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Analysis of clinical phenotypes of neuropathic symptoms in patients with type 2 diabetes: A multicenter study

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ABSTRACT

Aims/Introduction: We investigated the classification of diabetic peripheral neuropathy (DPN) patients by subjective symptoms, and identification of the relationship between the patterns and intensities of symptoms and the clustered groups of DPN patients.

Materials and Methods: This multicenter study analyzed epidemiological data and sensory symptoms of 649 patients with DPN. Cluster analysis was carried out to identify subgroups of patients with characteristic symptom profiles. Factor analysis was carried out to investigate the symptom patterns of the clustered groups of DPN patients.

Results: Three clusters of patients with DPN were identified: severe symptoms with decreased quality of life (cluster 1, n = 119, 18.3%), predominantly insensate symptoms with relatively good quality of life (cluster 2, n = 318, 49.0%), and moderate pain intensity and decreased quality of life (cluster 3, n = 204, 31.4%). The frequency of symptoms on each item of the Michigan Neuropathy Screening Instrument questionnaire showed a similar distribution according to pain intensities along with the three clusters.

Conclusions: Our study supports the hypothesis that diversity in sensory symptoms exists in patients with DPN. Heterogeneity in DPN patients should be taken into account for a more stratified or individualized treatment approach. Based on a multicenter study, we identified three clusters of patients with DPN. Our research supports the hypothesis that diversity in sensory symptoms exists in patients with DPN. Heterogeneity in DPN patients should be taken into account for a more stratified or individualized treatment approach.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is one of the most common complications of diabetes, and is a significant cause of morbidity, mortality and diminished quality of life (QOL). A previous study reported that the prevalence of neuropathy in patients with type 2 diabetes was 33.5%[1], and the prevalence of painful DPN is 43.1% in patients with DPN in Korea[2]. DPN is a heterogeneous disease with widely varying pathology, suggesting differences in perception and recognition of sensory symptoms among patients. Although numerous pharmacological

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agents have been proven to be effective for patients with DPN, they are often ineffective and poorly tolerated. This is mainly due to difficulties in objectifying DNP symptoms in real practice as a result of its diverse symptoms or pain patterns and the subjective description of symptoms by patients. Therefore, a comprehensive approach for DPN management is necessary by classifying or subtyping patients according to subjective symptoms and objective test results. However, few studies have classified DPN patients according to subjective symptoms and identified the characteristics of the patient groups with similar symptoms.

The present study aimed to establish clustered groups of DPN patients with a composite of subjective symptoms, and clinical impacts on pain severity, sleep disturbance and QOL. Furthermore, our objective was to identify the relationship between the intensity levels of symptom patterns and clustered groups of DPN patients, and to evaluate the clinical significance of the currently used composite symptom score questionnaire.

METHODS

Study population and design

Patients with type 2 diabetes aged >19 years from 10 hospitals in Korea were included in this nationwide, multicenter, cross-sectional, observational study from January 2017 to May 2017. Inclusion criteria comprised of the following: (i) patients aged >19 years, classified as type 2 diabetes mellitus according to the 2017 American Diabetes Association guidelines or those who are being treated with diabetes medications, including insulin; (ii) patients who have access to medical records and data during the entire study period; and (iii) patients whose symptoms and QOL have been assessed or documented by several questionnaires. Exclusion criteria comprised of: (i) type 1 diabetes; (ii) causes of neuropathy other than diabetes (such as vitamin B_{12} deficiency, chronic alcohol abuse, drug-induced neuropathy); (iii) severe renal disease or liver disease; (iv) advanced malignancy, active infection; (v) cervical or lumbar spondylosis; and (vi) pregnancy, lactation or childbearing age without use of safe contraception. Participants filled in questionnaires about demographic data (such as age, sex, diabetes duration in years), alcohol, smoking, glycemic control and comorbidities. Clinical history of major cardiovascular events (ischemic heart disease, stroke and peripheral vascular disease) and diabetes complications (retinopathy, nephropathy) were collected from medical records. The list of medications for diabetes mellitus and DPN, and laboratory data obtained within 3 months before enrollment were collected from available sources.

Measures

Data regarding neuropathy symptoms, QOL and perception of overall health status of the patients were collected by trained healthcare workers using specific questionnaires in each hospital. All questionnaires were administered through face-to-face interview with healthcare professionals.

