Numbness and paresthesia in bilateral toes and soles, and disproportional sweating restricted to face and trunk are suitable symptoms useful for the diagnosis of diabetic symmetric polyneuropathy

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ABSTRACT

Aims/Introduction: In order to diagnose diabetic symmetric polyneuropathy (DSPN) more simply and accurately, we identified symptoms that correlated with neurological functions and existed more frequently in diabetic than non-diabetic subjects.

Materials and Methods: The relationships between 10 symptoms (numbness or paresthesia in toe and sole, numbness in hand, pain in foot or hand, coldness in legs, painful leg cramp, dizziness on standing, sweating restricted to face/trunk and frequent constipation/diarrhea) and clinical background, defined as DSPN and cardiovascular autonomic neuropathy (CAN) by the criteria proposed in the statement of the American Diabetes Association, and seven quantitative nerve function data were evaluated in 593 diabetic patients in Wakayama Medical University Hospital (WMUH). Furthermore, the prevalence of various symptoms was examined by three questionnaires: a WMUH survey (999 diabetic outpatients), a Nationwide survey (1524 male diabetic outpatients under a primary-care physician) and a Control survey (501 non-diabetic subjects).

Results: Bilateral ‘numbness in toe and sole’, ‘paresthesia in toe and sole’, ‘pain in foot’ and ‘sweating restricted to face/trunk’ were significantly associated with diabetes duration, retinopathy, probable and confirmed DSPN, possible and advanced CAN, and all or six nerve functions. Questionnaire surveys clarified that symptoms that are not rare (>15%) and more frequent in diabetic than non-diabetic subjects were bilateral ‘numbness in toe and sole’, ‘paresthesia in toe and sole’, ‘coldness in legs’, ‘dizziness on standing’ and ‘sweating restricted to face/trunk’.

Conclusions: Therefore, bilateral ‘numbness in toe and sole’, ‘paresthesia in toe and sole’ and ‘sweating restricted to face/trunk’ are suitable symptoms useful for the diagnosis of DSPN.

KEY WORDS: Diabetic symmetric polyneuropathy, Specific symptoms, Prevalence

INTRODUCTION

Diabetic symmetric polyneuropathy (DSPN) is the most common disorder of heterogeneous diabetic neuropathies1. Early and accurate diagnosis of DSPN is necessary to prevent its progression through appropriate management. Although recognizing symptoms is important for the initial diagnosis of DSPN, many symptoms in diabetic patients might be caused by something other than DSPN. In the latest statement of the American Diabetes Association (ADA), minimal criteria for DSPN were proposed and diagnostic criteria for cardiovascular autonomic neuropathy (CAN) were also described in the report2. Symptoms that are suitable and useful for diagnosis of DSPN should contain the following five features: (i) a close relationship with DSPN and CAN defined in the latest ADA statement2; (ii) a significant association with duration of diabetes or diabetic retinopathy; (iii) a close relationship with objective quantitative nerve functions; (iv) a higher prevalence in diabetic patients than in non-diabetic subjects; and (v) common or not rare symptoms.

The aim of the present study was to identify the suitable symptoms for the diagnosis of DSPN that satisfied the aforementioned five conditions.

MATERIALS AND METHODS

Investigation 1. Characteristic Symptoms of DSPN Subjects and Their Symptoms

A total of 593 Japanese diabetic patients (372 male, 221 female) who received a medical interview, physical examination and multiple quantitative nerve function tests were studied. Of these,
Objective nerve functions were evaluated by the Achilles tendon reflex (ATR) in the knee-standing position and quantitative nerve function tests. Quantitative nerve function tests consist of seven tests: motor nerve and F-wave conduction velocity (MCV, FCV) in the ulnar nerve, sensory nerve conduction velocity and action potential (SCV, SNAP) in the median nerve, coefficient of variation of R-R intervals in electrocardiogram during deep breathing (CVdb), a fall in systolic blood pressure during head-up tilt (ΔBP) and 125 Hz quantitative vibratory perception threshold at the big toe (VPT125). Methods of neurological examination were described previously. We judged the nerve function data impaired as follows: MCV, FCV, SCV, SNAP, logarithmic CVdb and VPT125 were distributed normally, values exceeding the range of means ± 2 SD of the age-matched healthy subjects in our institution were judged as impaired. Abnormal ΔBP was defined by the American Autonomic Society criteria. Namely, a fall in systolic blood pressure of more than 20 mmHg and/or a fall in diastolic blood pressure of more than 10 mmHg were judged to be abnormal values.

We then diagnosed DSPN and CAN according to the modified criteria of the latest ADA statement. Subjective symptoms were excluded from the criteria, because the aim of the present study was to examine the reliability of symptoms. Probable DSPN was defined by abnormalities in both the ATR and VPT125. Confirmed DSPN was defined by one or two abnormalities in ATR and VPT125, and nerve conduction abnormalities, which were diagnosed by more than one impaired value in both the ulnar and median nerve. Possible CAN was defined by one or more impairment in CVdb and ΔBP. Advanced CAN was defined by impairment in both the CVdb and ΔBP.

