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Comparison of diabetic and idiopathic sensory polyneuropathies with respect to nerve fibre affection and risk factors

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ABSTRACT

Background and purpose Chronic distal sensory or sensorimotor polyneuropathy is the most common pattern of polyneuropathy. The cause of this pattern is most often diabetes or unknown. This cross-sectional study is one of the first studies to compare the demographics, cardiovascular risk factors and clinical characteristics of diabetic polyneuropathy (DPN) with idiopathic polyneuropathy (IPN).

Methods Patients with DPN were included from a sample of 389 patients with type 2 diabetes mellitus (T2DM) enrolled from a national cohort of patients with recently diagnosed T2DM (Danish Centre for Strategic Research in Type 2 Diabetes cohort). Patients with IPN were included from a regional cohort of patients with symptoms of polyneuropathy referred for workup at a combined secondary and tertiary neurological centre (database cohort).

Results A total of 214 patients with DPN were compared with a total of 88 patients with IPN. Patients with DPN were older (67.4 vs 59 years) and had a longer duration of neuropathy symptoms. Patients with DPN had greater body mass index (32 vs 27.4 kg/m^2) and waist circumference (110 cm vs 97 cm); higher frequency of hypertension diagnosis (72.9% vs 30.7%); lower total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels; and a higher prevalence of use of statins (81.8% vs 19.3%). DPN was associated with a slightly higher autonomic score and total score on the Neuropathy Symptom Score; lower frequency of hyperalgesia, allodynia and decreased vibration on quantitative sensory testing; lower intraepidermal nerve fibre density count and higher frequency of small-fibre neuropathy.

Conclusion DPN and IPN showed clear differences in neuropathy characteristics, indicating that these two entities are to be regarded as aetiologically and pathogenetically distinct.

Key messages

What is already known on this topic

- To our knowledge, this is one of the first studies to compare cardiovascular and clinical neuropathy characteristics of the two most common distal symmetric polyneuropathies, diabetic polyneuropathy (DPN) and idiopathic polyneuropathy (IPN).

What this study adds

- This study shows that DPN is associated with a greater involvement of small fibres and a less frequency of evoked pain phenomena, that is, dynamic mechanical allodynia and hyperalgesia.

How this study might affect research, practice or policy

- The difference in neuropathy characteristics implies that the pathogenesis of DPN and IPN is distinct. The difference in neuropathy subtypes and evoked pain phenomena implies the importance of intact small fibres as a main driver of neuropathic pain.

INTRODUCTION

Polyneuropathy is a common neurological condition with a prevalence of 1% in the general population and rising to 7% in the elderly.[1] The most common pattern is that of a chronic distal, predominantly or purely sensory polyneuropathy. Diabetic polyneuropathy (DPN) accounts for 32%–53% and idiopathic polyneuropathy (IPN), defined as polyneuropathy with no clear aetiology, accounts for 24%–27% of such cases.[2]

DPN is shown to be associated with both non-modifiable and modifiable cardiovascular risk factors.[3 4] The pathogenesis of DPN remains unresolved.[5] IPN is also shown to be associated with cardiovascular risk factors,[6 7] with hypertension and abdominal obesity being the two most consistent factors.[8]

Sensory nerve fibres comprise fibres of different diameter. Large fibres are responsible for touch, vibration and joint position sensation, while small fibres are responsible for thermal and pain sensation.[9] Based on the preferential fibre diameter involved, DPN and IPN can be subtyped into small-fibre neuropathy (SFN), large-fibre neuropathy (LFN) and mixed-fibre neuropathy (MFN).[10]

To our knowledge, only one study has previously compared DPN with IPN.[11] The study compared limited aspects confined to demographics and neuropathy severity. In this study, we aimed to compare DPN to IPN in relation to demographics, lifestyle and cardiovascular characteristics, and neuropathy phenotype. We hypothesise that a similar neuropathy phenotype could indicate a common pathogenesis.

METHODS

Design, setting and participants

This is a cross-sectional study comparing DPN in patients with recently diagnosed type 2 diabetes mellitus (T2DM) with IPN in patients with recently diagnosed IPN.

DPN cohort

The patients with DPN were included from the Danish Centre for Strategic Research in Type 2 Diabetes cohort.[12 13] This sample has been described in detail previously.[14 15] A total of 389 patients were enrolled during a 2-year period from 1 October 2016 to 30 October 2018. Inclusion and exclusion criteria are shown in figure 1.

