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The Diagnostic Value of Neuropathy Symptom and Change Score, Neuropathy Impairment Score and Michigan Neuropathy Screening Instrument for Diabetic Peripheral Neuropathy

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Key Words
Diabetes mellitus · Diabetic peripheral neuropathy · Neuropathy symptom and change · Neuropathy impairment score · Michigan neuropathy screening instrument

Abstract
Aims: This study aims to evaluate the diagnostic capabilities of neuropathy symptom and change (NSC) score, neuropathy impairment score (NIS) and Michigan neuropathy screening instrument (MNSI) in diagnosing diabetic peripheral neuropathy (DPN). ***Methods:*** A total of 131 patients with type II diabetes received NSC, NIS and MNSI scoring systems. Electromyography/nerve conduction velocity (EMG/NCV) test was taken as gold standard. Correlations between EMG/NCV test and the 3 scorings, and their sensitivity, specificity, positive and negative predictive values, accuracy and kappa (κ) value were analyzed. ***Results:*** The prevalence of DPN was 43.5% according to EMG/NCV findings. EMG/NCV test was significantly positive correlated with all the 3 scorings, highest with NIS scoring ($r = 0.653$, $p < 0.001$). Compared with EMG/NCV test, NSC score was most sensitive (85.96%) but least specific (77.03%); NIS score had lower sensitivity (59.65%) but best specificity (98.65%) and accuracy (81.68%). Both had high concordance with EMG/NCV test ($\kappa = 0.61$). Sensitivity, specificity and accuracy of MNSI were highest (70.18, 98.65 and 80.15%) at the cutoff values of >1.0, >2.5 and >1.5, respectively ($\kappa = 0.58$). ***Conclusions:*** Both NSC and NIS were accurate and reliable diagnostic methods for DPN. The combined application of NSC and NIS was recommended in DPN diagnosis.

Introduction

As one of the common complications of diabetes mellitus (DM), diabetic peripheral neuropathy (DPN) is an important reason for foot ulceration, as well as morbidity and mortality [1, 2]. It occurs in patients who have type I or type II DM [3]. Previous researches have reported that the worldwide prevalence of DPN in diabetics was as high as up to 54% [4]. Hence, screening and early diagnosis of DPN would provide a crucial opportunity for these patients with DM to improve foot care promptly in case of the onset of significant morbidity.

Nerve conduction study (NCS) is considered a reference standard in diagnosing DPN, because of the advantages of objectivity, sensitivity and reliability [5, 6]. It consists of both nerve conduction velocity (NCV) and needle electromyogram (EMG) [7]. However, NCS is often as-

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sociated with time consumption, inconvenience and high cost. Recently, several clinical scoring systems, such as neuropathy symptom and change (NSC) score, neuropathy impairment score (NIS) and Michigan neuropathy screening instrument (MNSI), have been developed as diagnostic methods to screen the presence and severity of DPN [8–11]. Though NSC, NIS or MNSI have been studied for their reliability and accuracy elsewhere [12–14], most of these studies did not refer to all the 3 clinical scoring systems as well as their correlation with EMG/NCV test.

This study was designed to evaluate the diagnostic values of NSC, NIS and MNSI by assessing the performance characteristics of the 3 clinical scoring systems (sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs), accuracy, kappa (κ) value) with EMG/NCV test as gold standard. The correlations of the 3 clinical scoring systems with EMG/NCV test were also evaluated.

Patients and Methods

Patients

This study was conducted in the Community Health Services center of Jing'an area, Shanghai, China. Patients with type II DM on basis of the American Diabetes Association criteria [15] were eligible for inclusion, and a total of 131 patients who had a visit from January 2013 to May 2014 were recruited consecutively. Cerebrovascular disease, lumbar spondylosis, toxic peripheral neuritis, infective polyneuritis, chronic alcoholism, vasculitis, systemic lupus erythematosus, uremia, foot ulcer, infection and edema were all excluded from this study according to patient history, physical examination and laboratory findings.

The study was approved by Regional Ethics Committee, and informed consent was obtained from all parents.

