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RESEARCH REPORT

The Utah Early Neuropathy Scale: a sensitive clinical scale for early sensory predominant neuropathy

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Abstract Early neuropathy is often sensory predominant and prominently involves small-diameter nerve fibers. Established neuropathy examination scales such as the Michigan Diabetic Neuropathy Scale (MDNS) and the Neuropathy Impairment Score–Lower Leg (NIS-LL) focus primarily on large-fiber sensory and motor function. Here, we validate the Utah Early Neuropathy Scale (UENS), a physical examination scale specific to early sensory predominant polyneuropathy. Compared with other scales, the UENS emphasizes severity and spatial distribution of pin (sharp) sensation loss in the foot and leg and focuses less on motor weakness. UENS, MDNS, and NIS-LL were compared in 215 diabetic or prediabetic subjects, with (129) or without neuropathy (86), and repeated in 114 neuropathy subjects after 1 year of follow-up. Neuropathy severity was also evaluated with nerve conduction studies, quantitative sensory testing, quantitative sudomotor axonal reflex testing, and intraepidermal nerve fiber density determination. The UENS had a high degree of interrater reliability (interclass correlation of 94%). UENS correlated significantly to MDNS and NIS-LL ($p < 0.01$), and more significantly than MDNS or NIS-LL to confirmatory tests. In this cohort, UENS had a superior profile to receiver operating characteristic analysis across a range of scores, with a sensitivity (92%) higher than MDNS (67%) or NIS-LL (81%), without sacrificing specificity. UENS more closely correlated with change in ancillary and small-fiber neuropathy measures over 1 year follow-up than did MDNS or NIS-LL. UENS is a sensitive and reproducible clinical measure of sensory and small-fiber nerve injury and may be useful in trials of early neuropathy.

Key words: diabetes, examination scales, prediabetes, sensory neuropathy

Introduction

Neuropathy physical examination scales are frequently used as the primary outcome measure in clinical trials. A variety of validated scales semiquantitatively assess sensation, strength, and reflexes. Commonly used examination scales, such as the Michigan Diabetes Neuropathy Scale (MDNS) and the lower extremity portion of the Neuropathy Impairment Score (NIS-LL), are designed to be applicable across a broad range of neuropathy types and severity, and balance contribution of motor and sensory findings to the examination score. However, this balanced approach may sacrifice sensitivity to mild neuropathy and the ability to recognize early neuropathy progression. These scales lack a mechanism for measuring anatomic spread of sensory loss, an important clinical aspect of early neuropathy progression.

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Peripheral neuropathy is often recognized by patients or their physicians at a time when symptoms outweigh physical signs. Sensory symptoms, paresthesias, sensory loss, and neuropathic pain are common initial complaints *(Notermans et al., 1993; Gorson and Ropper, 1995; The Italian General Practitioner Study Group, 1995)*. Sensory symptoms and signs predominate in the most common forms of neuropathy, those related to early diabetes *(Dyck and Dyck, 1999; Feldman et al., 1999)*, prediabetes *(Novella et al., 2001; Singleton et al., 2001a; 2001b; Sumner et al., 2003)*, or idiopathic neuropathy (in which no clear cause can be identified) *(Gorson and Ropper, 1995; Wolfe and Barohn, 1998; Wolfe et al., 1999; Smith and Singleton, 2004)*. Although injury to all fiber calibers and types occurs, small-diameter unmyelinated or lightly myelinated nociceptive and autonomic fibers are often prominently affected in these common neuropathies *(Holland et al., 1998)*.

There is an increasing interest in recognizing and treating neuropathy early in its course. Human trials of rational therapies to slow or reverse diabetic neuropathy, including angiotensin converting enzyme inhibitors, nerve growth factors, and aldose reductase inhibitors *(Greene et al., 1999)* have been largely unsuccessful, despite promising results of these medications in animal diabetic models *(Yagihashi et al., 2001)*. One likely contributor to this failure has been selection of study subjects with relatively advanced neuropathy *(Pfeifer and Schumer, 1995; Pfeifer et al., 1997)*. Partly as a consequence of these criticisms, recent clinical trials of alpha-lipoic acid have focused on diabetic subjects with new-onset mild disease *(Ziegler et al., 2004)*.

There is a need for a sensitive clinical examination scale that more faithfully reflects the small-fiber loss common in early neuropathy. The Utah Early Neuropathy Scale (UENS) was developed specifically to detect and quantify early small-fiber sensory neuropathy and to recognize modest changes in sensory severity and distribution. We find that the UENS correlates well with the NIS-LL or MDNS but is more sensitive in detection of neuropathy.

