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RESEARCH REPORT

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Small and large fiber sensory polyneuropathy in type 2 diabetes: Influence of diagnostic criteria on neuropathy subtypes

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Abstract

Diabetic polyneuropathy (DPN) can be classified based on fiber diameter into three subtypes: small fiber neuropathy (SFN), large fiber neuropathy (LFN), and mixed fiber neuropathy (MFN). We examined the effect of different diagnostic models on the frequency of polyneuropathy subtypes in type 2 diabetes patients with DPN. This study was based on patients from the Danish Center for Strategic Research in Type 2 Diabetes cohort. We defined DPN as probable or definite DPN according to the Toronto Consensus Criteria. DPN was then subtyped according to four distinct diagnostic models. A total of 277 diabetes patients (214 with DPN and 63 with no DPN) were included in the study. We found a considerable variation in polyneuropathy subtypes by applying different diagnostic models independent of the degree of certainty of DPN diagnosis. For probable and definite DPN, the frequency of subtypes across diagnostic models varied from: 1.4% to 13.1% for SFN, 9.3% to 21.5% for LFN, 51.4% to 83.2% for MFN, and 0.5% to 14.5% for non-classifiable neuropathy (NCN). For the definite DPN group, the frequency of subtypes varied from: 1.6% to 13.5% for SFN, 5.6% to 20.6% for LFN, 61.9% to 89.7% for MFN, and 0.0% to 6.3% for NCN. The frequency of polyneuropathy subtypes depends on the type and number of criteria applied in a diagnostic model. Future consensus criteria should clearly define sensory functions to be tested, methods of testing, and how findings should be interpreted for both clinical practice and research purpose.

KEYWORDS

diabetic polyneuropathy, large fiber neuropathy, mixed fiber neuropathy, small fiber neuropathy, type 2 diabetes mellitus

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1 | INTRODUCTION

Original work by Adrian and Zotterman in the 1920s,[1] where they demonstrated a subclassification of nerve fibers into A, B, and C fibers associated with different sensory and motor functions paved the way for today's classification of neuropathies into different categories. Neuropathies can be classified in different ways[2]; a simple clinical description divides neuropathies into small fiber neuropathy (SFN), large fiber neuropathy (LFN), and mixed fiber neuropathy (MFN).[3] Particular interest has been devoted to small fiber neuropathies, which are conditions characterized by selective damage to unmyelinated (C) and thinly myelinated (Aδ) sensory and autonomic nerve fibers.[4-9] The clinical picture of SFN is characterized by positive and negative symptoms and/or signs related to pain, temperature, and autonomic functions.[7,9] In addition to pure SFN, small fiber damage may also occur in patients with large fiber abnormalities, such as diabetic neuropathy.[10-13] The diagnosis of SFN is not easy and represent a challenge because in contrast to LFN there is no agreed objective neurophysiological measure for small fiber involvement. Without a gold standard for classifying SFN, a series of different definitions and classifications have therefore been suggested,[10,12-15] which in part may explain the large variation in frequency of SFN in different samples reported in the literature (7%-54%).[10,12,14]

Based on the fact that there is no gold standard for the diagnosis of SFN in diabetic neuropathy,[16] the Toronto Consensus Criteria[17] comprised a hierarchical classification similar to the principle previously used for defining neuropathic pain.[18] According to the Toronto Consensus Criteria, three categories are described: (a) possible diabetic SFN defined as the presence of length-dependent symptoms and/or signs of small fiber damage; (b) probable diabetic SFN as length-dependent symptoms, clinical signs of small fiber damage together with normal sural nerve conduction; and (c) definite SFN as length-dependent symptoms, clinical signs of small fiber damage, normal sural nerve conduction study, and altered intraepidermal nerve fiber density and/or abnormal thermal threshold by quantitative sensory testing (QST) at the foot.[17] However, it is not specified what symptoms and signs are required to fulfill these criteria, and how the signs exactly should be examined. In this study we aimed to determine the influence of different diagnostic criteria on the frequency of neuropathy subtypes (SFN, LFN, and MFN) in a sample of carefully phenotyped type 2 diabetes patients that all had either probable or definite DPN according to the Toronto Consensus Criteria.[17]

2 | METHODS AND AIMS

2.1 | Design, setting, and participants

This study was a nested cross-sectional study based on a previous clinical study[19] of patients from the Danish Center for Strategic Research in Type 2 Diabetes (DD2) cohort.[11,20] DD2 is an ongoing cohort of patients with recently diagnosed type 2 DM that currently comprises more than 8000 patients. A total of 389 patients from the DD2 cohort agreed to be enrolled during a 2-year period, from October 2016 until October 2018 in a previous clinical study.[21] A subsample of the 389 patients was included in this study based on the following inclusion criteria: (a) no clinical evidence of DPN, or (b) a clinical diagnosis of either probable or definite DPN according to the Toronto Consensus Criteria.[17] Patients with possible DPN, subclinical DPN, neuropathy due to other causes than DM, and patients with symptoms due to other neurological disease than neuropathy were excluded from this study. A flow diagram of patient inclusion is shown in Figure 1.

2.2 | Data collection

Symptoms, bedside clinical examination, quantitative sensory testing (QST), intraepidermal nerve fiber density (IENFD), and nerve conduction studies (NCS) were used to subtype DPN patients in SFN, LFN, and MFN.

2.2.1 | Symptoms

We used a focused interview with predefined questions to obtain information on the presence and localization of neuropathy symptoms, type of neuropathy symptoms (negative vs positive) and nature of positive symptoms (painful vs non-painful). Negative symptoms were predefined as numbness or any other description of sensation loss, and positive symptoms as prickling, stabbing, tingling, itching, and/or any other description of positive sensory disturbance. Symptoms which occurred distally and bilaterally were considered as symptoms of DPN.

