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Clinical neuropathy scales in neuropathy associated with impaired glucose tolerance

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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 rather 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.
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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

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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.

1. Research design and methods

1.1. 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).

1.2. 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 (Tesfaye et al., 2010), with symptoms of neuropathy for two years or less. The etiology of neuropathy was IGT based on standardized American Diabetes Association (ADA) criteria (Anonymous, 2013).

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) (Bril, 1999), Michigan Diabetic Neuropathy Score (MDNS) (Feldman et al., 1994), modified Toronto Clinical Neuropathy Score (mTCNS) (Bril & Perkins, 2002), Total Neuropathy Score-clinical (TNS-C) (Cornblath et al., 1999), the Utah Early Neuropathy Score (UENS) (Singleton et al., 2008), and the Neuropathy Disability Score (NDS) (Young, Boulton, MacLeod, Williams, & Sonksen, 1993). 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 [Grafco #3039-3c; Graham-Field Health Products], cold perception using metal thermal disks (Dyck, Curtis, Bushek, & Offord, 1974) 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 (Peltier et al., 2009). 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 (Anonymous, 2013). 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 (Tesfaye et al., 2010). 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: mildly reduced sensory nerve action potential amplitudes, mildly abnormal 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 (Peltier et al., 2009; Russell, 2005). IENFD was determined using preparation of the biopsy and measurement according EFNS guidelines as previously published (Lauria et al., 2010; Tesfaye et al., 2010).

Large fiber neuropathy was defined as the presence of abnormal NCS, obtained in all subjects, or 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.

1.3. Statistical design

Analysis was performed using SPSS version 22. Receiver operating characteristic (ROC) curves were calculated and compared as previously described (DeLong, DeLong, & Clarke-Pearson, 1988). 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.

2. Results

2.1. 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).

2.2. 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

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