SENSITIVITY OF FOUR SIMPLE METHODS TO SCREEN CHINESE PATIENTS FOR DIABETIC PERIPHERAL NEUROPATHY

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Abstract

Context. Diabetic peripheral neuropathy (DPN) is a common complication associated with long-term type 2 diabetes mellitus, although early diagnosis can improve prognosis.

Objective. Our objective was to develop a simple protocol for early diagnosis of DPN in Chinese type 2 diabetic patients.

Subjects and Methods. A total of 209 type 2 diabetic patients were included; these patients were categorized as symptomatic and asymptomatic group based on their symptoms. Clinical data of these patients were recorded and they were screened for DPN by vibration perception threshold test (VPT), 10-G nylon monofilament test, temperature identification, and the tendon reflex test.

Results. The total combined rate of patients who were tested positive for DPN with all four screening methods was 68.7%. Patients tested positive for DPN were significantly older and had a longer disease duration than those who were tested negative ($p < 0.01$); however, glycated hemoglobin levels, presence of hypertension, and gender did not differ significantly between them ($p > 0.05$). Among screening methods, the highest positive rate observed among patients screened with the VPT test was 63.64% as compared to other tests. The total positive rate for temperature discrimination, 10-G monofilament and tendon reflex test were 26.79%, 11.96 % and 17.22 % respectively. In asymptomatic group VPT showed the highest positive rate for DPN (48.41%).

Conclusions. The combination of four simple methods can improve the detection rate of DPN and identify subclinical cases. Abnormal vibration perception was the most common feature of DPN and it was associated with both disease duration and the age of the patient.

Key words: Diabetic peripheral neuropathy, vibration perception threshold, monofilament, temperature identification, tendon reflex, type 2 diabetes.

INTRODUCTION

China had the highest number of diabetes patients aged between 20-79 years worldwide in 2013, with approximately 98.4 million people suffering from the disease (1). The estimated prevalence of diabetes globally for all age-groups was 2.8 % in 2000 and is predicted to rise to 4.4 % by 2030 (2). Diabetes is a precursor for microangiopathies including peripheral neuropathy, which is a common chronic complication of diabetes and a factor leading to disability and amputation in diabetic patients.

A study based on 3359 people from Guangdong province, China, reported that 33 % of study participants tested positive for diabetic peripheral neuropathy (DPN) (3), which results in their being subject to a higher risk of morbidity. A cross-sectional hospital-based study conducted in 4 major Chinese cities (Shanghai, Chengdu, Beijing and Guangzhou) showed that 17.8 % of patients with diabetes mellitus type 2 have DPN (4). In contrast to China, the prevalence of DPN in Type 2 diabetic patients in the UK was far higher at 32.1 % (5) and the prevalence in the USA was as high as 49 % (6). The morbidity rate of DPN among Chinese, however, was predicted to be 46.6 % and culpable factors such as HbA1c, hyperlipidemia and retinopathy were significantly implicated (7).

The degree of pathological severity and clinical symptoms are often inconsistent, so early detection of diabetic peripheral neuropathy represents a great diagnostic challenge. Up to 50 % of DPN patients remain asymptomatic and so variation in clinical presentation causes considerable trouble when diagnosing it correctly (8). Considering that 82 % of diabetic patients with foot wounds have DPN (9),

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early detection and diagnosis of DPN is imperative in preventing the development and progression of complications. Early diagnosis will also lead to better prognostic value of the treatment.

There are different diagnostic modalities available to detect DPN (10), but the variable rate of detection is largely attributed to the method selection and also variance in performing these methods. Previous studies have demonstrated that 45 % of participants had DPN based on the Michigan Neuropathy Screening Instrument (MNSI) while the detection rate using the 128-Hz tuning fork and 10-g Semmes Weinstein monofilament (SWM) was nearly the same (32.6 % and 31.4 %, respectively). These rates are significantly higher than that for the ankle reflex test (23.1 %). However, the prevalence of DPN determined by these two tests combined (38.79 %) was higher than that through the single test (11). The point estimates of the positive likelihood ratios for vibration testing by the on-off method, vibration testing by the timed method, the SWME and superficial pain sensation test are 26.6, 18.5, 10.2, and 9.2, respectively. The point estimates of the negative likelihood ratios are 0.33, 0.51, 0.34, and 0.50, respectively (12).

Unlike a previous study which evaluated the differences in painful neuropathic pain in type II diabetic patients using Leeds Assessment of Neuropathic Symptoms and Signs Scale, thermal and vibratory Quantitative Sensory Testing and, EMG supported Diabetic Neuropathy Score (13), this study sought to determine the combinatorial sensitivity of four methods, vibration perception threshold test (VPT), temperature discrimination, sense of touch and tendon reflex, in the early detection of DPN among Chinese diabetes patients.

