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Clinical Neuropathy Scales in Neuropathy Associated with Impaired Glucose Tolerance

Lindsay A. Zilliox, Sandra K. Ruby, Sujal Singh, Min Zhan, and James W. Russell¹

¹Department of Neurology, Maryland VA Healthcare System and University of Maryland, Baltimore, MD

Abstract

AIMS—Disagreement exists on effective and sensitive outcome measures in neuropathy associated with impaired glucose tolerance (IGT). Nerve conduction studies and skin biopsies are costly, invasive and may have their problems with reproducibility and clinical applicability. A clinical measure of neuropathy that has sufficient sensitivity and correlates to invasive measures would enable significant future research.

METHODS—Data was collected prospectively on patients with IGT and symptomatic early neuropathy (neuropathy symptoms < 2 years) and normal controls. The seven scales that were examined were the Neuropathy Impairment Score of the Lower Limb (NIS-LL), Michigan Diabetic Neuropathy Score (MNDS), modified Toronto Clinical Neuropathy Scale (mTCNS), Total Neuropathy Score (Clinical) (TNSc), The Utah Early Neuropathy Scale (UENS), the Early Neuropathy Score (ENS), and the Neuropathy Disability Score (NDS).

RESULTS—All seven clinical scales were determined to be excellent in discriminating between patients with neuropathy from controls without neuropathy. The strongest discrimination was seen with the mTCNS. The best sensitivity and specificity for the range of scores obtained, as determined by using receiver operating characteristic curves, was seen for the mTCNS followed by the TNSc. Most scales show a stronger correlation with measures of large than small fiber neuropathy.

CONCLUSIONS—All seven scales identify patients with neuropathy. For the purpose of screening potential patients for a clinical study, the mTCNS followed by the TNSc would be most helpful to select patients with neuropathy.

Keywords

neuropathy; diabetes; impaired glucose regulation; clinical scales; screening tools

Corresponding Author: James W. Russell, M.D., M.S., Department of Neurology, University of Maryland, School of Medicine, 3S-129, 110 South Paca Street, Baltimore, MD 21201-1595, Tel: 410-3283100; Fax: 410-3288981, JRussell@som.umaryland.edu.

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There is no widely accepted or highly sensitive clinical primary endpoint measure for the neuropathy associated with impaired glucose tolerance (IGT). Furthermore, the diagnosis of mild large fiber or small fiber neuropathies is often costly and involves invasive procedures such as nerve conduction studies (NCS) and skin biopsies for the measurement of the intraepidermal nerve fiber density (IENFD). In turn, this leads to high expenses for conducting clinical studies in patients with IGT. The lack of sensitivity significantly affects the power analysis for a study and increases the likelihood that the study will be “negative”. A clinical measure of neuropathy that is sensitive enough to detect early neuropathies and that correlates to invasive measures of small fiber neuropathy would be a great advantage to clinical research in diabetes and could potentially lower the size and cost of future trials.

There are multiple clinical neuropathy scales available, but many of them test components of the neuropathy examination that may not be affected, or only minimally affected, in early or small fiber neuropathies. For example, scales often include deep tendon reflexes, proprioception and motor dysfunction. These scales may be less sensitive to early and small fiber neuropathies that are associated with IGT.

Currently, it is unknown which of the available clinical scales performs best in patients with neuropathy due to IGT. Current areas of clinical research are targeted at patients with early neuropathy, which may be most amenable to therapies and early diagnosis may be crucial to the success or failure of these trials. Neuropathy associated with IGT can initially present with non-specific symptoms and minimal objective findings on clinical examination. Thus, diagnosis of neuropathy may be missed or delayed. Furthermore, because NCSs are often normal, non-invasive and reliable measures are needed to monitor the neuropathy.

The purpose of this study was to determine which of seven clinical neuropathy scales were best able to detect the presence of an early neuropathy (defined as having symptoms of neuropathy for two years or less) in subjects with IGT. In addition, we compared the individual scale scores to measurements of the IENFD, quantitative sudomotor axon reflex (QSART), sural nerve amplitude and the peroneal nerve conduction velocity.