### Association of Symptoms With Clinical Background, Defined Types of DSPN and CAN and Objective Nerve Functions

Relationships between the prevalence of symptoms and background data, such as age, duration, HbA1C, and retinopathy, and types of DSPN and CAN, including probable DAPN, confirmed DSPN, possible CAN and advanced CAN, were evaluated among the groups divided by these parameters. Actual data of seven nerve function tests were also compared between symptomatic and asymptomatic patients to clarify the relationship between subjective symptoms and objective nerve functions.

Data are expressed as percentage and means ± SD. Statistical analyses were carried out by chi-squared test for a 2 × 2 or 2 × 3 contingency table and ANOVA followed by Scheffe’s method as a post-hoc test using statistical software (Statview-J5.0; Hulinks, Tokyo, Japan).

### Investigation 2. Prevalence of Symptoms in Diabetic and Non-Diabetic Subjects

#### Research Design and Subjects

In order to clarify the prevalence of symptoms characteristic to DSPN, three self-administered questionnaires were carried out. The first survey was carried out on 999 outpatients (508 male, 467 female, 23 unknown) of the special diabetes clinic in WMUH (WMUH survey). The second survey was carried out as part of a nationwide survey that was mainly aimed at assessing the prevalence of erectile dysfunction; the sample analyzed for the present study was 1524 male diabetic outpatients under primary-care physicians (Nationwide survey). The third survey was taken by 501 non-diabetic individuals (311 male, 168 female, 22 unknown) who underwent corporate health screening examinations (Control survey). Male subjects in the Control survey were analyzed separately (Male Control survey).

#### Questionnaires

All participants who consented to the questionnaires did so voluntarily. All surveys were filled out at the distribution site of questionnaire forms and the completed forms were returned to researchers. The question items of the WMUH and Control surveys were the same as the aforementioned items in...
Table 1 | Prevalence of subjective symptoms and diminished Achilles tendon reflex in 593 diabetic patients by sex, age, duration, diabetic retinopathy and HbA_{1c}

|                          | Sex           | Age (years) | Duration (years) | Diabetic retinopathy | HbA_{1c} (%) |
|--------------------------|---------------|-------------|------------------|----------------------|--------------|
|                          | Female (n=221)| Male (n=372) |                  |                      |              |
| Age (years)              | 20-49         | 50-59       | 60-64            |                      |              |
| Female                   | n=166         | n=218       | n=209            |                      |              |
| Male                     | n=137         | n=216       | n=203            |                      |              |
| Duration (years)         | 0-5           | 6-14        | 15-19            |                      |              |
| Male                     | n=128         | n=164       | n=172            |                      |              |
| Female                   | n=119         | n=159       | n=168            |                      |              |

Subjective symptoms

Number in toe and sole

No symptom

Number in toe and sole

Unilateral

Bilateral

Paresthesia in toe and sole

No symptom

Unilateral

Bilateral

Pain in foot

No symptom

Unilateral

Bilateral

No symptom

Unilateral

Bilateral

Coldness in legs

No symptom

Symptomatic

Painful leg cramp

No symptom

Symptomatic

Dizziness on standing

No symptom

Symptomatic

Swelling restricted to face/neck

No symptom

Symptomatic

Frequent constipation/diarrhea

No symptom

Symptomatic

Objective neuro function test

Achilles tendon reflex

Normal

Decreased

Blatantly decreased

Blatantly decreased

No 0.05 analyzed by chi-squared test for 2 x 2 contingency table. *P < 0.05, **P < 0.01, ***P < 0.001 analyzed by chi-squared test for 2 x 3 contingency table. The value for HbA_{1c} (%) was estimated as a NGSP equivalent value (%) calculated by the formula HbA_{1c} (%) = HbA_{1c} (JDS) (%) + 0.4%.
### Table 2: Prevalence of subjective symptoms and diminished Achilles tendon reflex in 593 diabetic patients by defined diabetic symmetric polyneuropathy and cardiovascular autonomic neuropathy

