Tibial nerve somatosensory evoked potentials at various stages of peripheral neuropathy in insulin dependent diabetic patients

Dan Ziegler, Hansjörg Mühlen, Karsten Dannehl, F Arnold Gries

Abstract

To determine whether central nervous conduction deficits are related to the degree of peripheral neuropathy somatosensory evoked potentials (SEP) were measured after tibial nerve stimulation in 51 healthy subjects aged 39.3 (SE 2.0, range 21-71) years and 100 insulin dependent diabetic patients aged 37.3 (1.5, 18-73) years. Five criteria were used for staging of peripheral neuropathy: nerve conduction; thermal discrimination threshold; vibration perception threshold; tendon reflexes; and neuropathic symptoms. Thirty seven patients had fewer than two abnormalities among the first four criteria and no symptoms (stage 0 = no neuropathy), 37 had 2 or more abnormalities but no symptoms (stage 1 = subclinical neuropathy); 26 had 2 or more abnormalities in conjunction with symptoms (stage 2 = symptomatic neuropathy). Multiple regression analysis was used to define the age and height dependent limits of normal of SEP at the 97.5th and 2.5th centiles. In five patients with stage 1, seven patients with stage 2, but no patient with stage 0 the individual SEP components were unrecordable. The relative frequencies of abnormally prolonged or non-evokable popliteal N₈ latency as well as cortical N₃₃ latency and N₃₃/P₄₀ amplitude increased significantly from stage 0 (3-30%) to stage 1 (22-62%) and stage 2 (46-84%) ($p < 0.05$ for each component and stage). The numbers and percentages of abnormal recordable spinal N₂₂₋₃₀ and supraspinal N₃₀₋₃₃ interpeak latencies were two (6.3%) and four (11.8%) in patients with stage 0, but these rates did not increase in subjects with stage 1 or 2. The components of SEP were significantly associated with the indices of peripheral and autonomic function tests. There were no major relations between the latencies of SEP and duration of diabetes or prevailing glycaemic control. These findings suggest that the degree of dysfunction along the somatosensory afferent pathways in insulin dependent diabetic patients depends on the stage of peripheral neuropathy; is not related to the degree of glycaemic control or duration of diabetes; and can be characterised mainly by an alteration of the cortical sensory complex and peripheral transmission delay, while spinal and supraspinal con-

duction deficits are detected infrequently.

(*J Neurol Neurosurg Psychiatry* 1993;56:58-64)

Clinically manifest and subclinical peripheral somatosensory and autonomic nerve dysfunction have been extensively characterised in diabetic patients.¹ In contrast, less attention has been directed toward impairment of the central nervous system. Postmortem studies in diabetic patients have shown diffuse degenerative lesions in the central nervous system, including demyelination and loss of axon cylinders in the posterior columns,^{2,3} degeneration of cortical neurons,⁴ and abnormalities in the midbrain and cerebellum^{4,5} that have been called diabetic myelopathy³ and diabetic encephalopathy.^{4,6}

Recent studies that evaluated central nervous system function in diabetes using somatosensory evoked potentials (SEP) in response to stimulation of the median,⁷⁻¹⁴ peroneal,¹⁵ tibial,^{7,10-13} or sural nerves¹⁶ have shown controversial results regarding the existence of spinal or supraspinal (central) conduction deficits. As most of these studies included patients without clinical evidence of peripheral neuropathy,^{7,10-12,14} there is as yet no information on the extent of central nervous dysfunction in relation to the degree of peripheral nerve involvement.

In the present study somatosensory potentials were evoked by tibial nerve stimulation to evaluate proximal, spinal, and central nerve conduction in different stages of peripheral neuropathy; staging criteria similar to those recently proposed by Dyck¹⁷ were used. In addition, we studied the relation between SEPs and several indices of peripheral and autonomic nerve function as well as the influence of variables such as age, height, duration of diabetes, and prevailing glycaemic control.

Patients and methods

After informed consent had been obtained, 100 insulin dependent diabetic patients admitted to the Diabetes Research Institute participated in the study. Fifty one healthy subjects served as controls. Criteria for entry into the study included serum C peptide concentrations below 0.3 ng/ml after stimulation with 1 mg intravenous glucagon or a history of hyperglycaemia or ketonuria with requirement for insulin from the diagnosis onward; mani-

Diabetes Research Institute,
Heinrich-Heine-University,
Düsseldorf, Germany
Dan Ziegler
Hansjörg Mühlen
Karsten Dannehl
F Arnold Gries

Correspondence to:
Dr Dan Ziegler, Diabetes-
Forschungsinstitut an der
Heinrich-Heine-
Universität, Auf'm
Hennekamp 65, 4000
Düsseldorf 1, Germany

Received 21 June 1991
and in revised form
25 October 1991.
Accepted 29 April 1992

festation of diabetes before the age of 40; and duration of diabetes for more than one year. Patients were excluded if they had evidence of neuropathy other than of diabetic origin; were taking drugs known to influence peripheral, autonomic, or central nervous function; or had cerebrovascular dysfunction or peripheral vascular disease (intermittent claudication, ankle pressure index < 1 , or lack of foot pulses). The nerve function measurements were performed in the absence of ketonuria for at least one week.

