes into account the findings of neurological examination and neurophysiological assessments: the higher the composite score the more severe the neuropathy. In all subjects, assessments to stage the severity of neuropathy were made within 7 days of MRI.

MRI protocol

All subjects underwent MRI of the cervical spine using a standard spinal phased-array receive only radiofrequency coil on a system operating at 1.5 T (Eclipse; Philips Medical Systems, Cleveland, OH). T2-weighted imaging was performed axially from C1 to T2 using a gradient echo technique (echo time 17.9 ms, repeat time 800 ms; slice thickness 4 mm; in-plane resolution 0.78 × 0.96 mm). Spinal cord cross-sectional area was measured at the level of disc space C2/C3 in all subjects (17). Total imaging time was 15 min.

Data analysis

Before the analysis was performed, an experienced neuroradiologist (P.D.G.) reviewed the standard images acquired (axial T2, sagittal T1 and T2) to exclude any anatomical abnormalities. A simple 4-point scoring system was used to quantify the degree of degenerative vertebral disease affecting subjects in this study (normal = 0, thecal indentation only = 1, thecal indentation touching the spinal cord = 2, and spinal cord compression = 3) (17).

The average of spinal cord area measurements (nerve roots were excluded) from three slices at the level of C2/C3 was then calculated (17). In the pilot study, cord area measurements were performed at three different levels of the spinal cord (C2/C3, C6/C7, and T9/T10) and demonstrated a significant difference in cord area at C2/C3. Hence, we focused our attention at this level in this larger adequately powered study. Furthermore, at this level, cerebrospinal fluid tends to encircle the cord, facilitating the semiautomated computerized thresholding method used to measure cord cross-sectional area. In addition, positioning the patient to ensure that the cord at this level is in the middle of the bony canal (i.e., not touching the bone) is easy as the neck is kept in a more comfortable neutral position. An assessor (D.S.), who was blinded to subject identity, performed the analysis. Because variations in slice prescription and intersubject anthropometric (age, height and weight) differences can introduce errors/differences in spinal cord area, corrections were made for all of these variables to isolate the effect of diabetes only. Variations in slice positioning will result in the artificial scaling of structures in the image acquired. As all structures in an image will experience the same amount of artificial scaling, dividing the absolute cord area by the anteroposterior diameter of the spinal canal will account for this variation. This correction ratio of spinal cord area (spinal cord area index [SCAI]) serves as an index of cord atrophy and has been used in the subsequent analyses.

Statistical analysis

All analyses were performed using the statistical package SPSS 11.1. Baseline characteristics were described as means and SD for normally distributed variables and as medians and interquartile range for variables with a skewed distribution. Action potentials were undetectable in 18 patients for the sural nerve and in 4 patients for the peroneal nerve. Hence, in these circumstances, we excluded the values for sural and peroneal nerve conduction velocity and distal latency from all statistical analyses.

We used ANCOVA to compare differences between groups (nondiabetic control subjects, those with HSMN type1A, and no DPN, subclinical DPN, and clinically detectable DPN groups), by calculating mean SCAI per group adjusted for age, height, weight, and HbA_{1c} (A1C). By adjusting the mean SCAI for age, height, weight, and A1C, we account for the possible confounding effects these baseline characteristics may have on the changes of SCAI among the groups. Hence, only changes attributed to diabetes were reported. The relation between mean SCAI and individual attributes of nerve function (e.g., nerve conduction velocities, vibration detection threshold, and others), NCSs and NSSs was analyzed in more detail among subjects with diabetes ($n = 81$) using linear regression. Data distributions were checked, and those that were skewed were transformed before linear regression analysis.

To assess the effects of observer experience, 18 subjects were randomly selected and reanalyzed by two observers (experienced [D.S.] and novice [C.J.E.]) to determine the intra- and interobserver variation. These 18 subjects were also rescanned after being repositioned on the scanner to determine the scan-rescan variation.