Materials and Methods

The UENS was performed simultaneously with the MDNS and NIS-LL and correlated with several confirmatory measures of neuropathy in a total of 215 study subjects with either diabetes or prediabetes using American Diabetes Association diagnostic criteria *(American Diabetes Association, 2003)*. Subjects were participants in one of two National Institutes of Health-funded studies: Impaired Glucose Tolerance Neuropathy (IGTN) pilot clinical study (R01 NS40458) or the Cutaneous Measures of Neuropathy in Diabetes (CMND) study (R01 DK064814). Participant University Institutional Review Boards approved both studies, and each subject signed a consent form prior to enrollment. The IGTN study was a three-site (University of Michigan, Yale University, University of Utah), National Institute of Neurological Disease and Stroke-funded study designed to characterize the neuropathy associated with IGT, and to develop and select neuropathy progression measures appropriate to IGTN. Sixty-nine subjects were enrolled. IGTN subjects were recruited from patients presenting to endocrinology or neurology clinics at each university. Most IGTN subjects (approximately 60) were referred to neuromuscular clinics for evaluation of otherwise idiopathic polyneuropathy and subsequently discovered to have IGT. The remainder of the subjects were IGT patients referred to the study from endocrinology or general medicine clinics when they were recognized to have a distal polyneuropathy. All IGTN subjects had clinically evident peripheral neuropathy at the time of study enrollment.

The CMND study enrolls subjects with diabetes, with or without early neuropathy. Subjects with advanced neuropathy (symptoms >5 years) are excluded. CMND subjects are recruited from a large community-based primary care network. The University of Utah Health Network (UUHN) includes 10 primary care clinics in the Salt Lake City metropolitan area, with more than 300,000 visits yearly. The UUHN patient database is queried, and informational letters sent to a random selection of patients of the appropriate age with ICD-9 diagnostic codes consistent with diabetes. Interested patients respond and are screened by telephone, then enrolled at an intake visit if they meet inclusion criteria. The first 146 CMND subjects enrolled were included in this analysis. Demographic data for study subjects is provided in Table 2.

Subjects in both study cohorts had identical evaluations for neuropathy, consisting of symptom questionnaires, focused physical exam scales, nerve conduction studies (NCS), skin biopsy for intraepidermal nerve fiber density (IENFD) determination, quantitative sudomotor axon reflex testing (QSART), and quantitative sensory testing (QST), described in greater detail below. The UENS examination form is reproduced in Fig. 1, together with instructions for its performance. A safety pin and standard 128 Hz tuning fork are required to perform the UENS, which takes about 3 min. Nickel-plated steel, size #2 (4.5 cm, 1¾ inch) safety pins (Grafco® #3039-3c; Graham-Field Health Products) were used for all studies.

The UENS was developed over 2 years using an iterative process in which individual elements of the