Five criteria were used for characterisation and staging of peripheral neuropathy: delay in motor or sensory nerve conduction in two or more of four nerves tested; raised metacarpal or malleolar vibration perception threshold; increased thermal discrimination threshold on the thenar eminence or the dorsum of the foot; bilateral absence of knee or ankle tendon reflexes; and neuropathic symptoms such as symmetrical pain, paraesthesia, or numbness in the distal lower or upper limbs.

Peripheral neuropathy was defined using a staging approach similar to the one suggested by Dyck.¹⁷ Stage 0 (no neuropathy) consisted of two or fewer findings among the first four criteria in the absence of neuropathic symptoms; stage 1 (asymptomatic = subclinical neuropathy) of two or more findings among the first four criteria in the absence of neuropathic symptoms; and stage 2 (symptomatic = clinical neuropathy) of two or more findings among the first four criteria in the presence of neuropathic symptoms.

Figure 1 Example of a recording of typical components of somatosensory evoked potentials to tibial nerve stimulation in a healthy subject.

ANALYTICAL METHODS

Glycosylated haemoglobin (HbA_{1c}) was determined with high performance liquid chromatography using a Diamat analysing system (Bio-Rad, Munich). The normal range for this laboratory is $< 6.3\%$ of total haemoglobin. Capillary blood was taken on the day of the nerve function measurements; heparinised capillaries ($20 \mu\text{l}$) were used and glucose was measured by the hexokinase method on an ACP 5040 autoanalyser (Eppendorf, Hamburg). Mean blood glucose concentration was calculated from five values (fasting, postprandial, before lunch, before supper, and at bedtime). Fasting and stimulated (seven minutes after 1 mg intravenous glucagon) C peptide was analysed by radioimmunoassay using a RIA-mat C peptide (Byk-Mallinckrodt, Dietzenbach) within the range of $0.3\text{--}30 \text{ ng/ml}$. Urinary albumin excretion rate was determined from 24 hour samples by using the immunonephelometric technique (Array Protein System, Beckman, Fullerton, California).

Eye examinations were carried out by fundoscopy at the department of ophthalmology of the Düsseldorf University Clinic.

SOMATOSENSORY EVOKED POTENTIALS

SEPs were measured with a Mistral EP system (Medelec, Woking). They were recorded after square wave electrical stimulation of the right tibial nerve at the ankle with surface electrodes. The stimulus duration was $0.1\text{--}0.3 \text{ ms}$ and the frequency was 2 Hz . The stimulus intensity was adjusted to produce a twitch and plantar flexion of the toe muscles. The recording electrodes (Ag/AgCl) were placed over the tibial nerve at the popliteal fossa (N_8), over the spine at the lumbar L_1 area (N_{22}) against an abdominal reference, at the posterior midline of the neck at the second cervical vertebra (N_{30}), and on the scalp at Cz' , overlying the parietal sensory cortex contralateral to the stimulated leg according to the 10–20 system. The reference electrode was placed in a frontal position on the midline at Fz . The ground electrode was wrapped around the right calf with an elasticated strap in contact with the skin. The components recorded are thought to be generated in the tibial nerve (N_8), the dorsal gray of the lumbar cord at the root entry zone (N_{22}), thalamus, nuclei gracilis or medial lemniscus (N_{30}), and the primary sensory cortex. The cortical response is characterised by a W shaped complex consisting of two or three negative (N_{33} , N_{50} , N_{75}) and two positive (P_{40} , P_{60}) waves.¹⁸ A typical SEP recording is shown in figure 1. Note that the initial cortical negative N_{33} component is missing. In addition to the individual latencies, the interpeak latencies N_{8-22} , N_{22-30} , N_{30-33} , N_{22-33} , and N_{33-75} as well as the amplitudes N_{33}/P_{40} , P_{40}/N_{50} , N_{50}/P_{60} and P_{60}/N_{75} were calculated.

The impedance of the electrodes was maintained below 4Ω . The signals were filtered within a frequency band of $1\text{--}3000 \text{ Hz}$ and amplified ($50 \mu\text{V/division}$). The analysis time was 100 ms . The mean (SD) number of the responses averaged was $477 (24)$ in the healthy subjects and $505 (12)$ in the diabetic group. To

Table 1 Clinical characteristics of healthy subjects and diabetic patients without peripheral neuropathy (stage 0) and with subclinical (stage 1) and symptomatic (stage 2) peripheral neuropathy. Values are means (SE) unless otherwise stated

	Control (n = 51)	Stage 0 (n = 37)	Stage 1 (n = 37)	Stage 2 (n = 26)
Sex (m/f)	18/33	22/16	21/17	13/11
Age (years)	39.3 (2.0)	29.0 (1.7)*	40.2 (2.4)	43.9 (3.0)
Height (cm)	173 (1.4)	173 (1.1)	167 (4.3)	171 (2.4)
Weight (kg)	67.9 (1.6)	68.8 (1.5)	70.8 (1.7)	71.9 (2.3)
Duration of diabetes (years)		10.6 (1.4)†	14.6 (0.3)	15.7 (2.0)
Glycated haemoglobin (%)		8.8 (0.4)	9.1 (0.3)	8.9 (0.4)
Actual blood glucose (mmol/l)		7.1 (0.3)	7.8 (0.5)	8.9 (0.7)‡
Mean blood glucose (mmol/l)		7.8 (0.5)	8.4 (0.3)	8.2 (0.4)
Injectons/day		3.1 (0.3)	3.5 (0.3)	3.6 (0.3)
Median (range) excretion of albumin in urine (µg/min)		5.4 (1.1–189)	9.0 (1.8–396)	26.0 (1.6–2627)‡
% of patients with retinopathy		0	9.5§	44.4‡