In addition, we also investigated the underlying risk factors attributed to DPN.

SUBJECTS AND METHODS

General information

A total of 209 type 2 diabetic patients were included in this study who attended the outpatient clinic of Endocrinology Department at Wuhan Union Hospital from October 2014 to March 2015. These patients were categorized as symptomatic (83 cases) or asymptomatic (126 cases) based on their peripheral neuropathy symptoms. Out of 209 type 2 diabetic patients, 123 were males and 86 were females. All these patients were aged between 20 and 82 years, with an average of 55.04 ± 12.29 years. The duration

of diabetes of these patients ranged from 0 to 30 years, with a mean of 5.9 ± 6.17 years. On the basis of lifestyle intervention, 115 patients were treated with oral antihyperglycemic agents (OHA), 59 patients with OHA plus insulin and remaining 35 patients with insulin alone. For the treatment of neuropathy, 72 patients received Mecobalamine (Takeda Pharmaceutical Co., Japan) alone, 82 patients received Epalrestat (Yangzhijiang Pharmaceutical Co., Jiangshu, China) alone, 31 patients received both drugs and remaining 24 patients received no drug. This study excluded patients exhibiting poor general condition, alcoholism, mental and psychological disorders, long-term sedative use, and central or peripheral neuropathy due to other causes. The research protocol has been approved by Ethics Committee of the Wuhan Union Hospital and it conforms to the provisions of the Declaration of Helsinki in 1964, all examinations were conducted after obtaining informed consent from participants.

METHODS

Sense of touch (10g monofilament test)

Three types of monofilaments (4.17, 5.07 and 6.10) are used in the diagnosis of DPN. The forces required to bend these monofilaments are 1, 10, and 75 g, respectively (14). Among them, the 5.07/10-g monofilament has been described as the best indicator for determining loss of protective sensation (15). Patients were supine with bare feet. With closed eyes, patients were asked to respond when monofilament pressure could be detected on each foot. A total of 20 examination sites were recorded, including the halluces, middle toe, little toe, head of the metatarsal bone, heel, and back of foot. The nylon filament was placed perpendicularly adjacent to the skin with enough pressure to bend the nylon about 1 cm. The contact time was 2 seconds. Each site was examined with a gap of 2-3 seconds between sites. Patient responses were considered abnormal if 8 or fewer points touched per side were detected.

Sense of vibration

We used a biothesiometer (Eisai Pharmaceutical Co. Ltd, Japan) to quantitatively measure the vibration perception threshold (VPT). Patients rested for 10 min in the supine position on an examination bed to completely relax the body. The instrument amplitude was set to zero, then the operator adjusted the vibration pressure to a proper value and placed the vibration stimulation equipment (about 450 grams) vertically on

the halluces (2.5 cm from the front of the toenail) while preventing the probe from moving over the surface of the skin. We progressively increased the vibration amplitude from zero to a barely detectable vibration amplitude (threshold) at which the patient was just able to feel the vibration sensation. It has been proven that the best cut-off value is 10.54 V (16). Thresholds between 0 and 10 volts were considered normal, 11 to 15 volts mildly abnormal, 15 to 25 volts moderately abnormal, and > 25 volts severely abnormal.

Temperature discrimination

We used a thermesthesiometer (Eisai Pharmaceutical Co. Ltd, Japan) with a cool metal probe on one end and a warm polyester probe on the other. Patients were instructed to lie back, close their eyes and relax, and then were asked to determine if the end of the instrument touched to the back of their feet felt warm or cool. An inability to distinguish cool from warm was considered an abnormal test result.

Tendon reflex

Patients were instructed to lie on their backs and stay relaxed. A reflex hammer was used to gently tap the quadriceps femoris tendon (knee reflex) and calcaneus tendon (ankle reflex) with moderate strength. The resulting muscle contractions were assessed as either present or absent and then compared.

Examination conditions

All examinations were conducted by specialists in a suitable and consistent environment under ideal temperature to prevent errors.

Statistical analyses

We used SPSS for Windows (version 10.0, SPSS, Inc., Chicago, IL, USA) to process the data. Numerical variables were analyzed using Student's t

test and presented as a value $\pm$ standard deviation, while categorical variables were analyzed using Pearson's chi-square test.