|                           | Probable DSPN | Confirmed DSPN | Possible CAN | Advanced CAN |
|---------------------------|---------------|----------------|--------------|--------------|
|                           | No            | Yes            | No           | Yes          | No           | Yes          |
|                           | n = 367 (%)   | n = 214 (%)    | n = 377 (%)  | n = 162 (%)  | n = 270 (%)  | n = 297 (%)  |
| Subjective symptoms       |               |                |              |              |              |              |
| Numbness in toe and sole  |               |                |              |              |              |              |
| No symptom                | 289 (78.8)    | 108 (50.5)     | 287 (76.1)   | 76 (46.9)    | 209 (77.4)   | 174 (58.6)   |
| Unilateral                | 13 (3.5)      | 11 (5.1)       | 20 (5.3)     | 4 (2.5)      | 16 (5.9)     | 10 (3.4)     |
| Bilateral                 | 65 (17.7)     | 95 (44.4)**    | 70 (18.6)    | 82 (50.6)**  | 45 (16.7)    | 113 (38.0)** |
| Paresthesia in toe and sole|              |                |              |              |              |              |
| No symptom                | 324 (88.2)    | 146 (46.8)     | 331 (87.8)   | 105 (64.8)   | 239 (88.5)   | 221 (74.4)   |
| Unilateral                | 9 (2.5)       | 11 (5.1)       | 11 (2.9)     | 1 (0.6)      | 7 (2.6)      | 6 (2.0)      |
| Bilateral                 | 34 (9.3)      | 64 (29.9)**    | 35 (9.3)     | 56 (34.6)**  | 24 (8.9)     | 70 (23.6)**  |
| Numbness in hand          |               |                |              |              |              |              |
| No symptom                | 317 (86.3)    | 167 (50.3)     | 319 (84.6)   | 130 (80.3)   | 227 (84.1)   | 243 (81.8)   |
| Unilateral                | 19 (5.2)      | 10 (4.7)       | 20 (5.3)     | 7 (4.3)      | 13 (4.8)     | 15 (5.1)     |
| Bilateral                 | 31 (8.5)      | 37 (17.3)**    | 38 (10.1)    | 25 (15.4)    | 30 (11.1)    | 39 (13.1)    |
| Pain in foot              |               |                |              |              |              |              |
| No symptom                | 332 (90.5)    | 162 (57.5)     | 337 (89.3)   | 117 (72.2)   | 242 (89.0)   | 241 (81.1)   |
| Unilateral                | 7 (1.9)       | 5 (1.9)        | 7 (1.9)      | 5 (3.1)      | 4 (1.5)      | 8 (2.7)      |
| Bilateral                 | 28 (7.6)      | 47 (22.0)**    | 33 (88.8)    | 40 (24.7)**  | 24 (8.9)     | 48 (16.2)**  |
| Pain in hand              |               |                |              |              |              |              |
| No symptom                | 357 (97.3)    | 202 (54.4)     | 365 (96.8)   | 131 (84.5)   | 257 (95.2)   | 288 (87.0)   |
| Unilateral                | 6 (1.6)       | 1 (0.5)        | 5 (1.3)      | 1 (0.6)      | 6 (2.2)      | 1 (0.3)      |
| Bilateral                 | 4 (1.1)       | 11 (5.1)**     | 7 (1.9)      | 8 (4.9)*     | 7 (2.6)      | 8 (2.7)      |
| Coldness in legs          |               |                |              |              |              |              |
| No symptom                | 89/125 (71.2) | 28/46 (60.9)   | 67/93 (72.0) | 30/45 (66.7) | 49/67 (71.6) | 58/93 (62.4) |
| Symptomatic               | 36/125 (28.8) | 18/46 (39.1)   | 26/93 (28.0) | 15/45 (33.3) | 19/67 (28.4) | 35/93 (37.6) |
| Painful leg cramp         |               |                |              |              |              |              |
| No symptom                | 261/348 (75.0)| 132/194 (68.0)| 251/358 (70.1)| 113/146 (77.4)| 191/257 (74.3)| 198/275 (72.0)| 340/469 (72.5)| 50/68 (73.5)| 14/22 (63.6)| 8/22 (36.4) |
| Symptomatic               | 87/348 (25.0) | 62/194 (32.0)  | 107/358 (29.9)| 33/146 (22.6)| 66/257 (25.7)| 77/275 (28.0)| 129/469 (27.5)| 18/68 (26.5) |
| Dizziness on standing     |               |                |              |              |              |              |
| No symptom                | 293/366 (80.3)| 144/210 (86.6)| 301/357 (80.3)| 101/158 (63.9)| 222 (82.2)   | 205/291 (70.4)| 388/495 (78.4)| 47/74 (63.5)| 107/495 (21.6)| 27/74 (34.5)** |
| Symptomatic               | 72/366 (19.7) | 66/210 (34.1)**| 74/357 (21.7)| 57/158 (36.1)**| 48 (17.8)   | 86/291 (29.3)**| 403/493 (81.7)| 47/74 (63.5)| 27/74 (34.5)** |
| Sweating restricted to face/trunk | | | | | | | | |
| No symptom                | 301/366 (82.2)| 152/208 (73.1)| 311/376 (82.7)| 107/156 (68.6)| 227 (84.1)   | 218/291 (74.9)| 403/493 (81.7)| 47/74 (63.5)| 27/74 (34.5)** |
| Symptomatic               | 65/366 (17.8) | 56/208 (26.9)**| 65/376 (17.3)| 49/156 (31.4)**| 48 (15.9)   | 73/291 (25.1)**| 90/493 (18.3)| 27/74 (34.5)** |
| Frequent constipation/diarrhea | | | | | | | | |
| No symptom                | 335/366 (91.5)| 172/208 (82.7)| 339/376 (90.2)| 128/156 (82.1)| 247 (91.5)   | 247/291 (84.9)| 444/493 (90.1)| 58/74 (78.4)| 16/74 (21.6)** |
| Symptomatic               | 31/366 (8.5)  | 36/208 (17.3)**| 37/376 (9.8) | 28/156 (17.9)**| 23 (8.5)    | 44/291 (15.1)* | 49/493 (9.9) | 16/74 (21.6)** |

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Investigation 1. In the Nationwide survey, two questions, ‘Do you feel numbness in your hand? Numbness in hand’ and ‘Do you feel pain in your hand? Pain in hand’ were omitted, and sensory symptoms in the lower leg were limited to bilateral symptoms. Private information was not included for each question item.

Prevalence of the symptoms was compared between the WMUH and Nationwide, WMUC and Control, and Nationwide and Male control surveys. Statistical analyses were carried out by chi-squared-test for a $2 \times 2$ contingency table using statistical software (Statview-J5.0; Hulinks).

