Journal of Diabetes and Its Complications 33 (2019) 107397

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Sex differences in neuropathy & neuropathic pain: A brief report from the Phase 2 Canadian Study of Longevity in Type 1 Diabetes

Nancy Cardinez [a,1,2], Leif E. Lovblom [a,1], Andrej Orszag [a], Vera Bril [b], David Z. Cherney [c,2], Bruce A. Perkins [a,*,2]

[a] Division of Endocrinology and Metabolism, Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada
[b] Ellen and Martin Prosserman Centre for Neuromuscular Diseases, Division of Neurology, Department of Medicine, University Health Network, University of Toronto, Toronto, Canada
[c] Division of Nephrology, Department of Medicine, University Health Network, University of Toronto. Toronto, Ontario, Canada

ARTICLE INFO

Article history:
Received 27 February 2019
Received in revised form 26 April 2019
Accepted 4 June 2019
Available online 20 June 2019

Keywords:
Sex
Type 1 diabetes
Neuropathy
Gender
Neuropathic pain
Pain

ABSTRACT

To evaluate previous results from a questionnaire-based study, we studied objective neuropathy measures to determine sex differences in the prevalence of neuropathy and neuropathic pain in longstanding type 1 diabetes. Despite better neuropathy measures in females compared to males, we confirmed a trend towards higher neuropathic pain in females.

1. Introduction

Neuropathy and neuropathic pain are common complications in type 1 diabetes (T1D).[1,2] Previous research has implied that females experience greater prevalence of neuropathic pain regardless of having neuropathy; however such studies generally used subjective measures of neuropathy.[3] Less is known about sex-based differences in neuropathy in longstanding T1D utilizing gold-standard measures. We aimed to determine if sex differences in the prevalence of neuropathic pain and neuropathy exist in a cohort of participants with longstanding T1D (≥50 years of duration) using objective measures of neuropathy from the Phase 2 Canadian Study of Longevity in Type 1 Diabetes Study.

2. Methods

2.1. Study design

In this cross-sectional study, we studied a subset of 75 participants with ≥50 years of T1D (Phase 2) who participated in our Phase 1 questionnaire study (Canadian Study of Longevity in T1D — a national registry to determine factors associated with resistance to the development of complications in longstanding T1D). The 75-participant subset underwent a two-day in hospital deep-phenotyping visit where they also completed nerve conduction studies (NCS) for neuropathy.

For this secondary analysis, neuropathy is termed NEUROPATHY$_{NCS}$ and defined according to the Toronto consensus criteria i.e. 1) the presence of 1 or more neuropathic symptoms or signs, and 2) the presence of an abnormality in 1 or more NCS variables in sural and peroneal testing.[4,5] Neuropathic pain was determined from participants' report of allodynia or pain, tingling or burning in the extremities (from the Michigan Neuropathy Screening Instrument Questionnaire [MNSI-Q]), or self-reported use of neuropathic pain medications. The MNSI-Q score of ≥3 is valid for identification of neuropathy and, for current purposes, the score permits identification of neuropathic pain.[3,6] The study was approved by the Research Ethics Board at Mount Sinai Hospital and University Health Network (Canada).

2.2. Statistical analysis

Comparisons were made using the Student's *t*-test, the Wilcoxon rank-sum test, or the χ^2-test, depending on variable distribution. The presence of neuropathic pain was compared between sexes: this was done in the whole cohort (using the χ^2-test) and when stratified by the presence of NEUROPATHY$_{NCS}$ (using the χ^2-test or Fisher's exact test when fewer than five participants were in any given category).

* Corresponding author at: Professor-Endocrinology & Metabolism, Department of Medicine, University of Toronto, Clinician Scientist, Lunenfeld-Tanenbaum Research Institute, Director Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, L5209-60 Murray Street Box 16, Toronto, Ontario M5T3L9, Canada.
E-mail address: bruce.perkins@sinaihealthsystem.ca (B.A. Perkins).
[1] Indicates co-primary authors.
[2] Indicates co-senior authors.

https://doi.org/10.1016/j.jdiacomp.2019.06.002
1056-8727/

Table 1
Phase 2: clinical characteristics & neuropathy measures.