2.2.2 | Bedside clinical examination

Bedside clinical examination was performed for the lower extremities by the primary investigator at each center (MI and SSG, both trained and board-qualified neurologists).

Hypoalgesia and hyperalgesia to pinprick was tested using the sharp end of a broken wooden cotton stick (Aarhus) and a sterile Neurotip (Odense) (Owen Mumford, Oxford, UK). The Neurotip was attached to the end of a Neuropen (Owen Mumford, Oxford, UK) to ensure a consistent pressure of 40 g. The sharp end of the broken wooden cotton stick was hold loosely between the thumb and index finger allowing the stick to slide ensuring a relatively constant pressure. The prick was applied randomly to the dorsum of the proximal phalanx of the great toe with the proximal anteromedial thigh used as reference as performed in a standard neurological examination.[22] Hypo- and hyperalgesia were evaluated qualitatively by asking the patient to state whether the sensation was significantly/considerably different compared to the reference site.

Temperature sensation was tested using warm and cold thermal rollers (Somedic AB, Hörby, Sweden) with standard temperatures of

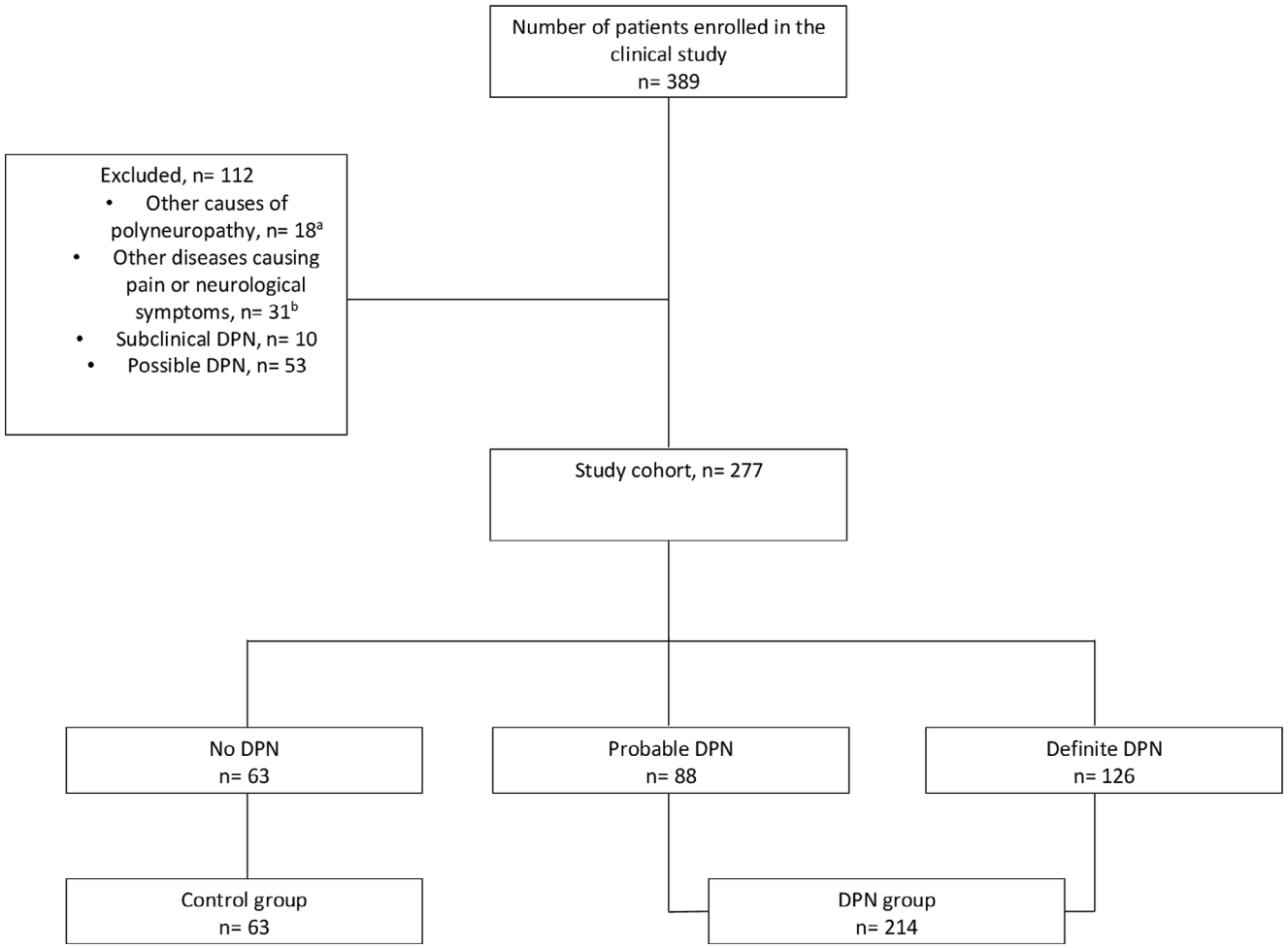

FIGURE 1 Flow diagram of patient inclusion. DPN, Diabetic Polyneuropathy. a: Chemotherapy- or alcohol-induced polyneuropathy, chronic inflammatory demyelinating polyneuropathy, sarcoidosis, vitamin B12 deficiency, infection with human immunodeficiency virus, and psoriasis arthritis. b: Spinal stenosis, arthritis (osteo-, psoriasis, borrelia-), herniated disc, multiple sclerosis, fibromyalgia, peripheral arterial disease, stroke, transversal myelitis, sequela from trauma and operations (in the back and feet), pes planus transverse, progressive supranuclear palsy, and restless leg syndrome

40°C and 20°C, respectively, applied to the dorsum of the foot and great toe. The proximal thigh was used as reference site. For all assessments, the foot temperature was ensured to be >28°C. An abnormal result was defined as an absent or decreased sensation for either warm or cold stimulus.