RESULTS

Investigation 1. Characteristic Symptoms of DSPN

The prevalence of symptoms and diminished ATR by sex, age, diabetes duration, diabetic retinopathy and HbA1c are shown in Table 1. Unilateral and bilateral symptoms were separately analyzed. Bilateral ‘numbness in toe and sole’, ‘paresthesia in toe and sole’, ‘pain in foot’ and ‘sweating restricted to face/trunk’ were significantly associated with duration and retinopathy. However, unilateral symptoms of these question items were not associated with duration and retinopathy. Bilaterally diminished ATR was significantly associated with age, duration and retinopathy. Although ‘painful leg cramp’ was significantly associated with duration, an increase in the prevalence in parallel with increasing duration was not observed.

Probable DSPN, confirmed DSPN, possible CAN and advanced CAN were observed at 36.8% (214/581), 30.1% (162/539), 52.4% (297/567) and 13.1% (75/574) in diabetic patients, respectively. The prevalence of symptoms and diminished ATR by probable DSPN, confirmed DSPN, possible CAN and advanced CAN are shown in Table 2. Bilateral ‘numbness in toe and sole’, ‘paresthesia in toe and sole’, ‘pain in foot’, ‘dizziness on standing’, ‘sweating restricted to face/trunk’ and ‘frequent constipation/diarrhea’ were significantly associated with all DSPN and CAN. Unilateral symptoms of sensory symptoms in the lower limb were not associated with DSPN and CAN at all.

Table 3 shows the data of seven quantitative nerve function tests in subdivided groups by symptoms and ATR. Data in the patients with bilateral ‘numbness in toe and sole’ were significantly deteriorated compared with those in asymptomatic patients in all nerve function tests. In contrast, data in the patients with unilateral ‘numbness in toe and sole’ were not significantly different from those in asymptomatic patients in all nerve function tests. Therefore, it was considered that not unilateral, but bilateral ‘numbness in toe and sole’ was significantly related to all nerve functions examined. In the same way, the relationships between other symptoms or ATR and nerve functions were examined. As a result, not unilateral, but bilateral ‘numbness in toe and sole’, ‘paresthesia in toe and sole’ and diminished ATR were significantly related to all nerve functions. Similarly, bilateral ‘pain in foot’ and ‘sweating restricted to face/trunk’ were significantly related to six of seven nerve functions. ‘Frequent constipation/diarrhea’, bilateral ‘pain in hand’ and ‘dizziness on standing’ were related to five, four and three
## Table 3 | Difference in objective quantitative nerve functions between the patients with and without subjective symptoms or diminished Achilles tendon reflex