RESULTS

Comparison of screening methods

Of 209 patients with diabetes, the total combined DPN positive rate of the four methods was 68.70 % (144 cases). Of these, 91.57 % (77 cases) and 53.17 % (67 cases) of patients in the symptomatic and asymptomatic groups, respectively, tested positive for DPN. The VPT positive rate alone was the highest with 63.64 % (133 cases). In the symptomatic group, 75.91% (63 cases) of patients showed moderate to severe abnormalities based on their VPT result (Tables 1 and 2).

Correlation between individual screening results and duration of diabetes

Of the 209 cases, 63 had a clinical duration of less than 1 year, 47 had clinical duration of 1-5 years, 44 of 5-10 years, and 55 had clinical duration of more than 10 years. The rate of abnormal findings among VPT, temperature discrimination, and tendon reflex gradually increased with duration of diabetes. Differences between groups according to duration of diabetes were statistically significant ($P < 0.05$), but differences in sense of touch were not significant ($P > 0.05$) (Table 3).

Analysis of factors related to DPN

Age and duration of diabetes differed significantly between the symptomatic and asymptomatic groups ($P < 0.01$). However, as shown in Table 4, glycosylated hemoglobin level (HbA1c level), the presence of hypertension, and gender did not differ significantly between groups ($P > 0.05$).

Table 1. The results of the four screening methods

	Total Positive Rate	Symptomatic Group (N=83)	Asymptomatic Group (N=126)
VPT	133 (63.64 %)	72 (86.75 %)	61 (48.41 %)
Temperature Discrimination	56 (26.79 %)	34 (40.96 %)	22 (17.46 %)
10-G Monofilament	25 (11.96 %)	14 (16.87 %)	11 (8.73 %)
Tendon Reflex	36 (17.22 %)	22 (26.51 %)	14 (11.11 %)
Total Screening Abnormality	144 (68.70 %)	77 (91.57 %)	67 (53.17 %)

Table 2. Quantitative analysis of the vibration perception threshold test screening results

Total Cases	Mild Abnormalities	Moderate Abnormalities	Severe Abnormalities	Negative Results
Symptomatic Group (83 Cases)	9 (10.84 %)	26 (31.33 %)	37 (44.58 %)	11 (13.25 %)
Asymptomatic Group (126 Cases)	17 (13.49 %)	22 (17.46 %)	22 (17.46 %)	66 (52.38 %)

Table 3. Correlation between individual screening results and duration of diabetes

Duration	Total Cases	VPT Abnormality	Temperature Discrimination Abnormality	10-G Monofilament Test	Tendon Reflex
<1 Year	63	34 (53.97 %)	12 (19.05 %)	6 (9.52 %)	10 (15.87 %)
1-5	47	24 (51.06 %)	8 (17.02 %)	8 (17.02 %)	5 (10.64 %)
5-10	44	31(70.45 %)	16 (36.36 %)	5 (11.36 %)	9 (20.45 %)
>10	55	43 (78.18 %)	20 (36.36 %)	6 (10.91 %)	13 (23.64 %)
P Value		<0.05	<0.05	>0.05	<0.05

Table 4. Analysis of factors related to diabetic peripheral neuropathy

Variables	Positive Group	Negative Group	P Value
Total Cases	144	65	
Gender (M/F)	81/53	42/23	>0.05
Age (Years)	58.2±10.81	46.98±13.64	<0.01
Duration (Year)	6.68±6.50	4.10±5.02	<0.01
HbA1c (%)	9.10±2.60	8.48±2.73	>0.05
Hypertension	65/79	23/42	>0.05

DISCUSSION

Peripheral neuropathy is the most common chronic complication of diabetes and contributes to increased morbidity and mortality. Early diagnosis and timely intervention can, however, minimize its impact. Until now, there has been no effective screening method for the early stages nor has there been universal and easily recognized DPN diagnostic standards. Nerve tissue biopsies can provide objective evidence of the nature and severity of damaged nerves, but are time consuming, cause trauma, and also carry the risk of severe side effects. Patients are therefore reluctant to undergo the procedure; thus, it is currently used only in experiments. Nerve conduction velocity studies played an important role in screening in the past (17), but they are expensive, time consuming, and painful, which have limited their widespread use. Ultimately, there is a compelling need for a screening method that better suits the needs of the huge number of diabetes patients in our country.

The VPT test focuses on quantitative detection of the minimum detectable vibration level and has been widely used for DPN screening in both developed countries (18) and in China. The 10-g monofilament test together with the temperature test and tendon reflex examination are widely used to examine superficial and deep feeling and physiological reflexes, which can quickly reveal abnormalities in sense of touch, temperature discrimination, and physiological reflexes (19). Since a nervous system lesion caused by diabetes may affect more than one neuron system, a combination of the four examination methods used in this study may be useful for DPN screening. To our knowledge, no such combination test has yet been reported in Chinese

population. In this study, we combined the VPT, 10-g monofilament test, temperature discrimination, and tendon reflex examinations to test superficial and deep feeling and tendon reflex, which illustrate the characteristics commonly affected in diabetic patients. The present study was designed to identify common neuropathies and their associated factors in order to provide evidence of the utility of these tests for early diagnosis, prevention, and treatment of DPN.