Symptoms of DPN were assessed using the Michigan Neuropathy Screening Instrument questionnaire (MNSI), a structured examination involving inspection of the feet and evaluation of fine touch (using a Semmes–Weinstein 5.07 10-g monofilament), vibration perception (using a 128-Hz tuning fork) and ankle reflexes. In addition, the diagnosis of neuropathic pain was made using another validated screening tool, the painDETECT questionnaire. It evaluates pain intensity, pain pattern and pain quality. By summing up the scores given in each domain, a final score between −1 and 38 can be achieved, with higher scores indicating more likely neuropathic pain[3]. Trained technicians examined the feet of participants for deformities, dry skin, callus and ulcerations. Also, muscle strength reflexes were tested using a hammer at the Achilles tendon on both ankles. Vibration sense tests were carried out on the interphalangeal joints of both great toes, and the monofilament test at the dorsum of both great toes[4].

Diagnosis of DPN

DPN was diagnosed based on the presence of either of the following criteria: (i) an MNSI score ≥3; or (ii) symptoms of pain, burning, tingling and/or loss of sensation, and abnormal or decreased/absent ankle reflexes; and (iii) at least one of the tests for neuropathy is positive. Such criteria are based on the recommendations of the Toronto Diabetic Neuropathy Expert Group[5]. Most of the patients in this study were classified as probable DPN.

Patient-reported outcomes measures

Quality of life was assessed using the following questionnaires: the modified Korean version of the Brief Pain Inventory-Short Form (BPI-SF) to evaluate the severity and interference of pain with daily functioning; the six-item Medical Outcomes Study (MOS) Sleep Scale to measure overall sleep quality using a sleep problem index; the Korean version of the EuroQoL Health (EQ-5D) with a standardized five-item measure of health profiles; and the visual analog scale (VAS) to assess pain intensity.

BPI-SF

The modified BPI-SF Korean version used in the present study contains a four-item pain severity scale (worst, least, average and current pain) and a seven-item pain interference scale (general activity, mood, walking ability, normal work, relationships with others, sleep and enjoyment of life). Each BPI item is equidistantly bounded on a 0–10 numeric rating scale, having 0 as 'no pain' and 10 as 'pain as bad as you can imagine' for severity, or 'does not interfere' to 'completely interferes' for interference[2].

Six-item MOS-Sleep scale

A six-item version of the MOS-Sleep Scale was used in the present study. The six-item summary scale includes trouble falling asleep (MOS-7), awaken during sleep (MOS-8), awaken short

of breath or with headache (MOS-5), enough sleep to feel rested (MOS-4), amount of sleep needed (MOS-12) and trouble staying awake during day (MOS-9). The MOS-Sleep Scale measured sleep quality and problems over the previous 4 weeks. The patients responded on a 6-point scale, ranging from 1 for 'all of the time' to 6 for 'none of the time'. To represent a measure of overall sleep quality, a sleep problem index was calculated as the sum of points of all six sleep items[2].

EQ-5D

The EQ-5D was used to measure the health-related QOL of the patients. The descriptive system consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three response levels indicating 'no problem' (or 1), 'some problems' (or 2) and 'severe problems' (or 3). The sum of the scores of the five domains were used as a single preference-based index score (EQ-5D index)[2].

VAS

The VAS is based on self-reported measures of symptoms that are a 10-cm line with anchor statements on the left (no pain) and right (extreme pain). The patients were asked to mark their current pain level on the line. Measurements from the "no pain" anchor point of the scale to the patients' marks are recorded in centimeters and are interpreted as their pain. The score 10 represents the worst imaginable health state and 0 represents the best imaginable health state.

Statistical analysis

K-means cluster analysis was carried out using the scores from the following scales: MNSI (total score, 13); BPI-SF (total score, 40); six-item MOS sleep scale (total score, 36), EQ-5D (total score, 15) and VAS score (total score, 10). Two analytical approaches were applied to improve the reliability of the best cluster solution for the number of clusters in the dataset. First, we used Ward's method and dendogram for hierarchical cluster analysis to estimate the number of likely clusters within the studied population. Next, we identified the cluster number to minimize the total within-cluster sum of squares by iterating for all of the clusters of the K-means algorithm[6]. Results from both algorithms indicated that the optimal number of clusters was three. We then examined each variable for differences among the clusters.

Exploratory factor analysis was carried out to identify neuropathic symptom patterns using 12 of 15 items of the MNSI self-administered questionnaire (three questions excluded: questions number 4, 8 and 9 were excluded due to low communality in factor analysis).

The varimax rotation method was used to simplify the interpretations of summary factors. The Kaiser–Mayer–Olkin measure and Bartlett's test of sphericity were carried out to find sampling adequacy. Factors with eigenvalues >1 were considered. The significance level for interpretation of factor loadings was 0.40. Cronbach's alpha was calculated to measure the reliability of these factors. Finally, the summary factors were classified according to the loaded symptoms on a specific factor. Data analyses were carried out using SPSS Statistics for Windows, version 26.0 (SPSS Inc., Chicago, IL, USA); significance was set at $P < 0.05$. Continuous variables were presented as the mean ± standard deviation, and categorical data as frequencies and percentages were compared between clusters by ANOVA tests, or χ^2 or Fisher's exact tests.

