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Risk Factor Associations with Clinical Distal Symmetrical Polyneuropathy and Various Neuropathy Screening Instruments and Protocols in Type 1 Diabetes

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Abstract

Objective—To determine whether DSP and neuropathy-assessment instruments used by non-physicians have similar risk factors.

Research Design and Methods—Analyses were cross-sectional (n=176).

Results—Risk factors were similar for DSP and screening devices.

Conclusions—These data support the clinical utility of neuropathy screening devices used by non-physician personnel.

Keywords

Diabetic Neuropathy; NC-stat®; Vibratron; MNSI; Monofilament; Neurometer® CPT

2. Introduction

Diabetic neuropathy is a common microvascular complication in type 1 diabetes (T1D). The prevalence rate, after 40 years of diabetes, approaches 50% [1]. Various studies [2-3] have identified several modifiable cardiovascular risk factors, such as lipids, smoking, body mass index (BMI), and hypertension, which have been shown to predict clinically diagnosed neuropathy in T1D. In this cross-sectional analysis, we sought to determine whether the risk factors associations seen with clinical distal symmetrical polyneuropathy (DSP) were similar to those associated with abnormal responses on the various neuropathy assessment instruments and screening protocols which can be utilized by non-physician personnel in either clinical or research settings.

3. Research design and methods

Subjects were participants in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study, a prospective cohort of childhood T1D, diagnosed at Children's Hospital of Pittsburgh between 1950 and 1980 and first examined between 1986 and 1988. This report

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presents cross-sectional analyses from the 176 participants attending the 18 year examination (2004-2006) with data on the Vibratron II and two point-of-care devices, NC-stat® and Neurometer® CPT.

DSP

DSP was determined by a study-trained physician using the Diabetes Control and Complications Trial clinical examination protocol [4].

NC-stat® (NEUROMetrix, Inc.)

The NC-stat® is a validated [5] point-of-care device used in primary care practice [6] designed to perform standard noninvasive nerve conduction studies by non-specialist personnel. Compound muscle action potential (CMAP) for the peroneal motor nerve (F wave latency) and the sural nerve amplitude potential (SNAP) for the sensory nerve at the foot and ankle. The sensory raw score was thus analyzed two ways: ≥ 6 uV or < 6 uV, based on conventional criteria (SNAP), and any versus no response (NCstat sensory). The motor data was dichotomized as normal or abnormal (CMAP).

Vibratron II (Physitemp Instruments, Clifton, NJ)

Sensory thresholds were measured on the 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 [7]. Both age unadjusted (for continuous raw score) and adjusted (categorical) scores were used [8].

MNSI Examination

MNSI 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 appearance examination was conducted by a trained study technician while the evaluation of the ankle reflexes and vibration sensation were conducted by the same study physician. A score of ≥ 2 was considered a positive result [9].

Monofilament

Light touch perception was assessed using a 10-g Semmes-Weinstein monofilament (Sensory Testing Systems®, Baton Rouge, LA) on the dorsum of the great toe. This was done ten times for each foot with the subject's eyes closed. For the purposes of the current analyses, the score was dichotomized with 8-10 correct responses considered normal and 0-7 correct responses abnormal.

Neurometer® CPT (Neurotron, Inc.)

This portable point-of-care device, available in a subgroup of participants, 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). Resulting values below the normal range quantify hyperesthesia and above the normative range indicate hypoesthesia.

Participants completed a questionnaire concerning demographic and medical history information before each exam. Three seated blood pressure readings were taken with a random zero sphygmomanometer and the mean of the second and third readings used in analyses. [10]. Hypertension was defined as $\geq 140/90$ mmHg or use of antihypertensive medication. HbA1c was measured with the DCA 2000 analyzer (Bayer, Tarrytown, NY, USA). Total, high and low density lipoprotein cholesterol and triglycerides were determined

by the Cholestech LDX analyzer which measures lipids by an enzymatic method [11-14]. Renal function was estimated by the Cockcroft-Gault equation [15] and expressed as Glomerular Filtration Rate (GFR).

The waist/hip ratio (WHR) was determined as follows: waist circumference was determined, in duplicate, at the midpoint between the highest point of the iliac crest and the lowest part of the costal margin in the mid-axillary line and hip girth was determined at the level of the greater femoral trochanter. Estimated Glucose Disposal Rate (eGDR) was calculated using the equation: $eGDR = 24.395 - 12.97 (\text{waist to hip ratio}) - 3.388 [\text{hypertension status (140/90 mm Hg or on medications)}] - 0.601(\text{HbA1c})$ [16]. Cardiovascular Autonomic Neuropathy (CAN) was determined by means of the heart rate response to deep breathing, i.e., the expiration/inspiration (E/I) ratio which was calculated by the mean of the longest R wave to R wave (RR) interval during expiration and the shortest RR interval during inspiration over 6 cycles of deep breathing. CAN was considered to be present if the mean E/I was ≤ 1.1 .