| Symptom                              | MCV (ulnar n: m/s) | FCV (ulnar n: m/s) | SCV (median n: m/s) | SNAP (median n: μV) | CVdb (%) | ΔBP (mmHg) | VPT125 (dB) |
|--------------------------------------|--------------------|--------------------|---------------------|---------------------|----------|------------|-------------|
| **Numbness in toe and sole**         |                    |                    |                     |                     |          |            |             |
| No symptom                           | 381 51.6 5.0       | 340 594 47         | 355 577 53          | 337 209 13.1        | 386 42 28 | 386 99 15.0| 392 199 97  |
| Unilateral                           | 26 502 48          | 21 587 48          | 21 572 45           | 20 179 11.5         | 26 35 22  | 26 44 8.6  | 26 245 11.7|
| Bilateral                            | 154 477 5.6        | 142 557 5.4        | 139 540 60          | 140 141 14.0        | 160 28 20 | 157 161 17.4| 160 265 10.4|
| **Paresthesia in toe and sole**      |                    |                    |                     |                     |          |            |             |
| No symptom                           | 453 513 5.2        | 406 591 4.9        | 418 573 5.5         | 402 202 13.8        | 464 20 48  | 461 199 15.5| 468 207 103|
| Unilateral                           | 13 509 5.4         | 9 609 33           | 12 566 50           | 10 202 14.2         | 13 34 16  | 13 111 90  | 13 237 82  |
| Bilateral                            | 95 472 5.5         | 88 542 4.8         | 85 533 5.6          | 85 126 10.9         | 95 29 2.2 | 95 182 16.4| 97 274 9.6  |
| **Numbness in hand**                 | 0.023              | 0.006              | 0.12                | 0.18                | 0.07     | 0.0332     |             |
| No symptom                           | 470 505 5.3        | 418 584 5.0        | 432 569 5.4         | 415 193 13.6        | 475 38 27 | 472 104 15.5| 482 215 103|
| Unilateral                           | 27 515 6.1         | 25 590 6.2         | 24 557 6.6          | 25 159 12.1         | 27 39 33  | 28 84 140  | 28 222 103|
| Bilateral                            | 64 495 6.4         | 60 569 6.0         | 59 554 6.9          | 58 165 13.9         | 70 32 19  | 69 152 17.7| 68 250 10.8|
| **Pain in foot**                     |                    |                    |                     |                     |          |            |             |
| No symptom                           | 473 509 5.2        | 427 587 5.0        | 441 571 5.5         | 424 194 13.3        | 488 39 28 | 484 109 16.6| 498 210 103|
| Unilateral                           | 12 488 60          | 10 566 63          | 10 533 6.9          | 9 206 12.9          | 13 32 16  | 11 157 23.9| 12 267 8.9 |
| Bilateral                            | 71 479 6.2         | 66 561 6.0         | 64 540 6.5          | 65 145 14.8         | 71 29 18  | 74 136 15.3| 73 273 9.3  |
| **Pain in hand**                     |                    |                    |                     |                     |          |            |             |
| No symptom                           | 540 505 5.4        | 482 584 5.2        | 495 567 5.7         | 477 191 13.7        | 505 38 2.7 | 547 113 15.9| 557 217 10.5|
| Unilateral                           | 6 533 6.5          | 6 584 5.9          | 6 588 6.5           | 6 232 16.4          | 7 51 40  | 7 36 8.7  | 6 250 7.7  |
| Bilateral                            | 15 469 5.6         | 15 546 5.7         | 14 528 5.1          | 15 93 48            | 15 32 17  | 15 163 13.8| 15 269 69  |
| **Coldness in legs**                 | 0.017              | 0.020              | 0.024               | 0.0174             | 0.0148   | 0.026      |             |
| No symptom                           | 101 498 5.1        | 70 590 47          | 81 572 4.7          | 67 247 17.7         | 114 33 21 | 103 106 14.6| 111 191 98  |
| Symptomatic                          | 49 481 5.2         | 31 572 6.1         | 36 541 5.2          | 31 235 19.0         | 57 28 17  | 50 142 16.7| 51 199 11.3|
| Painful leg cramp                    | 0.025              | 0.056              | 0.39                | 0.032              | 0.34     | 0.05       |             |
| No symptom                           | 383 503 5.5        | 340 584 5.2        | 349 569 5.5         | 337 192 13.7        | 392 38 27 | 387 108 16.0| 394 212 10.4|
| Symptomatic                          | 143 509 5.3        | 130 587 5.2        | 134 564 5.8         | 128 204 13.8        | 147 37 26 | 143 123 15.6| 145 232 10.2|
| **Dizziness on standing**           | 0.07               | 0.11               | 0.0234              | 0.18                | 0.10     | 0.001      | 0.0186      |
| No symptom                           | 422 508 5.3        | 377 586 5.2        | 385 570 5.7         | 370 194 13.6        | 432 39 27 | 430 98 13.9| 435 213 100|
| Symptomatic                          | 133 488 5.4        | 120 577 5.3        | 124 557 5.4         | 122 175 13.5        | 135 34 26 | 133 158 20.3| 137 237 11.4|
| **Sweating restricted to face/trunk**|                    |                    |                     |                     |          |            |             |
| No symptom                           | 0.0008             | 0.0273             | 0.0062              | 0.0234             | 0.0173   | 0.0011     | 0.0146      |
| Symptomatic                          | 436 510 5.3        | 397 586 5.0        | 405 571 5.5         | 398 193 13.6        | 449 40 27 | 446 103 15.1| 451 213 100|
| Frequent constipation/diarrhea       | 0.0432             | 0.0188             | 0.006               | 0.041              | 0.0173   | 0.0011     | 0.0005      |

### Symptoms of diabetic polyneuropathy

- Numbness in toe and sole
- Paresthesia in toe and sole
- Numbness in hand
- Pain in foot
- Pain in hand
- Coldness in legs
- Dizziness on standing
- Sweating restricted to face/trunk
- Frequent constipation/diarrhea

### Analysis

- Significant differences were observed in various objective quantitative nerve functions between patients with and without specific subjective symptoms or diminished Achilles tendon reflex.

### Conclusion

The study highlights the correlation between objective nerve function measurements and subjective symptoms in patients with diabetic polyneuropathy, emphasizing the importance of comprehensive evaluations for accurate diagnosis and management.
Table 3 (Continued)

| Objective nerve function test | ATR (ulnar n: m/s) | FCV (ulnar n: m/s) | SCV (median n: m/s) | SNAP (median n: m/s) | CVdb (%)
|------------------------------|------------------|------------------|------------------|------------------|---------
| Normal                       | 167 ± 17.9       | 167 ± 18.1       | 169 ± 17.6       | 169 ± 17.6       | <0.0001 |
| Unilaterally decreased       | 145 ± 20.2       | 145 ± 20.2       | 146 ± 20.2       | 146 ± 20.2       | <0.0001 |
| Bilaterally decreased        | 365 ± 36.5       | 365 ± 36.5       | 365 ± 36.5       | 365 ± 36.5       | <0.0001 |

Table 4 shows the summarized relationships between symptoms, ATR and background characteristics, probable and confirmed DSPN, possible and advanced CAN, and seven nerve function data.

Discussion

In the present study, we examined which symptoms were suitable and helpful for diagnosis of DSPN among the 10

Investigation 2. Prevalence of Symptoms in Diabetic and Non-Diabetic Subjects

Table 5 shows the prevalence of symptoms in all participants of Investigation 1 and 2. The first row is the prevalence of symptoms in the out- and inpatients of WMUH who attended Investigation 1 and whose symptoms were obtained by interview.

In the comparison between Investigation 1 and the WMUH survey, the prevalence of unilateral ‘numbness in toe and sole’, unilateral ‘numbness in hand’, uni- and bilateral ‘pain in hand’, ‘painful leg cramp’ and ‘frequent constipation/diarrhea’ in Investigation 1 was significantly lower than that in the WMUH survey. In contrast, the prevalence of bilateral ‘numbness in toe and sole’ and bilateral ‘pain in foot’ in Investigation 1 was significantly higher than that in the WMUH survey.