*p < 0.05 v stage 1, stage 2, and controls; †p < 0.05 v stage 1 and 2; ‡p < 0.05 v stage 0; §p < 0.05 v stage 2.

avoid averaging of irrelevant signals, artifacts were automatically suppressed. To ensure the reproducibility of the wave forms, each test was performed twice in succession. The coefficients of variation of the short term test-retest reproducibility have been reported elsewhere.¹⁹

Latencies and cortical amplitudes that could not be recorded were considered as abnormal, and recordings that yielded poorly reproducible peaks were regarded as missing values. In case of the interpeak latencies only evokable responses were taken into account, and both poorly reproducible or non-evokable latencies were classified as missing values.

Normal ranges of SEP were determined in a group of 51 healthy subjects consisting of staff of the institute, medical students, and their relatives; their characteristics are listed in table 1. The same exclusion criteria that were used in the diabetic group were applied to the healthy subjects. Multiple regression analysis revealed that all latencies from N₈ to N₇₅ rose significantly with increasing age and height (p < 0.05), except for N₃₀, which was associated only with height. Interpeak latency N_{33–75} correlated significantly with age and N_{8–22} and N_{22–33} were related to height (p < 0.05). The remaining interpeak latencies and each of the cortical amplitudes were independent of age or height. The following regression formulas were used to define the age (x₁ given in years) dependent or height (x₂ given in cm) dependent upper limits of normal at the 97.5th percentiles of the individual SEP components (y) given in ms:

$$N_8: y = 0.058x_1 + 0.075x_2 - 4.567$$

$$N_{22}: y = 0.047x_1 + 0.111x_2 + 4.757$$

$$N_{30}: y = 0.124x_2 + 11.9$$

$$N_{33}: y = 0.032x_1 + 0.160x_2 + 8.835$$

$$P_{40}: y = 0.098x_1 + 0.208x_2 + 6.501$$

$$N_{50}: y = 0.074x_1 + 0.175x_2 + 22.53$$

$$P_{60}: y = 0.117x_1 + 0.107x_2 + 44.71$$

$$N_{75}: y = 0.139x_1 + 0.163x_2 + 49.98$$

$$N_{8–22}: y = 0.042x_2 + 8.616$$

$$N_{22–33}: y = 0.053x_2 + 5.291$$

$$N_{33–75}: y = 0.105x_1 + 33.12.$$

Limits of normal at the 97.5th percentile obtained for components that were independent of age and height were: N_{22–30}, 10.7 ms; N_{30–33}, 5.3 ms. Amplitudes (2.5th percentile): N₃₃/P₄₀, 0.6 µV; P₄₀/N₅₀, 0.6 µV; N₅₀/P₆₀, 0.7 µV; and P₆₀/N₇₅, 1.5 µV.

Peripheral and autonomic nerve function tests

Nerve conduction studies were performed with

an EMG 2000 electromyograph (Schwarzer-Picker, Munich) using surface electrodes. Motor nerve conduction velocity (MNCV) was measured in the right median and peroneal nerves, and sensory nerve conduction velocity (SNCV) was determined in the right median and sural nerves at local skin temperatures of 33–34°C as previously described.²⁰ Normal ranges were obtained from 60 healthy subjects aged 21–64 years. Median MNCV and SNCV decreased significantly with increasing age (p < 0.05), and peroneal MNCV and sural SNCV were inversely related to height (p < 0.05). The lower limits of normal at the 2.5th percentile were derived from the following regression formulas representing the association of nerve conduction (y), given in m/s, with either age (x₁, given in years) or height (x₂, given in cm): median MNCV, y = -0.14918x₁ + 54.89; median SNCV, y = -0.20349x₁ + 56.79; peroneal MNCV, y = -0.180x₂ + 75.22; and sural SNCV, y = -0.158x₂ + 71.98.

Thermal discrimination thresholds were measured on the right thenar eminence and the lateral aspect of the dorsum of the foot using the Marstock stimulator²¹ (Somedic, Stockholm) as previously described.²² Normal ranges were established in 70 healthy volunteers aged 17–64 years. The age (x) dependent upper limit of normal at the 97.5th percentile for the thermal discrimination threshold (y) on the foot given in Δ°C was defined by the equation log y = 0.004x + 0.702. The normal range for the age independent threshold on the thenar eminence was < 3.0Δ°C.

Vibration perception thresholds were determined on the right second metacarpal bone and medial malleolus using the vibrometer²³ (Somedic, Stockholm) as previously described.²² Normal ranges were evaluated in 70 healthy subjects aged 20–64 years. The age (x) dependent upper limit of normal at the 97.5th percentile for malleolar vibration perception threshold (y) given in µm was defined by the formula log y = 0.006x - 0.193. The normal range for the age independent metacarpal vibration perception threshold was < 0.61 µm.