In this study, the total DPN screening positive rate was 68.7 %, while previously reported prevalence rates are 10 % to 50 % (20, 21). The positive rates in the symptomatic and asymptomatic groups were 91.57 % and 53.17 %, respectively, which are consistent with previous studies (22). These findings suggest that many patients had peripheral nerve damage before the onset of clinical symptoms and that this screening can detect subclinical lesions. Therefore, the combination of these four methods can be useful for the detection of early stage DPN. Early detection of DPN during the asymptomatic phase is very important because these patients can develop foot ulcers despite the absence of previously observed signs of disease. More than 80 % of amputations follow foot ulcer or injury (23).

Generally, diabetes-related nervous system impairment may start with myelinated and non-myelinated nerve fibers resulting in reduced pain and temperature discrimination, in conjunction with abnormalities in the sympathetic nerve fibers leading to local congestion, followed by a loss of sense of vibration due to damage to large myelinated fibers. We found a VPT positive rate of 63.64 %, much higher than that of temperature discrimination, sense of touch, and tendon reflex, which suggests that vibration impairment may occur before the damage to other

sensory systems. This positivity difference may also be due to technical and sensitivity differences between tests. For example, VPT can quantitatively analyze the deep sensation and hence it is more sensitive compared to the other 3 detection methods. However, elucidation of the specific mechanism involved requires further study.

We found that VPT appears to be the most sensitive of these tests for the detection of DPN and so can be used for early detection of peripheral neuropathy. These findings are consistent with previous studies that have proven that VPT is a very important diagnostic method for subclinical neuropathy and it is a predictor for foot injuries (24). On the other hand, according to other research, the prevalence of DPN diagnosed with VPT was 34.9 % and compared with VPT, ankle reflex was the most sensitive (90.7 %) but least specific (37.3 %). The tuning fork and monofilament tests respectively had lower sensitivity (62.5 % and 62.8 %) but better specificity (95.3 % and 92.9 %) and accuracy (78.9 % and 77.9 %) (25). We also observed 7 cases with no obvious abnormalities in all four screening tests among 83 patients who felt pain and/or experienced the “ants climbing” or needling sensation. This was probably attributed to the irritation caused by damage or ischemic spasm of small nerve fibers can quickly recover, making them difficult to be detected with these screening methods. However, the specific reason remains unknown.

Poor glycemic control and modifiable cardiovascular risk factors such as raised triglyceride, smoking, hypertension and body mass index are associated with neuropathy (26). In diabetes, increased blood glucose causes the enhanced activation of the polyol pathway, oxidative stress and the non-enzymatic glycation (27), these factors underline the development of neuropathy in diabetes. The clinical studies like the United Kingdom Prospective Diabetes Study (UKPDS) post-trial and the Diabetes Control and Complications Trial (DCCT)-Epidemiology of Diabetes Interventions and Complications (EDIC) (DCCT-EDIC) trial have demonstrated that early diabetes control resulted in sustained benefits of fewer complications, suggesting the presence of a metabolic memory effect (28, 29). These findings explain why our study did not observe significant difference in HbA1c, gender, or hypertension between asymptomatic and symptomatic patients. While this study did find that DPN positivity increased with age, this association was probably attributable to two reasons. First, Pacinian corpuscles, which sense vibration, may degenerate and lose sensitivity with age.

Second, most elderly patients in this study had a long duration of diabetes, which also increased the positivity rate. However, the exact correlations and mechanisms need to be further studied.

In conclusion, the four screening methods evaluated in this study not only identify abnormalities of the peripheral nervous system in symptomatic patients, but also reveal subclinical lesions in asymptomatic subjects. Since these tests are simple, practical, economical, and painless, a combination test is suitable for widespread screening for early stage DPN. However, because abnormal vibration perception is the most easily identified feature of early stage DPN, clinicians should attach great importance of VPT results. Early diagnosis of DPN allows timely intervention to prevent severe complications.

Conflict of interest

The authors declare no potential conflict of interest.

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Disclosure

The authors do not have any financial interests related to the material in the manuscript to disclose. The funding organizations are public institutions and had no role in the design and conduct of the study; collection, management, and analysis of the data; or preparation, review, and approval of the manuscript.

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