RESULTS

Participant flow

Eligibility for the study was assessed for 203 subjects with diabetes. Of these, 105 were eligible according to the study criteria and were willing to undergo neurophysiological assessments, and 81 subsequently underwent MRI. Seventeen

Table 1—*Demographic and neurophysiological parameters of study*

	No DPN	Subclinical DPN	Clinical DPN	Nondiabetic control subjects	HSMN
n	19	23	39	24	8
Age (years)*	37.9 ± 9.4	44.3 ± 10.4	51.1 ± 8.2	47.6 ± 13.1	52.6 ± 15.4
Height (cm)	177.3 ± 5.5	176.1 ± 7.4	175.2 ± 6.9	175.6 ± 5.4	176.3 ± 5.6
Weight (kg)	88.3 ± 12.5	82.8 ± 12.7	81.7 ± 13.3	81.4 ± 14.0	80.9 ± 14.2
A1C*	7.82 ± 0.9	8.02 ± 1.1	8.63 ± 0.9	NA	NA
Duration of diabetes (years)*	17.8 ± 9.5	22.0 ± 10.6	27.2 ± 9.8	NA	NA
Sural velocity	43.8 (4.7)	37.3 (4.3)	25.0 (35)	44.6 (9.5)	ND
Sural amplitude	10.6 (4.9)	4.7 (2.6)	0.1 (4.1)	11.1 (9.6)	ND
Peroneal velocity	43.2 (3.2)	38.3 (3.1)	34.7 (5.8)	44.8 (6.4)	ND
Tibial velocity	43.3 (2.7)	38.3 (7.3)	35.2 (5.1)	41.1 (7.5)	ND
Heart rate variability on diabetes	1.4 (0.32)	1.3 (0.34)	1.2 (0.29)	1.4 (0.3)	ND
Peroneal amplitude	5.2 (3.4)	4.3 (3.0)	1.6 (2.9)	6.3 (2.8)	ND
Vibration JND	15.7 (3.62)	18.6 (3.76)	21.9 (4.46)	17.3 (3.51)	ND
NCS	0.0 (0.0)	4.0 (3.0)	13.0 (12)	NA	NA
NSS	0.0 (0.0)	0.0 (1.0)	3.0 (3.0)	NA	NA

Data are means ± SD or median (interquartile range) for variables with a skewed distribution. Sural sensory nerve conduction velocity (sural velocity, ms^{-1}), sural sensory nerve action potential (sural amplitude, μV), common peroneal nerve conduction velocity (peroneal velocity, ms^{-1}), tibial motor nerve velocity (tibial velocity, ms^{-1}), R-R variability with heart rate deep breathing (heart rate variability on diabetes), common peroneal compound muscle action potential (peroneal amplitude, μV), and vibration "just noticeable difference" (vibration JND) of the subjects (no DPN, diabetic subjects with no neuropathy; subclinical DPN, diabetic subjects with early neuropathy; clinical DPN, diabetic subjects with established neuropathy; nondiabetic control subjects; HSMN, subjects with HSMN type 1). *Demographic characteristics statistically significantly different between the groups (ANOVA). NA, not applicable; ND, not detectable.

withdrew from the study before imaging, and 7 had contraindications to MRI. Twenty-four nondiabetic healthy control subjects and 8 subjects with HSMN type1A were also recruited.

Baseline characteristics

Table 1 shows demographic details and the results of the neurophysiological and MRI assessments for the three diabetic groups (no DPN, subclinical DPN, and clinically detectable DPN), nondiabetic control subjects, and subjects with HSMN type1A.

SCAI measurements per group

Figure 1 shows the mean SCAI per group, after adjustment for age, height, and weight. Diabetic subjects with no neuropathy (no DPN group) had a mean SCAI (67.5 mm [95% CI 64.1–70.9]) similar to that of the nondiabetic control subjects (69.2 mm [66.3–72.0], $P = 0.47$) and the subjects with HSMN type1A (71.07 mm [65.3–76.9], $P = 0.31$). Further analysis revealed that both clinically detectable DPN (57.2 mm [54.9–59.6]) and subclinical DPN (62.4 mm [59.5–65.3]) groups had a significantly lower mean SCAI compared with no DPN subjects ($P < 0.001$ and $P = 0.03$, respectively). The difference between clinically detectable DPN and subclinical DPN groups was statistically significant ($P = 0.006$). When compared with HSMN type1A, diabetic subjects with subclinical DPN and clinically detectable DPN had lower mean SCAIs ($P = 0.01$ and $P < 0.001$, respectively). The test for an inverse linear trend across the three diabetic groups showed $P = 0.001$.