The SPSS/PC statistical software (SPSS, Chicago, IL) was used for all analyses. The Kolmogorov-Smirnov test was used to assess normality with variables being log-transformed as appropriate. Group differences were tested with χ^2 tests for categorical variables and with student's t-test and ANOVA, with Bonferroni's correction for multiple comparisons, for continuous variables. GLM were used to adjust the continuous variables for sex. Forward stepwise adjusted (sex, diabetes duration, height, smoking status, HDL cholesterol, nonHDL cholesterol, HbA1c, and hypertension) logistic regression models were constructed for each screening device and clinical protocol to assess independent associations with DSP. The Akaike's Information Criterion (AIC), which measures the goodness of fit of a statistical model, was then calculated to determine the best model.

4. Results and Discussion

The main demographic and clinical participant characteristics, stratified by neuropathy status, are listed in Table 1a. All continuous variables, with the exception of age and duration of diabetes, were sex adjusted. Participants with physician-diagnosed DSP, or who were abnormal on the NC-stat®, the Vibratron II, MNSI, and monofilament were older ($p < 0.05$) and had a longer duration of diabetes ($p < 0.05$), with the exception of the monofilament where no such difference was noted. There were no difference by sex for any neuropathy status with the exception of the NC-stat® (motor) ($p < 0.01$), where cases were more likely to be male, and also the NC-stat® (sensory), but this difference was borderline ($p = 0.07$). HbA1c was higher in participants diagnosed with DSP and with abnormal NC-stat® (all categories) and MNSI ($p < 0.05$) results. Moreover, HbA1c was marginally higher in participants testing positive for the monofilament ($p = 0.09$). Systolic blood pressure and CAN were higher in every abnormal category ($p < 0.05$). GFR was significantly lower for participants positive for clinical DSP ($p < 0.05$), as well as those classified as abnormal for the NC-stat® (motor, $p < 0.01$). Participants abnormal for NC-stat® (sensory) and monofilament had a lower GFR, but the difference was borderline ($p = 0.06, 0.08$ respectively). There was no difference in GFR for those participants testing positive for the NC-stat® (SNAP), Vibratron II, and MNSI. In Table 1b, similar characteristics for the Neurometer® CPT subgroups are shown with no differences in age, duration of diabetes, sex, height, or HbA1c noted, with the exception of the 5 Hz frequency where participants classified with hypoesthesia were significantly older than participants classified as normal ($p < 0.05$). There was also a significant trend for hypertension ($p < 0.01$) in the 5 Hz frequency, with proportions increasing from normal to hypoesthesia.

Separate logistic models for DSP, controlling for the same physiologic risk factors for DSP, as well as each neuropathy measure, were examined (Table 2). Duration of diabetes and

HbA1c were the sole significant physiologic correlates of DSP (OR=1.13 and 1.39, respectively, all $p<0.01$), while the addition of the NC-stat® (SNAP or Motor) and the Neurometer® CPT (categorical and dichotomized) did not significantly improve the fit of the model. However, the addition of the MNSI, NCstat (Sensory), Vibratron II, and monofilament all contributed to the improvement of the model, with the MNSI (OR=4.73, $p<0.01$) providing the best fit, perhaps reflecting both the similarity of the exam components and the physician examiner. Major limitations of this study include that no variation of any testing modality (e.g. different monofilament weights) were addressed, which may have yielded different results, and the nature of the “Gold Standard” (Physician Exam).

In conclusion, these results suggest (with the exception of the Neurometer® CPT 2000 Hz and 250 Hz) that the risk factor profiles for the screening devices and clinical DSP are similar, supporting their clinical utility.

