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Clinical Diagnosis of Diabetic Polyneuropathy With the Diabetic Neuropathy Symptom and Diabetic Neuropathy Examination Scores

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OBJECTIVE — To evaluate the discriminative power of the Diabetic Neuropathy Symptom (DNS) and Diabetic Neuropathy Examination (DNE) scores for diagnosing diabetic polyneuropathy (PNP), as well as their relation with cardiovascular autonomic function testing (cAFT) and electro-diagnostic studies (EDS).

RESEARCH DESIGN AND METHODS — Three groups (matched for age and sex) were selected: 24 diabetic patients with neuropathic foot ulcers (DU), 24 diabetic patients without clinical neuropathy or ulcers (DC), and 21 control subjects without diabetes (C). In all participants, the DNS and DNE scores were assessed and cAFT (heart rate variability [HRV], baroreflex sensitivity [BRS]), and EDS were performed (Nerve Conduction Sum [NCS] score; muscle fiber conduction velocity: fastest/slowest ratio [F/S ratio]).

RESULTS — Both the DNS and the DNE scores discriminated between the DU and DC groups significantly ($P < 0.001$). The DNE score even discriminated between DC and C ($P < 0.05$). Spearman's correlation coefficients between both DNS and DNE scores and cAFT (HRV −0.42 and −0.44; BRS −0.30 and −0.29, respectively) and EDS (NCS 0.51 and 0.62; F/S ratio 0.44 and 0.62, respectively) were high. Odds ratios were calculated for both DNS and DNE scores with cAFT (HRV 4.4 and 5.7; BRS 20.7 and 14.2, respectively) and EDS (NCS 5.6 and 16.8; F/S ratio 7.2 and 18.8, respectively).

CONCLUSIONS — The DNS and DNE scores are able to discriminate between patients with and without PNP and are strongly related to cAFT and EDS. This further confirms the strength of the DNS and DNE scores in diagnosing diabetic PNP in daily clinical practice.

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One of the major risk factors for the development of diabetic foot complications is distal symmetric sensorimotor polyneuropathy (PNP) (1,2). For diagnosing PNP, no gold standard is available. The San Antonio consensus panel has recommended that at least one measurement should be performed in five different diagnostic categories (3). These are symptom scoring, physical examination scoring, quantitative sensory testing (QST), cardiovascular autonomic function testing (cAFT), and electro-diagnostic studies (EDS).

Because none of the existing symptom and physical examination scores for diabetic PNP completely fulfilled methodological criteria for diagnostic tests, the Diabetic Neuropathy Symptom (DNS) and Diabetic Neuropathy Examination (DNE) scores were developed (4,5). (DNS guidelines can be found in an online appendix at http://care.diabetesjournals.org.) The construct validity of these scores was studied in relation to Semmes Weinstein monofilaments and vibration perception threshold testing (both forms of QST) because of their predictive value to the development of diabetic foot complications (6–9).

cAFT has an important prognostic value for the prediction of diabetic foot complications (8,10,11) and mortality due to cardiovascular problems (12,13). The prognostic value of EDS is less clear, although EDS are supposed to be the most sensitive diagnostic tool for diabetic PNP (14). The relation between the DNS and DNE scores and cAFT and EDS, respectively, has not been studied.

The objective of this study was to assess the discriminative power of the DNS and DNE scores for diagnosing diabetic PNP, as well as their relation with cAFT and EDS, respectively.

RESEARCH DESIGN AND METHODS

Patients

All participants were recruited from the Diabetes Outpatient Clinic (University Hospital Groningen) and the Rehabilitation Center Beatrixoord Haren after informed consent was obtained. To study the discriminative power of the DNS and DNE scores, three groups of subjects were studied. Patient records were consecu-

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Abbreviations: BRS, baroreflex sensitivity; cAFT, cardiovascular autonomic function testing; DNE, Diabetic Neuropathy Examination; DNS, Diabetic Neuropathy Symptom; EDS, electro-diagnostic studies; F/S ratio, fastest/slowest ratio; HRV, heart rate variability; MFCV, muscle fiber conduction velocity; NCS, Nerve Conduction Sum; PNP, polyneuropathy; QST, quantitative sensory testing; RV, reference value.