The coefficient of variation of heart rate variability was determined in the supine position at rest using a microcomputer based technique (Neurocard-Analyzer, Argustron, Mettmann, Germany)²⁴ as previously described.²⁰

Table 2 Peripheral and autonomic nerve function tests in healthy subjects and diabetic patients without (stage 0) and with subclinical (stage 1) and symptomatic (stage 2) peripheral neuropathy.

	Control (n = 51)	Stage 0 (n = 37)	Stage 1 (n = 37)	Stage 2 (n = 26)
Mean (SE) of nerve conduction velocity:				
Median motor (m/s)	58.0 (0.6)*	56.3 (0.5)	50.1 (0.8)†	48.1 (1.4)
Peroneal motor (m/s)	50.8 (0.5)*	48.1 (0.7)	43.6 (0.9)†	40.0 (1.3)‡
Median sensory (m/s)	59.4 (0.7)*	55.5 (1.2)	49.9 (1.6)†	46.6 (1.9)
Sural sensory (m/s)	52.4 (0.5)*	50.0 (0.5)	43.5 (1.5)†	40.7 (2.0)
Median (range) of vibration perception threshold:				
Metacarpal (μ m)	0.27 (0.10–0.66)*	0.17 (0.09–0.54)	0.47 (0.11–7.0)†	0.69 (0.12–7.24)
Malleolar (μ m)	0.40 (0.20–0.91)*	0.38 (0.11–0.98)	0.86 (0.16–17.9)†	1.75 (0.22–68.0)‡
Median (range) of thermal discrimination threshold:				
Thenar eminence ($^{\circ}$ C)	2.0 (1.1–3.5)*	1.8 (1.2–2.8)	3.0 (1.4–4.8)†	3.3 (1.0–13.6)
Dorsum of the foot ($^{\circ}$ C)	4.0 (1.9–6.7)*	4.1 (1.4–6.0)	8.0 (3.2–18.1)†	11.5 (3.6–21.4)‡
Median (range) of heart rate variation:				
At rest (%)	5.21 (1.89–13.3)*	4.45 (1.87–9.83)	2.58 (0.53–11.8)†	2.21 (0.78–6.44)‡
During deep breathing (%)	9.33 (2.36–20.4)*	6.77 (3.37–12.0)	2.59 (0.58–9.24)†	2.68 (0.84–8.64)
Mean (SE) of pupillary dilation velocity (mm/s)	1.02 (0.03)*	0.89 (0.03)	0.72 (0.04)†	0.83 (0.13)

*p < 0.05 v stage 2; †p < 0.05 v control; ‡p < 0.05 v stage 1.

Infrared pupillometry was performed using a computer based TV pupillometer system, series 1000 (G + W Applied Science Laboratories, Waltham, Massachusetts) as previously published.²⁰ The computer calculated the pupillary dilation velocity and pupillary reflex latency. These indices were measured on each eye, and the results were expressed as the mean of both values.

CLINICAL EVALUATION

Neurological examination included registration of typical symptoms of polyneuropathy such as pain, paraesthesia, or numbness; examination of tendon reflexes; motor power; and perception of pin pricks and joint position.

STATISTICAL ANALYSIS

The results of the clinical data, peripheral and autonomic nerve function tests, and SEP recordings were expressed by the arithmetical mean (SE) or median (range). In case of the latencies of SEP, non-evokable potentials were assigned to the corresponding maximum values, while the values of unrecordable cortical amplitudes were considered as 0 μ V. The Mann-Whitney test and the *t* test for two independent samples were applied to test differences between groups of similar age and

height. Qualitative data were given as relative frequencies and were statistically analysed with the χ^2 test. Multiple and single linear regression analyses were used to study associations between variables. The level of significance was defined as 0.05 for all statistical tests.

Results

The clinical characteristics of the patients allocated to the different stages of peripheral neuropathy and of the healthy subjects studied are shown in table 1. There were no significant differences between controls and patients at stages 1 and 2 for any of the variables listed. However, mean age was significantly lower in patients at stage 0 than at stages 1 and 2 as well as in controls, and duration of diabetes was significantly shorter at stage 0 than stages 1 and 2 ($p < 0.05$). In addition, actual blood glucose concentrations during the SEP measurements and urinary albumin excretion rate were significantly higher in patients at stage 2 than stage 0, and retinopathy was more common in patients with stage 2 neuropathy than stages 0 and 1 ($p < 0.05$).

The results of the peripheral somatosensory and autonomic nerve function tests are shown in table 2. The mean or median values of all tests were significantly impaired in the diabetic

Table 3 Median (range) latencies, interpeak latencies, and cortical amplitudes of somatosensory evoked potentials in healthy subjects and diabetic patients without (stage 0) and with subclinical (stage 1) and symptomatic (stage 2) peripheral neuropathy