Characteristic	Females n = 41	Males n = 32	*p*-Value
Age (years)	65.5 ± 8.1	66.7 ± 7.6	0.51
HbA_{1c} (%)	7.5 ± 1.0	7.2 ± 0.6	0.10
Systolic blood pressure (mmHg)	133 ± 14	132 ± 17	0.71
LDL cholesterol (mmol/L)	1.92 ± 0.52	1.79 ± 0.56	0.30
eGFR (mL/min/1.73 m^2)	67.4 ± 15.4	78.1 ± 17.7	**0.006**
TID duration (years)	53[52,57]	55[52,58]	0.26
Currently physically active	31 (76%)	27 (82%)	0.52
History of alcohol use	35 (83%)	26 (76%)	0.45
Smoking history	14 (34%)	17 (53%)	0.10
MNSI-Q	2[0,3]	2[1,3]	0.45
TCNS (total out of 19)	5.0[3.0,9.0]	7.0[4.5,11.5]	0.13
TCNS symptoms (out of 6)	1.0[0.0,2.0]	1.5[0.0,3.0]	0.52
TCNS signs (out of 13)	1.0[0.0,2.0]	2.0[1.0,3.0]	**0.013**
Nerve conduction studies			
Peroneal Amp (mV)	1.81 ± 1.56	1.78 ± 1.48	0.94
Peroneal CV (m/s)	37.62 ± 7.21	33.90 ± 8.55	**0.047**
Peroneal F-wave (ms)	61.99 ± 8.65	63.81 ± 6.45	0.33
Sural Amp (μV)	3.22 ± 3.13	2.58 ± 2.62	0.36
Sural CV (m/s)	37.23 ± 6.36	35.47 ± 6.03	0.23
Cooling detection thresholds (°C)	23.84 [21.40,27.32]	19.59 [15.58,26.01]	0.052
Vibration perception threshold, upper limb (V)	5.87 ± 2.27	6.71 ± 1.33	0.11
Vibration perception threshold, lower limb (V)	19.61 ± 9.22	27.89 ± 10.05	**0.003**
CNFL (mm/mm^2)	8.43 ± 4.52	8.08 ± 4.40	0.75
CNBD (branches/mm^2)	14.14 ± 16.50	13.12 ± 18.81	0.81
CNFD (fibres/mm^2)	10.11 ± 9.12	9.27 ± 8.93	0.70
LF/HF ratio	1.97 ± 1.67	3.08 ± 2.47	**0.03**
$NEUROPATHY_{NCS}$	34(83%)	31(97%)	0.058
Presence of neuropathic pain	12(29%)	7(21%)	0.39
Use of neuropathic pain meds	4(10%)	3(9%)	0.92
Complications			
Nephropathy	17(41%)	8(24%)	0.10
Retinopathy	23(56%)	16(47%)	0.44
CVD	10(24%)	5(15%)	0.30
Psychosocial			
PAID	9.6 ± 9.2	8.6 ± 11.6	0.69
GDS	1.8 ± 2.7	1.5 ± 2.3	0.90
Self-reported QoL			
Excellent	17(43%)	20(61%)	0.32
Good	16(40%)	11(33%)	
Normal	5(13%)	1(3%)	
Poor	2(5%)	1(3%)	

Data presented as mean ± SD, median [IQR] and n (%). Estimated glomerular filtration rate (eGFR), type 1 diabetes (TID), Michigan Neuropathy Screening Instrument Questionnaire [MNSI-Q]), Toronto Clinical Neuropathy Score (TCNS), Amp (amplitude), millivolt (mV), conduction velocity (CV), meter per second (m/s), millisecond (ms), microvolt (μV), Celsius (°C), volt (V), millimeter (mm), corneal nerve fibre length (CNFL), corneal nerve branch density (CNBD), corneal nerve fibre density (CNFD), low frequency/high frequency (LF/HF), cardiovascular disease (CVD), Problem Areas In Diabetes (PAID), Geriatric Depression Scale (GDS), Quality of Life (QoL).