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Table 1
a: Mean Risk Factors by Differing Neuropathy Assessments at the 18 Year Follow up Examination (n=176)

	DSP		NCStat@: SNAP		NCStat@: Sensory		NCStat@: Motor		Vibratron		MNSI		Mono [†]	
	NonCase (n=103)	Case (n=73)	NonCase (n=64)	Case (n=112)	NonCase (n=116)	Case (n=60)	NonCase (n=121)	Case (n=55)	NonCase (n=32)	Case (n=144)	NonCase (n=59)	Case (n=117)	NonCase (n=162)	Case (n=14)
Age (yrs)	41.6 (6.6)	46.0 [†] (7.0)	40.1 (6.5)	45.4 [†] (6.7)	42.1 (6.8)	46.1 [†] (6.9)	42.2 (6.9)	46.1 [†] (6.7)	40.3 (6.8)	44.2 [†] (7.0)	40.5 (6.4)	44.9 [†] (7.0)	43.1 (7.0)	48.1 [*] (6.3)
Duration of Diabetes (yrs)	33.7 (5.2)	37.7 [†] (6.9)	32.9 (5.6)	36.7 [†] (6.3)	34.4 (5.7)	37.2 [†] (6.9)	34.5 (5.9)	37.1 [†] (6.7)	33.3 (5.6)	35.8 [*] (6.4)	33.0 (5.0)	36.5 [†] (6.6)	35.1 (6.3)	37.7 (6.0)
Sex (%F)	49	53	53	50	56	42	60	31 [†]	66	48	51	51	51	50
Height (cm) [‡]	167.6 (9.6)	167.8 (9.9)	167.1 (9.7)	168.0 (9.7)	167.2 (9.7)	168.7 (9.2)	167.4 (9.6)	168.5 (8.9)	166.2 (9.0)	168.0 (9.7)	166.6 (10.0)	168.3 (9.5)	167.5 (9.6)	170.7 (10.4)
Weight (kg) [‡]	75.9 (14.5)	75.8 (14.0)	73.6 (14.8)	77.2 (13.9)	74.6 (14.0)	78.3 (14.4)	77.0 (14.6)	73.5 (13.6)	73.3 (11.7)	76.5 (14.7)	73.6 (14.5)	77.1 (14.1)	75.7 (13.4)	78.4 (22.8)
HbA1c(%) [‡]	7.3 (1.4)	7.7 [*] (1.3)	7.0 (1.0)	7.7 [†] (1.5)	7.3 (1.2)	7.8 [*] (1.6)	7.3 (1.2)	7.8 [*] (1.6)	7.3 (1.3)	7.5 (1.4)	7.1 (1.0)	7.6 [*] (1.5)	7.4 (1.4)	8.1 (1.0)
Waist Hip Ratio [‡]	.87 (.09)	.88 (.09)	.85 (.08)	.89 [†] (.09)	.86 (.08)	.89 [*] (.10)	.87 (.09)	.88 (.09)	.85 (.08)	.88 (.09)	.85 (.08)	.88 [*] (.09)	.87 (.09)	.90 (.12)
Estimated Glucose Disposal Rate (mg/kg/ min) [‡]	7.8 (2.3)	7.4 (2.3)	8.6 (1.7)	7.1 [†] (2.4)	8.1 (2.0)	6.8 [†] (2.5)	7.9 (2.1)	6.9 [†] (2.5)	8.4 (2.0)	7.5 [*] (2.3)	8.2 (2.0)	7.4 [*] (2.4)	7.7 (2.3)	6.9 (2.6)
HDL cholesterol (mg/dl) [‡]	57.9 (15.0)	59.8 (17.7)	60.6 (16.8)	57.6 (15.8)	58.8 (16.6)	58.5 (15.3)	58.9 (16.9)	58.3 (14.0)	57.9 (14.6)	58.9 (16.6)	60.2 (16.7)	57.9 (15.9)	58.9 (16.1)	56.8 (17.6)
nonHDL cholesterol (mg/dl) [‡]	113.6 (31.8)	119.2 (35.8)	112.8 (27.2)	117.8 (36.6)	116.3 (31.2)	115.2 (37.9)	114.2 (33.1)	119.7 (34.5)	128.3 (38.9)	113.2 [*] (31.8)	110.1 (28.0)	118.9 (35.7)	115.5 (33.2)	121.5 (37.7)
Hypertension(%)	26	27	16	33 [*]	20	40 [†]	21	38 [*]	16	29	24	28	26	29
Systolic Blood Pressure (mm/Hg) [‡]	112.1 (14.9)	118.9 [†] (13.9)	107.9 (10.9)	118.9 [†] (15.3)	112.1 (13.2)	120.4 [†] (16.1)	112.3 (12.9)	120.8 [†] (16.7)	109.2 (11.9)	116.2 [*] (15.1)	110.4 (13.7)	117.3 [†] (14.9)	113.8 (14.3)	128.6 [†] (14.2)
Diastolic Blood Pressure (mm/Hg) [‡]	67.4 (10.2)	67.0 (10.9)	66.9 (9.1)	67.4 (11.3)	67.4 (9.2)	66.8 (12.7)	67.4 (9.2)	66.7 (12.9)	67.7 (8.8)	67.1 (10.9)	68.3 (9.3)	66.6 (11.1)	67.3 (10.2)	66.6 (13.8)
Ever Smoke(%)	35	40	31	40	40	30	32	47	37	37	34	38	38	29
Glomerular Filtration Rate (mL/min/ 1.73m ² [‡]	100.9 (30.8)	88.6 [*] (31.6)	100.4 (27.0)	93.2 (33.9)	99.1 (27.8)	89.5 (37.7)	102.0 (28.3)	82.3 [†] (36.0)	102.3 (24.7)	94.4 (32.9)	101.1 (29.1)	93.1 (32.6)	97.1 (29.8)	81.3 (46.9)
Cardiovascular Autonomic Neuropathy [‡]	1.18 (.12)	1.11 [†] (.11)	1.21 (.14)	1.12 [†] (.10)	1.19 (.13)	1.08 [†] (.08)	1.18 (.13)	1.08 [†] (.08)	1.22 (.14)	1.14 [†] (.11)	1.20 (.13)	1.12 [†] (.11)	1.16 (.12)	1.08 [*] (.09)
Pulse Rate (bpm) [‡]	73.2 (11.1)	76.9 [*] (11.8)	72.5 (12.1)	75.9 (10.9)	73.9 (12.1)	76.2 (10.1)	73.8 (11.3)	76.8 (11.7)	74.2 (12.6)	74.8 (11.2)	75.1 (11.7)	74.5 (11.4)	74.5 (11.6)	77.3 (9.9)