Touch sensation was tested using a 10 g monofilament attached to the Neuropen (Owen Mumford, Oxford, UK) applied in an arrhythmic manner four times at the dorsal aspect of the proximal phalanx of each great toe with the patients eyes closed as described in the Toronto Clinical Neuropathy Score (TCNS).[23] Abnormality was defined as <4 applications felt for each toe.

Vibration was tested according to the Utah Early Neuropathy Scale (UENS) protocol[24] by first acquainting the subject to vibration (as opposed to pressure), then holding the maximally vibrated 128 Hz tuning fork to the dorsum of the great toe at the distal interphalangeal joint. Extinction of vibration in less than 10 seconds was considered as decreased vibration while lack of perception was considered as absent vibration.

Ankle reflexes were tested using a Tromner reflex hammer ****** (US Neurologicals LLC, USA) according to the Michigan Neuropathy Screening Instrument clinical part (MNSIc) protocol.[25] Reflexes were considered diminished if only elicited by distraction (Jendrassik maneuver) and absent if not elicited at all.

Proprioception was tested over the distal interphalangeal joint of the great toe and performed as in a standard neurological examination.[22] Abnormality was defined as decreased or absent proprioception.

Motor weakness and atrophy, which are considered to be late manifestations of DPN and preceded by involvement of large fiber sensory functions[26] were not included in the bedside clinical examination protocol.

2.2.3 | Quantitative sensory testing

QST was tested by certified study nurses certified by the German Research Network on Neuropathic Pain (DFNS) and done in accordance with a modified version of the DFNS protocol.[27]

Cold detection threshold (CDT) and warm detection threshold (WDT) were tested by the Thermal Sensory Analyzer (TSA, Medoc, Israel) on the dorsum of the right foot. The baseline temperature was 32°C and the contact area of the thermode about 9 cm^2. All thresholds were obtained with ramped continuously increasing or decreasing thermal stimuli (1°C/s) that were terminated when the patient pressed a button. Cut-off temperatures were 0°C and 50°C. The average threshold temperature of three measurements were entered into the database.

Mechanical detection threshold (MDT) was tested by a set of standardized von Frey hairs (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, and 512 mN) (Marstock^{nervtest}, Germany). We started by applying a von Frey hair with a force of 16 mN. Subsequently, von Frey hairs of the corresponding next lower intensity (8 mN) were applied until the patient did not feel any touch sensation. The equivalent force applied represented the first subthreshold stimulus intensity. Then the reversed procedure with increasing stimulus intensities were applied to determine the suprathreshold value. Both procedures were repeated until a total of five sub- and five suprathreshold values were obtained.

Vibration detection threshold (VDT) was tested by a 128 Hz tuning fork (Seagull) with mountable dampers reducing the frequency to 64 Hz. The tuning fork was placed on the medial bony prominence of the distal first metatarsal bone on the right side. The vibration detection threshold was determined with a series of three descending stimulus intensities as the last noticeable vibration on an 8/8 scale.

2.2.4 | Skin biopsy

IENFD was determined from a single 3-mm punch biopsy taken from 10 cm above the right lateral malleolus. All biopsies were analyzed by one skin biopsy expert (PK). The method of fixation, cryoprotection, and staining has been described in detail elsewhere.[28,29] IENFD measurements were performed exactly according to the European Federation of Neurological Societies' (EFNS) and the Peripheral Nerve Society (PNS) guidelines and compared to an international reference material.[30]

2.2.5 | Nerve conduction studies

NCS were performed by experienced examiners. Tibial, peroneal, and median nerves were examined unilaterally, and a unilateral ulnar nerve was additionally examined if the median nerve was abnormal. Sural nerves were examined bilaterally as described elsewhere.[31] For the NCS to be considered abnormal, two or more nerves including at least one sural nerve had to be abnormal. An abnormal nerve was defined as an abnormality on at least one of the following parameters (amplitude, conduction velocity, distal motor latency or F-wave latency).[31,32] These criteria have previously been shown to have a high specificity and acceptable sensitivity for detection of DPN.[32] The definition of DPN as a sensory (at least one sural nerve) polyneuropathy (two or more nerves abnormal) was also respected by these criteria.

2.3 | Definition of DPN

No DPN, possible DPN, probable DPN, and definite DPN were defined according to the Toronto Consensus Criteria.[17] Probable and definite DPN constituted the neuropathy group while no DPN constituted the control group. The methods used for diagnosing DPN are described in detail elsewhere.[21]

2.4 | Definition of DPN subtypes

We applied four different sets of criteria designated models 1 to 4 to the total group of neuropathy patients (probable and definite DPN) and to the definite DPN group separately (Figure 2). In all models, SFN diagnosis was defined as criteria of SFN being fulfilled and criteria of LFN not being fulfilled. LFN diagnosis was defined as criteria of LFN being fulfilled and criteria of SFN not being fulfilled. MFN was defined as SFN and LFN criteria being fulfilled simultaneously. Non- classifiable neuropathy (NCN) was defined as neuropathy in which none of the criteria of SFN, LFN, and MFN were fulfilled.