Research Design and Methods

Standard protocol approvals, registrations, and patient consents

All neuropathy and normal subjects were consented according to the ethical standards committees on human experimentation (University of Maryland and Maryland VA Health Care System).

Study design

Data was obtained prospectively from the University of Maryland Neuromuscular and Department of Neurology Database, and participants in ClinicalTrials.gov NCT00780559 and NCT01864460.

Early neuropathy is polyneuropathy as previously defined (1), with symptoms of neuropathy for two years or less. The etiology of neuropathy was (IGT) based on standardized American Diabetes Association (ADA) criteria (2).

Subjects with neuropathy were evaluated with the clinical neuropathy scales that have been widely used in the assessment of neuropathy: the Neuropathy Impairment Score of the lower limb (NIS-LL) (3), Michigan Diabetic Neuropathy Score (MDNS) (4), modified Toronto Clinical Neuropathy Score (mTCNS) (5), Total Neuropathy Score-clinical (TNS-C) (6), the Utah Early Neuropathy Score (UENS) (7), and the Neuropathy Disability Score (NDS) (8). The Early Neuropathy Score (ENS) was developed to assess key abnormalities in early neuropathy: (1) sensory loss (10 gram Semmes Weinstein type monofilament testing on the hallux [The tip of the monofilament is gently applied to the skin, bent slowly to approximately 3/4 of its extended length, then slowly released. The application occurs over approximately 2 seconds], vibration testing using a Rydel-Seiffer tuning fork on the interphalangeal joint of the hallux, pin perception on the hallux using a nickel-plated steel, size #2 safety pins [Grafc0 #3039-3c; Graham-Field Health Products], cold perception using metal thermal disks (9) on the dorsum of the foot); (2) ankle reflexes that are graded as reduced if they can only be obtained with reinforcement and absent if they cannot be obtained with reinforcement. Items are tested bilaterally, with 0 given for a normal result, 1 for a reduced result and 2 for an absent result. The scales were administered, using a standardized protocol, at the same time in each subject to allow for comparison between the scales.

Electrodiagnostic tests were performed on subjects with suspected neuropathy and included NCS, quantitative sensory testing (QST) [vibration detection threshold (VDT) and cold detection threshold (CDT)], and QSART performed as previously described (10). Subjects with clinical neuropathy also had skin biopsies performed at the calf and thigh and the IENFD was measured. The criteria for inclusion within the study for patients with IGT associated neuropathy were signs and symptoms of peripheral neuropathy and an abnormality in at least one of the following: NCS, QST, QSART, or IENFD. Laboratory testing included obtaining a 75 gram 2 hour oral glucose tolerance test and HbA1c testing performed using ADA criteria (2). Other tests included but were not confined to the following: electrolyte and liver function testing panel, B12 levels, methylmalonic acid levels, thyroid function tests, serum and urine protein electrophoresis and immunofixation, antinuclear antibody, and erythrocyte sedimentation rate. Other laboratory tests for neuropathy were performed where appropriate depending on the clinical evaluation.

The presence of neuropathy was determined using criteria for confirmed diabetic sensorimotor polyneuropathy according to guidelines published by the Toronto Diabetic Neuropathy Expert Group (1). Subjects with neuropathy met the following criteria (1) clinical neuropathy (signs and symptoms of neuropathy) diagnosed within two years of inclusion into the study (2) abnormal electrophysiological tests or IENFD (3) no evidence of demyelinating neuropathy (4) NCS could be normal with an abnormality of QST, QSART, or IENFD. NCS in the lower extremities were considered abnormal if any of the following were present: sensory nerve action potential amplitudes, sensory conduction velocities or onset latencies, mildly reduced compound motor action potentials, or minimally abnormal motor conduction velocities. QST was performed in the distal leg with the Case IV device, using a standard stepping algorithm. QST included measurement of the CDT and the VDT (10, 11). IENFD was determined using preparation of the biopsy and measurement according EFNS guidelines as previously published (1, 12).

