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Combining cutaneous silent periods with quantitative sudomotor axon reflex testing in the assessment of diabetic small fiber neuropathy

J.T. Kamel [a,c,*], S.J. Vogrin [a,c], R.J. Knight-Sadler [a,c], N.K. Willems [a,c], L. Seiderer [a,c], M.J. Cook [a,c], R.J. MacIsaac [b,c], L.J. Roberts [a,c]

[a] St. Vincent's Hospital, Centre for Clinical Neurosciences and Neurological Research, Melbourne, Australia
[b] Endocrinology & Diabetes, St. Vincent s Hospital, Melbourne, Australia
[c] Department of Medicine, The University of Melbourne, Parkville, Australia

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HIGHLIGHTS

- Routine electrophysiological testing cannot assess small nerve fiber types (Aδ and C). These fibers are commonly affected earlier in diabetic small fiber neuropathy (SFN).
- Non-invasive tests such as CSP and QSART can directly evaluate these fiber types.
- Combining these two tests can detect SFN from diabetes and impaired glucose tolerance.

ABSTRACT

Objective: Routine electrophysiological testing is often normal in the evaluation of painful diabetic neuropathy, as it is unable to detect dysfunction of thinly myelinated (Aδ) and unmyelinated (C) small fibers. Although cutaneous silent periods (CSP) and quantitative sudomotor axon reflex testing (QSART) respectively evaluate these fiber types in the extremities, these two tests have yet to be assessed together.
Methods: 26 patients with a clinical diagnosis of small fiber neuropathy (SFN) and 26 age-matched controls were assessed. Nine patients had Type I diabetes, nine had Type II diabetes, and eight had impaired glucose tolerance. The CSP onset latency and duration were recorded in each extremity. QSART was performed on the right side.
Results: 58% (15/26) of patients had abnormal sweat volumes obtained from QSART, while 50% (13/26) of patients had abnormal CSP responses. Combining these two tests increased the sensitivity of testing to 77% (20/26). Abnormalities were seen equally across all patient groups.
Conclusions: Combining CSP with QSART significantly increases the sensitivity of testing when assessing patients with SFN related to diabetes, or prediabetes.
Significance: For clinically suspected SFN, it is preferable to test more than one small fiber type, as each possess different structural and functional properties and may be heterogeneously affected between patients.

1. Introduction

Small fiber neuropathy (SFN) is a disorder that affects thinly myelinated Aδ-fibers and unmyelinated C-fibers. A common identifiable cause of SFN is diabetes, which frequently presents as a symmetric distal sensory polyneuropathy, with prominent positive sensory symptoms most commonly manifesting as the "burning feet" syndrome. It is now recognized that symptoms can also develop during even the early phases of glycemic dysregulation, prior to the onset of clinically detectable diabetes (Sumner et al., 2003). Routine electrophysiologic testing, including nerve conduction studies and electromyography, is often normal in the assessment of painful diabetic neuropathy, and is likely due to earlier involvement of small fibers, before abnormalities involving large

* Corresponding author at: Centre for Clinical Neurosciences and Neurological Research, St. Vincent's Hospital Melbourne, P.O. Box 2900, Fitzroy 3065, Melbourne, Australia. Fax: +61 3 9288 3350.
E-mail address: jordan.kamel@hotmail.com (J.T. Kamel).

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fibers can be detected by standard techniques (Singleton et al., 2001; Lacomis, 2002).

Various specialized modalities for testing SFN have been described previously, and validated for several different underlying aetiologies, including both diabetes and IGT. These include skin biopsy with intraepidermal nerve fiber density (IENFD) measurement (Kennedy et al., 1996), quantitative sensory testing (QST) (Magda et al., 2002), nociceptive evoked potentials (Casanova-Molla et al., 2011), microneurography (Ørstavik et al., 2006), and corneal confocal microscopy (Tavakoli et al., 2010). Although "gold standard" diagnostic criteria have been proposed, using a combination of IENFD, QST and clinical examination (Devigili et al., 2008), these were developed retrospectively, with IENFD testing limited to certain centers. There is also a degree of invasiveness associated with skin punch biopsy, with potential risk of infection, particularly in patients with diabetes who may have impaired wound healing.

Other diagnostic methods include cutaneous silent periods (CSP) testing and autonomic tests such as quantitative sudomotor axon reflex testing (QSART). The CSP involves measuring the brief suppression of voluntary muscle contraction after strong stimulation of a cutaneous nerve. There is strong evidence that thinly myelinated somatic Aδ-fibers are the afferent arm of this robust nociceptive spinal reflex (Floeter, 2003). QSART is a test that involves stimulation of eccrine sweat glands through iontophoresis of acetylcholine, which assesses the function of unmyelinated post-ganglionic sudomotor C-fibers (Sletten et al., 2010). Both CSP and QSART measure small fiber function in both the upper and lower extremities, and can demonstrate a length-dependent process. Although previous studies have shown a relatively low diagnostic sensitivity of the CSP (32.6%) (Koytak et al., 2011) and a modest diagnostic sensitivity of QSART (59–80%) (Lacomis, 2002), the two tests have not been studied in conjunction.