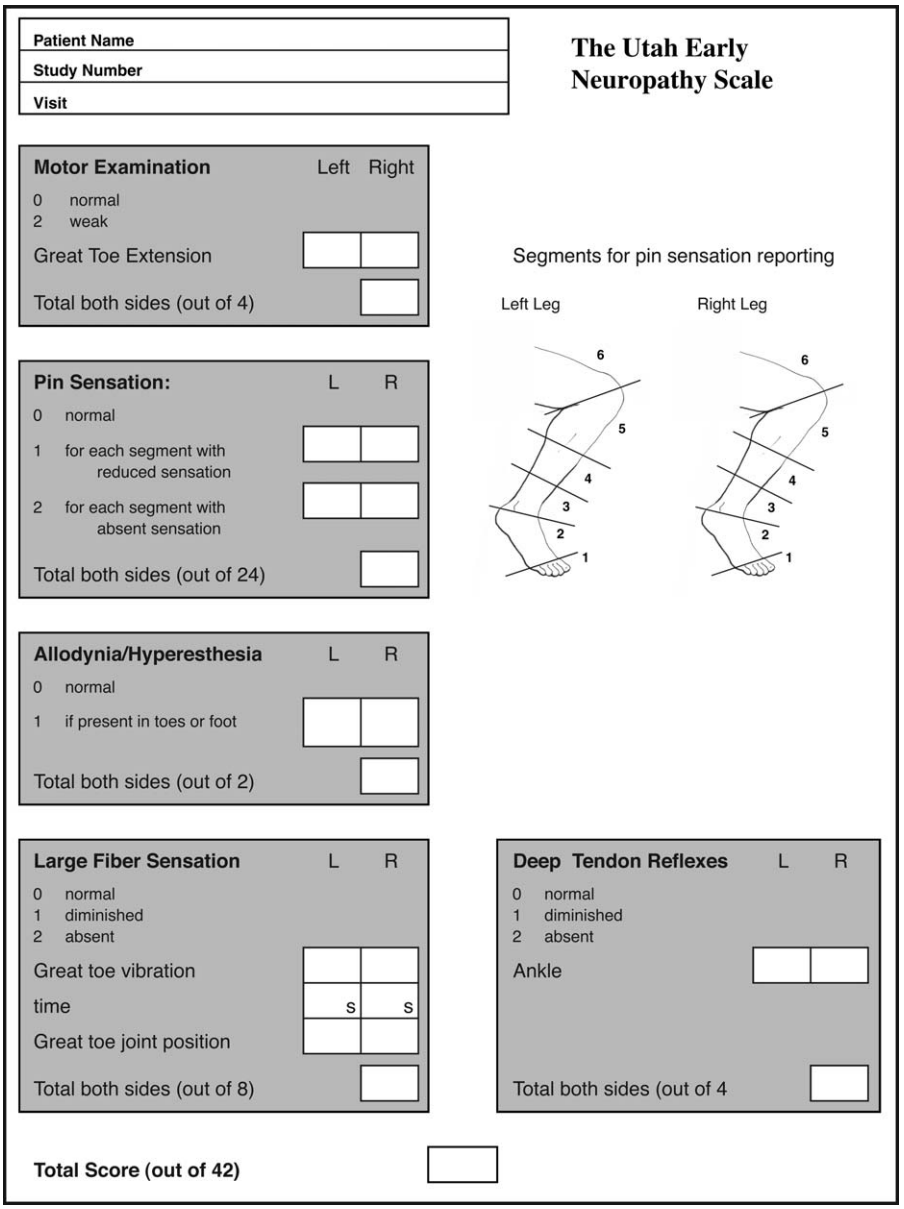

Figure 1. Performing the Utah Early Neuropathy Scale (UENS) examination. The UENS requires a number 2 (1¾ inch) safety pin and a 128 Hz tuning fork. Pin sensation is tested by first reviewing normal sharp sensation to pin on an unaffected portion of the skin. Once this is established, touch the dorsal surface of the foot and leg with the pin, working centripetally from the great toe in 1–2 cm increments while asking the subject to respond when they first feel "any sharpness," and again more proximally when the pin feels "as sharp as they would expect." Repeat to firmly establish these levels. On each side, 2 points are scored for each region in which the patient fails to feel any sharpness. One additional point is scored for each additional region in which the pin feels less sharp than expected. Only distal sensory loss is scored. So, for instance, a person who reported absent pin sensation to the mid foot dorsum (4 points) and reduced sensation to the low ankle (1 point) bilaterally would score a total of 10 points for this portion of the UENS. Vibration is tested by first acquainting the subject with vibration (as opposed to pressure) sensation, then holding the maximally vibrated tuning fork to the dorsum of the great toe at the distal interphalangeal joint. Extinction of vibration in less than 10 s is considered "diminished," while "absent" requires that the patient cannot detect the maximally vibrating tuning fork at the toe. The motor examination is limited to great toe dorsiflexion. Other aspects are as typically performed in neurological examination.

scale were evaluated for their reliability and sensitivity. Elements of the UENS adapted from other scales, such as 0-, 1-, or 2-point scoring for normal, reduced, and absent vibration or ankle deep tendon reflexes used in the MDNS, NIS, and NIS-LL (see below), have been previously validated for reliability.

Cutaneous sharp pain sensation is probably mediated by a combination of unmyelinated c-fiber

nociceptors, lightly myelinated Aδ, and more heavily myelinated Aβ fibers *(Lawson, 2005)*. Twenty-four of the 42 points in the UENS are devoted to a brief anatomical mapping of sensory loss to pin in the foot and lower leg. This anatomical concept was adapted from the examination scale incorporated in the Total Neuropathy Score *(Cornblath et al., 1999)*. Anatomical distribution of foot and leg segments, as shown in Fig. 1, were selected for their reproducibility across subjects (i.e, the boundary between scoring regions can be readily recognized and standardized to compare one patient with another), between examiners and over time. Scoring values for pin sensory loss were chosen to reflect both partial and complete loss of pin sensation in each segment to increase sensitivity. Preliminary testing using only complete loss of pin sensation in each segment found this method less sensitive to mild defects, but no more reliable between examiners. Receiver operating characteristic (ROC) curve analysis showed pin testing alone contributed much of the total sensitivity of the UENS (data not shown).

The MDNS is a 40-point examination scale developed and validated for evaluation of diabetic neuropathy *(Feldman et al., 1994)*. Subjects are tested for strength in finger spread, great toe extension, and foot dorsiflexion; deep tendon reflexes at biceps, triceps, patella, and Achilles; sensation is tested with vibration, 10 g monofilament pressure, and pin sensation at the great toe. For strength, deep tendon reflexes, monofilament, and vibration sensation, 1 point is given for reduction on either side and 2 points when the response is absent. For pin sensation at the great toe dorsum, 2 points per side are assigned if sharp sensation is absent. The MDNS examination was originally designed to be paired with NCS to confirm peripheral neuropathy but has been used as a stand-alone measure in clinical trials *(Abbott et al., 1998, Brown et al., 2004)*. An MNDS score of 6 or more is necessary to confirm neuropathy.