Of patients with clinically detectable DPN and subclinical DPN patients, 25.6 and 8.7%, respectively, had spinal cord atrophy as defined by a corrected spinal cord area <2 SD below that of normal control subjects. None of the diabetic

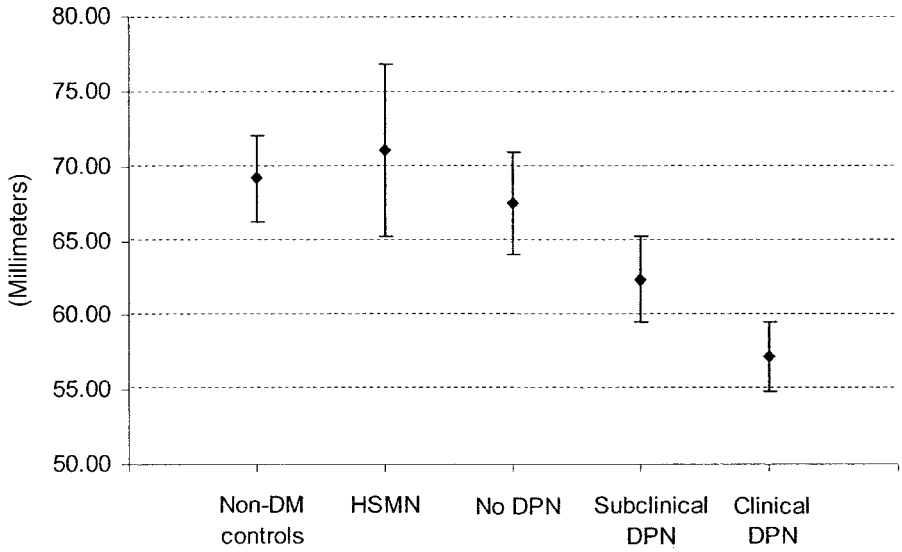

Figure 1— *Mean (♦) and 95% CI of SCAI per group corrected for slice positioning errors and adjusted for age, height, and weight: non-DM controls, nondiabetic control subjects* (n = *24); HSMN, subjects with HSMN type 1* (n = *8); no DPN, diabetic subjects with no neuropathy* (n = *19); subclinical DPN, diabetic subjects with early neuropathy* (n = *23); clinical DPN, diabetic subjects with established neuropathy* (n = *39). No DPN (mean 67.5 [95% CI 64.1–70.9]) vs. subclinical DPN (62.4 [59.5–65.3]),* P = *0.03; no DPN vs. clinical DPN (57.2 [54.9–59.6]),* P < *0.001; subclinical DPN vs. clinical DPN,* P = *0.006; no DPN vs. HSMN (71.07 [65.3–76.9]),* P = *0.31; no DPN vs. non-DM controls (69.2 [66.3–72.0]),* P = *0.47 (ANCOVA). SCAI is measured by dividing the spinal cord area by the anteroposterior diameter of the spinal cord.*

Table 2—*Relation between SCAI and clinical and neurophysiological assessments among subjects with diabetes*

	SCAI (adjusted for age, height, weight, and A1C)		
	β (95% CI)	Partial *r*	*P* value
Sural velocity	0.35 (4.83 to 34.4)	0.34	0.01
Sural amplitude	0.10 (−1.33 to 2.84)	0.10	0.47
Peroneal velocity	0.39 (−9.22 to 12.8)	0.04	0.75
Peroneal amplitude	−0.08 (−2.62 to 1.25)	−0.09	0.48
Tibial velocity	0.08 (−3.90 to 7.37)	0.08	0.54
Heart rate variability on DB	0.17 (−4.21 to 22.64)	0.17	0.17
Vibration JND	−0.20 (−18.5 to 3.09)	−0.17	0.16
NCS	−0.26 (−0.44 to −0.01)	−0.24	0.04
NSS	−0.30 (−1.56 to −0.15)	−0.28	0.02
Total neuropathy score	−0.28 (−0.33 to −0.02)	−0.26	0.03

See Table 1 for explanation of neurophysiological parameters. β is the linear regression coefficient, indicating the change in SCAI per unit change in each of the independent variables. Partial *r* is the partial correlation coefficient obtained from the linear regression model.

subjects without DPN had a corrected spinal cord area below this level.