In addition to QSART, there are other more traditional tests of autonomic integrity, and thus small fiber function. These include sympathetic skin responses (SSR), which measure the electrical activity of the skin after electrical, magnetic or other stimulation, although this does involve a polysynaptic response, including centrally mediated pathways rather than only efferent sudomotor C-fibers tested by QSART. Other tests based on cardiovascular autonomic function testing (AFT) can also be performed. These include tests of both cardiac parasympathetic pathways, including heart rate variation with deep breathing, Valsalva maneuver and standing, and sympathetic pathways, including blood pressure response to head-up tilt and sustained handgrip. The relative ease in which these tests can be performed may make them practical adjunctive tools for the detection of SFN in diabetes, as well as other conditions.

The aim of this study is to assess the clinical utility of CSP, QSART, SSR and AFT in detecting SFN related to glycemic dysregulation, and to compare the function of the different small fiber types that are assessed by these modalities.

2. Methods

2.1. Study population

In this study, we prospectively evaluated 26 patients with a clinically suspected diagnosis of painful small fiber neuropathy secondary to glycemic dysregulation. All patients had positive painful sensory symptoms in their feet (i.e. burning, prickling, hyperalgesia or allodynia) with the diagnosis of SFN supported by the clinical scales described below. Nine patients had Type I diabetes, nine had Type II diabetes, and eight patients had confirmed impaired glucose tolerance on formal oral glucose tolerance testing (OGTT). Normative values for CSP and QSART parameters were obtained from 26 age-matched healthy control participants. Participants were all under the age of 67. Height, weight and body mass index (BMI) were recorded in all participants. This study was approved by our local Human Research Ethics Committee.

2.2. Clinical evaluation

Patients that had any disorder other than diabetes or impaired glucose tolerance that could cause symptoms or signs of peripheral neuropathy were excluded. Participants were assessed for vitamin B12 or folate deficiency, hypertriglyceridemia, thyroid or other autoimmune diseases, malignancy, use of neurotoxic drugs, as well as a family history of inherited neuropathy. Details about the patient's diabetes or pre-diabetes, and neuropathy symptoms were taken, including their most up to date HbA1c, and when details needed to be obtained from their medical record, this was done with their consent.

All patients and control participants were first evaluated with the Michigan Neuropathy Screening Instrument (MNSI) (Feldman et al., 1994), which is a validated and sensitive screening tool for diabetic neuropathy. Many questions in the questionnaire component of this tool relate to symptoms of small fiber neuropathy in the legs and feet, including symptoms of burning, prickling, hyperalgesia and allodynia, particularly at night. Patients with a clinical MNSI score of >2 were included in the study, while those with a score $\leqslant 2$ were excluded. Control participants were only included if their MNSI score was $\leqslant 2$.

We then performed the Utah Early Neuropathy Scale on participants (Singleton et al., 2008), which was designed and validated to detect early small fiber neuropathy prior to the development of large fiber involvement in patients with either diabetes or prediabetes. This scale has a significant weight given to the presence of diminished cutaneous sharp pain sensation (with Neurotip™ pin) in the lower extremities, with 24 of the 42 points devoted to this, given that this sensory modality relies heavily on intact small fiber function, and more closely reflects the distribution of deficits in early sensory neuropathy than other scales.

After assessing patients for clinical signs of SFN, the Michigan Diabetic Neuropathy Score (MDNS) (Feldman et al., 1994) was then performed. This was used to identify and exclude patients that had significant large fiber dysfunction, in order to study patients with predominantly small fiber neuropathy as the cause of their painful symptoms. The first part of the MDNS is a clinical examination, which is then followed by routine nerve conduction studies. Vibratory threshold perception was assessed with a 128 Hz tuning fork. Light touch was assessed with a 10 g monofilament applied to the dorsum of the great toe. Deep tendon reflexes and muscle strength testing formed the remainder of the clinical examination score. Nerve conduction studies were performed using an electromyographic (EMG) device (Dantec Keypoint G4 Workstation), examining the right upper and lower extremities, and included median and peroneal motor studies, and sural, median and ulnar sensory studies. Abnormal parameters were defined as amplitudes, conduction velocities or latencies that exceeded two standard deviations from the normal values of our laboratory. Testing was performed with a target temperature of 32 °C in the upper extremity and 30 °C in the lower extremity. Participants were then given a composite score based on their clinical examination and nerve conduction study results. Patients with more than class 1 (mild) large-fiber neuropathy were excluded from the study. In addition, patients were required to have a normal sural sensory nerve response for age when compared to our laboratory's normal reference values.

Symptoms of autonomic failure were also graded by using a previously described scale (Low, 1993) as either: absent, with no autonomic symptoms; mild, with either impotence, marked