2.4.1 | Model 1

SFN diagnosis required an abnormality on ≥1 out of four small fiber measures (pinprick bedside, thermal sensation bedside, QST [CDT and/or WDT]), or IENFD). LFN diagnosis required an abnormality on ≥1 out of four large fiber measures (vibration bedside, ankle reflexes, QST [VDT and/or MDT], or NCS).

2.4.2 | Model 2

This model corresponds exactly to model 1 except for SFN and LFN diagnosis requiring an abnormality on ≥2 out of four measures respectively.

2.4.3 | Model 3

This model corresponded to the criteria proposed by Truini et al.[12] SFN diagnosis required the following four criteria: (a) the presence of distal thermal pain; (b) decreased pinprick and/or temperature sensation on bedside examination; (c) reduced IENFD and/or increased thermal threshold on either CDT and/or WDT; (d) normal NCS. Criteria for LFN and MFN were not defined.

2.4.4 | Model 4

This model corresponded to the criteria proposed by Devigili et al.[10] SFN diagnosis required ≥2 out of three small fiber measures:

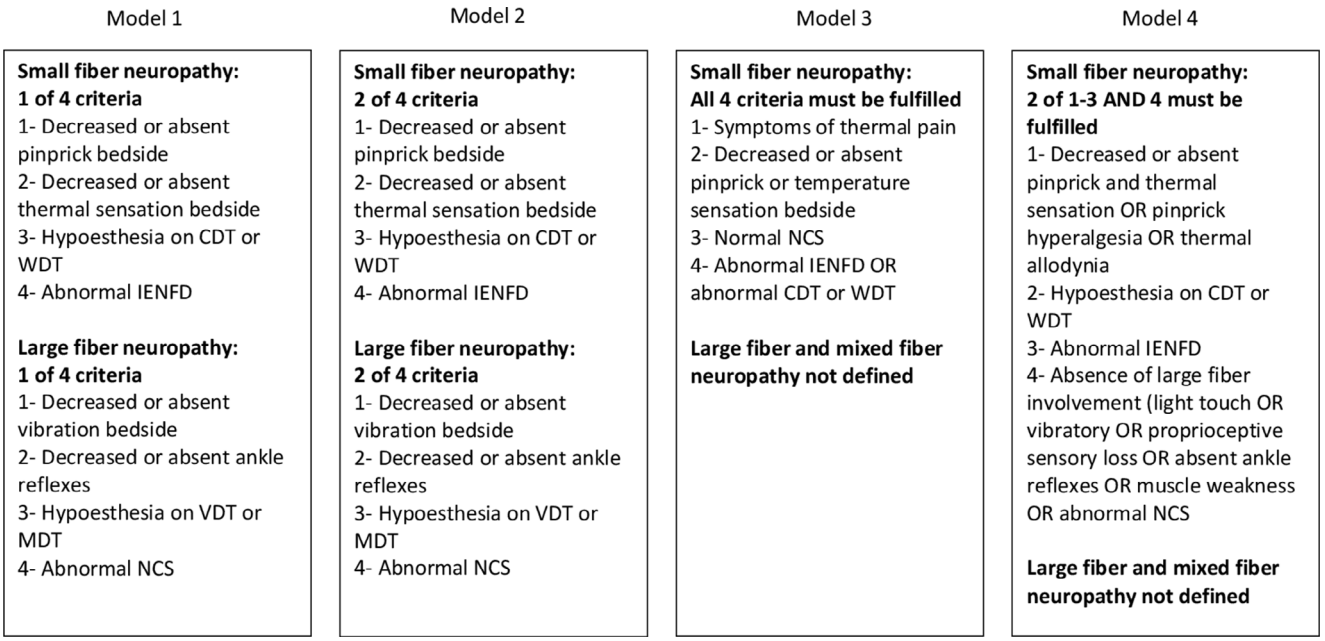

FIGURE 2 Four different models for defining polyneuropathy subtypes. IENFD, intraepidermal nerve fiber density; NCS, nerve conduction studies; CDT, cold detection threshold; WDT, warm detection threshold; VDT, vibration detection threshold; MDT, mechanical detection threshold

(a) abnormal bedside measure (decreased pinprick and thermal sensation combined, pinprick hyperalgesia, or thermal allodynia); (b) abnormal QST measure (increased CDT and/or WDT); (c) reduced IENFD. Furthermore, SFN diagnosis required the absence of any large fiber involvement (Figure 2). Criteria for LFN and MFN were not defined.

2.5 | Neuropathy severity

We used the TCNS[23] to measure the severity of DPN. This is a well validated score that based on symptoms and clinical signs divides neuropathy in four distinct categories: No neuropathy (score 0-5); mild neuropathy (score 6-8); moderate neuropathy (score 9-11); and severe neuropathy (score 12-19).

2.6 | Statistics

The frequency of polyneuropathy subtypes was stated as percentage out of total number of observations. Categorical variables were described as proportions with 95% confidence intervals. 95% confidence intervals were estimated as exact intervals using the Clopper-Pearson method. Interval variables were described using median and interquartile range. Stata 16 IC statistical software package was used for the descriptive statistics performed. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Aarhus University.[33,34] Double data entry was carried out.

2.7 | Ethics

The study was approved by the Regional Research Ethics Committee of Central Denmark Region (1-10-72-130-16). The Danish National Committee on Health Research Ethics (record number S-20100082) approved the DD2 project. The Danish Data Protection Agency (record number 2008-58-0035) approved the DD2 project and the study is registered at Aarhus University internal notification no. 62908-250. All participants gave written informed consent.