IPN cohort

Patients living in Funen in Denmark and referred consecutively from 1 January 2016 to 31 December 2019 to the department of neurology at Odense University Hospital (OUH) for suspicion of polyneuropathy were invited to participate in the study. Patients were excluded from enrolment if they had previously (>1 year prior to inclusion) been diagnosed with polyneuropathy, if they had cognitive disabilities or if they did not master Danish as

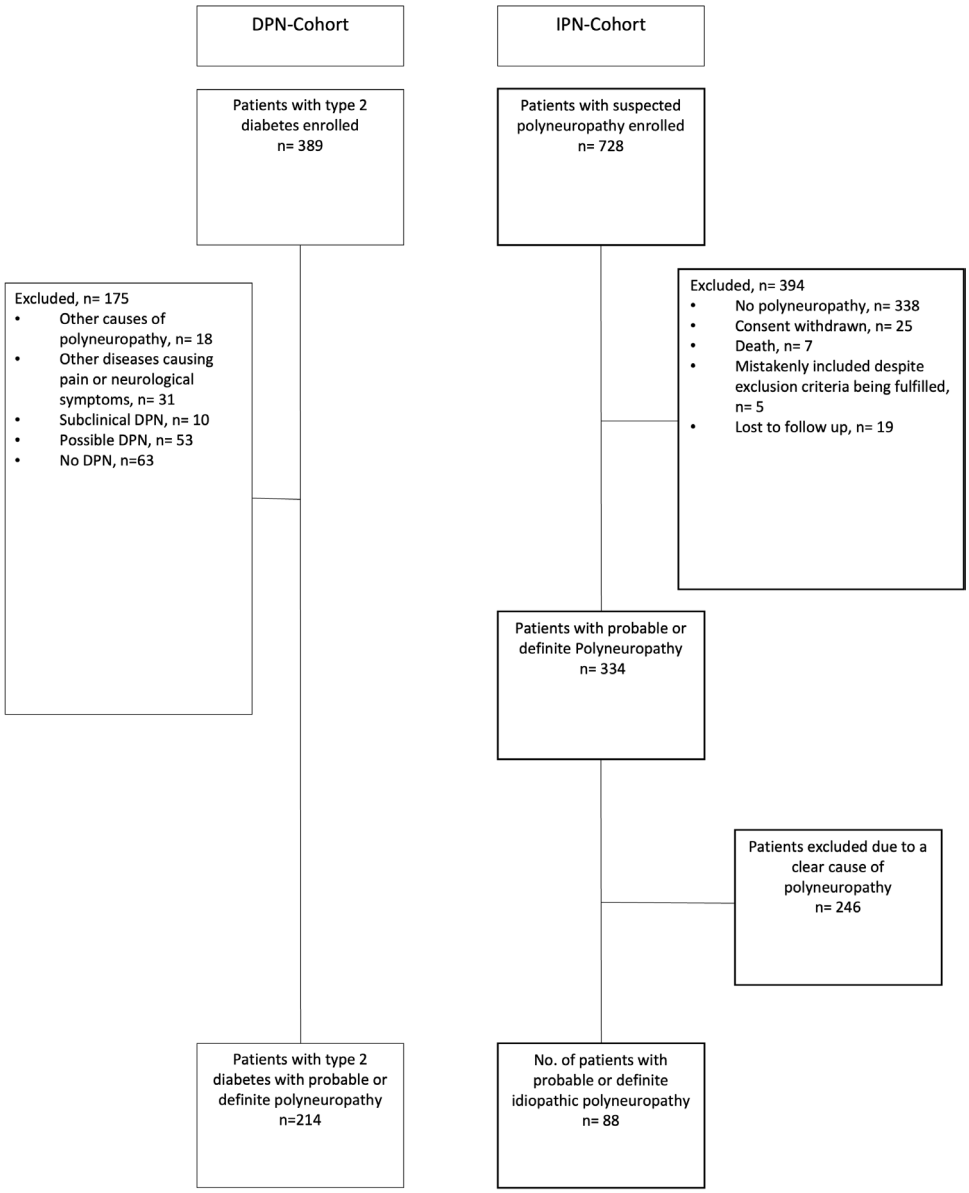

Figure 1 Flow diagram of patient inclusion. DPN, diabetic polyneuropathy; IPN, idiopathic polyneuropathy.

language. Inclusion and exclusion criteria are shown in figure 1.

Data collection

Each participant from both cohorts were examined thoroughly by a focused interview, clinical examination, neurological examination and a series of paraclinical examinations.

Interview (DPN and IPN cohorts)

All interviews were carried out by senior neurologists or residents in neurology. Patient history was obtained through a predefined interview with special focus on type (sensory, motor and/or gait disturbance), duration and localisation of symptoms.

We screened for cardiovascular risk factors such as hypertension, smoking, ischaemic heart and cerebrovascular diseases, and peripheral arterial disease.

Common aetiologies of polyneuropathy such as thyroid disease, exposure to toxic substances, autoimmune diseases, sarcoidosis, renal insufficiency, monoclonal gammopathy of undetermined significance and history of cancer were screened for through the interview. We screened the IPN cohort for a history of diabetes.

Neuropathy Symptom Score (NSS)[16] and the Neuropathic Pain Symptom Inventory (NPSI) questionnaire[17] were conducted as part of the interview.