	Control (n = 51)	Stage 0 (n = 37)	Stage 1 (n = 37)	Stage 2 (n = 26)
Latencies (ms):				
N ₈	9.7 (7.2–11.5)*	9.8 (8.0–11.3)	10.9 (7.8–14.5)†	13.1 (8.4–14.5)‡
N ₂₂	23.4 (19.9–27.1)*	23.7 (21.1–26.6)	24.8 (21.3–31.3)†	27.9 (20.5–31.3)‡
N ₃₀	31.3 (26.8–35.4)*	32.1 (26.6–36.5)	33.2 (27.1–45.7)†	41.7 (28.1–45.7)‡
N ₃₃	34.6 (31.4–42.6)*	35.7 (31.1–39.8)	37.5 (30.5–49.8)†	44.7 (31.6–49.8)‡
P ₄₀	41.8 (36.1–50.2)*	41.6 (35.9–47.7)	44.1 (36.3–54.9)†	50.2 (38.1–54.9)‡
N ₅₀	50.4 (43.6–56.8)*	51.0 (45.1–56.3)	54.5 (44.1–65.6)†	56.9 (47.7–65.6)‡
P ₆₀	61.3 (53.9–69.9)*	60.5 (55.3–68.0)	64.6 (56.3–77.5)†	67.0 (53.7–77.5)‡
N ₇₅	75.8 (64.1–87.5)*	73.8 (65.8–84.4)	77.5 (65.8–91.6)	79.4 (69.3–91.6)‡
Interpeak latencies (ms)				
N ₈₋₂₂	13.8 (11.6–16.3)	13.8 (12.0–16.1)	13.7 (9.9–16.8)†	14.6 (12.1–17.6)‡
N ₂₂₋₃₀	8.0 (5.1–11.3)	8.0 (5.5–11.3)	8.4 (6.0–14.7)	8.0 (4.5–14.4)
N ₃₀₋₃₃	3.8 (2.2–5.1)	3.3 (2.2–8.4)	3.7 (1.9–6.9)	3.7 (2.2–8.3)
N ₂₂₋₃₃	11.4 (9.3–16.4)	11.8 (8.6–15.3)	11.7 (9.2–21.1)	12.9 (9.4–21.7)‡
N ₃₃₋₇₅	40.2 (29.5–50.6)	38.1 (30.5–49.8)	38.8 (32.8–48.5)	38.1 (24.8–43.2)
Amplitudes (μ V):				
N ₁₃ /P ₄₀	2.2 (0.5–6.6)*	1.9 (0.3–5.7)	1.6 (0.5–7)	0.7 (0.3–4)‡
P ₄₀ /N ₅₀	3.1 (0.4–8.9)*	3.1 (0.4–10.2)	2.3 (0.6–7)†	0.7 (0.4–0)‡
N ₅₀ /P ₆₀	2.5 (0.6–7.4)*	2.4 (0.4–9.0)	1.8 (0.6–5)†	0.5 (0.3–6)‡
P ₆₀ /N ₇₅	4.1 (1.0–8.1)*	3.9 (1.0–8.8)	2.7 (0.5–7)†	1.7 (0.6–4)‡

Non-evokable potentials for latencies were assigned to the corresponding maximum values; for interpeak latencies were not considered; for amplitudes were assigned to 0 μ V.

*p < 0.05 for control v stage 1; †p < 0.05 for stage 1 v stage 2; ‡p < 0.05 for control v stage 2.

Table 4 Number (percentage) of abnormalities in latencies, interpeak latencies, and cortical amplitudes of somatosensory evoked potentials in diabetic patients without (stage 0) and with subclinical (stage 1) and symptomatic (stage 2) peripheral neuropathy

	Stage 0	Stage 1	Stage 2
Latencies:			
N_{33}	11/37 (29.7)*	21/34 (61.8)†	21/25 (84.0)‡
N_{30-33}	5/37 (13.5)*	17/35 (48.6)†	21/26 (80.8)‡
Interpeak latencies:			
N_{8-22}	2/32 (6.3)	3/19 (15.8)	1/10 (10.0)
N_{22-33}	4/34 (11.8)	2/21 (9.5)	2/12 (16.7)
Amplitudes:			
N_{33}/P_{40}	1/37 (2.7)*	8/36 (22.2)†	12/26 (46.2)‡
N_{50}/P_{60}	4/37 (10.8)*	8/35 (22.9)	14/26 (53.8)‡

For interpeak latencies, potentials that could not be evoked were not considered.

* $p < 0.05$ for stage 0 v stage 2; † $p < 0.05$ for stage 0 v stage 1; ‡ $p < 0.05$ for stage 1 v stage 2.

groups with subclinical (stage 1) or symptomatic (stage 2) peripheral neuropathy compared with the control group ($p < 0.05$). Moreover, patients with stage 2 had significant impairment of several peripheral nerve variables in the legs and a diminished variation in heart rate at rest when compared with those with stage 1 ($p < 0.05$).

The median values and ranges of the indices of SEP in the healthy subjects and diabetic patients without neuropathy (stage 0) and with subclinical (stage 1) and symptomatic (stage 2) peripheral neuropathy are shown in table 3. Each component of the latencies and cortical amplitudes was significantly impaired in patients with stage 1 or 2 peripheral neuropathy compared with the healthy subjects ($p < 0.05$). These differences were also found between patients with stage 1 neuropathy and those with stage 2 neuropathy ($p < 0.05$), except for P_{60} , N_{75} , and the N_{33}/P_{40} amplitude. There were no significant differences between the groups for the interpeak latencies, except for a prolongation of N_{8-22} and N_{22-33} in patients with stage 2 neuropathy compared with the controls, and N_{8-22} compared with patients at stage 1 ($p < 0.05$). In five patients with stage 1 neuropathy, seven patients with stage 2, but no patient with stage 0 neuropathy the individual components of SEP were completely unrecordable.

