Differences in Peripheral and Autonomic Nerve Function Measurements in Painful and Painless Neuropathy

A clinical study

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OBJECTIVE — To examine the differences in peripheral and autonomic nerve function measurements between diabetic patients without neuropathy (group 1, n = 38, mean age 50.9, range 29–71 years), with painless neuropathy (group 2, n = 32, mean age 49.2, range 30–71 years), and with painful neuropathy (group 3, n = 52, mean age 51.5, range 28–73 years).

RESEARCH DESIGN AND METHODS — The evaluation of neuropathy was based on clinical symptoms, signs, and quantitative sensory testing, including current perception threshold (CPT) with a neurometer and electrophysiology.

RESULTS — The Neuropathy Symptom Score and the Neuropathy Disability Score were higher in patients with painful neuropathy compared with patients with painless neuropathy (6.8 ± 2.7 vs. 0.5 ± 0.8 [mean ± SD], $P < 0.0001$, and 12.5 ± 6.2 vs. 8.6 ± 6.8, $P < 0.01$, respectively). In contrast, no differences were found in the quantitative sensory testing, including CPT measurements, the electrophysiological measurements, and the autonomic nerve system function tests in the two groups. Significant differences were found in all the above measurements when groups 2 and 3 were compared with diabetic patients without neuropathy (group 1). When all diabetic patients were considered as one group, significant correlations were found between CPT and the other peripheral nerve function assessments. In particular, peroneal nerve motor conduction velocity correlated with CPT at 2 kHz ($r = -0.48$, $P < 0.001$) and vibration perception threshold ($r = -0.50$, $P < 0.001$).

CONCLUSIONS — We conclude that no difference could be found in the function of small and large nerve fibers between painful and painless diabetic neuropathy using conventional tests currently used. The CPT evaluation failed to quantify painful symptoms, but it compared favorably with other quantitative sensory tests in quantifying peripheral neuropathy.

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CPT, current perception threshold; VPT, vibration perception threshold; TDT, thermal discrimination threshold; NSS, Neuropathy Symptom Score; NDS, Neuropathy Disability Score; PMCV, peroneal nerve motor conduction velocity.

The etiopathogenesis and natural history of painful diabetic neuropathy has not been established satisfactorily. Although initial studies suggested that pain was caused by selective involvement of small nerve fibers, subsequent studies failed to confirm these findings (1,2). In addition, because the perception of pain is subjective, there are no available techniques that can quantify the painful symptoms. However, preliminary reports have suggested that current perception threshold (CPT) measurements assessment can quantify painful symptoms such as hyperesthesia (3).

The main aim of the present study was to examine the differences in peripheral and autonomic nerve function in patients with painful and painless diabetic neuropathy. Toward this aim, we have studied diabetic patients without neuropathy, with painful neuropathy, and with painless neuropathy. We have also investigated the ability of CPT measurements to quantify painful symptoms.

RESEARCH DESIGN AND METHODS

— Three groups of patients with either type I or type II diabetes and one group of nondiabetic subjects were studied. Group 1 consisted of 38 diabetic patients (mean age 50.9, range 29–71 years) without diabetic neuropathy. Group 2 included 32 diabetic patients (mean age 49.2, range 30–71 years) with painless diabetic neuropathy, and group 3 included 52 diabetic patients with painful neuropathy (mean age 51.5, range 28–73 years). Group 4 consisted of 24 healthy subjects (mean age 47.9, range 37–69 years) with no evidence of peripheral neuropathy. The diabetic patients were randomly recruited from the general diabetes and diabetic impotence clinic and were all males. They were all matched for age, and groups 2 and 3 were matched for the duration of diabetes (mean duration 17, range 0.1–35 years vs. mean duration 14, range 0.3–43 years, NS). The duration of diabetes in group 1 (9.5 [range 0.4–28] years) was significantly