Clinical examination (DPN and IPN cohorts)

Height, weight, waist circumference and twice the blood pressure in supine position after 5 min of rest were measured. Study nurses, certified by the German Research Network on Neuropathic Pain in quantitative sensory testing (QST), examined all patients according to a reduced version of the full German protocol.[18] We determined the warmth detection threshold (WDT), cold detection threshold (CDT), vibration detection threshold (VDT) and mechanical detection threshold, and tested for the presence of mechanical pain sensitivity (MPS) and dynamic mechanical allodynia (DMA).

Neurological examination

DPN cohort

The two primary investigators (MI, Odense) and (SG, Aarhus), both board certified neurologists, carried out a focused examination of the lower extremities. The sensory modalities tested included pinprick, warm, cold, touch, and vibration. Ankle reflexes were tested.[14 15] The Utah Early Neuropathy Scale (UENS)[19] was conducted as part of the examination. The methods of examination and interpretation of findings are described in detail elsewhere.[14 20]

IPN cohort

Examination was carried out by senior neurologists or residents in neurology. Reflexes were scored as absent if they could not be elicited during Jendrassik manoeuvre and diminished if they were elicited only during Jendrassik manoeuvre or were reduced in comparison to more proximal reflexes. Vibration was tested with a 128 HZ tuning fork, light touch with a cotton wisp and pinprick with the sharp end of a disposable wooden pin. Thermal sensation for cold was either tested using thermorollers (Somedic AB, Hörby, Sweden) or the end of a tuning fork. Proximal parts of the lower extremities with normal sensation were used as reference. The UENS was performed as previously mentioned.

Nerve conduction studies (NCS)

DPN and IPN cohorts

The sural nerves were tested bilaterally. The tibial, peroneal and median nerves were examined unilaterally with the addition of a unilateral ulnar nerve in case the median nerve was abnormal.

Experienced laboratory technicians at OUH and a trained PhD student (AGK) at Aarhus University Hospital (AUH) performed the NCS as described elsewhere.[21–23] The NCS was interpreted as abnormal if ≥2 nerves including at least one sural nerve had ≥1 abnormal parameter.[24] An unpublished Danish national laboratory control group was used as reference for participants at both centres.

Skin biopsy

DPN and IPN cohorts

All biopsies taken were 3 mm punch biopsies from the distal lateral leg (10 cm above the lateral malleolus). The biopsies were fixated, cryoprotected and stained according to published guidelines described in detail elsewhere.[25 26] The staining, counting and interpretation of intraepidermal nerve fibre density (IENFD) were carried out by an experienced researcher (PK) at AUH for the DPN cohort and highly trained laboratory technicians at OUH for the IPN cohort. Consistency between the two sites was ensured by the laboratory technicians from Odense visiting the Aarhus site to align the methods of fixation, staining and counting of IENFD.

Laboratory

DPN cohort

Blood tests of glycosylated haemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol, and triglyceride were undertaken if no prior results (within 3 months) before inclusion were available. No other blood tests were performed for this cohort.

IPN cohort

Blood tests included the following first-line tests to screen for common aetiologies and risk factors of polyneuropathy: haemoglobin, electrolytes, red and white blood cells, HbA1c, kidney function tests, liver function tests, vitamin B_{12}, folic acid, homocysteine, methylmalonate, thyroid function, cholesterol profile, angiotensin-converting enzyme (ACE), anti-Ro (SS-A) and anti-La (SS-B) antibodies, rheumatoid factor, antinuclear antibodies and cryoglobulin. Oral glucose tolerance test was performed in patients with normal HbA1c to exclude glucose

intolerance. Second-line blood tests were performed on indication and included paraneoplastic blood tests, transglutaminase antibodies and genetic tests for hereditary polyneuropathies.

Cerebrospinal fluid (CSF) (only IPN cohort)

CSF was only examined in the case of demyelinating polyneuropathy or suspicion of inflammatory/autoimmune central nervous system (CNS) disease.

Imaging (only IPN cohort)

CT of the thorax and abdomen or whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) was performed as a standard test in patients with no clear aetiology on-first line blood tests to rule out occult cancer or sarcoidosis. MRI of the spinal cord and brain was conducted in cases where CNS disease was suspected as a possible cause of symptoms, and MRI of lumbar or entire spinal column was conducted in case spinal stenosis was suspected.

Definition of polyneuropathy

DPN cohort

We defined probable and definite DPN according to the Toronto Consensus Criteria.[27]

IPN cohort

The neuropathy criteria used for the IPN cohort were identical to the Toronto Consensus Criteria except that diminished reflexes were not regarded as a separate clinical sign distinct from diminished distal sensation.

No polyneuropathy was defined as symptom/symptoms explained by other diseases than polyneuropathy, or as symptom/symptoms alone without any supporting abnormalities on neither clinical examination nor NCS and skin biopsy. IPN was defined as a diagnosis of probable or definite polyneuropathy after exclusion of other aetiologies based on detailed history and ancillary tests.