Large fiber neuropathy was defined as the presence of abnormal NCS, obtained in all subjects, and an abnormal VDT consistent with the presence of neuropathy but normal IENFD, QSART, or CDT. Small fiber neuropathy was defined as a normal NCS and VDT with abnormal IENFD, QSART or CDT.

Normal subjects without neuropathy were recruited as part of the University of Maryland Neuromuscular or Neurology Database. All normal subjects were examined by one of the authors (JWR or LZ) and their medical records were carefully reviewed to exclude subjects with neurological or neuromuscular disorders, or other conditions that may affect sensory or motor function. Normal subjects had a normal neuromuscular examination.

Statistical Design

Analysis was performed using SPSS version 22. Receiver operating characteristic (ROC) curves were calculated and compared as previously described (13). Internal consistency for the construct items was determined using Cronbach's alpha. Statistical significance was defined as a two-tailed P value < 0.05, and data is presented as the mean $\pm$ the standard error of the mean.

Results

General clinical features of the subjects

A total of 113 subjects, 81 with neuropathy and 32 normal controls, were included in this study. Table 1 shows the age, gender, etiology by neuropathy subtype, and mean scores in the seven examined neuropathy scales for all subjects as well as for the subgroups of those with large fiber vs. small fiber neuropathy. Neuropathy score data represents the mean $\pm$ standard error of the mean. There were 31 women (mean age = 61.13 $\pm$ 1.80 years) and 50 men (mean age = 62.04 $\pm$ 1.33 years) with IGT associated neuropathy. In the control group, there were 23 women (mean age = 53.14 $\pm$ 2.28 years) and 9 men (mean age = 54.78 $\pm$ 3.90 years) (Table 1). In the neuropathy group there were 26 subjects with a large fiber neuropathy and 25 subjects with a small fiber neuropathy (Table 1).

ROC for the clinical neuropathy scales

In assessing the scores on various clinical scales of neuropathy in subjects with IGT associated neuropathy as well as normal controls, the ROC sensitivity/specificity analysis indicated that the mTCNS and the TNSc showed the greatest sensitivity and specificity, among all of the examined scales, for detecting subjects with neuropathy from the control subjects. These two scales also performed best in detecting subjects with large fiber neuropathy as well as small fiber neuropathy (Fig. 1). The area under the ROC for neuropathy subjects as well as for subjects with either large or small fiber neuropathy are compared in Table 2. Significance compares the ROC area under the curve for each scale to the ROC with the smallest area under the curve (MDNS). All scales showed an excellent accuracy in discriminating between subjects with neuropathy and controls without neuropathy.

Comparing the AUCs for each scale to the AUC for the MDNS, which was the scale with the smallest AUC, there was a significant difference for the mTCNS score for subjects with neuropathy ($P<0.01$) and subjects with a small fiber neuropathy ($P<0.05$). There was not a significant difference for subjects with large fiber neuropathy between the AUC for the mTCNS and the MDNS. For subjects with neuropathy there was also a significant ($P<0.05$) difference for the ENS score and for small fiber neuropathy with the NDS ($P<0.05$). The AUC for other neuropathy scales were not significantly different. When a cohort of subjects with newly diagnosed type 2 diabetes were included in the analysis, there was no significant difference in the ROC AUC for the diabetic subjects compared to the IGT subjects. The positive and negative predictive values for each scale based on a cutoff with $>95\%$ specificity is shown in Table 3. The TCNS had the highest sensitivity and corresponding specificity of the tested scales.

Validation of the clinical neuropathy scale scores with IENFD and NCS

Using the coefficient of determination, there was much stronger correlation between each of the scales and measures of large fiber function (Table 4). All of the scales, except for the mTCNS, had a significant association with the sural sensory nerve action potential amplitude and all of the scales had a significant association with measurement of the peroneal nerve motor conduction velocity and VDT. The strongest correlation for all three measures of large fiber function was with the ENS. None of the examined neuropathy scales showed a significant association with the IENFD at the distal leg or thigh or with the CDT (Table 4). The TNSc, NIS-LL, ENS, UENS, NDS and MDNS scales demonstrated a weak but significant association with the QSART in the foot, which is a measure of small fiber neuropathy.