Relations between SCAI and neurophysiological assessments

Table 2 shows the relations between SCAI and neurophysiological assessments, NCS, and NSS among subjects with diabetes. Adjusting for age, height, weight, and A1C, we found that higher sural conduction velocities were associated with larger SCAIs. The amplitudes in both sural and peroneal nerves were not related to SCAI at a statistically significant level. SCAI was inversely related to DPN NCS, with each point associated with a cord area index reduction of 0.26 (95% CI 0.45 to −0.01). The associations of SCAI with heart rate variability and vibration detection threshold were not statistically significant.

Reproducibility

The intraobserver SD and coefficient of variation (CV) for the experienced observer were 0.01 and 1.0%, respectively. The novice observer had a SD of 0.02 and a CV of 2.0% for repeated measurements of the same image. The interobserver reproducibility CV was 1.4% with SD of 0.014. The CV and SD of the measurements on the scan-rescan series of images were 2.0% and 0.02, respectively. The intraclass correlation coefficient was 0.97 (95% CI 0.88–0.99). There were no significant differences in the scores for degenerative disc disease among the five groups studied. None of the subjects recruited had spinal cord compression.

CONCLUSIONS — DPN has traditionally been considered a disease of the peripheral nerve only, with potentially important areas such as the spinal cord being largely overlooked. In a pilot study, using an MRI technique, we demonstrated that the cervical spinal cord area was significantly reduced in subjects with clinically detectable DPN compared with that in normal control subjects (10). In this larger study we confirmed the results of the pilot study and, more importantly, also demonstrated that spinal cord atrophy is an early process, which is present not only in subjects with clinically detectable DPN but also in subjects with relatively modest impairments of nerve function (subclinical DPN). The significant inverse linear trend across diabetic groups and the continuous relations found with the NCS indicate a continuing loss of spinal cord area as the disease progresses. Significant correlations were also found between the SCAI and neurophysiological parameters. The mean SCAI was not significantly different between age- and sex-matched nondiabetic control subjects and diabetic subjects without DPN. In contrast, unlike DPN, subjects with HSMN type1A, who served as a severe neuropathy control group, had SCAI results similar to those of nondiabetic control subjects.

Absolute spinal cord area measurements are well recognized to be affected by anthropometric differences among subjects, scan setup, and slice prescription (i.e., ensuring that the scan plane is perpendicular to the long axis of the cord). We accounted for these variations by calculating the corrected index of spinal cord area (SCAI) before adjusting group means for age, weight, and height. Such "normalization," as used in studies of brain atrophy (18), is an individualized index of cord atrophy and, hence, is important in this cross-sectional study in which intersubject comparisons are performed. In addition, systematic errors were minimized by using a semiautomated computerized technique for measuring absolute cord cross-sectional areas (17). Taking these steps improved both the precision and accuracy and, hence, the reliability of the measurement technique.

Consensus reports on the definition of DPN agree that a combination of neuropathic symptoms, signs, and electrodiagnostic findings provide the most accurate way of detecting and staging the severity of DPN (19–21). Thus, our staging approach, defining the subgroup with no neuropathy (no DPN) as the absence of symptoms and signs of neuropathy together with no neuropathic test abnormalities and the subgroup with clinically detectable neuropathy (clinically detectable DPN) as asymptomatic subjects with abnormalities in both neuropathic tests and clinical examination and subjects with symptomatic neuropathy, is valid. More importantly, we also studied a subgroup of subjects with early neuropathy (subclinical DPN), comprising individuals with neither the symptoms nor the clinical signs of DPN but who had at least two neuropathic test abnormalities. In addition, we also used the NCS to quantify the severity of DPN in this study. Composite scores have recently been shown to be the best way to demonstrate subtle and latent functional worsening of nerve conduction even before nerve conduction test criteria for DPN have been met (22). This monotone worsening of nerve conduction is indicative of subclinical or early DPN. Thus, the detection and accurate quantification of DPN, crucial for

study of this condition, was performed using a combination of symptoms, signs, and neurophysiological assessments based on well-validated methods (11–16).