Definition of polyneuropathy subtypes

The same definition was used for both the DPN and IPN cohorts. SFN and LFN criteria were based on a model previously presented by Itani *et al*[15] (figure 2). SFN was defined as the criteria of SFN being fulfilled and the criteria of LFN not being fulfilled. LFN was defined as criteria of LFN being fulfilled and criteria of SFN not being fulfilled. MFN was defined as criteria of SFN and LFN being fulfilled simultaneously. The neuropathy was labelled as non-classifiable neuropathy when none of the three subtype criteria were fulfilled.

Statistics

Categorical variables were described with frequency and percentage of observations. Interval variables were described with median and IQR. Univariate analysis was conducted using rank-sum test for interval variables, χ^2 test for categorical variables with proportions of ≥5, and Fisher's exact test for categorical variables with proportions of <5. Multivariate analysis with adjustment for age, sex and duration of neuropathy symptoms was conducted using logistic regression for categorical variables and linear regression for interval variables. A significance level of 0.05 was chosen. We used the Stata V.16 IC statistical software. Study data were collected and managed using Research Electronic Data Capture tools hosted at Aarhus University for the DPN cohort and at the University of Southern Denmark for the IPN cohort.[28 29]

Small fiber neuropathy:
≥ 1 of 4 criteria
1- Decreased or absent pinprick bedside
2- Decreased or absent thermal sensation bedside
3- Hypoesthesia on CDT or WDT
4- Abnormal IENFD

Large fiber neuropathy:
≥ 1 of 4 criteria
1- Decreased or absent vibration bedside
2- Decreased or absent ankle reflexes
3- Hypoesthesia on VDT or MDT
4- Abnormal NCS

Figure 2 Criteria applied for the subtyping of diabetic and idiopathic polyneuropathy. CDT, cold detection threshold; IENFD, intraepidermal nerve fibre density; MDT, mechanical detection threshold; NCS, nerve conduction studies; VDT, vibration detection threshold; WDT, warm detection threshold.

RESULTS

DPN cohort

A total of 389 patients with T2DM were enrolled (figure 1). We excluded 175 patients: 63 without DPN, 53 with possible DPN, 10 with subclinical DPN, 31 with other diseases causing neuropathy-like symptoms and 18 with other causes of polyneuropathy than T2DM. A total of 214 patients with probable or definite DPN were included in the present study.

IPN cohort

A total of 728 patients with symptoms of polyneuropathy were enrolled to clinically verify a diagnosis of polyneuropathy and to determine the underlying cause of symptoms (figure 1). A total of 394 patients were excluded: 338 with no polyneuropathy and 56 not completing cross section. A total of 334 patients were verified to have a diagnosis of probable or definite polyneuropathy. A total of 246 patients were excluded due to the finding of a clear cause of polyneuropathy. A total of 88 patients with no cause of polyneuropathy despite extensive workup were included as our IPN group.

Table 1 Demographics, lifestyle, and cardiovascular and neuropathy characteristics of DPN compared with IPN