Internal consistency of internal reliability and frequency of the scale domains

Internal consistency reliability testing was performed using Cronbach's alpha for neuropathy subjects in this study. Table 5 shows the internal consistency for each of the scales considered in this study. For each item on the scale, the value represents the effect on the overall scale value for Cronbach's alpha if the specific domain were removed from the scale. The table shows the overall construct validity and scores for individual domains. The mTCNS shows the greatest scale reliability followed by the ENS. Within the domains, sensory signs show the greatest validity. Motor symptoms, motor signs and allodynia subscales show poor scale validity. Allodynia measured in the UENS was infrequent and this domain had poor construct validity.

Discussion

The current study compares seven commonly used neuropathy scales in order to determine which scale best distinguishes subjects with IGT associated neuropathy from control subjects without neuropathy and to determine the sensitivity and specificity of the scales in this population. This is important because currently there is no agreement on which scale should be used in clinical neuropathy trials. Patients included in this study were those with IGT and early neuropathy, with reported symptoms present less than two years. These participants would be potential subjects for future research studies of therapies for similar

types of neuropathy, as the neuropathy is typically mild and may be reversible. However, this population of patients with early neuropathy can be difficult to identify due to a predominantly small fiber involvement causing symptoms, but a relative lack of findings on examination or NCS. For these reasons, a clinical scale that is cost-effective, easy to administer, and sensitive enough to distinguish patients with neuropathy would be a great advancement. Furthermore, there is no agreed upon gold standard test for the presence or absence of early neuropathy.

NCSs are reproducible, reliable, and objective measures of peripheral neuropathy and are frequently used as endpoint measures in trials of peripheral neuropathy. However, the use of NCSs has been questioned due to the fact that only large fiber function is evaluated, the meaning of minimal changes in NCSs is unclear, and expected changes in NCSs over time are poorly defined. Skin biopsies for measurement of IENFD are also often used as endpoint measures for small fiber or early neuropathies. However, in addition to being costly and invasive, the biopsies need to be interpreted in an experienced laboratory with established age and gender matched normative values (12). Both NCSs and skin biopsies are time consuming and costly, which make them poor screening tools. In addition they are surrogate measures and do not directly measure clinically relevant features of neuropathy. In fact, clinical endpoints are preferable to surrogate markers to determine efficacy of therapeutic agents and are much easier to use in ambulatory settings.

There are currently several validated clinical neuropathy scales available. However, it has not been determined which scale is best to detect patients with IGT associated neuropathy from the general population. Many scales were designed to be used for a broad range of neuropathy types and severities, which may lead them to be less sensitive to early neuropathies.

The MDNS was developed to confirm the presence of neuropathy in patients who were first screened with the Michigan Neuropathy Screening Instrument. The MDNS was found to correlate with neuropathy measures such as vibration thresholds, autonomic function testing and NCSs (4). The NDS measures the ankle reflex and distal sensation at the great toe and showed a strong correlation with the vibration perception threshold (8). The NIS-LL was modified from the NDS specifically for distal polyneuropathy and only includes examination of the lower extremities since an abnormal neuropathy evaluation is more likely in the lower extremities. The NIS-LL focuses on motor activity and it gives relatively little weight to small fiber function, which potentially limits its use in patients with small fiber predominant neuropathy. The UENS was designed to detect early small-fiber sensory neuropathy and recognize small changes in sensation. It focuses on the sensory examination and includes minimal muscle and reflex examination; testing only the extensor hallucis longus strength and ankle reflexes. The UENS was found to correlate with the NIS-LL and MDNS but was more sensitive in the detection of neuropathy. Distal reduction in pin sensation was found to be the most sensitive feature on physical examination in neuropathy subjects evaluated with the UENS (7).

The mTCNS was validated relative to the Toronto Clinical Neuropathy Score (TCNS) in a population of patients with diabetes for 13 ± 8 years and mild to moderate severity diabetic

sensorimotor polyneuropathy (defined as a sural sensory nerve action potential amplitude of 1.0 μ V or more). The TCNS was found to be valid against sural nerve fiber density in diabetic sensorimotor polyneuropathy (5). The TCNS was modified to emphasize the significant sensory dysfunction seen in early diabetic neuropathy in order to improve its sensitivity and specificity. The mTCNS was found to correlate with summed sensory amplitudes from NCS, but less strongly than the TCNS (14). The TNS was originally used in studies of toxic neuropathies but was validated in subjects with diabetic polyneuropathy of varying severity (mild, moderate, and severe) (6).

