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The assessment of clinical distal symmetric polyneuropathy in type 1 diabetes: A comparison of methodologies from the Pittsburgh Epidemiology of Diabetes Complications Cohort

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ABSTRACT

Distal symmetrical polyneuropathy (DSP) is the most common type of diabetic neuropathy, but often difficult to diagnose reliably. We evaluated the cross-sectional association between three point-of-care devices, Vibratron II, NC-stat®, and Neurometer®, and two clinical protocols, MNSI and monofilament, in identifying those with DSP, and/or amputation/ulcer/neuropathic pain (AUP), the two outcomes of major concern. This report presents data from 195 type 1 diabetic participants of the Epidemiology of Diabetes Complications (EDC) Study attending the 18-year examination (2004–2006). Participants with physician-diagnosed DSP, AUP or who were abnormal on the NC-stat, and the Vibratron II, MNSI, and monofilament were older ($p < 0.05$) and had a longer duration of diabetes ($p < 0.05$). There was no difference by sex for DSP, AUP, or any testing modality, with the exception of NCstat (motor). The Vibratron II and MNSI showed the highest sensitivity for DSP (>87%) and AUP (>80%), whereas the monofilament had the highest specificity (98% DSP, 94% AUP) and positive predictive value (89% DSP, 47% AUP), but lowest sensitivity (20% DSP, 30% AUP). The MNSI also had the highest negative predictive value (83%) and Youden's Index (37%) and currently presents the single best combination of sensitivity and specificity of DSP in type 1 diabetes.

1. Introduction

Neuropathy, a common complication of type 1 and type 2 diabetes mellitus, may affect 28–70% of patients, depending upon the population characteristics, diabetes duration and diagnostic methodology used [1–6]. Although all types of peripheral nerves can be involved, it is usually sensory dominant with eventual involvement of motor nerve fibers [7]. Distal symmetrical polyneuropathy (DSP), which predisposes patients to variable pain, sensory disturbance, motor dysfunction, ulcers, and gangrene, is the most common type of diabetic neuropathy [8–10]. DSP, however, is difficult to diagnose because it is frequently subtle and requires clinical judgment and/or expensive and subsequent unpleasant testing modalities like nerve conduction. Patients may also be asymptomatic for years and diagnosis may only be apparent with a complication like painless foot ulcer. As over 80% of amputations follow a foot ulcer or injury and the total annual cost of DSP and its complications is estimated to be between $4.6 and $13.7 billion [11], early reliable identification of individuals at risk is a public health issue as well as a clinical concern [8].

In the Pittsburgh Epidemiology of Diabetes Complications Study (EDC), a 20 year prospective cohort of childhood onset type 1 diabetes, we have reported strong relationships of DSP with foot ulcers/amputation [12], coronary artery disease [13], and coronary artery calcification [14]. DSP risk factors comprised hypertension, diabetes duration, and glycosylated hemoglobin [15]. Other studies have reported similar findings with neuropathy [16–19].

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Unfortunately, there is no diagnostic gold standard for DSP and the use of multiple testing modalities is recommended [20]. Current standards of medical care by the American Diabetes Association recommend that all patients with diabetes should be screened annually for DSP using a variety of tests such as pinprick, sensation, vibration perception (using a 128 Hz tuning fork), 10 g (Semmes–Weinstein) monofilament pressure sensation at the distal halluces, and ankle reflexes [8]. No specific protocol is given, however, and a number of newer point-of-care instruments, Neurometer R-CPT (Neurotron, Inc.) and NC-stat (NEUROMetrix, Inc.), are now also available, in addition to older devices like the Vibratron II assessment of vibratory sensation, and clinical protocols like the Michigan Neuropathy Screening Index (MNSI), and monofilament. These instruments and protocols might enable more widespread technician screening and possibly earlier diagnosis, than would be possible using formal physician exams or nerve conduction studies.

In this cross-sectional analysis, we thus evaluated the Vibratron II, NC-stat (NEUROMetrix, Inc.) and Neurometer R-CPT (Neurotron, Inc.) devices, and the MNSI and monofilament protocols as indicators of clinically diagnosed DSP. The common outcome or ''Gold Standard'' to which they were all thus compared was a standard clinical exam protocol replicating use in general clinical practice. We also studied the other device/protocol associations against the NC-stat as an alternative (nerve conduction-based) Gold Standard. Finally, we examined the associations of these measures with the major clinical outcomes of neuropathy that are of concern to the patient and healthcare provider, i.e., presence of ulcer/amputation and/or neuropathic pain.