The relative frequencies of abnormalities of

the main SEP components in patients without peripheral neuropathy (stage 0) and in those with subclinical (stage 1) and symptomatic neuropathy (stage 2) are given in table 4. The percentages of abnormal prolonged latencies increased significantly from stage 0 to stage 1 and from stage 1 to stage 2 ($p < 0.05$). The percentages of abnormally prolonged interpeak latencies were lower and did not differ significantly among the three groups. In contrast, abnormally reduced cortical amplitudes were significantly more frequent in patients with neuropathy in stage 2 than in those in stage 0 and stage 1 ($p < 0.05$). Moreover, the percentage of abnormal N_{33}/P_{40} but not N_{50}/P_{60} amplitude was significantly higher in patients with neuropathy in stage 1 than in those without neuropathy ($p < 0.05$). When unrecordable cortical potentials were not considered in the calculation, significant differences between patients with stage 0 and 2 were still found: N_{33}/P_{40} (1/36 (2.8%) v 5/19 (26.3%), $p < 0.05$) and N_{50}/P_{60} (4/36 (11.1%) v 7/19 (36.8%), $p < 0.05$).

To clarify to what degree and whether the individual variables of peripheral somatosensory and autonomic nerve function are associated with the indices of SEP, linear regression analysis was applied to the test results in the 100 diabetic patients studied. The highest significant correlations were noted between the latencies of SEP and nerve conduction as well as thermal discrimination threshold in the legs and heart rate variability ($r = -0.30$ to -0.67 , $r = 0.46$ to 0.56 , and $r = -0.32$ to -0.53 , respectively; all $p < 0.05$). The associations with the remaining variables were weaker, but they reached statistical significance, except for metacarpal vibration perception threshold. Interpeak latencies and the N_{33}/P_{40} amplitude were most consistently related to peroneal motor nerve conduction velocity, thermal discrimination threshold on the foot, heart rate variability, and malleolar vibration perception threshold, but the correlation coefficients were lower than for the latencies. The associations of N_{33} latency, N_{30-33}

Figure 2 Associations of N_{33} latency, N_{30-33} interpeak latency, and N_{33}/P_{40} amplitude with heart rate variation at rest (upper panel) and thermal discrimination threshold on the foot (lower panel) in the diabetic patients studied.

interpeak latency, and N_{33}/P_{40} amplitude with heart rate variation at rest and thermal discrimination threshold on the foot are shown in figure 2.

Multiple linear regression analysis in the 100 diabetic patients showed that there was a significant association of the described components of SEP with increasing age independent of height ($p < 0.05$), except for N_{8-22} , N_{22-30} , N_{33-75} , and N_{33}/P_{40} . The results of SEP were also significantly associated with increasing height, independent of age ($p < 0.05$), except for N_{8-22} , N_{30-33} , N_{33-75} , and N_{33}/P_{40} . In contrast, SEP were associated with increasing duration of diabetes independently of age and height only for the N_{33}/P_{40} and P_{40}/N_{50} amplitudes.

Finally, there were no significant associations between the results of the individual components of SEP and glycated haemoglobin ($r = -0.03$ to 0.13 ; NS), blood glucose concentration during the SEP recordings ($r = -0.15$ to 0.06 ; NS), and mean blood glucose concentration during the day of the nerve function recordings ($r = -0.13$ to 0.14 ; NS).

Discussion

The results of the present study show that the extent of abnormalities of somatosensory evoked potentials to tibial nerve stimulation are related to the stage of peripheral nerve dysfunction in insulin dependent diabetic patients. Using age dependent or height dependent limits to define normal ranges for the various indices of SEP, we found common peripheral conduction deficits and reduced amplitudes of the cortical sensory complex and, less commonly, abnormal spinal or supraspinal transmission time in patients with or without peripheral neuropathy. However, it should be noted that in several patients with peripheral neuropathy no interpeak latencies could be estimated because of unrecordable SEP components. The alteration of the amplitudes of the cortical sensory complex may reflect either central or peripheral nerve dysfunction, or both. As in healthy subjects, age and height were the major determinants for the prolongation of latencies and reduction of cortical amplitudes in insulin dependent diabetic patients. In contrast, prevailing glycaemic control assessed by glycated haemoglobin and blood glucose concentrations as well as the duration of diabetes did not have a major effect on the results of the SEP recordings.

Previous studies that assessed central nervous function using potentials evoked to stimulation of the nerves in the arm or leg have yielded controversial results. Two earlier reports have described an abnormal conduction along the spinal cord in 12 of 30 and in 10 of 40 diabetic patients without clinical evidence of peripheral neuropathy,^{7 15} but, nerve conduction in the supraspinal segment from the cervical cord to cortex⁷ and over the caudal part of the spinal cord¹⁵ were normal in all patients. Recent reports of relatively small groups of patients without neuropathy have

shown relatively low frequencies of abnormalities of the spinal transmission time in three of 14, one of 14, and five of 16 diabetic subjects studied, and abnormal prolongation of the conduction time in supraspinal segments in only one of 14, one of 34, and three of 30 diabetic patients.^{10 12 13} In diabetic patients with symptomatic peripheral neuropathy a prolongation of the supraspinal N_{14-20} interval to median nerve stimulation has been shown in one study,¹⁴ but this finding could not be confirmed by others.^{9 16} The relatively low frequency of abnormally prolonged spinal and supraspinal interpeak latencies in the present study in subjects with or without peripheral neuropathy is consistent with most of the reports mentioned. In a considerable number of patients with subclinical or symptomatic neuropathy, however, no stable SEP recording could be identified. Hence, due to methodological limitations, the percentages of central and spinal conduction abnormalities reported could be underestimated.