Polyneuropathy entity	DPN	IPN	Univariate P value*	Multivariate P value†
Demographics				
Participants	N1=214	N2=88		
Male, n (%)‡	136 (63.6)	50 (56.8)	0.27	
Age (years), median (IQR)§	67.4 (59.0–72.3)	59 (49–70)	<0.001	
Duration of neuropathy symptoms (years), n (%)¶			0.02	0.01
0–5	112 (65.1)	70 (79.5)		
>5	60 (34.9)	18 (20.5)		
Lifestyle and cardiovascular characteristics				
BMI (kg/m^2)	32.0 (27.7–36.0)	27.5 (24.4–29.8) (1)	<0.0001	<0.001
Waist circumference (cm)	110 (99–120) (1)	97 (87–108) (1)	<0.0001	<0.001
SBP (mm Hg)	138 (129–151)	134 (122–145) (1)	0.02	0.15
DBP (mm Hg)	83 (77–90)	81 (74–91) (1)	0.32	0.17
Hypertension, n (%)	156 (72.9)	27 (30.7)	<0.001	<0.001
HbA1c (mmol/mol)	50 (45–57) (3)	36 (34–37) (1)	<0.0001	<0.001
Cholesterol (mmol/L)	4.0 (3.4–4.6) (3)	5.2 (4.4–6.0) (1)	<0.0001	<0.001
LDL (mmol/L)	1.9 (1.5–2.4) (10)	3.1 (2.3–3.6) (1)	<0.0001	<0.001
HDL (mmol/L)	1.2 (1.0–1.4) (3)	1.4 (1.1–1.7) (1)	<0.0001	<0.001
Statin users, n (%) (missing)	171 (81.8) (5)	17 (19.3)	<0.001	<0.001
Alcohol overuse, n (%)	23 (10.8)	5 (5.8)	0.18	0.28
Current smokers, n (%) (missing)	33 (15.6) (2)	19 (21.6)	0.20	0.57
Peripheral artery disease, n (%)	10 (4.7)	4 (4.6)	1.0.	0.6
Macrovascular disease, n (%)	51 (25.0) (10)	12 (13.6)	0.03	0.26
Neuropathy measures				
UENS total score	9.0 (5.0–16.0)	8.0 (3.0–14.0) (1)	0.02	0.41
NSS				
Bulbar paresis	0.0 (0.0–0.0)	0.0 (0.0–0.0) (1)	0.02	
Extremity paresis	0.0 (0.0–0.0)	0.0 (0.0–0.0) (1)	0.2	
Sensory positive	2.0 (1.0–2.0)	2.0 (1.0–2.0) (1)	0.74	
Sensory negative	0.0 (0.0–1.0)	0.0 (0.0–1.0)(1)	<0.001	
Autonomic	1.0 (0.0–1.0)	0 (0.0–0.0) (1)	<0.0001	
Total	3.0 (2.0–4.3)	2.1 (2.0–3.2) (1)	0.01	0.002
NPSI**				
Total score	28 (13.5–42.5) (1)	28(15-39)(1)	0.65	0.27
Evoked pain score	6 (0–12) (1)	3 (0–8) (1)	0.09	0.04
QST, n (%) (missing)				
Increased VDT	107 (55.4) (21)	61 (69.3)	0.03	<0.01
Increased MDT	71 (33.6) (3)	35 (39.8)	0.31	0.1
Increased CDT and/or WDT	62 (29.4) (3)	33 (37.5)	0.17	0.08
DMA	14 (6.6)	18 (20.5)	<0.001	<0.01
Increased MPS	11 (5.2) (3)	16 (18.2)	<0.001	<0.01
IENFD (fibres/mm)	3.2 (1.5–5.5) (28)	4.9 (3.6–6.2)	<0.0001	<0.001

Continued

Table 1 Continued

Polyneuropathy entity	DPN	IPN	Univariate P value*	Multivariate P value†
Abnormal IENFD, n (%) (missing)	95 (51.1) (28)	26 (29.6)	<0.01	<0.001
Abnormal NCS, n (%) (missing)	78 (37.1) (4)	35 (39.8)	0.67	0.25

*P value of <0.05 chosen as level of significance. Rank-sum test, χ^2 test and Fisher's exact test were used as appropriate.
†P value of <0.05 chosen as level of significance. Linear regression is used for interval variables and logistic regression for categorical variables with adjustment for age and sex for all variables.
‡All categorical variables are stated as frequency with percentage in parentheses and missing in parentheses if present, n (%) (missing).
§All interval variables are stated as median with IQR between brackets and missing between parentheses if present, median (IQR) (missing).
¶A total of 174 out of 214 patients with DPN have symptoms of polyneuropathy, whereas all patients with IPN are symptomatic. Duration of symptoms is missing for two patients with DPN. The frequencies are stated as proportions out of all patients with non-missing on duration of neuropathy symptoms.
**NPSI total score and evoked pain score for 97 patients with DPN and 52 patients with IPN with distal pain in both feet.
BMI, body mass index; CDT, cold detection threshold; DBP, diastolic blood pressure; DMA, dynamic mechanical allodynia; DPN, diabetic polyneuropathy; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; IENFD, intraepidermal nerve fibre density; IPN, idiopathic polyneuropathy; LDL, low-density lipoprotein; MPS, mechanical pain sensitivity; NCS, nerve conduction studies; NPSI, Neuropathic Pain Symptom Inventory; NSS, Neuropathy Symptom Score; QST, quantitative sensory testing; SBP, systolic blood pressure; UENS, Utah Early Neuropathy Score; VDT, vibration detection threshold; WDT, warmth detection threshold.

Demographics

We compared the demographic, lifestyle and cardiovascular characteristics of DPN to IPN (table 1). We found no difference in sex, whereas patients with DPN were older (67.4 vs 59.o years) and had longer duration of neuropathy symptoms.

Lifestyle and cardiovascular characteristics

In a multivariate analysis adjusting for the effects of age and sex, DPN was associated with greater body mass index (BMI) (32.0 kg/m^2 vs 27.4kg/m^2) and waist circumference (110 cm vs 97cm); higher frequency of hypertension diagnosis (72.9% vs 30.7%); lower total (4.0 mmol/L vs 5.2mmol/L), LDL (1.9 mmol/L vs 3.1mmol/L) and HDL (1.2 mmol/L vs 1.4mmol/L) cholesterol levels; and a higher prevalence of use of statins (81.8% vs 19.3%).