Clinical Data and Laboratory Test

The clinical profile regarding age, gender and mean duration of DM were collected. These patients were also evaluated for blood fasting sugar by glucose oxidase method (GOX0560, Shanghai Jingyuan Medical Appliances Co., Ltd., China), total cholesterol by CHOD-PAP method (CH00560, Shanghai Jingyuan Medical Appliances Co., Ltd., China), triacylglycerol by GPO-PAP method (TGP0560, Shanghai Jingyuan Medical Appliances Co., Ltd., China), high density lipoprotein by the International Reagents Corporation method (21200AMZ00404000, DaiichiPure Chemicals Co., Ltd., Tokyo, Japan), glycosylated hemoglobin Alc by high performance liquid chromatography (HLC-723G7, Tosoh Co., Tokyo, Japan).

Neurological Examination and Symptom Assessment

All the patients underwent the 3 simple tests: NSC, NIS and MNSI scoring (table 1). The neurological examination and symptom assessment was conducted by 2 assistant physicians, and a physician administered these produces. The NSC [16] consists of questions regarding the type of pain or slight illness, location and time of symptoms, arousal from the sleep and maneuvers that relieved symptoms. An NSC of 3–4 points was considered a mild neuropathy symptom, 5–6 points as medium neuropathy symptom and 7–9 points as severe neuropathy symptom. The NIS [17–19] includes the ankle reflex, vibration, pin-prick and temperature (cold tuning fork) sensations at the great toes. Bilateral lower limbs were independently evaluated with a maximum score up to 10 points. Patient with an NIS of 3–5 points was considered with mild neuropathy signs, 6–8 points as medium neuropathy signs and 9–10 points as severe neuropathy signs. Then DPN was diagnosed with an NIS score of ≥6, or an NIS score of 3–5 associated with an NSC score of ≥5. The MNSI [14] consisted of 2 parts: appearance

Table 1. Scores assigned during the 3 simple test procedures

Tests	Description
NSC score	
Types of pain or slight illness?	0 = absent, 1 = fatigue, cramping or aching, 2 = numbness, burning or prickling sensations
Location of the above symptoms?	0 = elsewhere, 1 = calves, 2 = feet
Time of the above symptoms?	0 = daytime alone, 1 = both day and night, 2 = nocturnal exacerbation
Arousal from the sleep?	0 = absent, 1 = present
Maneuvers that relieved symptoms?	0 = sitting or lying down, 1 = standing, 2 = walking
NIS[a]	
Ankle reflex	0 = normal, 1 = present with reinforcement, 2 = absent
Vibration sensation (128-Hz tuning fork) at the great toe	0 = present, 1 = reduced/absent
Pin-prick sensation at the great toe	0 = present, 1 = reduced/absent
Temperature sensation (cold tuning fork) at the great toe	0 = present, 1 = reduced/absent
MNSI[b]	
Appearance of feet[c]	0 = normal, 1 = abnormal
Ulceration	0 = present, 1 = absent
Ankle reflexes	0 = present, 0.5 = present with reinforcement, 1 = absent
Vibration perception (128-Hz tuning fork) at the great toe	0 = present, 0.5 = reduced, 1 = absent

[a] Maximum total score for each foot is 5 and for both feet is 10.
[b] Maximum total score for each foot is 4 and for both feet is 8.
[c] Includes deformity, dry skin, callus, infection or fissures.

of feet (deformity, dry skin, callus, infection or fissures) and examination of foot ulceration, ankle reflex and vibration perception with a 128 Hz tuning fork. Evaluation of each parameter was made at both sides with a maximum score of 8 points. The diagnostic criterion of DPN was a MNSI examination score of ≥2 [10].

Neurophysiologic Tests

Nerve conduction studies were taken as a gold standard for the diagnosis of DPN in this study. All the tests were recorded by a Dantec Keypoint 4-channel EMG device (Skovlunde, Denmark), including sensory NCV of median nerve in both upper extremities and superficial peroneal nerve in both lower extremities, motor NCV of common peroneal nerve, M-wave of median nerve, F-waves and H-reflexes of tibial nerve. The skin temperature at the legs was maintained at or above 30°C. Based on NCV and EMG findings compared with the normal values in our department, DPN was confirmed or excluded in each patient.