3 | RESULTS

A total of 277 (88 with probable DPN, 126 with definite DPN, and 63 with no DPN) out of 389 diabetes patients were included for this study (Figure 1). One hundred and twelve patients were excluded: 31 patients due to comorbidities causing symptoms not easily discernible from neuropathy, 18 patients due to other causes of neuropathy than diabetes, 10 patients due to subclinical neuropathy and 53 patients with possible DPN.

3.1 | Overview of clinical findings in no DPN and DPN based on IENFD and NCS findings

Table 1 shows an overview of polyneuropathy symptoms and abnormal findings on bedside clinical examination and QST among DPN patients stratified on the basis of NCS and IENFD results, and among diabetes patients with no DPN.

TABLE 1 Clinical findings in diabetes patients with no polyneuropathy and in diabetes patients with polyneuropathy based on the results of intraepidermal nerve fiber density and nerve conduction studies

	No DPN[a]	DPN[a,b]			
IENFD	NR	Normal	Abnormal	Normal	Abnormal
NCS	NR	Normal	Normal	Abnormal	Abnormal
No. of patients	63	70	47	19	47
No. with reduced and/or absent sensation on bedside clinical examination, n (%) [95% CI]					
Pinprick sensation	2 (3.2) [0.4-11.0]	24 (34.3) [23.3-46.6]	24 (51.1) [36.1-65.9]	7 (36.8) [16.3-61.6]	35 (74.5) [59.7-86.1]
Temperature sensation	18 (28.6) [17.9-41.3]	53 (75.7) [64.0-85.2]	38 (80.9) [66.7-90.9]	10 (52.6) [28.9-75.6]	37 (78.7) [64.3-89.3]
Touch sensation	2 (3.2) [0.4-11.0]	27 (30.0) [19.6-42.1]	19 (40.4) [40.1-69.8]	5 (26.3) [9.1-51.2]	30 (63.8) [48.5-77.3]
Vibration sensation	11 (17.5) [9.1-29.1]	39 (55.7) [43.3-67.6]	33 (70.2) [26.4-55.7]	10 (52.6) [28.9-75.6]	40 (85.1) [71.7-93.8]
Proprioception	6 (9.5) [3.6-19.6]	28 (40.0) [28.5-52.4]	28 (59.6) [44.3-73.6]	8 (42.1) [20.3-66.5]	38 (80.9) [66.7-90.9]
Ankle jerks	NR	37 (52.9) [40.6—64.9]	25 (53.2) [38.1-67.9]	10 (52.6) [28.9-75.6]	34 (72.3) [57.4-84.4]
No. with increased QST thresholds, n (%) [95% CI] (missing)[c]					
Cold detection	7 (11.3) [4.7-21.9] (1)	19 (27.5) [17.5-39.6] (1)	10 (21.3) [10.7-35.7]	3 (15.8) [3.4-39.6]	15 (31.9) [19.1-47.1]
Warm detection	1 (1.6) [0.04-8.5]	4 (5.7) [1.6-14.0]	8 (17) [7.6-30.8]	1 (5.3) [0.1-26.0]	6 (12.8) [4.8-25.7]
Mechanical detection	1 (1.6) [0.04-8.5]	22 (31.4) [20.9-43.6]	11 (23.9) [12.6-38.8] (1)	5 (27.8) [9.7-53.5] (1)	23 (48.9) [34.1-63.9]
Vibration detection	13 (27.1) [15.3-41.8] (15)	30 (47.6) [34.9-60.6] (7)	20 (46.5) [31.2-62.3] (4)	11 (68.8) [41.3-89.0] (3)	30 (69.8) [53.9-82.8] (4)
No. with polyneuropathy symptoms, n (%) [95% CI]					
Painful symptoms	NR	41 (58.6) [46.2-70.2]	31 (66.0) [50.7-79.1]	5 (26.3) [9.1-51.2]	32 (68.1) [52.9-80.9]
Non-painful symptoms	NR	27 (38.6) [27.2-51.0]	14 (29.8) [17.3-44.9]	12 (63.2) [38.4-83.7]	13 (27.7) [15.6-42.6]
No symptoms	NR	11 (15.7) [8.1-26.4]	6 (12.8) [4.8-25.7]	9 (47.4) [24.4-71.1]	6 (12.8) [4.8-25.7]

Abbreviations: DPN, diabetic polyneuropathy; IENFD, intra epidermal nerve fiber density; NCS, nerve conduction studies; NR, not relevant; QST, quantitative sensory testing.

[a]95% CI can only be compared in rows across groups as observations are independent of each other whereas 95% CI in columns across clinical findings cannot be used due to observations being dependent.

[b]The remaining 31 out of 214 DPN patients were not included in the overview due to missing results on NCS and/or IENFD preventing classification among the four groups.

[c]Proportions and 95% CI calculated after exclusion of missing values.

In patients with no DPN, abnormal findings were seen at bedside clinical examination and QST, for example, bedside temperature sensation and VDT were most frequently abnormal (28.6% and 27.1%, respectively) whereas bedside touch and pinprick sensation, and WDT and MDT were least frequently abnormal.

In patients with DPN, pinprick sensation was more likely to be affected in patients with abnormal-IENFD/abnormal-NCS (74.5%) compared to patients with normal-IENFD/normal-NCS (34.3%). We did not find any difference among DPN groups for bedside temperature sensation. Touch, vibration, and proprioception were more likely to be affected in patients with abnormal-IENFD/abnormal-NCS (63.8%, 85.1%, and 80.9%, respectively) compared to patients with normal-IENFD/normal-NCS (30.0%, 55.7%, and 40%, respectively). Proprioception was more likely to be affected in patients with abnormal IENFD/abnormal NCS (80.9%) compared to patients with normal IENFD/abnormal NCS (42.1%). We did not find any difference in abnormal ankle jerks, QST findings or polyneuropathy symptoms among the four DPN groups.