b: Mean Risk Factors by Differing Neurometer® CPT Frequencies at the 18 Year Follow up Examination (n=134)									
2000 Hz				250 Hz			5 Hz		
	Normal (n=48)	Hypo [†] (n=5)	Hypo [†] (n=81)	Normal (n=35)	Hyper [*] (n=9)	Hyper [*] (n=75)	Normal (n=9)	Hypo [†] (n=46)	
	41.9 (6.8)	45.2 (8.3)	44.3 (6.7)	42.6 (6.5)	40.5 (9.83)	44.1 (6.6)	40.4 (9.4)	45.5 ^{††} (7.1)	
Age(yrs)									

Duration of Diabetes (yrs)	34.0 (6.1)	36.6 (5.2)	35.9 (6.2)	34.2 (5.1)	34.4 (6.4)	35.6 (6.5)	34.3 (5.8)	33.6 (5.8)	36.8 (6.7)
Sex (% F)	50	60	47	40	44	51	53	44	41
Height (cm)	167.0 (8.9)	161.2 (12.5)	168.1 (9.7)	168.8 (8.2)	168.5 (9.9)	167.3 (9.8)	166.1 (9.6)	170.7 (7.9)	169.5 (9.0)
Weight (kg)	76.9 (12.9)	70.0 (16.7)	76.3 (14.8)	76.8 (14.5)	74.5 (9.7)	76.4 (14.5)	76.7 (14.1)	74.0 (8.6)	76.3 (15.2)
HbA1c(%)	7.2 (1.1)	7.8 (1.5)	7.7 (1.6)	7.4 (1.2)	6.6 (1.1)	7.6 (1.5)	7.6 (1.5)	7.0 (1.4)	7.3 (1.2)
Waist Hip Ratio	.89 (.07)	.89 (.09)	.88 (.09)	.90 (.08)	.87 (.08)	.88 (.09)	.88 (.08)	.89 (.07)	.89 (.09)
Estimated Glucose Disposal Rate (mg/kg/min) [‡]	7.4 (2.2)	7.5 (1.7)	7.4 (2.4)	7.6 (2.1)	7.6 (2.3)	7.3 (2.4)	7.8 (2.2)	7.1 (2.0)	6.9 (2.5)
HDL cholesterol (mg/dl)	56.2 (14.2)	56.0 (18.6)	58.8 (15.7)	55.3 (13.5)	63.6 (15.6)	58.5 (15.8)	58.4 (15.6)	62.7 (16.6)	56.3 (14.9)
nonHDL Cholesterol (mg/dl)	120.9 (33.3)	119.4 (30.5)	116.1 (33.4)	120.6 (28.6)	95.8 (27.9)	119.2 (35.2)	121.3 (30.9)	101.0 (36.1)	115.6 (36.5)
Hypertension (%)	33	20	26	20	44	31	16	44	46 [§]
Systolic Blood Pressure (mm/Hg)	115.7 (14.7)	113.2 (14.0)	115.6 (15.7)	117.5 (12.9)	110.0 (21.9)	115.6 (15.5)	113.5 (12.9)	113.9 (21.4)	119.3 (17.2)
Diastolic Blood Pressure (mm/Hg)	68.8 (9.5)	67.2 (8.4)	67.3 (10.8)	69.6 (8.2)	63.1 (7.7)	67.7 (11.2)	68.0 (8.9)	64.9 (7.5)	67.8 (12.8)
Ever Smoke (%)	35	40	42	26	57	42	39	56	37
Glomerular Filtration Rate (mL/min/1.73m ²) [‡]	91.9 (29.2)	90.0 (18.5)	98.5 (33.0)	94.6 (26.6)	94.1 (34.3)	96.4 (33.0)	99.9 (25.6)	94.6 (32.9)	89.5 (33.6)
Cardiovascular Autonomic Neuropathy	1.17 (.13)	1.17 (.21)	1.13 (.11)	1.19 (.15)	1.14 (.11)	1.13 ^{††} (.11)	1.15 (.12)	1.19 (.17)	1.13 (.11)