In the comparison between the WMUH survey and the Nationwide survey, all symptoms except for ‘numbness in toe and sole’ in the former survey were significantly more frequent than those in the latter survey.

Then, we compared the prevalence of symptoms between diabetic and non-diabetic subjects. Although a significantly higher prevalence of outpatients from the diabetes clinic (WMUH survey) compared with the non-diabetic subjects (Control survey) were observed with all bilateral sensory symptoms and other symptomatic items, the prevalence of unilateral symptoms of ‘paresthesia in toe and sole’, ‘numbness in hand’ and ‘pain in foot’ was not different between the two surveys. The prevalence of symptoms in male diabetic outpatients under primary-care physicians (Nationwide survey) was compared with that in male non-diabetic subjects (Male Control survey). Though the prevalence of ‘painful leg cramp’ and ‘frequent constipation/diarrhea’ in the Nationwide survey was not significantly different from that in the Male Control survey, all other symptoms were more frequently observed in the Nationwide survey than the Male Control survey.

Relatively common symptoms (>15%) in the WMUH or Nationwide surveys were bilateral ‘numbness in toe and sole’, ‘paresthesia in toe and sole’, ‘coldness in legs’, ‘painful leg cramp’, ‘dizziness on standing’, ‘sweating restricted to face/trunk’ and ‘frequent constipation/diarrhea’.

DISCUSSION

In the present study, we examined which symptoms were suitable and helpful for diagnosis of DSPN among the 10
**Table 4** | Significant association of subjective symptoms and Achilles tendon reflex with clinical background characteristics, defined types of diabetic symmetric polyneuropathy and cardiovascular autonomic neuropathy by American Diabetes Association statement and quantitative nerve functions

| Clinical background | Defined types of DSPN and CAN | Quantitative nerve functions |
|---------------------|-------------------------------|------------------------------|
| Sex Age Duration Retinopathy HbA1c | DSPN DSPN CAN CAN DSPN DSPN CAN CAN DSPN DSPN CAN CAN | MCV FCV SCV SNAP CV-db ΔBP VPT125 |

| Subjective symptoms | Clinical background | Defined types of DSPN and CAN | Quantitative nerve functions |
|---------------------|---------------------|-------------------------------|------------------------------|
| Numbness in toes and soles | • | • | • |
| Paresthesia in toe and sole | • | • | • |
| Numbness in hands | • | • | • |
| Pain in feet | • | • | • |
| Pain in hands | • | • | • |
| Coldness in legs | • | • | • |
| Painful leg cramp | • | • | • |
| Dizziness on standing | • | • | • |
| Sweating restricted to face/trunk | • | • | • |
| Frequent constipation/diarrhea | • | • | • |
| Objective nerve function test | | | |
| Diminished Achilles tendon reflexes | • | • | • |

(•) Significant association was observed. ΔBP: a fall in systolic blood pressure during head-up tilt; CAN, cardiovascular autonomic neuropathy; CV-db, coefficient of variation of R-R intervals in electrocardiogram; DSPN, diabetic symmetric polyneuropathy; FCV, F wave conduction velocity; MCV, motor nerve conduction velocity; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential during deep breathing; VPT125; 125 Hz quantitative vibratory perception threshold at the big toe.

Symptomatic items. The main results were as follows: significant relationships with probable DSPN, confirmed DSPN, possible CAN and advanced CAN defined by the criteria in the latest ADA statement were observed in six symptoms – bilateral ‘numbness in toe and sole’, bilateral ‘paresthesia in toe and sole’, bilateral ‘pain in foot’, ‘dizziness on standing’, ‘sweating restricted to face/trunk’ and ‘frequent constipation/diarrhea’; significant associations with duration of diabetes and diabetic retinopathy were observed in four symptoms – bilateral ‘numbness in toe and sole’, bilateral ‘paresthesia in toe and sole’, bilateral ‘pain in foot’ and ‘sweating restricted to face/trunk’; significant relationships with all or six in seven objective quantitative nerve function tests were observed in four symptoms – bilateral ‘numbness in toe and sole’, bilateral ‘paresthesia in toe and sole’, bilateral ‘pain in foot’ and ‘sweating restricted to face/trunk’; a higher prevalence in diabetic patients than in non-diabetic subjects was observed in many symptoms other than unilateral sensory symptoms, ‘painful leg cramp’ and ‘frequent constipation/diarrhea’; common or not rare symptoms (<15%) were bilateral ‘numbness in toe and sole’, bilateral ‘paresthesia in toe and sole’, ‘coldness in legs’, ‘painful leg cramp’, ‘dizziness on standing’, ‘sweating restricted to face/trunk’ and ‘frequent constipation/diarrhea’.

From the first, second and third results, bilateral ‘numbness in toe and sole’, bilateral ‘paresthesia in toe and sole’, bilateral ‘pain in foot’ and ‘sweating restricted to face/trunk’ were thought to correlate with the severity of diabetic chronic complication and nerve function deterioration. The fourth and fifth results confirmed the higher prevalence of the aforementioned four symptoms in diabetic patients compared with non-diabetic subjects, and clarified that bilateral ‘pain in leg’ was not frequent (approximately 10%). Taking into account all of the aforementioned findings, we might be able to conclude that bilateral ‘numbness in toe and sole’, bilateral ‘paresthesia in toe and sole’ and ‘sweating restricted to face/trunk’ are suitable symptoms useful for the diagnosis of DSPN, whereas bilateral ‘pain in foot’ is well associated with the severity of nerve dysfunctions in diabetic patients and a clinically important symptom. We also confirmed a close relationship between diminished ATR and severity of diabetic chronic complication and deterioration in quantitative nerve function tests. These findings are clinically well known; nevertheless, the reports that examine the characteristic symptoms of DSPN based on multiple objective neurological tests are rare.