We found that all seven of the examined clinical neuropathy scales performed well and were able to distinguish patients with IGT associated neuropathy from the control population with a high degree of sensitivity and specificity. However, the mTCNS followed by the TNSc had the greatest sensitivity and specificity for neuropathy as well as large and small fiber neuropathy subgroups. This may be because the mTCNS and the TNSc are the only two scales that include questions regarding sensory symptoms. The mTCNS includes the sensory examination but does not contain a motor or reflex exam. The TNSc puts more weight on the sensory examination but includes the strength and reflex examination as well.

Interestingly, when a cohort of subjects with newly diagnosed type 2 diabetes were included, there was no significant difference in the ROC sensitivity/specificity analysis for the diabetic subjects compared to the IGT subjects. A study of recently diagnosed type 2 diabetic patients found that early nerve damage in diabetic patients was characterized by involvement of both small and large fibers (15). Similarly, several studies of patients with IGT and neuropathy have shown that the neuropathy in this patient population also shows both large and small fiber dysfunction (7, 10, 16–18).

Although none of the examined scales demonstrated an association with the IENFD, the TNSc, NIS-LL, ENS, UENS, and MDNS did have a significant association with measurement of the QSART at the foot. There was a stronger association between most of the scales and measures of large fiber function including the sural sensory nerve action potential amplitude, peroneal motor conduction velocity, and the vibration detection threshold. This is not a surprising finding since most of the scales include clinical measures of large fiber function and were validated using tests of large fiber function such as nerve conduction studies.

Overall, the mTCNS demonstrated the greatest scale reliability. In particular, sensory signs had the greatest validity. In comparison motor symptoms, motor signs, and allodynia subscales demonstrated poor scale validity. For patients with IGT and neuropathy, where there is generally a mild sensory polyneuropathy with few motor findings, a scale showing high construct reliability would include sensory signs. In support of this, questionnaires about symptoms alone have been shown to perform poorly compared to the clinical examination and it has been suggested that questionnaires should not be used as a stand-alone test and that symptoms alone are a poor measure of neuropathy (4, 19). Furthermore, the assessment of autonomic function in the TNSc is too imprecise to add to the construct validity. A more precise measure of autonomic dysfunction in peripheral neuropathy, for

example the Survey of Autonomic Symptoms, may be a more valid scale to assess small fiber or autonomic function (20).

These conclusions would likely not be generalizable to other types of neuropathy where motor abnormalities are prominent or the neuropathy is more severe and the reflexes are significantly affected. Thus, in a clinical trial it is important that the scale be developed specifically to assess the typical neuropathic abnormalities present in the specific subjects enrolled in the trial.

The control subjects in this study were individuals without neuropathy. However, a control group of individuals with IGT but without neuropathy would have been ideal. Additionally since the majority of the controls were spousal controls they did not undergo electrodiagnostic studies and skin biopsies in addition to a physical examination. Due to this limitation only participants with symptomatic neuropathy were chosen for inclusion in the current study.

A more systematic approach to developing a scale to measure outcomes in early or mild diabetic neuropathy is needed. For example, a new scale designed for this population and using modeling with item response theory (IRT) (21) may improve early diagnosis and detect small changes in outcome. Thus far, these goals have been elusive using currently available scales developed using classical test theory. Based on results from the current study, items that assess sensory symptoms, sensory signs, and reflexes would be important in modeling an IRT built scale.

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Figure 1.