* <0.05

[‡] p<0.01

[¶] Monofilament;

[‡] Sex Adjusted;

data is mean (standard deviation)

* Hyperesthesia

[‡] Hypoesthesia

[§] Cochran-Armitage Test for Trends

^{††} significance between normal & hypoesthesia

Table 2

a: Physiologic Correlates of DSP and Point-of-Care Devices, Vibratron II, MNSI, and Monofilament at the 18 year Follow Up Examination (n=176)

		Exp(β)	CI	p	AIC
Model 1	Physiologic Risk Factors Only				
	Duration of Diabetes	1.13	1.1-1.2	<0.01	217.1
	HbA1c	1.39	1.1-1.8	<0.01	
Model 2	NCstat® - SNAP				
	Duration of Diabetes	1.13	1.1-1.2	<0.01	217.1
	HbA1c	1.39	1.1-1.8	<0.01	
Model 3	NCstat® - Sensory				
	Duration of Diabetes	1.12	1.0-1.2	<0.01	213.2
	HbA1c	1.33	1.0-1.7	<0.05	
	NCstat-Sensory	2.35	1.2-4.7	<0.05	
Model 4	NCstat® - Motor				
	Duration of Diabetes	1.13	1.1-1.2	<0.01	217.1
	HbA1c	1.39	1.1-1.8	<0.01	
Model 5	VIBRATRON II				
	Duration of Diabetes	1.12	1.1-1.2	<0.01	215.6
	HbA1c	1.37	1.1-1.8	<0.05	
	Vibratron II	2.39	.92-6.2	.075	
Model 6	MNSI				
	Duration of Diabetes	1.11	1.0-1.2	<0.01	203.6
	HbA1c	1.28	.99-1.6	.061	
	MNSI	4.73	2.1-10.8	<0.01	
Model 7	MONOFILAMENT				
	Duration of Diabetes	1.13	1.1-1.2	<0.01	210.3
	HbA1c	1.35	1.0-1.7	<0.05	
	Monofilament	7.69	1.6-37.1	<0.05	
b: Physiologic Correlates of DSP and Neurometer® at the 18 Year Follow Up Examination (n=134)					
		Exp(β)	CI	p	AIC

		Exp(β)	CI	P	AIC
Model 1	Physiologic Risk Factors Only				163.0
	Duration of Diabetes	1.15	1.1-1.2	<0.01	
	HbA1c	1.49	1.1-1.9	<0.01	
Model 2 *	2000 Hz				163.0
	Duration of Diabetes	1.15	1.1-1.2	<0.01	
	HbA1c	1.49	1.1-1.9	<0.01	
Model 3 *	250 Hz				161.5
	Duration of Diabetes	1.14	1.1-1.2	<0.01	
	HbA1c	1.46	1.1-1.9	<0.05	
Model 4 *	5 Hz				160.5
	Duration of Diabetes	1.14	1.1-1.2	<0.01	
	HbA1c	1.45	1.1-1.9	<0.05	
Model 5 †	2000 Hz				163.0
	Duration of Diabetes	1.15	1.1-1.2	<0.01	
	HbA1c	1.49	1.1-1.9	<0.01	
Model 6 †	250 Hz				
	Duration of Diabetes	1.14	1.1-1.2	<0.01	161.5
	HbA1c	1.46	1.1-1.9	<0.01	
Model 7 †	5 Hz				160.1
	Duration of Diabetes	1.14	1.1-1.2	<0.01	
	HbA1c	1.45	1.1-1.9	<0.05	

Sex, Height, Smoking, HDL, nonHDL, & Hypertension were available for all models

* Normal versus Hyperesthesia+Hypoesthesia

† Normal versus Hyperesthesia versus Hypoesthesia