3.2 | Impact of different diagnostic models on frequency of polyneuropathy subtypes

We compared the effect of four different diagnostic models on the frequency of polyneuropathy subtypes in the total DPN group (probable and definite DPN) (Figure 3A) and in the definite DPN group (Figure 3B). SFN frequency was compared across all four diagnostic models while LFN, MFN, and NCN frequency was only possible to compare between models 1 and 2 as criteria for these subtypes were not defined in models 3 and 4.

In the total DPN group, SFN showed a 9-fold variation in frequency [Range interval: 1.4%-13.1%], LFN a 2-fold variation [9.3%-21.5%], MFN a 1.5-fold variation [51.4%-83.2%], and NCN a 14.0% variation [0.5%-14.5%] in frequency across diagnostic models. In the definite DPN group, SFN showed an 8-fold variation in frequency [1.6%-13.5%], LFN a 4-fold variation [5.6%-20.6%], MFN a 1.5-fold variation [61.9%-89.7%], and NCN a 6.3% variation [0.0%-6.3%] in frequency across diagnostic models. MFN followed by LFN were the most common subtypes across models for both the total and definite DPN groups. The lowest frequency of NCN was seen in model 1 for both groups.

3.3 | Impact of neuropathy severity on frequency of polyneuropathy subtypes

We examined the effect of neuropathy severity as measured by the TCNS on frequency of polyneuropathy subtypes by applying model 1 (Supporting Information). We showed an increase in MFN from

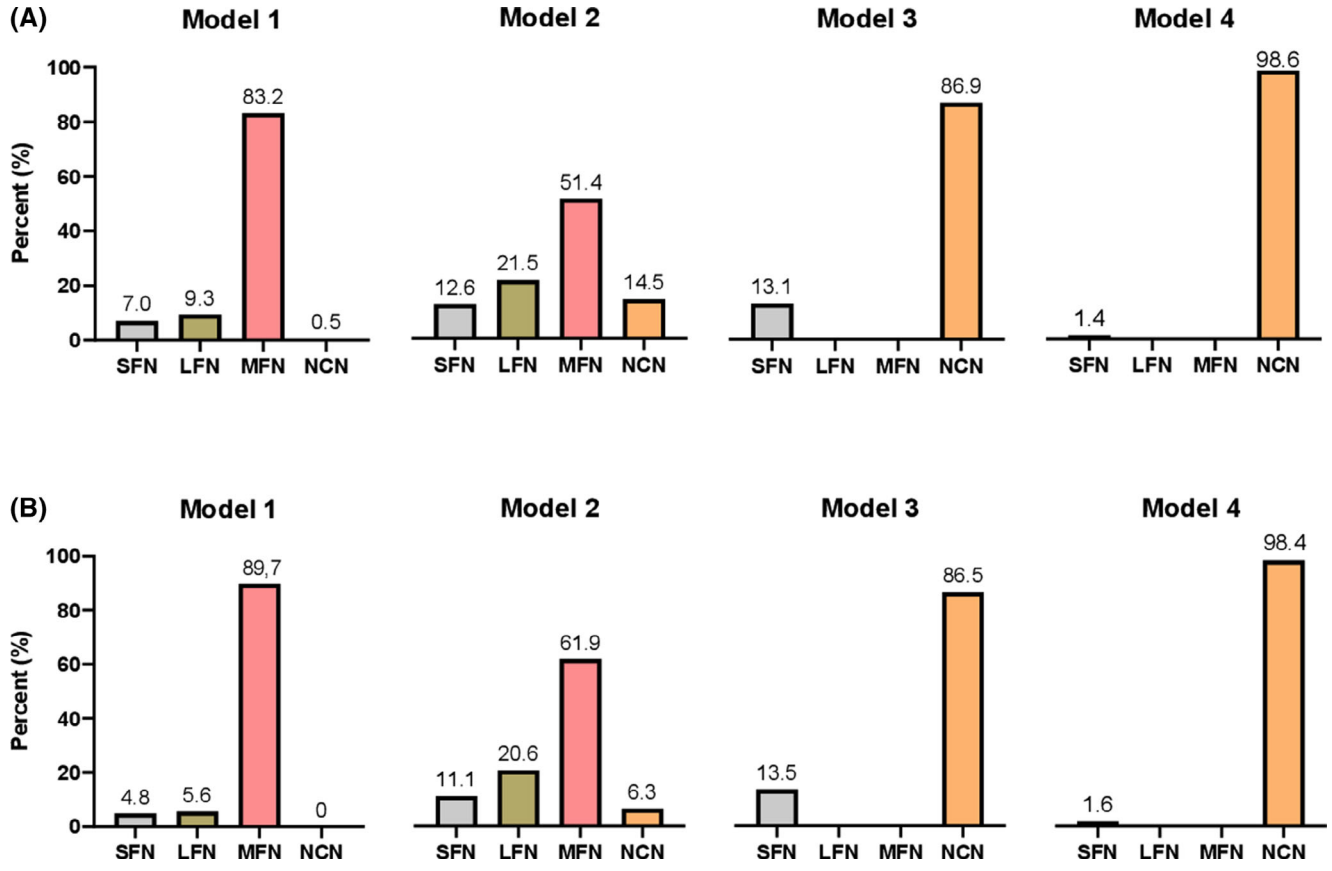

FIGURE 3 The proportion of polyneuropathy subtypes in four different diagnostic models applied to all 214 DPN patients (3A) and to 126 patients with definite DPN (3B). SFN, small fiber polyneuropathy; LFN, large fiber polyneuropathy; MFN, mixed fiber polyneuropathy; NCN, non classifiable polyneuropathy

59.4% for TCNS 0%-5% to 100% for TCNS >12. The frequency of SFN and LFN decreased respectively from 20.3% to 18.8% for TCNS 0%-5% to 0.0% for TCNS >12.