The findings of this study demonstrate that the neuropathic process in humans is not confined to the peripheral nerve and may also involve the spinal cord. The fact that this involvement appears to occur early in the neuropathic process is disturbing. Even at the subclinical DPN stage, extensive and perhaps even irreversible damage may have occurred. Indeed, with these results in mind, it is not surprising that so far the variety of therapeutic options attempted in DPN have been unsuccessful (23).

However, the underlying reason for reduction in cord size is not clear. The spinal cord consists of a number of nerve tracts within its white matter. The major ascending and descending spinal cord pathways are the *1*) spinothalamic, *2*) dorsal column, *3*) corticospinal, *4*) spinocerebellar, and *5*) autonomic pathways. Cord area reduction may be the result of a "dying back" phenomenon caused by peripheral nerve axonopathy. However, it is also possible that the effect of diabetes-induced microvascular dysfunction is concomitant spinal cord involvement leading to the observed spinal cord atrophy.

A group of patients with HSMN type1A, an inherited form of neuropathy, was studied to represent a disease control group as *1*) HSMN is recognized to predominantly affect the peripheral nervous system, and, unlike diabetes, *2*) vascular factors have not been implicated in its pathogenesis (24,25). It has been shown in postmortem studies that this demyelinating form of peripheral neuropathy is also accompanied by axonal atrophy and loss of anterior horn and dorsal root ganglion cells together with degeneration of the posterior columns in the spinal cord (26). However, the smaller SCAI observed in subclinical and clinical DPN compared with HSMN type1A in this study suggests that the impact of diabetes is generalized, concomitantly affecting the peripheral and central nervous systems. The significant correlation between neurophysiological parameters and SCAI in DPN supports this suggestion.

There is increasing evidence from epidemiological to nerve biopsy and in vivo studies in humans for the involvement of microvascular factors in the pathogenesis of axonal loss in the peripheral nerve (2,27–31). Nerve biopsy and in vivo studies in humans have revealed the presence of endoneurial microangiopathy (3), impaired nerve blood flow, and nerve hypoxia (31). Additionally, the severity of peripheral nerve fiber loss correlates with the degree of endoneurial microangiopathy (28,29). Postmortem findings of microvascular disease within the spinal cord (32), similar to that seen in the peripheral nerve (33), suggest that the same pathogenic mechanisms may be involved in both areas. It is, therefore, likely that the metabolic insult of diabetes (hyperglycemia, insulin resistance, dyslipidemia, hypertension, and so on) (34,35) has a generalized effect on the nervous system with similar vascular processes and axonopathy (neuronal loss) resulting in the observed spinal cord atrophy in DPN. From the observations of this study, it is premature to speculate on the underlying pathophysiological processes affecting the spinal cord in DPN. There are, however, somatosensory and motor evoked potential studies in diabetes that have shown prolongation not only of peripheral conduction time but also of the central conduction time, especially in spinal cord structures (36). These findings may suggest that the reduction in mean SCAI observed in both subclinical and clinically detectable DPN may be a consequence of "central length dependent injury" within the spinal cord. To understand the exact pathophysiology of this myelopathy in DPN, however, further morphological studies are needed.

Our secondary objective was to evaluate the effectiveness of this technique as an early marker for DPN, as we currently have no "microalbuminuria equivalent" for DPN. By the time DPN is clinically detectible, severe peripheral nerve fiber loss and endoneurial microangiopathy are present (37). Furthermore, unlike other microvascular complications of diabetes, the early diagnosis of DPN currently depends on a combination of detailed clinical and neurophysiological assessments, which not only are time consuming and costly but also have major limitations including high interobserver variability, insensitivity to changes over time, and nonlinearity of the measured parameters (11,38). Our findings suggest that spinal cord cross-sectional area measurement using this quick, noninvasive, and operator-independent MRI technique may serve as an additional tool in the early detection and accurate quantification of DPN. However, longitudinal prospective studies are now required to determine the natural history of spinal cord involvement in DPN.

Acknowledgments— This study was supported by a grant from Diabetes UK.

We thank all the volunteers, the MRI radiographers, and Drs. Andrew Gibson and Marios Hadjivassiliou for the providing the patients with hereditary sensory motor neuropathy.