The standard univariable odds ratio (OR) for the presence of neuropathic pain was calculated (with male sex used as the reference), then adjusted for presence of $NEUROPATHY_{NCS}$ (Cochrane-Mantel-Haenszel test). An α-level of 0.05 was used, and 95% confidence intervals for odds ratios were determined. As this was a secondary analysis, a priori sample size calculations were not performed.

3. Results

Of the 75 participants enrolled, 73 participants had sufficient data for analysis. There were 56.2% females and 43.8% males (Table 1). Males and females had similar age (66.7 ± 7.6 and 65.5 ± 8.1 years, $p = 0.51$), while males had numerically lower HbA_{1c} (7.2 ± 0.6 vs 7.5 ± 1.0%, $p = 0.10$) and longer T1D duration (55 [52, 58] vs 53 [52, 57] years, $p = 0.26$), though comparisons for these two variables were not statistically significant. $NEUROPATHY_{NCS}$ was more prevalent among males (97 vs 83%, $p = 0.058$), neuropathic pain was more commonly reported in females; however this trend did not reach statistical significance (29 vs 21%, $p = 0.39$, see Fig. 1). The use of neuropathic pain medications was similar between sexes (10% females vs 9% males, $p = 0.92$).

Specific nerve tests revealed that females had better nerve function than males. Peroneal conduction velocity in females was faster (37.62 ± 7.21 vs 33.90 ± 8.55 m/s, $p = 0.047$; reference value ≫40 m/s).[7] Lower limb vibration perception thresholds were better in females (19.61 ± 9.22 vs 27.89 ± 10.05 V, $p = 0.003$; reference value ≪15 V).[7] LF/HF ratio was lower in females (1.97 ± 1.67 vs 3.08 ± 2.47, $p = 0.03$; age and gender reference values 2.97 ± 3.18 [females], 4.77 ± 5.34 [males]).[8] Cooling detection threshold was better in females (23.84 [21.40, 27.32] °C vs 19.59 [15.58, 26.01], $p = 0.052$; reference value ≫ 22.8 °C).[9] Females had a tendency to greater odds 1.60 (95% CI 0.55–4.64, $p = 0.39$) of having neuropathic pain. After adjusting for the presence of $NEUROPATHY_{NCS}$, the OR was 1.65 (95% CI 0.61–5.54, $p = 0.28$).

4. Discussion

In participants with longstanding T1D who completed objective neurological examinations, $NEUROPATHY_{NCS}$ was generally more prevalent among males compared to females. Among females there was a tendency to greater presence of neuropathic pain. This observed trend towards a higher prevalence of neuropathic pain among females though not statistically significant, aligns with qualitative research findings that did not use objective measures of neuropathy. Taken together, results indicate that females experience greater neuropathic pain compared to males despite neuropathy generally occurred more frequently in males.[2,9–11]

In our previous questionnaire study that evaluated sex differences in neuropathic pain reporting among 361 participants with longstanding TID, we observed that females had a higher reported prevalence of