Neuropathy characteristics

We compared the clinical, NCS and IENFD characteristics of DPN to IPN (table 1). DPN was associated with slightly higher total neuropathy scores on both UENS (9.0 vs 8.0) and NSS (3.0 vs 2.1); a slightly higher autonomic score on NSS (1.0 vs 0.0); lower frequency of increased MPS, DMA and abnormal VDT; and lower IENFD count. In a multivariate analysis, adjusting for the effects of age and sex, the difference in total UENS score did not remain significant. In multivariate analysis adjusting for sex and age, DPN was associated with a higher evoked pain score on NPSI.

To adjust for asymptomatic patients with DPN, we performed a subgroup analysis comparing symptomatic DPN to IPN (table 2). In a multivariate analysis adjusting for the effects of age, sex and duration of neuropathy symptoms, DPN was associated with a slightly higher autonomic score and total symptom score on the NSS; lower frequency of increased MPS, DMA and abnormal VDT on QST; and lower IENFD count. There was a tendency for higher evoked pain score on NPSI and lower frequency of abnormal NCS in the DPN group.

Polyneuropathy subtypes

We compared the frequency of polyneuropathy subtypes in DPN with that in IPN (figure 3). The frequency of SFN was higher for both the total DPN (7.0 vs 5.7%) and symptomatic DPN group (8.0 vs 5.7%), respectively. There was a tendency of higher frequency of LFN in the IPN group compared with the symptomatic DPN group (p=0.07).

DISCUSSION

This study shows that the neuropathy characteristics of DPN differ from those of IPN. DPN is associated with slightly higher autonomic and total symptom scores on NSS; lower frequency of DMA, increased MPS and abnormal VDT on QST; lower IENFD count; higher frequency of SFN; and a tendency for lower frequency of LFN compared with IPN.

Demographics

We found no difference in sex between DPN and IPN. Patients with DPN were older than patients with IPN and DPN had a longer duration of symptoms. Sachedina and Toth compared 210 patients with DPN to 228 patients with IPN and found no difference in sex, age or duration of symptoms between the two groups.[11] In our study, a higher age and longer duration of symptoms in DPN can possibly be explained by a difference in patient selection. DPN is shown to develop prior to a diabetes diagnosis.[4] The probable and definite DPN groups were

Table 2 Subgroup comparison of 174 symptomatic patients with DPN to 88 patients with symptomatic IPN

Neuropathy measures*†	Symptomatic DPN (n=174)	Symptomatic IPN (n=88)	P value‡ Univariate analysis	P value§ Multivariate analysis
UENS total score	10.0 (5.0–18.0)	8.0 (3.0–14.0) (1)	**<0.01**	**0.3**
NSS				
Bulbar paresis	0.0 (0.0–0.0)	0.0 (0.0–0.0) (1)	**0.02**	
Extremity paresis	0.0 (0.0–0.0)	0.0 (0.0–0.0) (1)	**0.16**	
Sensory positive	2.0 (2.0–2.0)	2.0 (1.0–2.0) (1)	**<0.01**	
Sensory negative	0.0 (0.0–1.0)	0.0 (0.0–1.0) (1)	**<0.001**	
Autonomic	1.0 (0.0–1.0)	0 (0.0–0.0) (1)	**<0.0001**	
Total	3.0 (2.1–4.3)	2.1 (2.0–3.2) (1)	**<0.0001**	**<0.001**
NPSI¶				
Total score	28.0 (13.5–42.5) (1)	28.0 (15.0–39.0) (1)	**0.65**	**0.43**
Evoked pain	6.0 (0.0–12.0) (1)	3.0 (0.0–8.0) (1)	**0.09**	**0.06**
Pain, n (%)	97 (55.8)	52 (59.1)	**0.61**	**0.95**
QST, n (%) (missing)				
Increased VDT	88 (53.7) (10)	61 (69.3)	0.02	<0.01
Increased MDT	61 (35.7) (2)	35 (39.8)	0.52	0.21
Increased CDT and/or WDT	55 (32.2) (3)	33 (37.5)	0.4	0.35
DMA	13 (7.5)	28 (20.5)	<0.01	0.01
Increased MPS	11 (6.4) (3)	16 (18.2)	<0.01	0.03
IENFD (fibres/mm)	3.1 (1.2–5.3) (27)	4.9 (3.6–6.2)	<0.0001	<0.001
Abnormal IENFD, n (%) (missing)	80 (54.4) (27)	26 (29.6)	<0.001	<0.001
Abnormal NCS, n (%) (missing)	59 (34.5) (3)	35 (39.8)	0.4	0.06