RESULTS

Pain location and treatment pattern of the study participants

In the questionnaire regarding pain areas described by patients, painful sensation in the front of feet was reported by 69.9% ($n = 448$) of the patients with DPN, followed by 40.9% ($n = 262$) in the back of feet, and approximately 20% in the anterior legs between the ankle and knee (Appendix A). Most of the DPN patients complained of bilateral pain mainly in the lower extremities. In the treatment pattern of patients with DPN, anticonvulsants, such as gabapentin and pregabalin, were the most commonly used medications for pain control, whereas alpha-lipoic acid was most commonly used as a potentially disease-modifying therapeutic drug, followed by gamma-linoleic acid (Appendix B).

Clinical characteristics of the three identified clusters

The vast majority of patients (98.7%) were included in the clusters resulting from the present cluster analysis. The three identified clusters (clusters 1, 2 and 3) included 119 (18.3%), 318 (49.0%) and 204 (31.4%) patients, respectively. Baseline characteristics per cluster are summarized in Table 1. Cluster 1 had a higher proportion of women, and patients had a higher body mass index and fasting blood glucose (FBG) and triglyceride compared with the patients in cluster 2 and 3. Patients in cluster 1 had longer duration of diabetes and diabetic neuropathy than those in cluster 2 or cluster 3. There were no significant differences among groups in any of the baseline parameters, such as age, glycated hemoglobin, low-density lipoprotein cholesterol, creatinine, systolic blood pressure and treatment pattern of diabetes.

According to foot examination findings, there were more patients with foot deformities in cluster 2 than cluster 1 and 3. There was no significant difference regarding patients with foot ulcers among the three groups. Cluster 1 had more patients with abnormal ankle reflexes and first toe vibration sensations than the other clusters. Also, cluster 1 had significantly more patients with abnormal findings in the 10-g monofilament test. The overall foot examination score was significantly higher for patients in cluster 1 (2.8 ± 2.4) than cluster 2 and 3 (1.5 ± 1.6, 1.9 ± 2.0, respectively, $P < 0.01$; Table 2).

Comparison of QOL according to symptom clusters

The BPI-SF measures, total score of the items for pain severity (worst, weakest, average, current pain) were numerically higher in cluster 1 than the other clusters. The score of each item for

Table 1 | Baseline characteristics of the three clusters

Variable	Total $n = 649$	Cluster 1 $n = 119$	Cluster 2 $n = 318$	Cluster 3 $n = 204$	*P*-value
Age (years)	65.8 ± 12.0	66.3 ± 12.2	65.6 ± 11.7	66.1 ± 12.1	0.087
Female, *n* (%)	355 (54.7)	82 (68.9)***	165 (51.9)	104 (51.0)	0.003
Duration of diabetes (years)	14.6 ± 9.5	16.6 ± 9.3**	15.1 ± 9.2	13.1 ± 9.7	0.003
Duration of DPN	6.1 ± 5.2	7.0 ± 4.3*	5.5 ± 4.3	6.6 ± 6.7	0.015
BMI	25.0 ± 3.8	26.2 ± 3.9***	25.0 ± 3.6	24.5 ± 4.0	0.001
Diabetes treatment					
Diet and exercise	5 (0.8)	1 (0.8)	2 (0.6)	2 (1.0)	0.110
OHA	339 (52.2)	56 (47.1)	165 (51.9)	112 (54.9)	
Insulin	40 (6.2)	13 (10.9)	14 (4.4)	11 (5.4)	
Insulin + OHA	250 (38.5)	44 (37.0)	133 (41.8)	73 (35.8)	
GLP-1 RA + OHA + insulin	15 (2.3)	5 (4.2)	4 (1.3)	6 (2.9)	
FBS	153.0 ± 60.8	174.1 ± 83.7***	144.2 ± 47.3	152.8 ± 58.6	<0.001
HbA1c	8.00 ± 1.72	8.0 ± 1.7	7.9 ± 1.5	8.1 ± 2.0	0.376
SBP	125.2 ± 15.00	125.4 ± 14.7	124.1 ± 14.4	126.8 ± 15.7	0.139
DBP	71.6 ± 11.3	72.8 ± 10.0*	70.4 ± 11.0	72.7 ± 12.2	0.031
Total cholesterol	155.6 ± 89.3	148.8 ± 40.4	154.8 ± 38.5	149.1 ± 35.7	0.216
Triglyceride	149.2 ± 84.0	164.2 ± 102.0**	151.5 ± 84.4	134.9 ± 67.8	0.009
HDL cholesterol	48.0 ± 14.0	46.6 ± 13.7	48.1 ± 14.6	48.9 ± 13.4	0.962
LDL cholesterol	79.5 ± 32.4	79.8 ± 33.7	79.2 ± 31.2	79.0 ± 33.3	0.383
Creatinine	1.2 ± 1.3	1.4 ± 1.4	1.1 ± 1.2	1.1 ± 1.3	0.164
History of diabetic foot ulcer	17 (2.6)	3 (2.5)	7 (2.2)	7 (3.4)	0.700
History of amputation of lower limb	12 (1.8)	2 (1.7)	4 (1.3)	6 (2.9)	0.363

