Clinical diagnosis of diabetic polyneuropathy with the diabetic neuropathy symptom and diabetic neuropathy examination scores

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

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.
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

**Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>DU</th>
<th>DC</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>57.3 ± 11.4</td>
<td>52.2 ± 12.0</td>
<td>58.2 ± 9.9</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>14/10</td>
<td>13/11</td>
<td></td>
</tr>
<tr>
<td>Mean duration of diabetes (years)</td>
<td>16.9 ± 12.0</td>
<td>13.1 ± 9.8</td>
<td></td>
</tr>
<tr>
<td>Type 1/type 2 diabetes</td>
<td>5/19</td>
<td>8/16</td>
<td></td>
</tr>
<tr>
<td>Mean HbA1c (%)</td>
<td>8.3 ± 1.1*</td>
<td>7.5 ± 0.8</td>
<td></td>
</tr>
</tbody>
</table>

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

**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.

**cRAFT**

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(ms²). 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 diabetics, 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 Ile 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

<table>
<thead>
<tr>
<th></th>
<th>DU</th>
<th>DC</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>DNS (% &gt;1 point = abnormal)</td>
<td>96%</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>DNE (% &gt;3 points = abnormal)</td>
<td>100%</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td>NCS (% &gt;1 point = abnormal)</td>
<td>85%</td>
<td>32%</td>
<td>15%</td>
</tr>
<tr>
<td>F/S ratio (% &gt;1.0 = abnormal)</td>
<td>91%</td>
<td>33%</td>
<td>10%</td>
</tr>
<tr>
<td>BRS (% &lt;3 ms/mmHg)</td>
<td>52%</td>
<td>0%</td>
<td>11%</td>
</tr>
<tr>
<td>HRVtp (% &lt;median)</td>
<td>95%</td>
<td>57%</td>
<td>50%</td>
</tr>
<tr>
<td>Neuropathy Sum score (% &gt;1 point)</td>
<td>100%</td>
<td>47%</td>
<td>40%</td>
</tr>
</tbody>
</table>

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).

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...
Diagnosis of PNP: the DNS and DNE scores

Table 4—Correlation (Spearman’s rho) and odds ratios (95% CI) of DNS and DNE scores with EDS and cAFT, respectively

<table>
<thead>
<tr>
<th></th>
<th>DNS score</th>
<th>DNE score</th>
<th>NCS</th>
<th>F/S</th>
<th>BRs</th>
<th>HRVtp</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNS score</td>
<td>42.7 (8.4–215)</td>
<td>42.7 (8.4–215)</td>
<td>5.6 (1.7–18.2)</td>
<td>7.2 (2.3–22.3)</td>
<td>20.7 (2.5–172)</td>
<td>4.4 (1.5–12.8)</td>
</tr>
<tr>
<td>DNE score</td>
<td>0.67*</td>
<td>0.67*</td>
<td>16.8 (3.8–74)</td>
<td>18.8 (5.0–71)</td>
<td>14.2 (2.8–74)</td>
<td>5.7 (1.8–17.8)</td>
</tr>
<tr>
<td>NCS</td>
<td>0.51*</td>
<td>0.62*</td>
<td>13.9 (3.6–53)</td>
<td>0.60*</td>
<td>4.0 (0.7–24.4)†</td>
<td>4.4 (1.3–14.7)</td>
</tr>
<tr>
<td>F/S ratio</td>
<td>0.44*</td>
<td>0.62*</td>
<td>0.60*</td>
<td>0.60*</td>
<td>4.0 (0.7–24.4)†</td>
<td>4.4 (1.3–14.7)</td>
</tr>
<tr>
<td>BRs</td>
<td>−0.30†</td>
<td>−0.29†</td>
<td>−0.32†</td>
<td>−0.32†</td>
<td>22.4 (2.7–186)</td>
<td></td>
</tr>
<tr>
<td>HRVtp</td>
<td>−0.42*</td>
<td>−0.44*</td>
<td>−0.37†</td>
<td>−0.37†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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 measure 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 neuropathic pain 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 BR >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 Symptom 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 Symptom 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.

References