The NIS-LL represents a focused version of the full Neuropathy Impairment Score for use in length-dependent peripheral neuropathy but has also been combined with electrophysiological tests as a comprehensive score *(Dyck et al., 1997)*. Both scales have been extensively validated, and the NIS-LL has been used in recent clinical trials of nerve growth factor and ruboxistaurin in diabetic neuropathy *(Apfel et al., 2000; Tesfaye et al., 2007)*. For the NIS-LL, all tests are performed and scored bilaterally. Strength for ankle and toe dorsiflexion and plantarflexion is graded on a 4-point scale based on percent weakness. Reflexes at knee and ankle are graded 0–2 with corrections for age. Sensation at the distal joint of the great toe is tested with touch pressure, pin sensation, vibration, and joint position, and graded 0 (normal), 1 (reduced), or 2 (absent) for each modality. The total possible bilateral score is 56 (32 motor, 8 reflex, 16 sensory), and no specific diagnostic threshold for neuropathy has been set.

For all study subjects, common alternative causes of neuropathy were excluded with testing for vitamin B12, TSH, anti-nuclear antibodies, serum protein electrophoresis, and immunofixation *(Smith and Singleton, 2004)*. Potential subjects with a family history of neuropathy (independent of diabetes) or with a disease known to be associated with neuropathy (e.g., hepatitis C, systemic lupus erythematosis) were excluded.

To test interrater reliability, the UENS was performed on sequential days by two separate blinded physician examiners for 20 subjects with peripheral neuropathy. Subjects reported severity of neuropathic pain using two validated measures, a 100 mm visual analogue scale (VAS) and the Gracely pain scale *(Max et al., 1992)*.

For the purposes of calculating sensitivity of examination scales, subjects were defined as having polyneuropathy if they had symptoms of neuropathy confirmed by abnormalities of at least two confirmatory electrodiagnostic, electrophysiological, or histological tests. Symptoms of neuropathy were elicited by the investigators through direct interview with subjects. Reports of persistent numbness or paresthesias developing symmetrically in the feet, and progression from distal to proximal involvement were required historical elements. Examination signs were specifically excluded from the neuropathy threshold definition because of concern for a self-referential bias in comparing examination scales.

Confirmatory studies were performed in a standardized fashion for each subject. NCS included left sural sensory and peroneal motor responses. NCS were considered abnormal if subjects exhibited any one or more of the following: low-amplitude sural sensory nerve action potential, low-amplitude peroneal compound motor action potential, or slowed peroneal conduction velocity from distal to the fibular head to ankle. Skin temperature was maintained at $>32.0°C$. Consistent, age-specific normal values were applied to all subjects, and in the multicenter IGTN cohort, NCS results were reviewed for technical quality by a central laboratory at the University of Michigan.

QST for vibration and cold detection thresholds was performed at the foot using a CASE IV machine (WR Medical) and standardized 4.2.1 stepping algorithm. Results were expressed as age-adjusted percentiles for detection threshold using a data set derived from the Rochester Diabetic Neuropathy Study of Normal Subjects *(Dyck et al., 2005)* and provided with the device software by the manufacturer.

Detection thresholds more than the 95th percentile were considered abnormal.

QSART, a measure of autonomic mediated cutaneous sweat production in response to iontophoresed acetylcholine, was performed at left foot and distal leg using a QSweat machine (WR Medical) and a standardized protocol. Sweat volumes at each site were expressed in microliters and compared with percentile ranges for age- and sex-adjusted, anatomical site–specific sweat volumes derived from normal subjects in the Mayo Clinic Autonomic Reflex Laboratory *(Low and Mathias, 2005)*, with volumes less than fifth percentile judged abnormal.

Three millimeter punch skin biopsies were obtained from the ankle and proximal thigh, fixed, cut in 50-micron-thick sections, stained for the pan-axonal marker PGP 9.5, and examined microscopically in a blinded fashion to calculate IENFD according to standardized counting criteria *(Smith et al., 2005)*. IENFD at the distal leg was evaluated in considering whether an abnormality was present.

Statistical analysis

Intraclass correlation coefficients were used to assess interrater reliability of the UENS. Pearson's correlation coefficients were used to examine pairwise correlation between UENS, NIS-LL, MDNS, and other measures among subjects with neuropathy, both at baseline, and with change over time. Only subjects with neuropathy were used in these comparisons to avoid erroneously improved correlations due to comparison of scores in a large subset of subjects with examination scores at or near zero. Sensitivity and specificity of examination scales were calculated using standard formulae, and data for the full spectrum of possible neuropathy thresholds presented as ROC curves. Area under the ROC curve, SE, and 95th percentile CIs were calculated for each exam scale using SPSS statistical software (SPSS Inc.). Differences between correlations of UENS, NIS-LL, and MDNS with other factors at baseline, and change over 1 year were assessed using a *t* test applied to the appropriately transformed difference between two dependent Pearson correlations *(Cohen and Cohen, 1983)*.