4 | DISCUSSION

We found a considerable variation in polyneuropathy subtypes by applying different diagnostic models independent of the degree of certainty of DPN diagnosis. These findings suggest that both the type and number of criteria used has an effect on the frequency of neuropathy subtype. On the other hand, the degree of certainty of DPN diagnosis did not seem to have a major impact on frequency of polyneuropathy subgrouping. A higher neuropathy severity was associated with higher frequency of MFN and lower frequency of SFN and LFN.

In this study, we used a simple clinical approach to classify patients into whether they had exclusively small fiber, large fiber or mixed fiber involvement (Figures 2 and 3). In principle, all neuropathies should theoretically be possible to classify into one of these three categories.

Model 3, the model proposed by Truini and colleagues,[12] and model 4, the model proposed by Devigili and colleagues,[10] were only designed to identify SFN patients, with no criteria proposed for LFN and MFN. In our proposed models (models 1 and 2), it is clearly illustrated that a lower number of criteria needed to diagnose SFN and LFN is associated with a lower likelihood of NCN (0%-0.5% vs 6.3%-14.5%). The presence of NCN can be explained by the difference in criteria used to diagnose DPN (Toronto Consensus Criteria) and criteria used to subtype DPN. Symptoms of polyneuropathy and bedside tests of large fiber function such as touch sensation and proprioception were included in the diagnosis of DPN but not in the criteria for subtyping DPN.

The frequency of polyneuropathy subtypes did not depend on the degree of certainty of DPN diagnosis for any of the four diagnostic models (Figure 3). The only remarkable difference was the lower frequency of MFN and higher frequency of NCN in the total DPN group compared to patients with definite DPN in model 2. This is not surprising as patients with definite DPN per se implies abnormality of either NCS or IENFD which facilitates the fulfillment of subtype criteria for SFN, LFN, and MFN. It is reassuring that the distribution of subtypes is similar between the total DPN group compared to the definite DPN group indicating that probable and definite DPN are actually part of the same overall population.

The lack of gold standard diagnostic criteria for SFN makes the subtyping of DPN and other polyneuropathies difficult. It seems intuitively correct that the total number of criteria and type of criteria (symptoms, bedside signs, and QST signs) applied for SFN and LFN has to be equal in order to ensure an equal likelihood of diagnosis for the two subtypes (Figure 2). In addition, the number of criteria needed to be fulfilled for a diagnosis of either SFN or LFN has an important impact on the frequency of subtypes (Figure 3). The application of ≥1 criteria out of four (model 1A + 1B) instead of ≥2 criteria out of four (model 2A + 2B), makes it easier to fulfill the criteria of SFN and LFN simultaneously which is reflected in the higher frequency of MFN and lower frequency of the pure subtypes in model 1. An advantage of model 1 compared to model 2 is that it is better to exclude large fiber involvement in SFN (no large fiber criteria can be fulfilled) and small fiber involvement in LFN (no small fiber criteria can be fulfilled). On the contrary, model 2 has the advantage of a higher degree of certainty of small fiber involvement in SFN and large fiber involvement in LFN (2 criteria have to be fulfilled).

Truini and colleagues in their study restricted the diagnosis of SFN to patients with symptoms of thermal pain (cold or burning).[12] Although SFN is often associated with pain,[4,7,35] sensory symptoms of SFN have previously been stated not to be limited to symptoms of pain[7] which is also implied by our study in which 29.8% of patients with abnormal IENFD and normal NCS exhibited purely non-painful symptoms and 12.8% were asymptomatic (Table 1). Symptoms were not part of the two models that we proposed (models 1 and 2) whereas symptoms were part of the models proposed by Devigili et al (model 3) and Truini et al (model 4). We propose that future diagnostic criteria for the subtyping of DPN should not include symptoms as these are regarded as fiber unspecific. Symptoms should only be included as part of the diagnostic criteria of DPN as described for the Toronto Consensus Criteria.

Truini and colleagues and Devigili and colleagues included hyperesthesia phenomena in their diagnostic models.[10,12] Hyperalgesia and allodynia are broad terms that are pathophysiologically unclear as to whether they are caused by peripheral nerve damage, central sensitization, or perhaps both factors combined[36] why it can be challenged if it is correct to confine these phenomena to discrete fiber subtypes. In our opinion, hyperesthesia phenomena should not be included in the diagnostic criteria of DPN subtypes.

Abnormal bedside pinprick and thermal sensation were better associated to DPN with abnormal IENFD/normal NCS (59.6% for pinprick and 80.9% for thermal sensation) than thermal sensation on QST (21.3% for CDT and 17% for WDT). Increased thermal thresholds on QST have previously been shown only to be related to abnormal IENFD in 37.3% of patients.[10] We did not include findings on QST in the diagnosis of DPN which in part may explain the weak association shown here. Due to the poor correlation between IENFD and thermal thresholds on QST, we suggest that thermal thresholds on QST should be removed as class 1 evidence for definite SFN as described in Toronto Consensus Criteria.[17]

The presence of two or three signs on bedside large fiber sensory testing (ankle reflexes, vibration, and proprioception) have previously been shown to be the best predictor of electrophysiological evidence of peripheral neuropathy in both diabetes patients and patients without diabetes.[37] As mentioned earlier, we had to ensure an equal number of small fiber and large fiber signs why we only included two out of three signs in our diagnostic models (Figure 2). We chose ankle reflexes and vibration sensation as we empirically find these two modalities easier to test than position sensation. A reduction in a single sensory modality on bedside examination was found in some patients with no DPN (29% on temperature sensation and 17% on

vibration sensation) but was obviously less frequent than in patients with DPN. QST-based measurements were also found to be abnormal in patients with no DPN (27% on VDT and 11% on CDT). The explanation for these findings is not clear. One possibility is that the normal range for a sensory function has not been clearly defined that is, that the sample on which the normal range is based differs for example because of age.[38] Alternatively, it is possible that the non-DPN group already has a subclinical early nerve affection.