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

Table 1—*Patient characteristics*

	DU	DC	C
n	24	24	21
Mean age (years)	57.3 ± 11.4	52.2 ± 12.0	58.2 ± 9.9
Sex (M/F)	14/10	13/11	10/11
Mean duration of diabetes (years)	16.9 ± 12.0	13.1 ± 9.8	
Type 1/type 2 diabetes	5/19	8/16	
Mean HbA_{1c} (%)	8.3 ± 1.1*	7.5 ± 0.8	

Data are means ± SD. C, control subjects; DC, diabetic patients without neuropathy; DU, diabetic patients with neuropathic ulcer. *$P < 0.01$.

tively screened during our outpatient clinics for patients with previous neuropathic foot ulceration in whom peripheral vascular disease was not considered to have contributed to the foot ulcers. After this screening, they were recruited in a randomized order. The first group consisted of 24 diabetic patients known to have had neuropathic foot ulcers (DU group). These ulcers were purely neuropathic by origin, as confirmed by their localization (plantar surface of the foot at high-pressure points) and the absence of peripheral arterial disease, as described below. In the second group, 24 diabetic patients without clinical neuropathy or foot ulcers (DC group) were included. To confirm this, the 10-g Semmes Weinstein monofilament was tested on the plantar surface of the hallux and central at the heel. The ability to correctly sense the monofilament in six trials on both locations was defined as normal, whereas the inability to sense the monofilament correctly in one or more trials was defined as disturbed. The third group consisted of 21 control subjects with normal glucose tolerance (C group). All groups were matched for sex and age (within 5 years), and the diabetic groups were also matched for duration and type of diabetes (type 1/type 2 diabetes; type 1 diabetes was considered on clinical grounds when the onset of the disease was a ketoacidosis or before the age of 40 years). Subjects with a history of or clinically apparent cardiac disease, with electrocardiographic abnormalities, or who used β-blockers or calcium antagonists were excluded. Peripheral arterial disease was excluded by normal ankle-arm indexes (>0.90), toe-arm indexes (>0.70), and normal plethysmography (crest time 0.22 s) in all groups. Normal glucose tolerance of the control subjects was demonstrated by a fasting capillary blood glucose <6.1 mmol/l and a blood glucose <7.8 mmol/l 2 h after a 75-g oral glucose tolerance test. Details of the clinical characteristics of each group are given in Table 1.

Methods

The DNS and DNE scores (E.B.), cAFT (J.L.), and EDS (J.v.d.H.) were performed by different researchers who were blinded to participant group. The researchers were acting independently, and no information about the results was exchanged during the study. An overall Neuropathy Sum score, according to the San Antonio consensus, was composed.

DNS score

Both the DNS and DNE scores have been described in detail elsewhere (4,5). In short, the DNS score is a four-item validated symptom score, with high predictive value to screen for PNP in diabetes (4). Symptoms of unsteadiness in walking, neuropathic pain, paraesthesia, and numbness are elicited. The presence of one symptom is scored as 1 point; the maximum score is 4 points. A score of 1 or higher is defined as positive for PNP.

DNE score

The DNE score is a sensitive and validated hierarchical scoring system (5). The score contains two items concerning muscle strength, one concerning reflexes, and five concerning sensation (eight total items). Each item is scored from 0 to 2 (0 is normal and 2 severely disturbed). The maximum score is 16 points. A score of >3 points is defined as positive for PNP.