By using a staging approach we could discriminate increasing degrees of peripheral neuropathy by the percentages of abnormalities in latencies and cortical amplitudes of SEP. Patients with symptomatic neuropathy showed the most prominent prolongation of SEP latencies, primarily due to a peripheral conduction deficit, and consequently the spinal and first cortical components were also found prolonged. Relatively high rates of abnormal cortical latencies of SEP similar to those in this study have been reported previously,^{12 13 16} but it must be emphasised that these were attributable to a concomitant peripheral conduction delay.

The reduction of the cortical amplitudes shown in the present study in patients with neuropathy could not be seen in a previous study using potentials evoked to sural nerve stimulation.¹⁶ Diminished amplitudes of the cortical sensory complex were rare in patients without neuropathy but relatively common in those with symptomatic peripheral neuropathy. This finding may be directly related to the reduced peripheral input or it may mirror central nervous dysfunction. If the altered cortical amplitudes reflect the latter possibility, a structural but subclinical correlate in the cortex could be an underlying factor. In fact, a recent study using magnetic resonance imaging has shown subcortical lesions without evidence of cognitive impairment in insulin dependent diabetic patients with peripheral neuropathy.²⁵ On the other hand, the increase of the amplitude of the cortical complex of median nerve SEP following treatment with an aldose reductase inhibitor²⁶ suggests a more functional character of reduced cortical amplitudes.

No reports compared SEP to stimulation of the legs of diabetic patients with various stages of peripheral neuropathy. Previous studies using brainstem auditory and visual evoked potentials have shown equivocal results. Some authors have reported that abnormalities in brainstem auditory²⁷ and visual²⁸ evoked potentials were more frequent in patients with

clinically manifest neuropathy than in those without neuropathy, but others could not confirm these results.^{29,30} The reasons for such discrepancies could, for instance, be due to the inclusion of both types of diabetes, variable definitions of neuropathy, or to differences in methodology. The present study clearly shows that the components of SEP, including latencies, interpeak latencies, and cortical amplitudes, are associated with the indices of peripheral large or small fibre function and heart rate variation. Thus although spinal and supraspinal conduction slowing was detected relatively infrequently, these correlations support the concept of a diffuse involvement of the peripheral, autonomic, and central nervous systems in diabetic neuropathy.

Recently it has been claimed that abnormalities in SEP are associated with poor glycaemic control as assessed by glycated haemoglobin.¹⁰ In contrast, this study shows that neither glycated haemoglobin nor the mean or actual blood glucose concentrations during the neurophysiological sessions were significantly correlated with the results of the individual SEP recordings. Thus prevailing glycaemic control does not seem to be a major determinant for the outcome of SEP measurements. This view agrees with previous reports showing that somatosensory,¹² brainstem auditory,²⁹ and visual³⁰ evoked potentials were not related to the degree of glycaemic control. Moreover, multimodal evoked potentials including SEP tended to progress within an average follow up of 15.7 months despite a considerable improvement in glycaemic control.¹¹ In this study, the most consistent independent correlates for decreasing function along the somatosensory pathways in both healthy subjects and diabetic patients were increasing age and height.

In conclusion, we have shown that dysfunction along the somatosensory afferent pathways in insulin dependent diabetic patients is characterised by peripheral conduction deficits, often by absent spinal components, and reduced or absent amplitudes of the cortical sensory complex. These alterations were associated with the stage of peripheral neuropathy and with any of the standard indices of peripheral and autonomic nerve function as well as with age and height, but were largely unrelated to the degree of prevailing glycaemic control and duration of diabetes.

We thank M. Behler, H. Effertz-Umlauf, C. Gottschalk, and S. Witt for their excellent technical assistance and Professor H. Reinauer and coworkers for the measurement of the metabolic parameters, and Professor R. Sundmacher and colleagues for funduscopy. This study was supported by grants from the Bundesminister für Jugend, Familie und Gesundheit and the Minister für Wissenschaft und Forschung, Nordrhein-Westfalen.

- 1 Thomas PK, Eliasson SG. Diabetic neuropathy. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. *Peripheral neuropathy*. Philadelphia: W B Saunders, 1986: 1773-810.