This study has several strengths in comparison with some of other studies.[10,12-15] The sample was population-based as patients were invited from an ongoing national cohort of recently diagnosed type 2 DM.[11,20] This national cohort represents the whole spectrum of diabetes, from the well-regulated patients typically followed at primary physicians to the severely dysregulated patients followed at outpatient hospital clinics. The study was undertaken with the purpose to study DPN according to a standard protocol for clinical and paraclinical examinations. All patients were examined and interviewed by the same two experienced neurologists (MI in Odense & SG in Aarhus) according to renowned and validated methods. The examiners met to examine selected patients together in order to ensure consistency in the examination and interpretation of findings.

A potential limitation of our study was a relatively high proportion of missing skin biopsy data in 28 out of 214 DPN patients. These patients were not excluded from analysis but regarded as having a normal skin biopsy. This approach could potentially lead to an overestimation of LFN in model 2, and an underestimation of SFN in models 3 and 4. In model 2, IENFD was missing in 12 out of 46 LFN patients of which nine out of 12 patients had a single abnormal small fiber measure. Thus, the LFN estimate in model 2 could potentially be slightly overestimated by up to 4.2% if we assume all nine missing IENFD to be abnormal which is very unlikely. In models 3 and 4, respectively, the SFN estimate is expected to be valid as only four out of 186 and two out of 211 patients with NCN fulfilled the criteria of SFN except for a missing IENFD.

A cut-off of 10 seconds was used to distinguish between normal and abnormal vibration which could potentially overestimate abnormal vibration. This method has previously been applied as part of a well validated neuropathy score (UENS) without any adjustment for age and sex. In our study, none of the LFN and MFN had isolated abnormality on vibration why we do not expect this method to affect our results.

Pinprick was assessed using the Neurotip (Odense) and the sharp end of broken wooden cotton stick (Aarhus) which could be a source of variability. The Neurotip was attached to the end of the Neuropen ensuring a consistent pressure of 40 g. The precise pressure applied by the sharpened end of a broken wooden cotton stick was not possible to determine but relatively consistent pressure was attempted by holding the stick loosely between the thumb and index finger and exerting sufficient pressure on application allowing the stick to slide.

In this population-based cross-sectional study, we found the frequency of polyneuropathy subtypes based on fiber diameter to depend primarily on the type and number of criteria applied. The degree of certainty of DPN diagnosis did not have a great impact on frequency of polyneuropathy subtypes whereas higher neuropathy severity showed a clear convergence toward MFN.

In the absence of gold standard diagnostic criteria for the subtyping of DPN into SFN, LFN, and MFN, and because of the lack of knowledge on whether clinical criteria are completely subtype specific, there is a need for international consensus criteria to ensure standardization of clinical practice and comparability of research findings worldwide. This is especially highlighted by the advancement in the research field of neuropathic pain treatment in which a more detailed phenotypic and molecular assessment has paved the way for selection of subgroups of patients that may respond to a more specific treatment.[39,40]

In a recently ahead of print study, criteria for subtyping idiopathic distal sensory polyneuropathy (iDSP) have been proposed.[41] The proposed criteria suggest diagnosing iDSP as part of the subtyping process. The subtype criteria include symptoms and hyperesthesia phenomena such as hyperalgesia and allodynia. We propose that DPN diagnosis starts with a classification according to the Toronto Consensus Criteria, followed by a subtype classification that does not include symptoms or hyperesthesia phenomena as these are regarded as fiber type unspecific. Future consensus criteria for both DPN diagnosis and subtypes should clearly define the clinical sensory functions to be tested, the methods of testing, and the interpretation of findings on such tests as this would ensure consistency. It is advisable to distinguish between subtype criteria to be used in clinical practice and for research purposes. For research purposes, it is mandatory to include NCS and IENFD and to use specific and detailed criteria for subtyping of neuropathy that may vary depending on the specific research questions asked. For clinical practice, we propose to use a model similar to model 1 that is based on brief, simple, validated and reliable bedside tests supported by the results of NCS and skin biopsy, if available. Such a model is easy to administer in clinical practice and ensures that SFN and LFN are pure as SFN is ruled out if a single large fiber criterion is fulfilled and vice versa.

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AUTHOR CONTRIBUTION

Mustapha Itani: Design of the work, data collection, analysis, and interpretation, drafting the article, critical revision, and final approval of revised article.

Sif Gylfadottir: Design of the work, data collection, critical revision, and final approval of revised article.

Thomas Krøigård: Critical revision and final approval of revised article.

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Sören Möller: Data analysis and interpretation, critical revision, and final approval of revised article.

Henning Andersen: Critical revision and final approval of revised article.

Hatice Tankisi: Critical revision and final approval of revised article.

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Troels Staehlin Jensen: Design of the work, drafting the article, data interpretation, critical revision, and final approval of revised article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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