References

1. Boulton AJM, Malik RA, Arezzo JC, Sosenko JM: Diabetic somatic neuropathies. *Diabetes Care* 27:1458–1486, 2004
2. Tesfaye S, Chaturvedi N, Eaton SEM, Witte D, Ward JD, Fuller J, EURODIAB Prospective Complications Study Group: Vascular risk factors and diabetic neuropathy. *N Engl J Med* 352:341–350, 2005
3. Cameron NE, Eaton SE, Cotter MA, Tesfaye S: Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. *Diabetologia* 44:1973–1988, 2001
4. Dyck PJ, Giannini C: Pathologic alterations in the diabetic neuropathies of humans: a review. *J Neuropathol Exp Neurol* 55:1181–1193, 1996
5. Pryce TD: On diabetic neuritis with a clinical and pathological description of three cases of diabetic pseudo-tabes. *Brain* 16: 416, 1893
6. Leichtentritt H: Erkrankung peripherer nerven und des rucken-marks bei diabetes mellitus. *G Schade* 1–32, 1893
7. Williamson RT: Changes in the spinal cord in diabetes mellitus. *BMJ* 1:122, 1904
8. Reske-Nielsen E, Lundbaek K: Pathological changes in the central and peripheral nervous system of young long-term diabetics. II. The spinal cord and peripheral nerves. *Diabetologia* 4:34–43, 1968
9. Reske-Nielsen E, Lundbaek K, Gregersen G, Harmsen A: Pathological changes in the central and peripheral nervous system of young long-term diabetics: the terminal neuro-muscular apparatus. *Diabetologia* 6:98–103, 1970
10. Eaton SE, Harris ND, Rajbhandari SM, Greenwood P, Wilkinson ID, Ward JD, Griffiths PD, Tesfaye S: Spinal-cord involvement in diabetic peripheral neuropathy. *Lancet* 358:35–36, 2001
11. Grant IA, O'Brien P, Dyck PJ: Neuropathy tests and normative results. In *Diabetic Neuropathy*. 2nd ed. Dyck PJ, Thomas PK, Eds. Philadelphia, Saunders, 1999. p. 123–141
12. Dyck PJ, O'Brien PC, Kosanke JL, Gillen DA, Karnes JL: A 4, 2, and 1 stepping algorithm for quick and accurate estimation of cutaneous sensation threshold. *Neurology* 43:1508–1512, 1993