ROC curves were determined for (A) all neuropathy subjects (B) large fiber neuropathy and (C) small fiber neuropathy. The images represent the two neuropathy scales that showed the best sensitivity and specificity characteristics in determining the presence of neuropathy, the mTCNS and the TNSC. The MDNS (not shown) had the poorest sensitivity and specificity characteristics. The mTCNS area under the ROC (AUC) was significantly different from the MDNS for all subjects with neuropathy ($P<0.01$) and for small fiber neuropathy ($P<0.05$) but not for large fiber neuropathy. AUC for other neuropathy scales were not significantly different, except for the NDS that was significantly different from the MDNS for small fiber neuropathy ($P<0.05$).

Table 1

Age, Gender, Etiology and Neuropathy Scores in Subjects With and Without IGT Neuropathy

Type of Neuropathy	All neuropathy	Large Fiber	Small Fiber	No neuropathy
Age (years)	61.69 ± 1.06	65.00 ± 2.43	57.52 ± 1.53	53.61 ± 1.94
No. Female (%)	31 (38.3%)	9 (34.6%)	11 (44.0%)	23 (71.9%)
No. Male (%)	50 (61.7%)	17 (65.4%)	14 (56.0%)	9 (28.1%)
TNSc	8.38 ± 0.43	10.27 ± 0.84	6.24 ± 0.63	0.66 ± 0.29
NIS-LL	8.11 ± 0.67	11.48 ± 1.48	4.88 ± 0.74	0.22 ± 0.14
mTCNS	11.53 ± 0.65	13.96 ± 1.22	9.08 ± 1.15	0.47 ± 0.14
UENS	9.69 ± 0.85	14.13 ± 1.86	6.25 ± 1.10	0.41 ± 0.17
MDNS	9.99 ± 0.74	13.89 ± 1.51	5.92 ± 0.81	0.75 ± 0.23
ENS	9.25 ± 0.56	12.00 ± 1.17	6.64 ± 0.80	0.88 ± 0.26
NDS	6.26 ± 0.34	7.23 ± 0.91	4.77 ± 0.53	0.59 ± 0.18

Table 2

Comparison Between ROC for Different Types of Neuropathy

1. Area Under the ROC for All Subjects with Neuropathy				
Measurement Scale	Area	Lower Limit 95% CI	Upper Limit 95% CI	Significance
mTCNS	0.9983	0.9306	0.9939	0.0060
TNSc	0.9798	0.9439	1.0000	0.1572
NDS	0.9717	0.9451	0.9982	0.1237
ENS	0.9652	0.9356	0.9948	0.0426
NISLL	0.9623	0.9306	0.9939	0.0617
UENS	0.9483	0.9356	0.9948	0.5112
MDNS	0.9408	0.8995	0.9822	0.1237
2. Area Under the ROC for Subjects with Large Fiber Neuropathy				
Measurement Scale	Area	Lower Limit 95% CI	Upper Limit 95% CI	Significance
mTCNS	0.9986	0.9952	1.0000	0.1544
TNSc	0.9865	0.9606	1.0000	0.2718
ENS	0.9574	0.8956	1.0000	0.3835
NDS	0.9567	0.8964	1.0000	0.7437
NISLL	0.9467	0.8792	1.0000	0.4206
UENS	0.9411	0.8675	1.0000	0.7880
MDNS	0.9389	0.8560	1.0000	0.6044
3. Area Under the ROC for Subjects with Small Fiber Neuropathy				
Measurement Scale	Area	Lower Limit 95% CI	Upper Limit 95% CI	Significance
mTCNS	0.9959	0.9878	1.0000	0.0295
TNSc	0.9694	0.9178	1.0000	0.1324
NDS	0.9572	0.8993	1.0000	0.0367
ENS	0.9402	0.8756	1.0000	0.0730
NISLL	0.9355	0.8665	1.0000	0.1209
UENS	0.9205	0.8452	0.9958	0.2364
MDNS	0.8879	0.7910	0.9849	0.3175

Table 3

Sensitivity and Specificity for Tested Neuropathy Scales

	Cutoff	Sensitivity	Specificity	PPV	NPV	LRP	LRN
mTCNS	3.00	98.00	97.00	0.99	0.94	31.20	0.03
TNSc	5.00	81.00	97.00	0.99	0.66	25.90	0.20
UEENS	3.00	85.00	97.00	0.99	0.72	27.20	0.15
ENS	5.00	83.00	97.00	0.99	0.67	26.67	0.17
MDNS	5.00	80.00	100.00	1.00	0.65		0.20
NISLL	3.00	83.00	97.00	0.98	0.69	26.47	0.18
NDS	4.00	89.00	100.00	1.00	0.78		0.11

PPV = positive predictive value. NPV = negative predictive value. LRP = likelihood ratio positive. LRN = likelihood ratio negative.