Results

The UENS has an interrater reliability of 94% across 20 comparisons. Among subjects with neuropathy, initial UENS score closely correlates with that of the MDNS and NIS-LL ($p < 0.001$ for each), and change over 1 year follow-up ($p < 0.001$ for MDNS, $p = 0.02$ for NIS-LL). High reliability and close correlation with these established scales are necessary prerequisites for demonstrating the validity of the UENS. However, compared with MDNS or NIS-LL, the UENS is significantly more closely correlated with several ancillary measures of baseline neuropathy severity (Table 1).

Table 1. Correlation at baseline between examination scales, and with other measures of neuropathy severity in subjects with neuropathy.*

Exam scales	UENS	MDNS	NIS-LL
UENS	–	0.895 (<0.001)	0.863 (<0.001)
MDNS	–	–	0.880 (<0.001)
NIS-LL	–	–	–
Electrophysiology			
SSA	**−0.401 (0.002)**	−0.319 (0.002)	−0.249 (0.033)
PMA	−0.354 (0.001)	−0.311 (0.004)	−0.262 (0.017)
PMCV	**−0.278 (0.013)**	−0.183 (0.106)	−0.194 (0.087)
CDT	0.270 (0.014)	0.328 (0.002)	0.208 (0.059)
VDT	0.298 (0.006)	0.334 (0.003)	0.306 (0.005)
QSART			
Ankle	−0.179 (0.105)	−0.105 (0.343)	−0.068 (0.54)
Foot	**−0.331 (0.046)**	−0.087 (0.434)	−0.171 (0.123)
IENFD			
Distal leg	***−0.437 (0.001)***	−0.315 (0.008)	−0.186 (0.131)
Distal thigh	−0.239 (0.076)	−0.210 (0.087)	−0.204 (0.132)
Pain			
Gracely	**0.345 (0.001)**	0.279 (0.01)	0.214 (0.124)
VAS	**0.360 (0.002)**	0.211 (0.076)	0.199 (0.245)

UENS, Utah Early Neuropathy Scale; MDNS, Michigan Diabetic Neuropathy Scale; NIS-LL, Neuropathy Impairment Score−Lower Leg; SSA, sural sensory amplitude; PMA, peroneal motor response amplitude; PMCV, peroneal motor response proximal conduction velocity; CDT and VDT, cold and vibration detection thresholds; QSART, quantitative sudomotor axon reflex testing; IENFD, intraepidermal nerve fiber density; VAS, 100 mm visual analog scale.

*Data are expressed as correlation coefficient (p value). Correlation coefficients were compared using a *t* test applied to the appropriately transformed difference between two dependent Pearson correlations *(Cohen and Cohen, 1983)*. Measures for which UENS was significantly ($p < 0.05$) better correlated than one other exam scale are shown in bold, and those for which UENS was significantly better correlated than both MDNS and NIS-LL are bolded and italicized. In contrast, NIS-LL or MDNS were not significantly better correlated than UENS with any baseline measure.

The UENS more closely reflects the distribution of deficits in early sensory neuropathy than does the MDNS or NIS-LL. Point allocation of the UENS and MDNS are compared in Fig. 2B. The MDNS allocates points nearly evenly between tests of sensation, strength, and deep tendon reflexes. The UENS emphasizes sensory loss, and devotes 24 of its 42 points to an anatomical mapping of pin sensation in the foot and distal leg. Among our hyperglycemic neuropathy cohort, pin sensation at the foot is most frequently abnormal, while "large-fiber" sensory measures (vibration and joint position) are less often abnormal, and clinically evident weakness quite rare (Fig. 2A). This prominent early involvement of small unmyelinated peripheral nerve fibers is also reflected in the high prevalence of neuropathic pain and reduction in IENFD. Similar sensory and small-fiber predominance has been reported in patients with idiopathic neuropathy *(Wolfe et al., 1999; Smith and Singleton, 2004)*.

As shown in Fig. 2B, the allocation of points in the UENS more accurately reflects the point distribution among early neuropathy patients. Compared with the NIS-LL or MDNS, the UENS score more closely correlates with other measures of neuropathy severity in subjects with neuropathy and with severity of neuropathic pain (Table 1). Measures of small-fiber function (QSART and IENFD) are particularly likely to correlate with UENS score, reflecting its emphasis on small-fiber pin sensation.

The UENS has a greater diagnostic sensitivity at baseline than the MDNS or NIS-LL without sacrificing specificity. ROC analysis is shown in Fig. 3 together with areas under the curve, SEs, and 95th percentile CIs for each measure. UENS demonstrates superior diagnostic sensitivity and specificity across the spectrum of possible scores. Area under the ROC curve was greater for UENS than for other examination scales, though this difference did not reach statistical significance by comparison of SEs.