At present, we can use the minimal criteria for DSPN proposed in the ADA statement, in which probable DSPN seems to be most usable in daily medical practice. Probable DSPN was defined by the presence of a combination of symptoms and signs of neuropathy including any two or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes. Neuropathic symptoms were described as ‘sleep numbness’, pricking or stabbing, burning or aching pain in the toes, feet or legs. These are all bilateral sensory symptoms in the lower leg and corroborant with our findings.

The Michigan neuropathy screening instrument (MNSI) and abbreviated diagnostic criteria proposed by the Diabetic...
Table 5 | Prevalence of subjective symptoms in 593 diabetic out- and inpatients of Wakayama Medical University Hospital (WMUH) Investigation 1, 999 diabetic outpatients of WMUH survey, 1524 diabetic male outpatients in the Nationwide survey and 501 non-diabetic subjects in the Control survey (including 311 male non-diabetic subjects: Male Control survey)

| Symptom                        | Investigation 1 (Interviewed DM patients) | WMUH survey (DM patients) | Nationwide survey (Male DM patients) | Control survey (Non-DM subjects) | Male control survey (Male non-DM subjects) | Comparison between the surveys |
|--------------------------------|------------------------------------------|---------------------------|-------------------------------------|----------------------------------|------------------------------------------|-------------------------------|
|                                | n = 593 (%)                               | n = 965 (%)               | n = 1524 (%)                        | n = 500 (%)                      | n = 311 (%)                               |                               |
| Numbness in toe and sole       |                                          |                           |                                     |                                  |                                          |                               |
| No symptom                     | 402 (67.8)                               | 705 (73.1)                | 1206 (78.1)                         | 466/499 (93.8)                   | 292 (93.9)                                |                               |
| Unilateral                     | 26 (4.4)                                 | 78 (8.1)                  | ND                                  | 21/499 (4.2)                     | 13 (4.2)                                  | 0.0045                        |
| Bilateral                      | 165 (27.8)                               | 182 (18.8)                | 318 (20.9)                          | 10/499 (2.0)                     | 6 (1.9)                                   | <0.0001                       |
| Paresthesia in toe and sole    |                                          |                           |                                     |                                  |                                          |                               |
| No symptom                     | 480 (80.9)                               | 765/950 (80.5)            | 1330 (87.3)                         | 481/498 (96.6)                   | 297/309 (96.1)                           |                               |
| Unilateral                     | 13 (2.2)                                 | 32/950 (3.4)              | ND                                  | 6/498 (1.2)                      | 3/309 (1.0)                              | 0.18                          |
| Bilateral                      | 100 (16.9)                               | 153/950 (16.1)            | 193 (12.7)                          | 11/498 (2.2)                     | 9/309 (2.9)                              | 0.70                          |
| Numbness in hand               |                                          |                           |                                     |                                  |                                          |                               |
| No symptom                     | 494 (83.3)                               | 748/954 (78.4)            | ND                                  | 448 (89.6)                       | 275 (88.4)                               |                               |
| Unilateral                     | 29 (4.9)                                 | 88/954 (8.7)              | ND                                  | 31 (6.2)                        | 22 (7.1)                                 | 0.0049                        |
| Bilateral                      | 70 (11.8)                                | 123/954 (12.9)            | ND                                  | 21 (4.3)                        | 14 (4.5)                                 | 0.053                         |
| Pain in foot                   |                                          |                           |                                     |                                  |                                          |                               |
| No symptom                     | 505 (85.2)                               | 829/938 (88.4)            | 1363 (89.4)                         | 479/497 (96.4)                   | 297/309 (96.1)                           |                               |
| Unilateral                     | 13 (2.2)                                 | 36/938 (3.8)              | ND                                  | 13/497 (2.6)                     | 8/309 (2.6)                              | 0.007                         |
| Bilateral                      | 75 (12.6)                                | 75/938 (7.8)              | 161 (106)                           | 5/497 (1.0)                      | 4/309 (1.3)                              | 0.0017                        |
| Pain in hand                   |                                          |                           |                                     |                                  |                                          |                               |
| No symptom                     | 571 (96.3)                               | 856/951 (90.0)            | ND                                  | 484/497 (97.3)                   | 303/309 (98.0)                           |                               |
| Unilateral                     | 7 (1.2)                                  | 34/951 (3.6)              | ND                                  | 7/497 (1.4)                      | 3/309 (1.0)                              | 0.0044                        |
| Bilateral                      | 15 (2.5)                                 | 61/951 (6.4)              | ND                                  | 7/497 (1.4)                      | 3/309 (1.0)                              | 0.0006                        |
| Coldness in legs               |                                          |                           |                                     |                                  |                                          |                               |
| No symptom                     | 119/176 (67.6)                           | 652/951 (68.6)            | 1250 (82.0)                         | 420/499 (83.4)                   | 286/310 (82.3)                           |                               |
| Symptomatic                    | 57/176 (32.4)                            | 299/951 (31.4)            | 274 (180)                           | 79/499 (15.8)                    | 74/310 (23.7)                            |                              |
| Painful leg cramp              |                                          |                           |                                     |                                  |                                          |                               |
| No symptom                     | 403 (72.7)                               | 491/955 (51.4)            | 1130 (74.1)                         | 338/498 (67.9)                   | 218/309 (70.6)                           |                               |
| Symptomatic                    | 151 (27.3)                               | 464/955 (48.6)            | 394 (25.9)                          | 160/498 (32.1)                   | 91/309 (29.4)                            | <0.0001                      |
| Dizziness on standing         |                                          |                           |                                     |                                  |                                          |                               |
| No symptom                     | 447/585 (76.2)                           | 664/926 (71.7)            | 1277 (83.8)                         | 399/496 (80.4)                   | 273/308 (88.6)                           |                               |
| Symptomatic                    | 140/585 (23.8)                           | 262/936 (28.3)            | 247 (162)                           | 97/496 (19.6)                    | 35/308 (11.4)                            | 0.06                          |
| Sweating restricted to face/trunk|                                          |                           |                                     |                                  |                                          |                               |
| No symptom                     | 464/586 (79.2)                           | 713/925 (77.1)            | 1291 (84.7)                         | 451/495 (91.1)                   | 285/309 (92.2)                           |                               |
| Symptomatic                    | 122/586 (20.8)                           | 212/925 (22.9)            | 233 (15.3)                          | 44/495 (8.9)                     | 24/309 (7.8)                             | 0.34                          |
| Frequent constipation/diarrhea |                                          |                           |                                     |                                  |                                          |                               |
| No symptom                     | 518/586 (88.4)                           | 570/951 (59.9)            | 1262 (82.8)                         | 362/494 (73.3)                   | 244/309 (79.3)                           |                               |
| Symptomatic                    | 68/586 (11.6)                            | 381/951 (40.1)            | 262 (17.2)                          | 132/494 (26.7)                   | 65/309 (21.0)                            | <0.0001                      |