cAFT

Cardiovascular autonomic function was assessed by analysis of heart rate variability (HRV) and baroreflex sensitivity (BRS). All participants were studied in the morning. All measurements took place in a quiet room with the temperature kept constant at 22°C. Blood pressure was monitored by a Finapres (Ohmeda 2300; Ohmeda, Inglewood, CO) and heart rate by an electrocardiogram monitor (Hewlett-Packard 78351T; Hewlett-Packard, Palo Alto, CA). After 30 min of supine rest, the Finapres and electrocardiogram signals were sampled at 100 Hz and stored on a personal computer during 15 min. Offline, 300 s of each recording were analyzed by the CARSPAN program (IEC ProGamma; IEC, Groningen, the Netherlands), as previously described (15,16). After artifact correction and stationarity check, discrete Fourier transformation of systolic blood pressure and R-R interval length measurement were performed. HRV analysis was performed in accordance with the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (17). The total power frequency band of HRV was defined as 0.02–0.40 Hz. Because no reference values (RVs) of HRV are available, the median of the control group was used, 9.2 $\ln(ms^2)$. BRS was determined by the transfer function method and defined as the mean modulus between systolic blood pressure and HRV in the 0.07- to 0.14-Hz frequency band with at least 0.5 coherence, expressed in ms/mmHg (15,16,18). A BRS <3 ms/mmHg has shown high mortality rates in chronic heart failure and after myocardial infarction, but in diabetes, the prognostic value of the BRS is unknown (19,20). Therefore, in this study, a BRS <3 ms/mmHg was considered indicative for cardiovascular autonomic neuropathy.

Electro-diagnostic testing (EDS)

Nerve conduction studies were performed with standard surface stimulation and recording techniques using an electromyograph type Nicolet Viking IIe and IV with standard filter settings. All measurements were performed after warming in hot water (38°C) of forearm and lower leg during at least 15 min. Peak-peak amplitudes were used. RVs from our own laboratory were used, with abnormal values defined as >2 SD of normal mean values.

Motor nerve conduction velocity (RVs) were measured in the left median (thenar) (RV 58.5 ± 4.6 m/s [means ± SD]) and peroneal nerves (tibialis anterior) (RV 57.8 ± 7.1 m/s). Sensory nerve

Table 2—*Results of the tests for PNP for the three groups*

	DU	DC	C
n	24	24	21
DNS (% >1 point = abnormal)	96%	26%	24%
DNE (% >3 points = abnormal)	100%	13%	0%
NCS (% >1 point = abnormal)	85%	32%	15%
F/S ratio (% >1.9 = abnormal)	91%	33%	10%
BRS (% <3 ms/mmHG)	52%	0%	11%
HRVtp (% <median)	95%	57%	50%
Neuropathy Sum score (% >1 point)	100%	47%	40%

Data are means ± SD. C, control subjects; DC, diabetic patients without neuropathy; DU, diabetic patients with neuropathic ulcer. HRVtp, total power of HRV (abnormal defined as less than the median of the control group).

conduction velocities and amplitudes were measured antidromically with ring electrodes placed around the middle finger (median nerve) (RV 45.6 ± 3.7 m/s) and stimulation lateral of the Achilles tendon (sural nerve) (RV 47.4 ± 3.6 m/s). An overall Nerve Conduction Sum (NCS) score was defined as the number of these four nerves with an abnormal conduction velocity, ranging from 0 (all normal) to 4 (all abnormal).

Invasive muscle fiber conduction velocity (MFCV) measurements were performed in the tibialis anterior muscle at rest by means of needle electrodes adapted from a previously described method (21). In short, muscle fibers were directly stimulated in the distal part of the tibial anterior muscle by a small monopolar needle electrode (cathode) using a surface electrode as anode (filter settings 500 Hz–10 kHz, stimulation 0.2 ms, 1–2 mA). The resulting muscle fiber action potentials were detected at a known distance (50–60 mm) by a small concentric needle electrode. With this technique, action potentials supposed to represent individual muscle fibers were identified and the resulting conduction velocities were calculated. As parameters, the mean invasive MFCV and the fastest/slowest ratio (F/S ratio) representing the scatter of conduction velocities were used and compared with normative values from our own laboratory (3.17 ± 0.40; F/S ratio 1.47 ± 0.19, slowest 2.59 ± 0.40, fastest 3.78 ± 0.49).

Table 3—*The number of patients with normal (0) or abnormal scores (1–5) on the Neuropathy Sum (NS) score for the three groups*

NS score	0	1	2	3	4	5
DU (22)			1	12	6	3
DC (23)	12	7	3	1		
C (20)	12	6	2			

C, control subjects; DC, diabetic patients without neuropathy; DU, diabetic patients with neuropathic ulcer.