The UENS was designed to record change in anatomical distribution of pin sensory loss. Over 1 year of follow-up, change in UENS was significantly correlated with change in both MDNS [correlation coefficient (cc) 0.758, $p < 0.001$], and to a lesser degree NIS-LL (cc 0.425, $p = 0.02$). Over this short follow-up, change correlation was not significant for most measures using any examination scale. However, UENS change was significantly correlated ($p < 0.05$) with change in IENFD at the distal thigh (cc −0.659), change in neuropathic pain measured by VAS (cc 0.341) and Gracely scales (cc 0.276), and change in vibration detection threshold (cc 0.262). MDNS change was significantly correlated only with VAS change (cc 0.254), while change in NIS-LL correlated significantly with no other ancillary measure. Correlation coefficients were not significantly different between exam scales for change of any neuropathy measure.

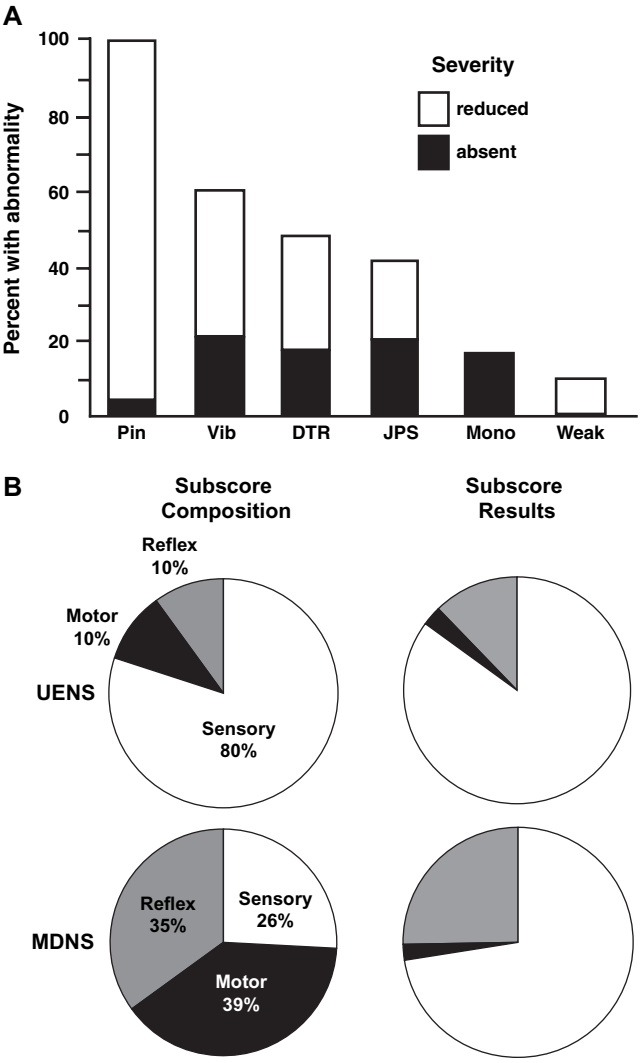

Figure 2. (A) Frequency of physical examination abnormalities for subjects with hyperglycemic neuropathy from left; sharp sensation to pin, vibration from 128 Hz tuning fork at the great toe, trace or absent deep tendon reflexes, joint position sense at great toe, pressure sensation from 10 g monofilament, and symmetric distal weakness. Sensory and small-fiber features predominate. The darkened portion of each bar represents the proportion of subjects for whom the examination measure was absent. (B) The point distribution of the UENS more closely reflects the sensory predominance of neuropathic features seen in early neuropathy than does the MDNS. The pie charts depict point distribution of the scales on the left: 80% of UENS points are sensory, compared with 26% of MDNS points. However, when applied to patients, subscore results are sensory predominant for both scales. The UENS composition more closely mirrors the distribution of examination signs observed in early neuropathy patients. Similar discrepancy is present with the NIS-LL (data not shown). UENS, Utah Early Neuropathy Scale; MDNS, Michigan Diabetic Neuropathy Scale; NIS-LL, Neuropathy Impairment Score–Lower Leg.

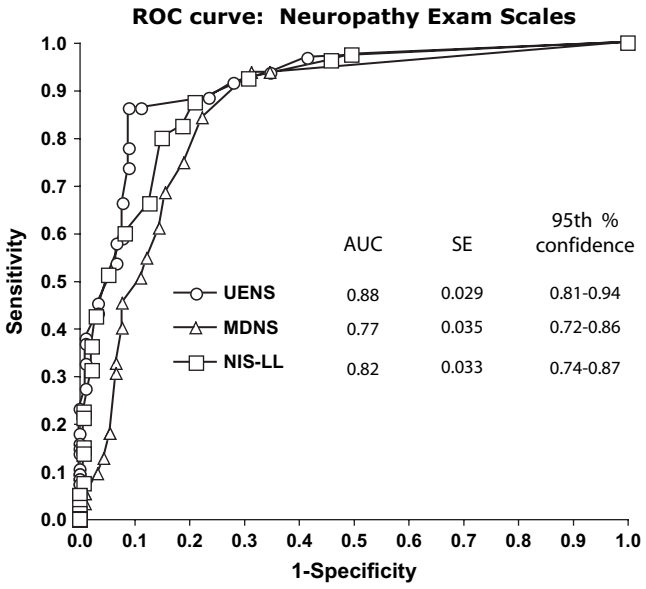

Figure 3. Receiver operating characteristic (ROC) curves demonstrate greater sensitivity and specificity for the UENS throughout its score. These differences do not reach statistical significance. UENS, Utah Early Neuropathy Scale.