Data are expressed as means ± standard deviation for continuous variables and frequency (%) for categorical variables. *$P < 0.05$ versus cluster 2. **$P < 0.05$ versus cluster 3. ***$P < 0.05$ versus cluster 2 and 3.

BMI, body mass index; DBP, diastolic blood pressure; DPN, diabetic peripheral neuropathy; FBS, fasting blood glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OHA, oral hypoglycemic agent(s); SBP, systolic blood pressure. [Correction added on September 15 2022, after first online publication: Values in "Total" and "Cluster 1" columns in Table 1 have been corrected.]

pain interference (general activity, mood, walking, normal work, relationship, sleep and enjoyment of life) was significantly higher in cluster 1 than the other clusters. The sleep problem index was significantly lower in cluster 1 than cluster 2 and 3. Therefore, patients in cluster 1 had more sleep disturbances than those of the patients in cluster 2 and 3. EQ-5D index and VAS were significantly higher in cluster 1 than the other clusters. Patients in cluster 2 had mild pain and relatively normal sleep patterns and QOL compared with patients in clusters 1 and 3 (Table 3).

Factor analysis

The Kaiser–Meyer–Olkin measure of sampling adequacy was 0.909, and Bartlett's test of sphericity was significant ($\chi^2 = 1{,}773.38$, $P < 0.01$) thus supporting the suitability of data for factor analysis. Five eigenvalues were >1, and this determined the five factors computed for all of the patients. Table 4 shows the five factors and their item loadings, with absolute values >0.4 identified. The results of factor analysis explained 78.37% of the total variance in the patients with DPN. Factor 1, capturing 18.35% of rotated variance, included number 14 ("Is the skin on your feet so dry that it cracks open?"), number 11 ("Are your symptoms worse at night?") and number 5 ("Do you ever have any prickling feelings in your legs or feet?"). Factor 2, capturing 16.84% of rotated variance, included number 10 ("Do you feel weak all over most of the time?") and number 13 ("Are you able to sense your feet when you walk?"). Factor 3, capturing 16.37% of rotated variance, included number 3 ("Are your feet too sensitive to touch?"), number 6 ("Does it hurt when the bed covers touch your skin?") and number 2 ("Do you ever have any burning pain in your legs and/or feet?"). Factor 4, capturing 16.16% of rotated variance, included number 15 ("Have you ever had an amputation?") and number 12 ("Do your legs hurt when you walk?"). Factor 5, capturing 10.66% of rotated variance, included number 1 ("Are your legs and/or feet numb?") and number 7 ("When you get into the bath or shower, are you able to tell the hot water from the cold water?"). The Cronbach's alpha of the factors 1, 2, 3, 4 and 5 were 0.785, 0.999, 0.653, 0.965 and 0.577, respectively.

Frequency of symptom patterns in each cluster

Participants' scores on the MNSI and painDETECT were significantly higher in cluster 1 than cluster 2 and 3 (Table 3). Figure 1 shows the frequencies of symptoms represented by