2. Method

2.1. Population

The subjects were participants in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, a prospective study of risk factors for complications of childhood onset (<17 years of age at diagnosis) type 1 diabetes, diagnosed (or seen within one year of diagnosis) at Children's Hospital of Pittsburgh between 1950 and 1980. This population has been shown to be epidemiologically representative of the Allegheny County type 1 diabetes population [21]. The EDC Study first examined participants between 1986 and 1988 and then biennially thereafter for 10 years and again at 18 years. This report presents cross-sectional data from 195 participants attending the 18 year examination (2004–2006) with available clinical exam data, Vibratron II testing, and NC-stat, which was introduced partway into the clinical examination period. As there was no assessment of neuropathy in the finger with the NCstat, this analysis is confined to the foot and especially the hallux. In a subgroup of 141 participants, the Neurometer was similarly evaluated.

2.2. Vibratory sensory thresholds: Vibratron II (Physitemp Instruments, Clifton, NJ)

Sensory thresholds were measured on the palmar aspect of the distal phalanx of the index finger and plantar aspect of the great toe on the dominant side of the body. The protocol uses the two alternative forced-choice methods, where the participant was required to indicate which of the two posts was vibrating as previously described [22]. The vibratory thresholds were examined as follows: the unadjusted for age raw score (continuous variable), and a categorical age-adjusted score. The criteria for the abnormal age-specific vibratory thresholds are >2.39, >2.56, and >2.89 vibration units for ages ≤35, 36–50, and >50 years, respectively [23].

2.2.1. NC-stat (NEUROMetrix, Inc.)

The NC-stat is a point-of-care device designed to perform standard noninvasive nerve conduction studies by non-technical personnel. The NC-stat device does not represent a new diagnostic technology but rather a further evolution of existing nerve conduction studies (NCS) methods. The testing was focused on the compound muscle action potential (CMAP) for the peroneal (motor F wave latency) nerve and the sural nerve amplitude potential (SNAP) for the sensory nerve at the region of the foot and ankle. Using a special alcohol and pumice prep pad, the foot was scrubbed and allowed to dry. For the tibial (sural) test, the electrode/biosensor was placed on the subject's ankle and the biosensor connected to the monitor, while for the peroneal (motor) the hallucis longus tendon was identified by having the patient flex his/her toes upward. The location was marked, the electrode/biosensor applied, and then the biosensor electrode was connected to the monitor. The NC-stat is equipped with a remote-on-call system which transmits the data from the monitor to the central reading center where a report was generated and sent to the clinic by fax. The testing took approximately 15 min. The sensory raw score was not normally distributed, despite log transformation, and thus analysed two ways: ≥6 μV or <6 μV, based on conventional criteria (SNAP), and any vs. no response (NCstat sensory). The latter stratification was based upon the limitations of the NCstat's sensory nerve amplitude which lacks signal detection for extremely low levels of sural nerve sensory amplitude and zeros all signals <2.1 μV. The motor data were dichotomized as normal or abnormal (CMAP).

2.2.2. Neurometer R-CPT (Neurotron, Inc.)

In a subgroup of participants (n = 141), the Neurometer R-CPT (Neurotron, Inc.), which was introduced later, was also available. The Neurometer is a portable point of care device which stimulates peripheral sensory nerve fibers in the great toe on the right foot at three frequencies, 2000 Hz (A_β fibers), 250 Hz (A_δ fibers), and 5 Hz (C fibers). Each frequency is repeated several times to ensure accuracy and reproducibility. The average time needed to complete the three tests was less than 5 minutes. The Neurometer reports values as the normal range (R-CPT Level, 6–13), hyperesthesia (R-CPT Level, 1–5), and hypoesthesia (R-CPT Level, 14–25). Due to the nonlinear scoring, analyses were performed having categorized participants as being normal, hyperesthesia, or hypoesthesia.

2.2.3. MNSI examination

MNSI examination is a structured clinical assessment of the feet to identify deformities, dry skin, calluses, infection, fissure, or ulcers (foot appearance), and evaluation of ankle reflexes and vibration sensation in the great toe. The foot