Table 4
Coefficient of Determination (R^2) Comparing Neuropathy Scales to IENFD and Electrophysiology

	Small Fiber Function				Large Fiber Function			
	IENFD (Distal Leg)	IENFD (Thigh)	Foot		CDT	Sural SNAP Amp.	Fibular MCV	VDT
			Distal Leg	QSART				
mTCNS	0.0028 (P=0.686)	0.0150 (P=0.360)	0.0079 (P=0.687)	0.0956 (P=0.117)	0.0009 (P=0.907)	0.0370 (P=0.096)	0.0642 (P=0.032)	0.1530 (P=0.048)
TNSc	0.0300 (P=0.186)	0.0116 (P=0.421)	0.0078 (P=0.688)	0.2020 (P=0.019)	0.0080 (P=0.724)	0.2320 (P<0.001)	0.1870 (P<0.001)	0.3540 (P=0.001)
NISLL	0.0000 (P=0.996)	0.0003 (P=0.898)	0.0686 (P=0.227)	0.2420 (P=0.011)	0.0242 (P=0.551)	0.2120 (P<0.001)	0.2780 (P<0.001)	0.3360 (P=0.002)
ENS	0.0049 (P=0.594)	0.0044 (P=0.620)	0.0920 (P=0.159)	0.2350 (P=0.010)	0.0081 (P=0.722)	0.1940 (P<0.001)	0.2120 (P<0.001)	0.4050 (P<0.001)
UENS	0.0018 (P=0.751)	0.0037 (P=0.647)	0.1030 (P=0.135)	0.1910 (P=0.023)	0.0003 (P=0.942)	0.1590 (P<0.001)	0.2490 (P<0.001)	0.3250 (P=0.002)
MDNS	0.0002 (P=0.923)	0.0005 (P=0.871)	0.1020 (P=0.137)	0.2670 (P=0.006)	0.00133 (P=0.886)	0.249 (P<0.001)	0.3220 (P<0.001)	0.3100 (P=0.003)
NDS	0.0044 (P=0.643)	0.0016 (P=0.785)	0.0017 (P=0.850)	0.1440 (P=0.051)	0.0343 (P=0.462)	0.1790 (P<0.001)	0.2690 (P<0.001)	0.3630 (P=0.001)

IENFD = intraepidermal nerve fiber density, QSART = quantitative sudomotor axon reflex test, CDT = cold detection threshold,

SNAP Amp. = sensory nerve action potential amplitude, MCV= motor conduction velocity, VDT = vibration detection threshold.

Table 5
Determination of Importance of Individual Domains in a Clinical Neuropathy Scale Using Reliability Statistics

	All Domains (1)	Sensory Symptoms (2)	Sensory Examination (3)	Motor Symptoms (4)	Motor Examination (5)	Autonomic Symptoms (6)	Reflexes (7)
mTCNS	0.83	0.90	0.76	NA	NA	NA	NA
ENS	0.82	NA	0.54	NA	NA	NA	0.96
MDNS	0.78	NA	0.72	NA	0.83	NA	0.67
NIS-LL	0.76	NA	0.60	NA	0.84	NA	0.70
UENS	0.70	NA	0.55	NA	0.73	NA	0.70
TNSc	0.67	0.64	0.62	0.68	0.69	0.68	0.63
NDS	0.64	NA	0.45	NA	NA	NA	0.93

The values in columns 2–7 indicate the effect on the overall Cronbach alpha for all domains (column 1). A reduced value in columns 2–7 indicates that if the domain were removed then the overall construct validity in column 1 would be reduced. If the value in columns 2–7 increases compared to the value in column 1, then removing the domain would increase the overall construct validity in column 1. UENS allodynia subscale: 0.73