Neuropathy Sum score

For this study, an overall score was composed of the DNS score (symptom score), DNE score (examination score), BRS (cAFT), and NCS (EDS). Because Semmes Weinstein monofilament testing was used in patient selection, these data, representing QST as the fifth category of the San Antonio consensus (3), were also available. These five tests together formed the Neuropathy Sum score. For each abnormal test result, 1 point was given; the maximum score was 5 points.

Statistics

The statistical package SPSS-PC 10.0 was used to compute the descriptive statistics: ANOVA, χ^2 tests, independent samples *t* test, Spearman's correlation coefficient, and odds ratios. Unless otherwise indicated, means ± SD are given. A *P* value <0.05 was considered statistically significant.

RESULTS — Table 1 shows the patient characteristics. There were no significant differences between the groups for mean age ($P = 0.15$) and sex ($P = 0.77$) and, for the DU and DC groups, duration ($P = 0.23$) and type of diabetes ($P = 0.33$). The mean HbA_{1c} of the DC group was significantly lower ($P < 0.01$) than that of the DU group.

Results of DNS and DNE scores for the three groups

For the DNS score, the scores (±SD) of the DU, DC, and C groups were 2.29 ± 1.23, 0.44 ± 0.84, and 0.38 ± 0.74, respectively. Differences between DU and both DC and C were significant, $P < 0.001$ in both cases, but not between DC and C. For the DNE score, the scores (±SD) of the DU, DC, and C groups were 8.90 ± 1.98, 1.46 ± 2.02, and 0.43 ± 0.81, respectively. Significant differences were found in all comparisons of the three groups, between DU and both DC and C groups, $P < 0.001$ in both cases, and between DC and C ($P < 0.05$).

There were no significant differences for DNS and DNE scores for type 1 and type 2 diabetic patients. There was a significant correlation between the DNS and DNE scores and HbA_{1c} (0.35, $P < 0.01$; 0.57, $P < 0.001$, respectively), as well as between the DNS and DNE scores and duration of diabetes (0.41, $P < 0.01$; 0.56, $P < 0.001$, respectively). There was no significant correlation between both scores and subject age.

Results of the PNP tests

Table 2 shows the percentage of patients in the three groups who scored abnormal on the individual diagnostic tests and on the Neuropathy Sum score. The DNS and DNE scores correctly identified the DU group in 96 and 100%, respectively, and the healthy control subjects in 76 and 100%, respectively. Almost one-half (47%) of the patients of the DC group and 40% of the C group scored at least 1 point on the Neuropathy Sum score, which means that they scored abnormal on at least one diagnostic category of the San Antonio consensus. Table 3 shows the specified results on the Neuropathy Sum score.

Relation of the DNS and DNE scores with cAFT and EDS

In Table 4, the correlation between the DNS and DNE scores and cAFT (BRS and HRV) and EDS (NCS and invasive MFCV) is shown. The odds ratios for these tests are also shown.

CONCLUSIONS — This study shows that the DNS and DNE scores are able to differentiate between subjects with and without neuropathy in diabetes. Previously, the construct validity of both scores was studied in relation to Semmes Weinstein monofilaments and vibration perception threshold testing (4,5)—two quantitative sensory tests known to be strong predictors for the development of

Table 4—*Correlation (Spearmans' rho) and odds ratios (95% CI) of DNS score and DNE scores with EDS and cAFT, respectively*

	DNS score	DNE score	NCS	F/S	BRS	HRVtp
DNS score		42.7 (8.4–215)	5.6 (1.7–18.2)	7.2 (2.3–22.3)	20.7 (2.5–172)	4.4 (1.5–12.8)
DNE score	0.67*		16.8 (3.8–74)	18.8 (5.0–71)	14.2 (2.8–74)	5.7 (1.8–17.8)
NCS	0.51*	0.62*		13.9 (3.6–53)	4.0 (0.7–24.4)‡	4.4 (1.3–14.7)
F/S ratio	0.44*	0.62*	0.60*		3.0 (0.7–11.7)‡	4.6 (1.5–14.2)
BRS	−0.30†	−0.29†	−0.22‡	−0.12‡		22.4 (2.7–186)
HRVtp	−0.42*	−0.44*	−0.37*	−0.32†	0.69*	