Table 2 | Characteristics of patient foot examination

Variable	Cluster 1 n = 119	Cluster 2 n = 318	Cluster 3 n = 204	P-value
Foot deformity (right)				
Absent	90 (75.6)	200 (63.3)	153 (75.4)	0.004
Present	29 (24.4)	116 (36.7)	50 (24.6)	
Foot deformity (left)				
Absent	92 (77.3)	205 (64.9)	160 (78.8)	0.001
Present	27 (22.7)	111 (35.1)	43 (21.1)	
Foot ulcer (right)				
Absent	113 (95.0)	311 (98.4)	195 (96.1)	0.103
Present	6 (5.0)	5 (1.6)	8 (3.9)	
Foot ulcer (left)				
Absent	114 (95.8)	313 (99.1)	196 (97.5)	0.088
Present	5 (4.2)	3 (0.9)	5 (2.5)	
Ankle reflex (right)				
Present	25 (25.3)	196 (66.9)	99 (52.9)	0.000
Reduced	61 (61.6)	90 (30.7)	79 (42.2)	
Absent	13 (13.1)	7 (2.4)	9 (4.8)	
Ankle reflex (left)				
Present	26 (26.3)	197 (67.2)	106 (56.7)	0.000
Reduced	62 (62.6)	87 (29.7)	72 (38.5)	
Absent	11 (11.1)	9 (3.1)	9 (4.8)	
Vibration in 1st toe (right)				
Normal	25 (25.3)	226 (77.1)	102 (54.5)	0.000
Impaired	44 (44.4)	53 (18.1)	55 (29.4)	
Absent	30 (30.3)	14 (4.8)	30 (16.0)	
Vibration in 1st toe (left)				
Normal	24 (24.2)	226 (77.1)	108 (57.8)	0.000
Impaired	45 (45.5)	54 (18.4)	48 (25.7)	
Absent	30 (30.3)	13 (4.4)	31 (16.6)	
10 g-Monofilament (right)				
Normal	44 (44.4)	242 (82.6)	137 (73.7)	0.000
Impaired	34 (34.3)	43 (14.7)	36 (19.3)	
Absent	21 (21.2)	8 (2.7)	14 (7.5)	
10 g-Monofilament (left)				
Normal	44 (44.4)	242 (82.9)	139 (74.7)	0.000
Impaired	35 (35.4)	42 (14.4)	32 (17.2)	
Absent	20 (20.2)	8 (2.7)	15 (8.1)	
Total score	2.8 ± 2.4***	1.5 ± 1.6	1.9 ± 2.0	0.000

Data are expressed as frequency (%) for categorical variables.
***P < 0.05 versus cluster 2 and 3.

results of factor analysis in the three cluster groups. Patients in cluster 1 reported high intensity on average for factor 3 and 4 dimensions (hypersensitivity, damaged), whereas patients in cluster 2 had high intensity for factor 2 and 5 dimensions (insensate, hypoesthesia). Patients in cluster 3 showed moderate intensity in all dimensions on average. Cluster 3 showed significantly more patients with reduced pain in response to symptomatic treatment in the past 24 h than other clusters (P = 0.01; Table 3). Based on cluster and factor analysis, the characteristics of the three clusters were defined as follows: cluster 1: high pain intensity, predominant positive symptoms of neuropathic pain, decreased QOL; cluster 2: predominant negative symptoms of neuropathic pain, relatively good QOL; and cluster 3: moderate pain intensity and moderate decreased QOL.

DISCUSSION

The present study showed that patients with DPN were clustered into three groups based on subjective neuropathic symptoms, and the clinical impacts of DPN on pain, sleep and QOL. Cluster 1 had a higher proportion of women, higher FBG, longer duration of diabetes and diabetic neuropathy than the other clusters, and were associated with the highest pain intensity and lowest QOL. Cluster 2 had a higher proportion of patients with negative neuropathic symptoms and showed relatively good QOL compared with other cluster patients. Patients in cluster 3 showed moderate pain intensity and QOL, and included a higher proportion of patients with reduced pain in response to symptomatic treatment than other clusters. These findings are consistent with previous studies in a large cohort of patients with DPN, in that patients presenting heterogeneous symptoms could be classified into several subgroups according to their neuropathic symptoms[7,8]. Regardless of cluster classification, patients mostly complained of pain in the lower extremities.

Approximately 30–50% of patients with diabetic neuropathy develop neuropathic pain, which can present as several different patterns[9]. The reason why some patients with diabetic neuropathy develop neuropathic pain whereas others do not is not fully understood. Neuropathic pain in DPN seems to be associated with female sex[10] and increasing age[11]. Metabolic problems including obesity[12], elevated glycated hemoglobin[13], type and duration of diabetes, and high alcohol intake, might increase the risk of developing neuropathic pain. Sensory phenotype and severity of neuropathic symptoms are also associated with DPN[14]. The present findings show that the patient cluster that complained of the most severe pain had a higher proportion of women, higher FBG and a longer duration of diabetes. This result is mostly consistent with the factors related to the development of neuropathic pain in DPN suggested in previous studies[15–18]. In particular, FBG was significantly higher in cluster 1 than other clusters. In general, DPN symptoms get worse at night. It is associated with an upregulated stress response during sleep by activation of sympathetic vascular control and poor subjective sleep quality. This result could be explained by high pain intensity playing a detrimental role in contributing to elevated FBG in cluster 1 than other clusters.