Table 1—*Results of peripheral and autonomic function tests*

	Group 1	Group 2	Group 3	Significance: Group 1 vs. 2	Significance: Group 1 vs. 3	Significance: Group 2 vs. 3
NSS	0.2 ± 0.5	0.5 ± 0.8	6.8 ± 2.7	<0.05	<0.0001	<0.0001
NDS	0.8 ± 1.7	8.6 ± 6.8	12.6 ± 6.4	<0.0001	<0.0001	<0.01
VPT (great toe, volts)	14.3 ± 7.0	27.0 ± 12.6	31.2 ± 12.0	<0.0001	<0.0001	NS
TDT (hand, °C)	0.26 ± 0.15	0.6 ± 0.9	0.5 ± 0.6	<0.01	<0.001	NS
TDT (foot, °C)	1.0 ± 2.6	6.9 ± 7.7	6.3 ± 7.8	<0.0001	<0.0001	NS
PMCV (m/s)	44.3 ± 5.3	36.6 ± 5.7	36.0 ± 7.5	<0.0001	<0.0001	NS
Orthostatic hypotension (mmHg)	2.6 ± 5.1	8.0 ± 9.1	9.2 ± 13.8	<0.001	<0.001	NS
R-R variation during deep breath (beats/min)	14 ± 8.1	8.7 ± 6.0	8.4 ± 6.7	<0.01	<0.01	NS
30:15 ratio	1.1 ± 0.1	1.08 ± 0.1	1.08 ± 0.1	<0.05	<0.05	NS

Data are means ± SD.

lower compared with both groups 2 and 3 ($P < 0.05$).

The clinical symptoms, signs, quantitative sensory testing (vibration perception threshold [VPT] and thermal discrimination threshold [TDT] for warm), electrophysiology, and autonomic nerve function tests were investigated in all diabetic patients.

The Neuropathy Symptom Score (NSS) and the Neuropathy Disability Score (NDS) were evaluated as has been described elsewhere (4). VPT was measured using a biothesiometer (Biomedical, Newbury, OH), and TDT for warm temperature was measured using a thermo-esthesiometer (Free University Hospital, Amsterdam, Netherlands). CPTs were measured at the pulp of the right great toe and the index finger using a neurometer device (Neurotron, Baltimore, MD). Three frequencies (5, 250, and 2,000 Hz) were tested on each site. The peroneal nerve motor conduction velocity (PMCV) was measured using a Medelec MS92A apparatus (Old Working, Surrey, U.K.).

Three autonomic nerve function tests were used: the drop of blood pressure after the change from lying to standing position, the heart rate variation during deep breathing, and the immediate heart rate response to standing. All tests were performed and interpreted according to previously described methods and thresholds of normality (5).

The diagnosis of peripheral neuropathy was based on the existence of pathological results in at least two of four main categories: clinical symptoms, signs, quantitative sensory testing (abnormal VPT, TDT, or both), and electrophysiology, according to the suggestions of the San Antonio Consensus Statement (6). To avoid bias in the selection of the patients with painful neuropathy, this group included all diabetic patients with NSS ≥3. In all but one patient of these groups, at least one more test was abnormal.

The Minitab statistical package (State College, PA) for electronic computers was used for the statistical analysis. The Kruskal-Wallis nonparametric analysis of variance test, the Mann-Whitney U test and the χ^2 test were used for comparisons between the four groups. The Spearman correlation coefficient r was used for the correlation of different parameters in the same group. The purpose of the study was explained to all patients, and the study was approved by the Central Manchester Health Authority Ethical Committee.

RESULTS— The NSS was significantly higher in the patients with painful neuropathy (group 3) (6.8 ± 2.7, mean ± SD) compared with groups 1 (0.2 ± 0.5, $P < 0.0001$) and 2 (0.5 ± 0.8, $P < 0.0001$), as would be expected from the selection criteria (Table 1). The NSS in group 2 was also significantly higher than in group 1 ($P < 0.05$).

Similar results were found in the NDS, which was significantly higher in group 3 compared with group 1 ($P < 0.0001$) and group 2 ($P < 0.01$). The NDS in group 2 was significantly higher than in group 1 ($P < 0.0001$).

VPT was similar in groups 2 and 3, but it was higher in both groups compared with group 1. Similar results were found for TDT in the foot and the hand. No difference existed between groups 2 and 3 at the dorsum of the foot, but TDT was higher in both groups compared with group 1 ($P < 0.0001$ for both groups).