*$P < 0.001$; †$P < 0.05$; ‡ = not significant. HRVtp, total power of HRV.

diabetic foot complications. In this report, the DNS and DNE scores are further validated with the EDS and cAFT. There is a strong relation between the DNS and DNE scores and EDS in both nerve and muscle fiber conduction studies. Furthermore, the relation of the DNS and DNE scores with cAFT is significant, although this is stronger for HRV than for BRS for both scores. These results further confirm the strength of the DNS and DNE scores in diagnosing diabetic PNP.

HRV and BRS are advanced measures that are able to detect early abnormalities in cAFT (10–13). The relation of HRV with the parameters for PNP (DNS and DNE scores, NCS, and F/S ratio of MFCV) is stronger than for BRS. While HRV measures the efferent part of the baroreflex arc, i.e., vagal and sympathetic nerve–mediated modulation of heart rate, BRS measures the relation between input (blood pressure sensed at the carotid arteries and aorta baroreceptors) and the output (modulations of heart rate, myocardial contractility, and peripheral arterial resistance) of the baroreflex. Thus, the differences in HRV and BRS in relation to diabetic PNP may be due to the fact that BRS assesses different aspects of cardiovascular reflex function than HRV. Interestingly, it has also been proposed that PNP and cAFT are distinct entities with a different pathogenesis (22), thereby explaining the previously noticed variable relation between cAFT and PNP.

The odds ratios for the DNS and DNE scores with NCS, MFCV (F/S ratio), HRV, and BRS are high, which means that the DNS and DNE scores are able to predict the results of these other diagnostic tests. By assessing the DNS and DNE scores at the outpatient clinic, a good indication is given for performing these more laborious and expensive and less patient-friendly laboratory tests. However, in our opinion, the necessity of complementary performance of cAFT and EDS with the DNS and DNE scores, as proposed in the San Antonio consensus, is debatable in clinical practice. No specific therapeutic interventions are available for neuropathy except strict glycemic control, symptomatic treatment of, for example, neuropathic pain, prevention, and instruction. For screening, prevention, and instruction, the performance of the DNS and DNE scores, eventually in combination with QST, may be sufficient.

As expected, performance of these various tests for diabetic PNP shows a high number of abnormalities among the group of patients with neuropathic ulcers. Although the percentage with abnormal BRS is rather low compared with the percentages of the other tests, these patients are expected to have a very poor prognosis due to their high risk of cardiovascular complications (19,20). In their treatment, hospitalization, and rehabilitation program, this should be taken into account. Strikingly, 48% of this group with obvious neuropathy has a BRS >3 ms/mmHg. This supports the hypothesis that cAFT might develop differently from PNP as an independent complication of diabetes.

In both the diabetic group without neuropathy and the control group, abnormal test results were found for most tests. This might be caused by lack of specificity of the tests, as shown in the control group, although it also shows that after careful and sensitive screening, more abnormalities can be found (also in diabetic patients not known to have neuropathy), as expected after checking the records. The results of the DNS and Neuropathy Sum scores are most striking. In our previous DNS score validation, we chose a cutoff value of >1 to define a sensitive measure for diabetic PNP. Our present values show that almost one-quarter of our control group scores were abnormal. The same problem will exist for other symptom scores, such as for the Neuropathy Symptom Score (NSS) (14,23), because these scores also score these four items of the DNS score. The Neuropathy Sum score, based on the five diagnostic categories as advised by the San Antonio consensus (3), also shows high percentages of participants, even in the control group, with abnormal test results. Therefore, one should consider the risk of overdiagnosis by using all five the diagnostic categories of the San Antonio consensus. Further research should be done to characterize an optimal set of diagnostic categories for diabetic PNP.

In conclusion, this report shows that the DNS and DNE scores allow discrimination between patients with and without diabetic PNP. Both scores are strongly related to EDS and cAFT. These results, together with the previously published results of the validation of both scores, further confirm the strength of the DNS and DNE scores in diagnosing diabetic PNP in clinical practice.

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