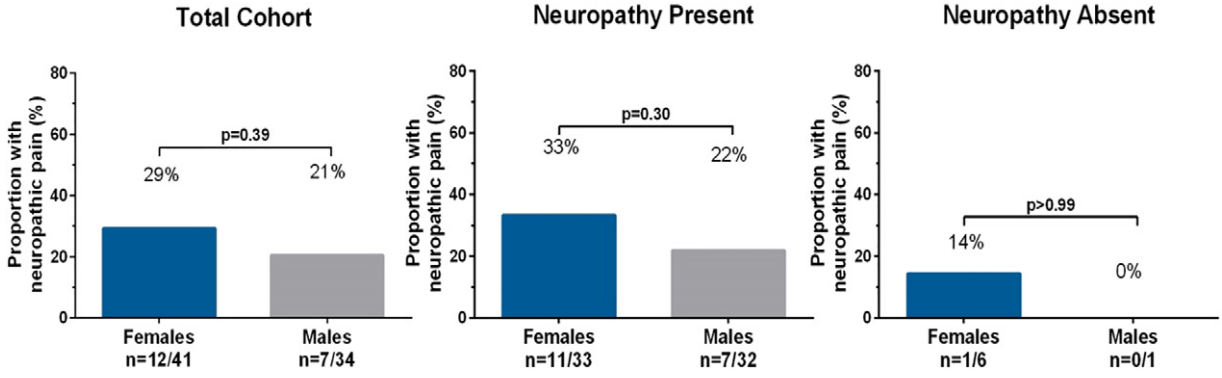

Fig. 1. Prevalence of neuropathic pain by sex.

neuropathic pain, the presence of neuropathy did not differ by sex, and females had a higher prevalence of neuropathic pain independent of the presence of neuropathy.[3] Though lacking statistical significance, the current findings in this smaller subset of the larger cohort are in concordance with previous observations. While our study did not explore the association of age on neuropathic pain reporting, the effect of age on neuropathy symptoms in TID has demonstrated an increase in the prevalence of painful symptoms with advancing age.[12]

Despite detailed neuropathic phenotyping, limitations include small sample size, potential selection (survivorship) bias as these findings represent individuals with longstanding TID and are not generalizable to individuals with TID of other age and diabetes duration, and may not be generalizable to T2D. Lack of a validated screening tool for neuropathic pain may explain the lower prevalence of neuropathic pain observed in our study when compared to other studies. We also acknowledge the cross-sectional nature of this study and cannot comment on longitudinal trends or causality.

5. Conclusion

In patients with longstanding T1D who underwent objective neuropathy testing, we found a trend towards higher neuropathic pain prevalence among females despite a seemingly increased prevalence of neuropathy among males. Further research using larger objective neuropathy datasets is required to further confirm these sex-specific differences.

Acknowledgements

We greatly appreciate our distinguished study participants, who have inspired our team and spent considerable time participating in this study. We will like to thank our colleagues who contributed to data acquisition for the Longevity cohort: Julie A. Lovshin, Vesta Lai, Leslie Cham, Josephine Tse, Yuliya Lytvyn, Genevieve Boulet, Mohammed A. Farooqi, Daniel Scarr, Alanna Weisman, Hillary A. Keenan, Michael H. Brent and Narinder Paul. N.C. and L.E.L. performed the statistical analysis and wrote the manuscript as primary authors. N.C., L.E.L., A.O., V.B., D.Z.C. and B.A.P. contributed to the discussion of the report draft. All authors reviewed the report for scholarly content. B.A.P. is the senior author and is the guarantor for the content of this study. Results of this study were presented at the European Association for the Study of Diabetes Meeting (Berlin, Germany; Oct 2018) and the American Diabetes Association Conference (Orlando, Florida; Jun 2018).

Funding statement

We are grateful to the support of JDRF Canada (Juvenile Diabetes Research Foundation operating grant 17-2013-312), its Canadian Clinical Trial Network and to Diabetes Canada for their non-financial support with study advertisement. We acknowledge the contributions of the Menkes Fund for supporting aspects of this research.

Declaration of Competing Interest

N.C. has received speaker honoraria from Astra Zeneca and consultation fees from Novo Nordisk and Antibody Research Inc. B.A.P. has received speaker honoraria from Medtronic Inc., Johnson and Johnson, Roche, Glaxo Smith Kline Canada, Novo Nordisk and Sanofi; has received research grant support from Medtronic and Boehringer Ingelheim; and serves as a consultant for Neurometrix. David Z. Cherney has received speaker honoraria from Janssen, AstraZeneca, Boehringer Ingelheim, Lilly and Merck and has received research grant support from AstraZeneca, Merck and Boehringer Ingelheim. Julie A. Lovshin has received grants from Sanofi and Merck, and speaking honorarium and/or consulting fees from Novo Nordisk, Eli Lilly, Merck, and AstraZeneca. The remaining authors have no relevant disclosures.

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