- 2 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* 1968;4:34-43.
- 3 Slager U. Diabetic myelopathy. *Arch Pathol Lab Med* 1978;102:467-9.
- 4 Olsson Y, Sävje-Söderbergh J, Sourander P, Angervall L. A patho-anatomical study of the central and peripheral nervous system in diabetics of early onset and long duration. *Path Europ* 1968;3:62-79.
- 5 Reske-Nielsen E, Lundbaek K, Rafaelsen OJ. Pathological changes in the central and peripheral nervous system of young long-term diabetics. I. Diabetic encephalopathy. *Diabetologia* 1965;1:233-41.
- 6 DeJong RN. The nervous system complications in diabetes mellitus with special reference to cerebrovascular changes. *J Nerv Ment Dis* 1950;111:181-206.
- 7 Gupta PR, Dorfman LJ. Spinal somatosensory conduction in diabetes. *Neurology* 1981;31:841-5.
- 8 Harkins SW, Gardner DF, Anderson RA. Auditory and somatosensory far-field evoked potentials in diabetes mellitus. *Int J Neurosci* 1985;28:41-7.
- 9 Collier A, Reid W, McInnes A, Cull RE, Ewing DJ, Clarke BF. Somatosensory and visual evoked potentials in insulin-dependent diabetics with mild peripheral neuropathy. *Diabetes Res Clin Pract* 1988;5:171-5.
- 10 Pozzessere G, Rizzo PA, Valle E, Mollica MA, Meccia A, Morano S, et al. Early detection of neurological involvement in IDDM and NIDDM. Multimodal evoked potentials versus metabolic control. *Diabetes Care* 1988; 11:473-80.
- 11 Pozzessere G, Rizzo PA, Valle E, Mollica MA, Sanarelli L, Morano S, et al. A longitudinal study of multimodal evoked potentials in diabetes mellitus. *Diabetes Res* 1989;10:17-20.
- 12 Nakamura Y, Takahashi M, Kitaguchi M, Kaido M, Imaoka H, Kono N, et al. Clinical utility of somatosensory evoked potentials in diabetes mellitus. *Diabetes Res Clin Pract* 1989;7:17-23.
- 13 Comi G, Martini A. Central nervous involvement in diabetic patients. In: Andreani D, Crepaldi G, DiMario U, Pozza G, eds. *Diabetic complications: early diagnosis and treatment*. Chichester: Wiley, 1987:145-55.
- 14 Van Gerven JMA, Arts R, Lemkes HHPJ. Somatosensory-evoked potentials (SSEPs) and electroneurography of sensory nerves in diabetic polyneuropathy (DN). *Transplant Proc* 1986;18:1592.
- 15 Cracco J, Castells S, Mark E. Spinal somatosensory evoked potentials in juvenile diabetes. *Ann Neurol* 1984; 15:55-8.
- 16 Vogel P. Zur Bedeutung sensibler evozierter Potentiale (SEP) in der Polyneuropathie-Diagnostik. *Fortschr Neurol Psychiatr* 1986;54:305-17.
- 17 Dyck PJ. Detection, characterization, and staging of polyneuropathy: assessed in diabetics. *Muscle & Nerve* 1988;11:21-32.
- 18 Stöhr M, Dichgans J, Diener HC, Buettner VW. *Evozierte Potentiale*. Berlin, Heidelberg: Springer-Verlag, 1982.
- 19 Ziegler D, Gries FA. Reproducibility of electrophysiologic tests. *Diabetes & Metabolism* 1990;16:373-6.
- 20 Ziegler D, Cicmir I, Wiefels K, Berger H, Gries FA. Peripheral and autonomic nerve function in long-term insulin-dependent diabetes. *Diabetes Res* 1987;4:9-14.
- 21 Fruhstorfer H, Lindblom U, Schmidt WG. Method for quantitative estimation of thermal thresholds in patients. *J Neurol Neurosurg Psychiatry* 1976;39:1071-5.
- 22 Ziegler D, Mayer P, Wiefels K, Gries FA. Assessment of small and large fiber function in long-term type 1 (insulin-dependent) diabetic patients with and without painful neuropathy. *Pain* 1988;34:1-10.
- 23 Goldberg JM, Lindblom U. Standardised method of determining vibratory perception thresholds for diagnosis and screening in neurological investigation. *J Neurol Neurosurg Psychiatry* 1979;42:793-803.
- 24 Morguet A, Springer HJ. Microcomputer-based measurement of beat-to-beat intervals and analysis of heart rate variability. *Med Progr Technol* 1981;8:77-82.
- 25 Dejgaard A, Gade A, Larsson H, Balle V, Parving A, Parving H-H. Evidence for diabetic encephalopathy. *Diabetic Med* 1991;8:162-7.
- 26 Jaspan JB, Towle VL, Maselli R, Herold K. Clinical studies with an aldose reductase inhibitor in the autonomic and somatic neuropathies of diabetes. *Metabolism* 1986; 35(suppl 1):83-92.
- 27 Goldsher M, Pratt H, Hassan A, Shenhav R, Eliachar I, Kanter Y. Auditory brainstem evoked potentials in insulin-dependent diabetics with and without peripheral neuropathy. *Acta Otolaryngol (Stockh)* 1986;102:204-8.
- 28 Mariani E, Moreo G, Colucci GB. Study of visual evoked potentials in diabetics without retinopathy: correlations with clinical findings and polyneuropathy. *Acta Neurol Scand* 1990;81:337-40.
- 29 Donald MW, Williams Erdahl DL, SurrIDGE DHC, Monga TN, Lawson JS, Bird CE, et al. Functional correlates of reduced central conduction velocity in diabetic subjects. *Diabetes* 1984;33:627-33.
- 30 Algan M, Ziegler O, Gehin P, Got I, Raspiller A, Weber M, et al. Visual evoked potentials in diabetic patients. *Diabetes Care* 1989;12:227-9.