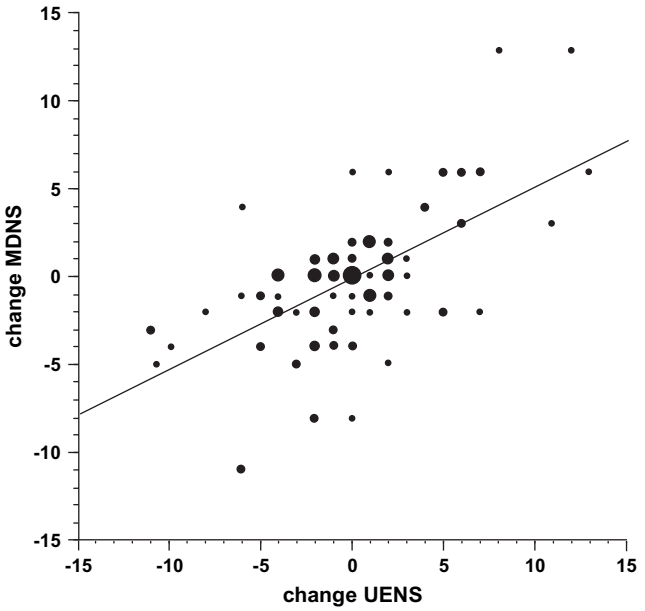

Figure 4. Change in the UENS is compared with change in MDNS over a 1 year follow-up for 114 subjects with hyperglycemic neuropathy. Change in the UENS was significantly correlated to change in the MDNS ($p < 0.001$) and $R^2 = 0.449$. IGTN subjects, all of whom received individualized diet and exercise counseling, tended to show improved (lower) scores, while diabetic CMND subjects, who received no prescribed therapy, showed worsening (higher) scores. The area of the circles is proportional to the number of subjects with each combination of score changes. Eighteen subjects had no change in either score. Linear best fit (solid line) and 95th percentile CIs (dashed lines) are shown. UENS changed approximately 2 points for every 1 point change in MDNS (dUENS = dMDNS(1.94) − 0.14). IGTN, Impaired Glucose Tolerance Neuropathy; CMND, Cutaneous Measures of Neuropathy in Diabetes; UENS, Utah Early Neuropathy Scale; MDNS, Michigan Diabetic Neuropathy Scale.

UENS was also more likely to record change in neuropathy severity (either worsened or improved) in this neuropathy cohort. Fig. 4 compares change in MDNS or UENS for the 114 neuropathy subjects for whom 1 year follow-up is available. UENS changed roughly 2 points for every one point of change in the MDNS (slope equation with the figure). In most cases where UENS changed but MDNS did not over 1 year of follow-up, UENS score change resulted from a change in the anatomical distribution of pin sensation.

Discussion

There is need for a simple, rapid, reproducible examination scale targeted to early sensory neuropathy. Our findings demonstrate that the UENS is a sensitive and valid measure of early neuropathy and its progression. The IGTN and CMND subject cohorts are appropriate for an analysis of examination scale sensitivity and specificity because for each subject, neuropathy has been extensively confirmed using ancillary electrodiagnostic, neurophysiological, and histological testing.

The most striking difference between the MDNS, NIS-LL, and UENS is the greater sensitivity demonstrated by UENS. By emphasizing pin (sharp) sensation, the UENS achieves greater sensitivity to presence of peripheral neuropathy. Previous studies indicate that loss of sharp sensation is a common early feature useful in defining the presence of sensory polyneuropathy *(McArthur, 1998; Smith and Singleton, 2004)*. Distal reduction in pin sensation was the most sensitive examination feature of neuropathy in our study subjects.

The UENS records change in neuropathy severity in part by mapping the anatomical distribution of pin sensory loss in the foot and leg. Most patients with early neuropathy report sensory loss that begins at the toes or soles of the feet and spreads slowly to affect proximal foot, then ankle, and lower leg. Conversely, resolution of reversible sensory neuropathy (e.g., following vitamin B12 supplementation) is associated with return of sensation first proximally and then distally in the leg. The UENS is designed to be sensitive to the changes in anatomic distribution common to sensory loss early in neuropathy progression. By comparison, the MDNS and NIS-LL register neuropathy progression primarily when a new sensory modality (vibration, monofilament pressure) becomes abnormal.