13. Dyck PJ, Zimmerman I, Gillen DA, Johnson D, Karnes JL, O'Brien PC: Cool, warm, and heat-pain detection thresholds: testing methods and inferences about anatomic distribution of receptors. *Neurology* 43:1500–1508, 1993
14. Pfeifer M: Cardiovascular assessment. In *Diabetic Neuropathy*. 2nd ed. Dyck PJ, Thomas PK, Eds. Philadelphia, Saunders, 1999, p. 171–183
15. Dyck PJ, Davies JL, Litchy WJ, O'Brien PC: Longitudinal assessment of diabetic polyneuropathy using a composite score in the Rochester Diabetic Neuropathy Study cohort. *Neurology* 49:229–239, 1997
16. Dyck PJ, Litchy WJ, Daube JR, Harper CM, Dyck PJ, Davies J, O'Brien PC: Individual attributes versus composite scores of nerve conduction abnormality: sensitivity, reproducibility, and concordance with impairment. *Muscle Nerve* 27:202–210, 2003
17. Losseff NA, Webb SL, O'Riordan JI, Page R, Wang L, Barker GJ, Tofts PS, McDonald WI, Miller DH, Thompson AJ: Spinal cord atrophy and disability in multiple sclerosis: a new reproducible and sensitive MRI method with potential to monitor disease progression. *Brain* 119: 701–708, 1996
18. Bigler ED, Tate DF: Brain volume, intracranial volume, and dementia. *Invest Radiol* 36:539–546, 2001
19. Boulton AJM, Gries FA, Jervell JA: Guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy. *Diabet Med* 15:508–514, 1998
20. American Diabetes Association, American Academy of Neurology: Consensus statement: Report and recommendations of the San Antonio Conference on Diabetic Neuropathy. *Diabetes Care* 11:592–597, 1988
21. England JD, Gronseth GS, Franklin G, Miller RG, Asbury AK, Carter GT, Cohen JA, Fisher MA, Howard JF, Kinsella LJ, Latov N, Lewis RA, Low PA, Sumner AJ, American Academy of Neurology, American Association of Electrodiagnostic Medicine, American Academy of Physical Medicine and Rehabilitation. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology* 64:199–207, 2005
22. Dyck PJ, O'Brien PC, Litchy WJ, Harper CM, Klein CJ, Dyck PJB: Monotonicity of nerve tests in diabetes: subclinical nerve dysfunction precedes diagnosis of polyneuropathy. *Diabetes Care* 28:2192–2200, 2005
23. Pfeifer MA, Schumer MP: Clinical trials of diabetic neuropathy: past, present, and future. *Diabetes* 44:1355–1361, 1995
24. Harding AE, Thomas PK: The clinical features of hereditary motor and sensory neuropathy types I and II. *Brain* 103:259–280, 1980
25. Llewelyn JG, Thomas PK, Gilbey SG, Watkins PJ, Muddle JR: Pattern of myelinated fibre loss in the sural nerve in neuropathy related to type 1 (insulin-dependent) diabetes. *Diabetologia* 31: 162–167, 1988
26. Smith TW, Bhawan J, Keller RB, DeGirolami U: Charcot-Marie-Tooth disease associated with hypertrophic neuropathy: a neuropathologic study of two cases. *J Neuropathol Exp Neurol* 39:420–440, 1980
27. Malik RA: The pathology of human diabetic neuropathy. *Diabetes* 46:S50–S53, 1997
28. Malik RA, Tesfaye S, Thompson SD, Veves A, Hunter A, Sharma AK, Ward JD, Boulton AJ: Transperineurial capillary abnormalities in the sural nerve of patients with diabetic neuropathy. *Microvasc Res* 48:236–245, 1994
29. Tesfaye S, Harris N, Jakubowski JJ, Mody C, Wilson RM, Rennie IG, Ward JD: Impaired blood flow and arterio-venous shunting in human diabetic neuropathy: a novel technique of nerve photography and fluorescein angiography. *Diabetologia* 36:1266–1274, 1993
30. Eaton SE, Harris ND, Ibrahim S, Patel KA, Selmi F, Radatz M, Ward JD, Tesfaye S: Increased sural nerve epineurial blood flow in human subjects with painful diabetic neuropathy. *Diabetologia* 46:934–939, 2003
31. Newrick PG, Wilson AJ, Jakubowski J, Boulton AJM, Ward JD: Sural nerve oxygen tension in diabetes. *Br Med J* 293: 1053–1054, 1986
32. Olsson Y, Save-Soderbergh J, Sourander P, Angervall L: A patho-anatomical study of the central and peripheral nervous system in diabetes of early onset and long duration. *Pathol Eur* 3:62–79, 1968
33. Tesfaye S, Malik R, Ward JD: Vascular factors in diabetic neuropathy. *Diabetologia* 37:847–854, 1994
34. Tesfaye S, Stevens L, Stephenson JM, Fuller JH, Plater M, Ionescu-Tirgoviste C, Nuber A, Pozza G, Ward JD: The prevalence of diabetic peripheral neuropathy and its relation to glycaemic control and potential risk factors: the EURODIAB IDDM complications study. *Diabetologia* 39:1377–1384, 1996
35. DeFronzo RA, Hendler R, Simonson D: Insulin resistance is a prominent feature of insulin-dependent diabetes. *Diabetes* 31:795–801, 1982
36. Suzuki C, Ozaki I, Tanosaki M, Suda T, Baba M, Matsunaga M: Peripheral and central conduction abnormalities in diabetes mellitus. *Neurology* 54:1932–1937, 2000
37. Malik RA, Veves A, Walker D, Siddique I, Lye RH, Schady W, Boulton AJ: Sural nerve fibre pathology in diabetic patients with mild neuropathy: relationship to pain, quantitative sensory testing and peripheral nerve electrophysiology. *Acta Neuropathol (Berl)* 101:367–374, 2001
38. Perkins BA, Bril V: Diabetic neuropathy: a review emphasizing diagnostic methods. *Clin Neurophysiol* 114:1167–1175, 2003