Contents lists available at ScienceDirect

Primary Care Diabetes

journal homepage: http://www.elsevier.com/locate/pcd

Original research

Evaluation of clinical tools and their diagnostic use in distal symmetric polyneuropathy

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ARTICLE INFO

Article history:
Received 31 January 2013
Received in revised form
2 April 2013
Accepted 3 April 2013
Available online 9 May 2013

Keywords:
Biothesiometer
Diabetes mellitus
Nerve fibres
Neuropathy
Skin biopsy

ABSTRACT

Aims: To compare the diagnostic usefulness of tuning fork, monofilament, biothesiometer and skin biopsies in peripheral neuropathy in individuals with varying glucose metabolism.
Methods: Normoglycaemic, impaired glucose tolerance (IGT) and type 2 diabetes (T2DM) individuals were recruited. Nerve conduction studies (NCS) and thermal threshold tests were performed. Vibrotactile sense was tested with a biothesiometer and a 128-Hz tuning fork. Touch/pressure perception was examined with a 10-g monofilament. Skin biopsies were performed and intraepidermal nerve fibres were quantified. Distal symmetric polyneuropathy (DSPN) was defined as neuropathy disability score ≥2 and abnormal NCS. Thermal threshold tests were used to define small nerve fibre neuropathy (sDSPN) in cases where NCS (large nerve fibres) were normal.
Results: The prevalence of DSPN and sDSPN in the whole group ($n = 119$) was 18% and 23%, respectively. For the biothesiometer, a cut-off of ≥24.5 V had a sensitivity of 82% and specificity of 70% (AUC = 0.81, 95% CI 0.71–0.91) when evaluating DSPN. An intraepidermal nerve fibre density cut-off of ≤3.39 fibres/mm showed a sensitivity of 74% and specificity of 70% in the detection of sDSPN, whereas the sensitivity of the tuning fork and the biothesiometer were relatively low, 46% and 67%, respectively. When combining skin biopsies with the tuning fork, 10 more sDSPN cases were identified. Adding skin biopsy to the combination of the tuning fork and biothesiometer increased the sensitivity of finding sDSPN cases, but not DSPN, from 81% to 93%.
Conclusion: Using a biothesiometer in clinical routine might be a sensitive method to detect large nerve fibre dysfunction in the lower extremity, whereas skin biopsies in combination with methods measuring vibrotactile sense could increase the diagnostic sensitivity of detecting peripheral neuropathy at an early stage.

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1751-9918/$ – see front matter
http://dx.doi.org/10.1016/j.pcd.2013.04.004

1. Introduction

Distal symmetric polyneuropathy (DSPN) is one of the most frequent complications of diabetes with a reported prevalence ranging from 30% to 50% [1,2]. DSPN can occur early in diabetes [3,4] with damage to peripheral nerve due to prolonged hyperglycaemia [5]. However, the condition may be unrelated to diabetes and result from other causes as well [6,7].

Neuropathy, being a clinical diagnosis, has been proposed to be accurately assessed when the combination of symptoms and signs together with nerve conductions studies are considered [8,9]. It has been proposed that DSPN could be confirmed in the presence of abnormal nerve conduction and symptom(s) *or* sign(s) of neuropathy [5,9].

Assessing DSPN in routine clinical practice, methods such as the tuning fork and the 10-g monofilament are frequently used to measure large nerve fibre function, i.e. vibrotactile and pressure sensation, respectively [10–12]. Biothesiometry for measuring vibration perception thresholds (VPT) is most often used for risk assessment of foot ulceration as a consequence of neuropathy [13,14]. In addition, skin biopsy with quantification of intraepidermal nerve fibre density (IENFD) has been suggested to be a useful method for assessing small nerve fibre neuropathy [15]. Still, it is uncertain whether these methods are sensitive and specific enough for detecting DSPN at an early stage, and whether the combination these methods provides any further diagnostic improvement and if the methods overlap.

Thus, our aim was to compare the diagnostic usefulness of the 128 Hz tuning fork, the 10-g monofilament, the biothesiometer and the skin biopsy in a well-defined population consisting of normoglycemic (NGT), impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) individuals.

2. Methods

2.1. Study population

Participants were recruited from November 2004 to April 2007 from the population-based Västerbotten Intervention Programme (VIP) [16]. The study population has been described elsewhere [17]. The glycaemic status of the NGT and IGT individuals was verified by two standardized oral glucose tolerance tests (OGTT). Participants with type 2 diabetes also performed an OGTT except those with fasting plasma glucose of >15 mmol/L. Of the 129 recruited participants, four withdrew, three were excluded due to vitamin B12 and folate deficiency and three were excluded due to stroke or sciatica. All participants gave informed consent and the regional ethical review board of Umeå University, Umeå, Sweden, approved the study.

2.2. Measurements

Height and weight were measured and BMI was calculated ($kg\,m^{-2}$). Blood pressure was measured with standard sphygmomanometer in supine position after 10 min' rest. Total cholesterol and triglycerides (Vitros 5.1 FS analyser, Johnson&Johnson, Raritan, NJ), HbA1c (HPLC, TOSOH, Tokyo, Japan), and fasting and 2-h plasma glucose (HemoCue, *HemoCue* AB, Ängelholm, Sweden) were measured in blood samples. HbA1c values were converted to the Diabetes Control and Complications Trial (DCCT) standard values using the formula: HbA1c (DCCT) = 0.923 × HbA1c (Mono S) + 1.345 and are presented in both the DCCT (%) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (mmol/mol) units. Conversion between DCCT and IFCC was done using the following equation: HbA1c (mmol/mol) = [HbA1c (%) − 2.15] × 10.929. Chronic alcoholism (evaluated by carbohydrate deficient transferrin and gamma glutamyl transferase), thyroid disease (thyroid stimulation hormone, thyroid hormones T_4 and $T_{3)}$, and vitamin B12 and folate deficiencies (homocystein, methylmalonic acid) were considered as other possible causes of polyneuropathy, and if present those participants were excluded.

2.3. Neurophysiological assessment

Standardized nerve conduction studies were performed on the tibial, peroneal and sural nerves at the clinical neurophysiology laboratory in Umeå University, Sweden. All nerve attributes measured were performed in one lower extremity [5]. The motor conduction velocity, amplitude and latency of the tibial and peroneal nerves were measured. The sensory conduction velocity, amplitude and latency of the sural nerve were measured. F-wave studies of the tibial and peroneal nerves were performed.

An experienced neurophysiologist, blinded to the group identity of all participants, performed all nerve conduction studies. The neurophysiologist considered the nerve attributes representative of neurophysiological abnormality in DSPN and determined whether the participants had evidence of abnormal nerve conduction or not. The limb temperature was monitored prior and during recordings using a skin surface probe; hot-water bath and hot-water blankets were used to keep the limb temperature above 31 °C when needed.

2.4. Thermal threshold testing

Thermal threshold tests were performed with the method of limits, using Thermotest® equipment (Somedic AB, Hörby, Sweden). Thermal stimulations were applied bilaterally to the dorsum of both feet, one at a time. The starting temperature was 32 °C for both the heat and cold sensation measurements. The rate of temperature change was 1 °C/s and 10 stimulations were applied for each thermal sensation. By using the method of limits (17), the individuals were told to give a response when perceiving a noticeable thermal sensation. The results are mean values and the standard laboratory cut-off values (adjusted for age and sex) were used for delimiting pathological findings: 40.6 °C for heat and 26.7 °C for cold perceptions (mean ± 2 SD). Only individuals with bilaterally abnormal thresholds were considered to have an abnormal outcome. The limb temperature was kept above 31 °C when needed.