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Cramps frequency and severity are correlated with small and large nerve fiber measures in type 1 diabetes

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HIGHLIGHTS

- Muscle cramps are very common, especially in type 2 diabetic polyneuropathy.
- Muscle cramps correlate with small and large nerve fiber measures in type 1 diabetes.
- Muscle cramp frequency and severity also correlate with conduction velocities in type 1 diabetes.

ABSTRACT

Objectives: To explore the correlations between different muscle cramp characteristics including cramp frequency and severity and clinical and large and small nerve fiber measures in patients with diabetes type 1 (DM 1) and 2 (DM 2).
Methods: Prospective cross sectional study of healthy controls and patients with DM 1 and DM 2 recruited between April 2009 and November 2012. Participants underwent clinical evaluation and large and small nerve fiber studies, and the frequency and correlations of muscle cramps were explored.
Results: 37 controls, 51 patients with DM 1, and 69 patients with DM 2 were studied. Muscle cramps were the most frequent symptom captured by the Toronto Clinical Neuropathy Score (TCNS) in all groups, up to 78% in patients with DM 2. In patients with DM 1, but not DM 2, muscle cramp frequency and severity were correlated with clinical (TCNS) and both large (electrophysiology and vibration perception thresholds) and small nerve fiber measures.
Conclusions: Muscle cramps are frequent in diabetes and are correlated with clinical and both small and large nerve fiber measures in DM 1, suggesting that their origin and propagation might extend beyond the motor nerve.
Significance: Muscle cramps correlate with nerve fiber measures in DM 1.

1. Introduction

Muscle cramps are defined as sudden sustained and painful contraction of a muscle or muscle group. Muscle cramps are common, with a higher prevalence in the elderly (Abdulla et al., 1999) and in patients with neuropathic conditions (Katzberg, 2015), and are often underreported (Naylor and Young, 1994). The pathogenesis of muscle cramps involves spontaneous discharges of motor nerves, but the exact site of origin of these discharges, and their physiological mechanism remain uncertain (Layzer, 1994). Although the prevailing hypothesis is that muscle cramps originate and are propagated at motor nerves (Layzer, 1994), muscle cramps have also been described in sensory and pure small fiber neuropathies (Lopate et al., 2013; Maxwell et al., 2014).

In the current study, we aimed to explore the frequency and severity of muscle cramps in patients with diabetes type 1 (DM 1) and type 2 (DM 2), and the correlations of muscle cramp characteristics with clinical and small and large nerve fiber measures. We hypothesized that patients with diabetes who experience muscle cramps will have greater burden of nerve impairment, and that muscle cramp frequency and severity will be inversely correlated with parameters of nerve function.

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2. Materials and methods

This cross sectional study consisted of healthy controls and patients with DM 1 and DM 2, recruited prospectively between April 2009 and November 2012 from the Diabetes and Endocrinology Clinic and the Diabetic Neuropathy Clinic at Toronto General Hospital, as part of an ongoing longitudinal cohort study funded by the JDRF (operating grant 17–2008–715) and a cross-sectional cohort study funded by the Canadian Diabetes Association (operating grant OG-3–10–3123- BP). The Research Ethics Board of the University Health Network approved the current study protocol, and all participants signed an informed consent.

The total cohort included 37 controls, 51 patients with DM 1, and 69 patients with DM 2. Healthy controls consisted of participants with no history of diabetes or polyneuropathy, and were excluded from the current study if their HbA1c values were >6.4%, as this result is consistent with a diagnosis of diabetes. The diagnosis of DM in the diabetic patient group was confirmed according to the American Association of Diabetes criteria based on one of four abnormalities: haemoglobin A1c (HbA1c), fasting plasma glucose, random elevated glucose with symptoms, or abnormal 2-h oral glucose tolerance test. Muscle cramp frequency and severity (measured by visual analog scale [VAS]), were evaluated by a questionnaire (Katzberg et al., 2014).

The study cohort underwent a comprehensive medical and neurological evaluation. The neurological assessment included clinical evaluation using the Toronto Clinical Neuropathy Score (TCNS) (Bril and Perkins, 2002), and both small and large nerve fiber studies. Large nerve fiber studies included nerve conduction studies (NCS), and vibration perception thresholds (VPT), while small nerve fiber studies included laser Doppler imaging (LDI), and cooling detection thresholds (CDT) (Abraham et al., 2016).

The TCNS (Bril and Perkins, 2002) is a validated scale for evaluating the presence and severity of diabetic sensorimotor polyneuropathy. The score ranges from a minimum of 0 to a maximum of 19 points, and scores sensory and motor symptoms, as well sensory and reflex examination findings at the lower limbs. TCNS $\leq$5 indicates no neuropathy, 6–8 mild neuropathy, 9–11 moderate neuropathy, and $\geq$12 severe neuropathy (Perkins et al., 2001).