Regarding foot examinations, the proportion of patients who showed abnormal findings in ankle reflex, vibration sensation and response to 10-g monofilament in cluster 1 was higher than cluster 2 and 3. This observation is consistent with the finding of a large-scale study carried out in the UK that showed the characteristics of painful DPN in patients assessed with the neuropathy symptom score and neuropathy disability score[15]. However, patients in cluster 2 had a significantly higher

Table 3 | Clinical characteristics and clinical impacts of diabetic peripheral neuropathy on pain, sleep and quality of life in three clustered groups

Variable	Cluster 1 *n* = 119	Cluster 2 *n* = 318	Cluster 3 *n* = 204	*P*-value
PainDETECT score	17.9 ± 7.0*,**	5.2 ± 3.7**	9.5 ± 5.6	0.000
MNSI score	9.2 ± 1.8*,**	4.3 ± 1.7**	6.1 ± 2.1	0.000
BPI				
Worst	7.1 ± 1.9*,**	2.3 ± 1.9**	5.8 ± 2.1	0.000
Weakest	5.0 ± 2.8*,**	1.1 ± 1.0**	3.2 ± 2.3	0.000
Average	6.6 ± 2.0*,**	2.0 ± 1.5**	5.0 ± 1.7	0.000
Current	6.3 ± 2.3*,**	1.1 ± 1.1**	4.4 ± 2.1	0.000
BPI total	25.0 ± 7.5*,**	6.5 ± 4.0**	18.4 ± 6.5	0.000
Treatment response (in the past 24 h)	30.2 ± 25.3	26.1 ± 30.5**	34.0 ± 28.0	0.010
Pain interference items†				
General activity	5.5 ± 2.8*,**	0.8 ± 1.3**	2.8 ± 2.3	0.000
Mood	6.1 ± 2.3*,**	1.2 ± 1.7**	2.9 ± 2.7	0.000
Walking	5.6 ± 2.6*,**	0.9 ± 1.4**	2.5 ± 2.4	0.000
Normal work	5.3 ± 2.7*,**	0.7 ± 1.2**	2.5 ± 2.4	0.000
Relationship	4.3 ± 3.0*,**	0.5 ± 0.9**	1.2 ± 1.8	0.000
Sleep	6.2 ± 2.9*,**	0.9 ± 1.5**	2.7 ± 2.7	0.000
Enjoyment of life	5.0 ± 3.1*,**	0.8 ± 1.2**	2.3 ± 2.5	0.000
MOS sleep scale‡				
Enough sleep to feel rested	2.7 ± 1.58***	3.6 ± 1.7	3.7 ± 1.6	0.000
Awaken short of breath or with headache	5.3 ± 1.1***	5.7 ± 0.7	5.7 ± 0.9	0.000
Feel drowsy during day	3.0 ± 1.2***	4.2 ± 1.3	3.9 ± 1.3	0.000
Trouble falling asleep	3.0 ± 1.7***	4.9 ± 1.5	4.4 ± 1.6	0.000
Awaken during sleep	3.1 ± 1.5***	4.9 ± 1.4	4.7 ± 1.6	0.000
Trouble staying awake during day	3.7 ± 1.5***	4.9 ± 1.3	4.8 ± 1.3	0.000
Snoring during sleep	3.7 ± 1.8***	4.4 ± 1.7	4.2 ± 1.8	0.000
Sleep problem index	19.2 ± 5.4***	26.8 ± 5.2	25.8 ± 5.37	0.000
EQ-5D§				
Mobility				
Some	89 (74.8)	44 (13.8)	73 (35.8)	0.000
Severe	6 (5.0)	0 (0)	1 (0.5)	
Self-care				
Some	43 (36.1)	6 (1.9)	11 (5.4)	0.000
Severe	1 (0.8)	0 (0)	1 (0.5)	
Usual activity				
Some	77 (64.7)	11 (3.5)	53 (26.0)	0.000
Severe	7 (5.9)	0 (0)	0 (0)	
Pain/discomfort				
Some	81 (68.1)	170 (53.5)	169 (82.8)	0.000
Severe	38 (31.9)	2 (0.6)	16 (7.8)	
Anxiety/depression				
Some	72 (60.5)	32 (10.1)	76 (37.3)	0.000
Severe	21 (17.6)	0 (0)	0 (0)	
EQ-5D index§	9.3 ± 1.8*,**	5.8 ± 0.9**	7.1 ± 1.3	0.000
VAS¶	6.2 ± 2.1*,**	1.2 ± 1.1**	4.4 ± 1.7	0.000

Data are expressed as means ± standard deviation for continuous variables and frequency (%) for categorical variables. *$P < 0.05$ versus cluster 2. **$P < 0.05$ versus cluster 3. ***$P < 0.05$ versus cluster 2 and 3. †Items were derived from the Brief Pain Inventory-Short Form (BPI). A 0–10 numeric rating scale was anchored at 0 for "no pain" and 10 for "pain as bad as you can imagine." ‡Item response on a 6-point scale ranging from 1 for "all of the time" to 6 for "none of the time;" dimensions of sleep quantity, "get the amount of sleep you needed;" and sleep adequacy, "get enough sleep to feel rested upon waking in the morning" were calculated backwards. §Items were from three levels indicating "no problem" (or 1), "some problems" (or 2) and "severe problems" (or 3), and EuroQoL Health (EQ-5D) index was the sum of scores of five dimensions. ¶Values from 0 to 10, where 0 represents the worst imaginable health state and 10 represents the best imaginable health state.
MOS, Medical Outcomes Study; MNSI, Michigan Neuropathy Screening Instrument; VAS, visual analog scale.