Prevalence of symptoms was analyzed by chi-squared test for 2 × 2 contingency table. Bilateral and unilateral symptoms was separately analyzed in the comparisons of Investigation 1 vs Wakayama Medical University Hospital (WMUH) survey and WMUH survey vs Control surveys. DM, diabetes mellitus; ND, no data; NE, not examined because of no data.

Statistically significant P-values (<0.05) were shown by boldfaced type.
Neuropathy Study Group in Japan (DNSGJ-criteria)\(^{10,11}\) are also used as convenient standards for DSPN screening. MNSI is used all over the world, and its survey sheet contains seven questions related to sensory disturbance in the legs. In the recent MNSI survey sheet distributed from the website of the Michigan Diabetes Research and Training Center, ‘legs and/or feet numb’, ‘burning and/or pricking pain in legs and/or feet’ and ‘decreased sensation of temperature’ were included, but ‘muscle cramp in legs and/or feet’ was excluded from neuropathic symptoms. Our data also showed that ‘painful leg cramp’ did not show a significant association with objective nerve functions.

Use of the DNSGJ-criteria is spreading in Japan. DSPN is usually diagnosed when two or more of three findings – sensory symptoms, bilaterally decreased ATR and bilaterally decreased vibratory sensation – are found. In the DNSGJ-criteria, bilateral numbness, pain, paresthesia or decreased sensation in toes and soles are used as symptoms considered to be as a result of DSPN; symptoms in only the upper extremities or only cold sense are excluded. These characteristics of the sensory symptoms of DSPN closely resemble with findings. The present study might provide supportive evidence to prove that the selection of sensory symptoms in the DNSGJ-criteria is warranted.

There are several problems or limitations in the present study. One problem is the accuracy of the response to the questions regarding neuropathic symptoms. We interviewed diabetic patients about symptoms in Investigation 1. The data are therefore thought to be more reliable than self-administered questionnaire surveys, because the interviewer explained the question in detail and might have excluded symptoms that were clearly of non-neuropathic origin. Although the degree of DSPN should be more severe in the patients of Investigation 1 than the patients who completed the surveys, the prevalence of unilateral sensory symptoms, ‘painful leg cramp’ and ‘frequent constipation/diarrhea’ were less frequent in patients of Investigation 1 than in those who completed the questionnaire surveys. We might have to take into account the possibility that the aforementioned symptoms are overestimated in a self-administered questionnaire survey.

Another problem is that the origin of the unilateral sensory symptoms is unknown. Because the nerve conduction and other quantitative nerve function data of the patients with unilateral sensory symptoms were not different from the data of asymptomatic patients, these symptoms seemed not to be caused by DSPN. The lower prevalence of unilateral symptoms in the interviewed patients than those in the patients who completed self-administered questionnaire surveys might suggest the possibility that these symptoms were caused by a disease other than peripheral neuropathy, such as inflammation or an orthopedic disorder. The interviewer might not have counted the unilateral symptom obviously caused by a disease other than DSPN as a positive response. Anyway, the unilateral sensory symptoms seem to not reflect the severity of DSPN.

We believe our data will contribute to devising simple, globally approved diagnostic criteria for DSPN.

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