Table 2. Baseline demographic and nerve function characteristics of subjects with and without neuropathy, using diagnostic criteria as described in the text.*

	No neuropathy, $N = 86$		Neuropathy, $N = 129$		
	Mean	SD	Mean	SD	Two-sided *t* test, p value
Subject characteristics					
Age	55.8	9.7	57.8	7.1	0.102
% female	50.0	–	54.2	–	0.578†
Body mass index	32.4	7.5	34.8	8.3	0.030
Neuropathy measures					
Exam scales					
UENS	1.39	2.29	9.24	6.10	<0.001
MDNS	0.83	1.76	6.62	5.13	<0.001
NIS-LL	0.91	1.82	7.23	5.51	<0.001
Electrophysiology					
SSA	11.6	6.6	5.0	5.4	<0.001
PMA	4.8	2.2	3.5	2.3	<0.001
PMCV	44.2	8.2	40.3	5.3	<0.001
CDT	53.1	27	78.8	23.8	<0.001
VDT	68.0	23.9	85.3	16.8	<0.001
QSART					
Ankle	1.11	0.77	0.76	0.73	0.001
Foot	0.94	0.72	0.67	0.73	0.008
IENFD					
Distal leg	4.6	2.7	1.7	2.3	<0.001
Distal thigh	6.8	3.51	4.52	2.99	<0.001
Pain					
Gracely	0.24	0.39	0.67	0.53	<0.001
VAS	6.3	13.8	24.2	27.3	<0.001

UENS, Utah Early Neuropathy Scale; MDNS, Michigan Diabetic Neuropathy Scale; NIS-LL, Neuropathy Impairment Score–Lower Leg; SSA, sural sensory amplitude; PMA, peroneal motor response amplitude; PMCV, peroneal motor response proximal conduction velocity; CDT and VDT, cold and vibration detection thresholds; QSART, quantitative sudomotor axon reflex testing; IENFD, intraepidermal nerve fiber density; VAS, 100 mm visual analog scale.
*Comparison of means for each measure was performed with Student's *t* test, and two-sided p values are shown.
†Fraction of female subjects in each group was compared using 2 × 2 contingency table analysis and Fisher's exact test. Two-sided p value is shown.

A variety of clinical examination scales for peripheral neuropathy are available; some, like the Charcot Marie Tooth Neuropathy Score, have been validated for evaluation of a particular neuropathy form *(Shy et al., 2005)*. Most weigh large-fiber sensory function and strength similar to the MDNS and many are longer and more time consuming. The MDNS was validated against the much more extensive Neuropathy Impairment Score. Integrated scores range from simple to very comprehensive. The Michigan Neuropathy Screening Instrument (MNSI) is a widely used clinical screening instrument valued for its simplicity. It consists of a brief symptom questionnaire and a subsequent 8-point examination scale *(Lunetta et al., 1998)*. Two points are assigned bilaterally for abnormalities of foot appearance (ulcers, amputations) and 1 point per side (in 0.5-point increments) for abnormalities of ankle reflexes or vibration at the great toe. A score greater than 2 in the setting of a positive questionnaire indicates neuropathy. The MNSI examination scale had a significantly smaller ROC curve area than the other scales evaluated (data not shown), suggesting this scale is not particularly sensitive to early neuropathy.

At the other end of the spectrum, the Total Neuropathy Score (TNS) is designed as a comprehensive neuropathy endpoint that summates symptoms, signs, and physiology in one score that may be used as a primary endpoint measure *(Cornblath et al., 1999)*. It includes an examination scale as well as points for sensory autonomic and motor symptoms, QST, and electrophysiological features. Like the UENS, the TNS factors anatomic distribution of pin sensory loss as a measure of neuropathy severity.

In general, it is best to choose a neuropathy rating scale that is specific for the neuropathy severity and disease being studied. The UENS was designed to reflect neuropathy severity and change in the narrow but common subset of patients with early sensory predominant neuropathy. As such, the UENS would not be appropriate to the evaluation of neuropathies with prominent weakness (acute inflammatory demyelinating polyradiculoneuropathy) or in those with more severe disease (advanced diabetic neuropathy). Instead, for motor and sensory mixed large- and small-fiber neuropathies of moderate severity, an examination scale like the NIS-LL or a comprehensive score like the TNS may be appropriate. These scores are not ideal for neuropathies of mild severity or for those involving specific fiber types or functions.

The UENS was designed specifically to meet the requirements of clinical evaluation in trials of early

neuropathy. Nerve conduction measures of neuropathy severity, such as change in peroneal motor conduction velocity or sural sensory amplitude, and direct histological measures (IENFD, sural nerve biopsy) have often been used as primary progression measures in diabetic neuropathy trials because they are objective, repeatable, and continuously variable. However, such surrogate measures have been criticized because they do not directly measure features of neuropathy clinically relevant to the patient *(Greene et al., 1999)*. The UENS, because of its sensitivity to early sensory loss and ability to record modest anatomic change in sensory function, is likely to be useful as future clinical trials seek to enroll and treat patients with milder neuropathy.

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