Table 4 | Factor loadings for Michigan Neuropathy Screening Instrument questionnaire items

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Cronbach's alpha
Number 14. Is the skin on your feet so dry that it cracks open?	0.954†	0.081	0.074	0.042	0.142	0.785
Number 11. Are your symptoms worse at night?	0.954†	0.081	0.074	0.042	0.142	
Number 5. Do you ever have any prickling feelings in your legs or feet?	0.456†	0.007	0.411	0.170	−0.107	
Number 10. Do you feel weak all over most of the time?	0.078	0.984†	0.034	0.081	0.106	0.999
Number 13. Are you able to sense your feet when you walk?	0.078	0.984†	0.034	0.081	0.106	
Number 3. Are your feet too sensitive to touch?	0.015	0.044	0.801†	0.207	0.144	0.653
Number 6. Does it hurt when the bed covers touch your skin?	−0.003	−0.068	0.784†	0.145	0.231	
Number 2. Do you ever have any burning pain in your legs and/or feet?	0.308	0.134	0.639†	0.050	−0.173	
Number 15. Have you ever had an amputation?	0.068	0.063	0.189	0.953†	0.088	0.965
Number 12. Do your legs hurt when you walk?	0.087	0.106	0.212	0.941†	0.081	
Number 7. When you get into the tub or shower, are you able to tell the hot water from the cold water?	−0.027	0.173	0.188	−0.019	0.763†	0.577
Number 1. Are your legs and/or feet numb?	0.231	0.029	−0.039	0.177	0.710†	
Factor's name	Painful	Insensate	Hypersensitivity	Damaged	Hypoesthesia	
Eigenvalue	2.202	2.020	1.965	1.939	1.279	
% Of variance explained	18.352	16.836	16.371	16.155	10.656	
% Cumulative variance	18.352	35.189	51.560	67.715	78.370	

Kaiser-Meyer-Olkin Measure of Sampling Adequacy = 0.909. Bartlett's Test of Sphericity. Chi-Square χ^2 = 1773.382 (df = 21, ***P < 0.01). Extraction Method: The principal axis factor, Rotation Method: Varimax rotation. †Factor loadings ≥0.40.

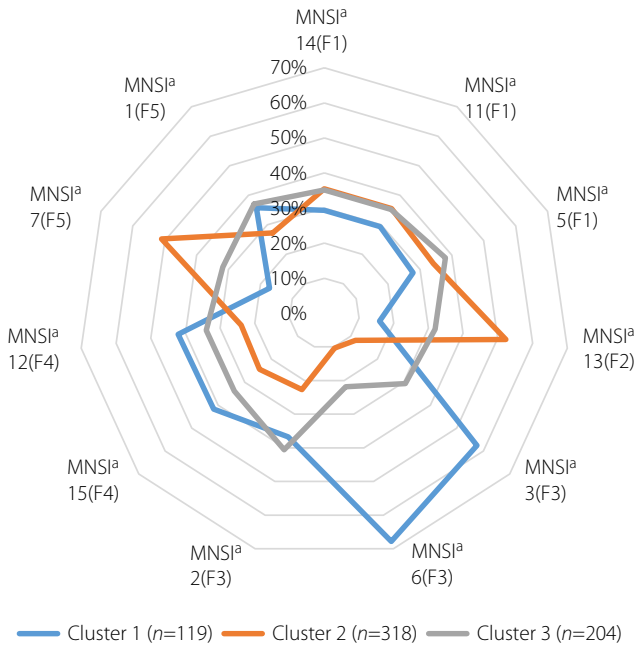

Figure 1 | Frequency (%) distribution of symptoms on the Michigan Neuropathy Screening Instrument questionnaire (MNSI) items among three clusters according to subgroups of symptom patterns. [a]P < 0.01. There was a significant difference across the clusters in all items.

proportion of patients with foot deformities. A substantial percentage of cluster 2 patients reported numbness or diminished sensation, and such negative symptoms might make it difficult to detect foot deformity and act as a risk factor for foot ulcers[19]. Diabetic neuropathy is well known as a risk factor for diabetic foot ulcers[20]. In the present study, the proportion of patients who had diabetic foot ulcers did not show a significant difference in each cluster. However, there is a possibility that the detection of changes in foot appearance might be delayed in patients with negative symptoms, thus more detailed foot observation and foot care education are needed in such patients[21].