*All categorical variables are stated as frequency with percentage in parentheses and missing in parentheses if present, n (%) (missing).
†All interval variables are stated as median with IQR between brackets and missing between parentheses if present, median (IQR) (missing).
‡P<0.05 chosen as level of significance. Rank-sum test, χ^2 test, and Fisher's exact test were used as appropriate.
§P<0.05 chosen as level of significance. Linear regression is used for interval variables and logistic regression for categorical variables with adjustment for age, sex and duration of neuropathy symptoms for all variables.
¶NPSI total score for 97 patients with DPN and 52 patients IPN with distal pain in both feet.
CDT, cold detection threshold; DMA, dynamic mechanical allodynia; DPN, diabetic polyneuropathy; IENFD, intraepidermal nerve fibre density; IPN, idiopathic polyneuropathy; MDT, mechanical detection threshold; MPS, mechanical pain sensitivity; NCS, nerve conduction study; NPSI, Neuropathic Pain Symptom Inventory; NSS, Neuropathy Symptom Score; QST, quantitative sensory testing; UENS, Utah Early Neuropathy Score; VDT, vibration detection threshold; WDT, warmth detection threshold.

invited to participate and included at a median duration from T2DM diagnosis of 5.8 (IQR 4.0–7.0) and 6.1 (IQR 4.5–7.4) years, respectively.[14] Patients with IPN were selected from a cohort of patients with self-volunteered polyneuropathy symptoms referred from primary physicians or private practising neurologists to further work up at a combined secondary and tertiary centre. Due to the self-volunteered nature of symptoms and the duration from patient referral to inclusion generally not exceeding 3 months, this could explain the lower age and shorter duration of symptoms in the IPN group.

Lifestyle and cardiovascular characteristics

Metabolic syndrome encompasses elements such as obesity, dyslipidaemia and hypertension[30] and is shown to be predictive of T2DM.[31] This explains the higher BMI, greater waist circumference, lower HDL cholesterol levels and greater number of patients with hypertension in DPN compared with IPN. International guidelines recommend the use of statins in T2DM for both primary and secondary prevention of cardiovascular disease.[32] The effects of such recommendations are clearly reflected in this study by a greater number of statin users in the DPN group, which also explains the lower levels of total cholesterol and LDL cholesterol in this group.

Neuropathy characteristics

We did not find any difference in total UENS score between DPN and IPN, which is in line with the study of Sachedina and colleagues.[11] The shown differences

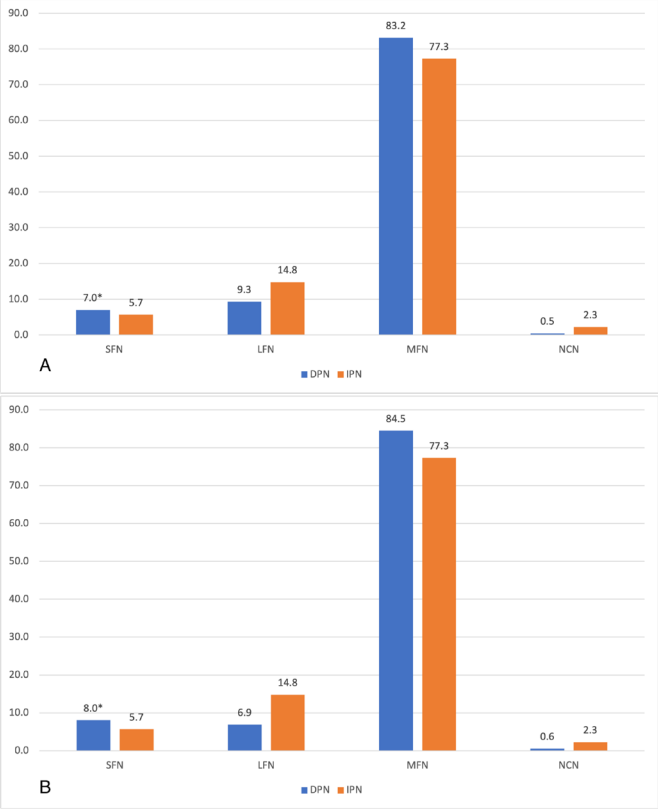

Figure 3 Frequency of polyneuropathy subtypes in the total group of DPN (A) and in the subgroup with symptomatic DPN (B) compared with IPN. *Significant difference in multivariate logistic regression adjusted for age and sex (A) and adjusted for age, sex, and duration of neuropathy symptoms (B). Frequencies are stated as percentage out of 214 patients with DPN and 88 patients with IPN (A), and as percentage out of 174 symptomatic patients with DPN and 88 patients with IPN (B). DPN, diabetic polyneuropathy; IPN, idiopathic polyneuropathy; LFN, large-fibre neuropathy; MFN, mixed-fibre neuropathy; NCN, non-classifiable polyneuropathy. SFN, small-fibre neuropathy.

in neuropathy characteristics between DPN and IPN could assumingly be due to difference in age, duration of neuropathy and/or the effect of asymptomatic patients with DPN. We adjusted for these potential sources of bias by comparing symptomatic DPN with IPN in a multivariate analysis adjusting for the effects of age, sex and duration of neuropathy. The differences in neuropathy characteristics remained significant except for evoked pain score on NPSI (p=0.06). In addition, these adjustments further strengthened the finding of a higher proportion of small-fibre affection in DPN compared with IPN.