No difference was found among all four groups in the CPT measurements at the index finger in all three frequencies. At the great toe, no differences were found in all three frequency measurements between groups 2 and 3. Also, no difference was found between groups 1 and 4 in all three frequencies. The 5-Hz measurements in group 3 were higher compared with group 1 (308 ± 387 vs. 95 ± 53, $P < 0.05$). The frequencies 250 Hz and 2 kHz in groups 2 (377 ± 352 and 575 ±

291, respectively) and 3 (356 ± 367 and 588 ± 287) were significantly higher compared with groups 1 (141 ± 87 and 365 ± 148) and 4 (133 ± 59 and 362 ± 116) ($P < 0.05$). The PMCV was also similar in groups 2 and 3, but it was significantly reduced in both groups compared with group 1 ($P < 0.0001$ for both groups).

The mean drop of blood pressure on assuming the standing position was similar in groups 2 and 3, and it was higher in both groups compared with group 1 ($P < 0.001$ for both groups). The heart rate variation was similarly reduced in groups 2 and 3 when compared with group 1. The mean R-R ratio of the 30:15 beats during immediate standing was also similarly reduced in groups 2 and 3. In group 1, all three tests were normal in 22 (58%) patients, one test was abnormal in 12 (32%) patients, and two tests were abnormal in 4 (10%) patients; in none of the patients were all three tests abnormal. In group 2, 13 (41%) patients had no abnormal tests, 12 (38%) patients had one abnormal test, 6 (19%) patients had two abnormal tests, and 1 (3%) patient had three abnormal tests. In group 3, no abnormal tests were found in 19 (37%) patients, one abnormal test was found in 17 (33%) patients, two abnormal tests were found in 15 (29%) patients, and all three tests were abnormal in 1 (2%) patient (NS for all groups).

When all diabetic patients were considered as one group, the VPT correlated with NSS ($r = 0.49$, $P < 0.001$), NDS ($r = 0.68$, $P < 0.001$), and PMCV ($r = -0.50$, $P < 0.001$). TDT at the dorsum of the foot correlated with NSS ($r = 0.23$, $P < 0.02$), NDS ($r = 0.48$, $P < 0.001$), and PMCV ($r = -0.51$, $P < 0.001$). CPT at 5 Hz correlated with NSS ($r = 0.19$, $P < 0.05$), NDS ($r = 0.31$, $P < 0.001$), and PMCV ($r = -0.31$, $P < 0.001$). CPT at 250 Hz correlated with NSS ($r = 0.19$, $P < 0.05$), NDS ($r = 0.38$, $P < 0.001$), and PMCV ($r = -0.30$, $P < 0.001$). CPT at 2 kHz frequency correlated with NSS ($r = 0.30$, $P < 0.001$), NDS ($r = 0.44$, $P < 0.001$), and PMCV ($r = -0.48$, $P < 0.001$).

CONCLUSIONS — In this study, we have examined the differences of peripheral and autonomic nerve function between painful and painless diabetic neuropathy. Our results failed to show any differences in the quantitative sensory testing, electrophysiology, or autonomic nerve function tests between patients with painful or painless neuropathy. The only differences that were found between the two groups were in the NSS, as expected from the selection criteria used, and in the NDS, which was increased in the group with painful neuropathy. Therefore, in disagreement with previous studies, we have failed to show any selective involvement of small fibers or the autonomic nervous system in painful neuropathy (7,8).

The CPTs were also equally increased in diabetic patients with painful and painless neuropathy. Thus, this technique was not proved to be useful in quantifying painful symptoms, and it followed the same pattern as the other two tests of the quantitative sensory testing. Despite this, the CPT measurements gave similar correlations with the other quantitative sensory testing results. More specifically, when compared with VPT, similar correlations were found to PMCV, which tests the large nerve fibers' function and has been shown to correlate with nerve structural damage (9).

In summary, we have failed to show any difference in the function of small and large nerve fibers between painful and painless diabetic neuropathy using the conventional tests currently used. These results do not support the hypothesis that in painless neuropathy there is a proportionately greater impairment of large fiber function. The CPT evaluation failed to quantify painful symptoms, but when compared with other quantitative sensory tests, it was found to be equally effective in quantifying neuropathy.

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