The patients in cluster 1 showed higher scores than patients in cluster 2 and 3 in all items of the painDETECT score, followed by cluster 3 and 2, respectively. In addition, the BPI-SF measurements showed a similar pattern. In the MOS Sleep Scale, cluster 1 had significantly worse sleep quality than clusters 2 and 3, whereas clusters 2 and 3 did not show a significant difference in sleep quality. According to these findings, study participants with predominantly positive symptoms and high pain intensity had higher pain interference scores, and more frequently reported sleep disturbance than participants with moderate or mild pain intensity. Patient responses to items of the MOS Sleep Scale in the present study supported the potential impact of nocturnal exacerbations due to pain on the various dimensions of sleep. EQ-5D index showed a significant difference between each cluster, and it was demonstrated that the proportion of patients in cluster 1 who had problems with motor skills, self-management and daily activities was higher than the patients in clusters 2 and 3. In particular, the proportion of patients complaining of anxiety or depression was significantly higher in cluster 1 compared with other

clusters. Based on these findings, a detailed evaluation of psychological performance might be required for patients who complain of positive symptoms and a high level of pain intensity. In addition, this result suggests that DPN phenotype classification can be useful for the attention and appropriate treatment of specific symptoms of each subtype.

In the present study, pain intensity seems to be the most important factor in classifying DPN patients into three clusters. The frequency of distribution of each symptom on the MNSI had comparable tendencies regarding pain intensities. The patients in cluster 1 had prominent symptom intensities, and a higher number of patients with symptoms related to 'painful' and 'hypersensitivity'. Such data are consistent with those of previous studies showing the heterogeneity of neuropathic pain in patients whose pain was assessed with the painDETECT[22] or the MNSI[23], which showed that patients with varied symptoms might be classified into several phenotypes based on neuropathy-related symptom profiles.

Although the present study was based on a large multicenter study, it had several limitations. First, as the diagnosis for DPN was not assessed with more reliable and quantitative methods, such as nerve conduction study, relatively more patients with possible or probable DPN might have been included than patients with confirmed DPN. Second, the effect of the type or dose of concurrent neuropathic medication on various neuropathic symptoms could not be evaluated. The cross-sectional design of this study made it difficult to explore the causal relationships between various DPN symptoms and the effects of medication or associated sequelae. Despite such limitations, the results of this study suggest that sensory phenotypes of DPN might lead to more individualized and effective treatment of patients with DPN. Future studies are required to replicate the findings of the present study. Also, whether a specific treatment approach is systematically associated with the altered clinical characteristics of DPN over time is worth investigating.

In conclusion, the present cluster and factor analyses support the hypothesis that diversity in sensory symptoms exists in patients with DPN. We identified three cluster groups based on sensory profiles and effects of DPN on QOL. The identification of patient subtypes with distinct symptom characteristics at baseline is important and shows that heterogeneity in patients with DPN should be taken into account for a more stratified or individualized treatment approach.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: This study was approved by the local ethics committees of each participating hospital (CUH 2017-06-004).

Informed consent: All participants enrolled provided written informed consent to the procedures in accordance with the Declaration of Helsinki.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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APPENDIX A

THE LOCATION OF NEUROPATHIC PAIN USING ON SCHEMATIC DIAGRAM REPRESENTING THE FRONT AND BACK VIEWS OF THE WHOLE BODY REGION

Pain location	Patient (*n*)	Pain location	Patient (*n*)	Pain location	Patient (*n*)	Pain location	Patient (*n*)
1	448	17	3	39	84	61	8
2	448	18	1	40	85	62	4
3	82	19	79	41	16	63	2
4	92	20	72	42	16	64	2
5	91	21	13	43	20	65	0
6	88	22	8	44	20	66	14
7	39	23	9	45	10	67	23
8	34	24	3	46	7		
9	23	25	3	47	5		
10	21	26	2	48	5		
11	0	27	2	49	3		
12	0	28	1	50	1		
13	2	29	15	51	39		
14	3	30	10	52	36		
15	0	31	2	53	4		
16	0	32	2	54	4		
17	3	33	0	55	3		
18	1	34	2	56	2		
19	79	35	262	57	1		
20	72	36	261	58	1		
21	13	37	53	59	0		
22	8	38	55	60	0		

APPENDIX B

THE PROPORTION OF MEDICATION USE FOR DIABETIC PERIPHERAL NEUROPATHY IN THE ENTIRE PATIENTS

Medication	Total (n = 498)
Antidepressants	58 (11.6)
Anticonvulsants	330 (66.3)
Alpha-lipoic acid	264 (53.0)
Gamma-linoleic acid	149 (30.0)
Opioids	15 (3.0)
None	54 (10.8)

Data are expressed as frequency (%).