NCS were performed according to the protocols of the Toronto General Hospital (University Health Network) electrophysiology laboratory, using the Sierra Wave instrument (Cadwell Laboratories Inc., Kennewick, WA, USA). Limb temperature was measured prior to nerve conduction studies, and if required, warming was performed to ensure a surface temperature of $\geq$32.0 °C in the hands and $\geq$31.0 °C in the feet. Surface stimulating and recording techniques were performed according to the standards of the Canadian Society of Clinical Neurophysiology and the American Association of Neuromuscular and Electrodiagnostic Medicine (Bolton et al., 2000). Distal latencies, amplitudes and conduction velocities were calculated automatically. Peroneal compound muscle action potential (CMAP) and sural sensory nerve action potential (SNAP) amplitudes were measured from baseline to negative peak, or from positive peak if present for sensory amplitudes. Sensory and motor distal latencies were measured from onset to initial deflection from baseline. Normal values were considered as >2 mV for peroneal CMAP amplitudes and >6 μV for sural SNAP amplitudes, and as >40 m/s for peroneal and sural nerve conduction velocities.

A Neurothesiometer (Horwell Scientific, London, UK) was used to assess VPT at the fingers and toes, using the method of limits (Claus et al., 1993). Mean VPT values were calculated in volts after three separate tests, and a random 'null stimulus' was inserted to ensure adherence and understanding. The stimulus was applied to the distal pulp of the first finger and toe on each side, asking subjects to indicate when vibration sensation was first perceived. Stimulus intensity was gradually increased up to a value at which the subject first detected vibration. Normal values were considered as <5 volts in the fingers, and <15 volts in the toes (Dimitrakoudis and Bril, 2002).

Heat-induced axon reflex-mediated neurogenic vasodilation was measured using laser Doppler imaging (LDI). After warming the foot dorsum to a standardized temperature of 32 °C with a warm blanket, the skin above the first metatarsal area was heated to 44 °C for 20 min by a skin-heating probe (Moor Instruments Ltd, Axminster, U.K.). Blood flow in the dermal capillaries was measured using the MoorLDI software (version 3.11), and the LDI flare area was calculated in centimeters squared. Normal values were >2 cm^2, based on local laboratory normative data (Abraham et al., 2016).

Cooling detection thresholds (CDT) were assessed using a method of limits by the TSA-II NeuroSensory Analyzer (Medoc Advanced Medical Systems, Ramat-Yishai, Israel). The temperature of the foot dorsum was decreased gradually up to the first level perceived by the patient as a cooler than the previous, using a stimulator with a starting temperature of 32 °C. This was repeated 5 times, and the mean of the five levels was determined and compared to age-dependent normative data, which are generally >22.8 °C (Farooqi et al., 2016). In addition, a catch trial with a null stimulus was inserted randomly during testing (Abraham et al., 2016).

2.1. Statistical analysis

Statistical analysis was performed using SAS version 9.2. Comparisons of demographic variables and large and small nerve fiber studies were made between DM 1 and DM 2 patients and between patients with and without muscle cramps using *t*-test or the χ2-test. The correlation between muscle cramps frequency and severity and various clinical and small and large fiber measures was assessed using Pearson correlation coefficients. A multivariate regression analysis was performed using muscle cramps frequency as an independent variable, and total TCNS, age, gender, and HbA1c as independent variables. *P* values <.05 were considered as statistically significant.

3. Results

The demographic, and clinical characteristics of healthy controls and patients with DM 1 and DM 2 are presented in Tables 1 and 2, and their large and small nerve fiber measures are presented in Table 3. Muscle cramps were more frequent than any other neuropathic symptom—captured by the TCNS—in all groups, reported in up to 78% of patients with DM 2. Patients with DM 2 were older, had higher muscle cramp frequency with a trend toward higher muscle cramp severity, and worse clinical and small and large nerve fiber measures compared with patients with DM 1. The TCNS was compatible with minimal neuropathy in controls and DM 1 patients, and with moderate polyneuropathy in DM 2 patients (Perkins et al., 2001). There were no demographic differences between patients with and without muscle cramps in patients with DM 1 and DM 2. In patients with DM 2, there were no differences between patients with and without muscle cramps; however, in the DM 1 group, there were significantly more sensory findings on examination in patients with muscle cramps compared to those without muscle cramps (Table 4). However, there were no differences between small and large nerve fiber measures in patients with and without muscle cramps in patients with DM 1 and DM 2 (Table 5). The frequency, and to a lesser degree the severity of muscle cramps, correlated with clinical and both small and large