Neuropathy subtypes

DPN had a more predominant involvement of pure small fibres compared with IPN. This was illustrated through a higher frequency of SFN in the DPN group. The latter finding was not reflected in the frequency of increased CDT and/or WDT, which was not different between DPN and IPN. Increased temperature thresholds on QST have previously been shown to be poorly related to abnormal IENFD.[15 33]

IPN showed a tendency to more predominant involvement of pure large fibres, which was illustrated through a tendency to higher frequency of LFN compared with DPN. The latter finding was also supported by higher frequency of increased VDT and a tendency for higher frequency of abnormal NCS in the IPN group.

DMA and increased MPS were more prevalent in the IPN group. The precise mechanisms underlying DMA and increased MPS remain open to debate.[34] One proposed mechanism is the sensitisation of second-order neurons in the dorsal horn by damaged nociceptive afferents leading to perceived pain when these second order neurons are activated through large myelinated A-beta fibres (DMA) and thinly myelinated A-delta fibres (MPS).[35] Another view is that provoked pain is elicited by sensitised peripheral nociceptors[36] or is elicited by a combination of central and peripheral sensitisations.[37] The higher frequency of DMA and increased MPS in IPN seems to support the importance of relatively spared but sensitised small fibres as the main driver for evoked pain phenomena.

Limitations

The difference in patient selection, DPN selected from a national cohort and IPN from a regional cohort, could be a potential source of bias. However, the population of Funen comprises around 41% of the population in the Region of Southern Denmark, which is the third largest region regarding population size out of the five regions in Denmark. In addition, the Danish healthcare system is a universal tax-funded system with free access to healthcare services across all regions of Denmark.[38] Thus, we expect the population of Funen to be relatively representative of the national population.

Intuitively, patients with painful polyneuropathy are expected to have a higher probability of referral to further workup at secondary and tertiary centres, which could be a potential source of selection bias contributing to the higher proportions of allodynia and hyperalgesia in the IPN group. There was no difference in total or evoked pain score on the NPSI nor in the frequency of reported pain between DPN and IPN. Thus, we do not find the difference in patient selection to be a source of bias.

The difference in laboratory evaluation between DPN and IPN is a potential limitation. Screening blood tests with the highest diagnostic yield in patients with polyneuropathy of unknown cause are HbA1c, vitamin B_{12} and monoclonal protein.[39] In patients with an established diabetes diagnosis, the diagnostic yield of additional blood tests is limited (7.8% for vitamin B_{12} and 1.9% for monoclonal protein).[40] Most patients with diabetes in Denmark are followed up closely with clinical and laboratory evaluation by either primary physicians or outpatient diabetes clinics due to the free access healthcare system in Denmark. This is reassuring, as the few patients with diabetes with a potential additional cause of

polyneuropathy would be expected to have such causes disclosed by routine follow-up. Therefore, we expect the detailed history of current and previous comorbidities in the diabetes cohort to be sufficient to rule out most additional causes of polyneuropathy.

The relatively high proportion of missing VDT and IENFD in the DPN group compared with no missing in the IPN group is a limitation. The missing VDT could perhaps overestimate the difference in SFN as an abnormal VDT is expected to shift patients from SFN to MFN. However, VDT was only missing in one patient with SFN, which is why this factor is not expected to affect our results. On the contrary, IENFD was missing in three patients with LFN which could underestimate the difference in LFN as an abnormal IENFD would shift the patients from LFN to MFN increasing the difference in LFN between DPN and IPN.

Another limitation was the registration of duration of neuropathy symptoms as a categorical variable with relatively large intervals (0–5 years and >5 years). This could potentially lead to an underestimation of the effect of this variable on multivariate analysis compared with a registration of this variable as interval variable.

Finally, although standardised methods were used, the fact that patients in the cohorts were examined by different investigators is a potential limitation.

CONCLUSION

In this cross-sectional study, we compared the neuropathy characteristics of the two most common sensory polyneuropathies, DPN and IPN. We found DPN to be associated with higher symptom scores and a greater involvement of pure small fibres, whereas IPN was associated with a tendency to greater involvement of pure large fibres and a higher frequency of pain phenomena such as DMA and hyperalgesia. We hypothesised that considerable similarities between DPN and IPN could indicate a similar pathogenesis. However, DPN and IPN showed clear differences in neuropathy characteristics, indicating that these two entities are to be regarded as aetiologically and pathogenetically distinct. There is growing evidence of the importance of metabolic factors in the pathogenesis of DPN,[5] whereas the understanding of aetiology and pathogenesis in IPN remains undiscovered with emerging evidence of a possible role of low-frequency genomic variants.[41] Future studies should focus on the role of rare genetic mutations and non-hereditary genomic variants in the pathogenesis of IPN.

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