Statistics Analyses

The measurement data were presented as mean ± SD and enumeration data as percent. The correlation between NSC/NIS score, MNSI score and EMG/NCV test were assessed using Spearman's rank correlation analysis. Subsequently, sensitivity, specificity, PPV, NPV and accuracy of NSC/NIS score, MNSI score and EMG/NCV test as well as κ value were all determined by a 4-fold table. Statistically significant difference was set at $p < 0.05$. A κ value of >0.75 was considered as excellent concordance, κ of 0.4–0.75 as moderate-high concordance and κ of <0.4 as poor concordance [20]. All the statistical analyses were performed with Stata version 10.0 software (Stata Corporation, College Station, Tex., USA).

Results

This study included 54 men and 77 women. The mean age was 68.9 ± 6.9 years (range 53–85 years). The disease duration was 10.3 ± 14.9 years. Of the 131 patients, 57 (43.5%) patients were diagnosed with DPN according to EMG/NCV findings. The clinical and biochemical characteristics of the DPN and non-DPN patients are shown in table 2. Patients developing DPN had lower body mass index (BMI 25.4 ± 8.6 kg/cm^2) than those without DPN (28.3 ± 7.9 kg/cm^2, $p = 0.047$).

On basis of the Spearman's rank correlation analysis, significant positive correlation was observed between the EMG/NCV test and NSC score, NIS score and MNSI score ($p < 0.001$; table 3), among which the NIS score showed the great correlation with EMG/NCV test ($r = 0.653$, $p < 0.001$).

Table 4 gives the sensitivity, specificity, PPV, NPV and accuracy of each diagnostic test. When compared with EMG/NCV test, which was considered as the gold standard, NSC score was the most sensitive (85.96%) but least specific (77.03%). The NIS score had lower sensitivity (59.65%) but best specificity (98.65%) and accuracy (81.68%). Both of them were more reliable and accurate diagnosis for DPN, with high concordance with EMG/NCV test (κ = 0.61). The diagnostic performance of MNSI score was weighted to emphasize different cutoff points. Sensitivity was 70.18% at a cutoff value of above 1.0 and decreased to 36.84% at a cutoff value >2.5. While specificity increased from 81.08 to 98.65%. The PPV increased from 74.07 to 95.45% and NPV dropped from 77.92 to 66.97%. The highest accuracy (80.15%) was at the cutoff value of >1.5 (κ = 0.58).

Table 2. Clinical and biochemical characteristics of the study population with DM

	DPN	Non-DPN	p value
Number (%)	57 (43.5)	74 (56.5)	
Gender (M/F)	24/33	30/44	
Age, years	69±16.3	68±14.9	0.715
Duration of DM, years	9±6.3	11±5.4	0.053
BMI, kg/cm^2	25.4±8.6	28.3±7.9	0.047
Systolic blood pressure, mm Hg	134±26.9	133±28.6	0.840
Diastolic blood pressure, mm Hg	80±16.4	79±12.6	0.704
Fasting plasma glucose, mmol/l	8.3±7.9	8.4±9.3	0.948
Hemoglobin A1c, %	8.0±3.9	7.9±3.6	0.879
Triglyceride, mmol/l	1.81±0.98	1.94±1.23	0.514
Total cholesterol, mmol/l	5.86±2.03	5.65±2.35	0.592
High-density lipoproteins, mmol/l	1.47±0.71	1.36±0.54	0.333
Low-density lipoprotein, mmol/l	1.62±1.36	1.68±1.59	0.820

Table 3. Correlations between EMG/NCV test and NSC, NIS and MNSI scores

	r	p value
NSC score	0.625	<0.001
NIS score	0.653	<0.001
MNSI score		
>1.0	0.500	<0.001
>1.5	0.618	<0.001
>2.0	0.548	<0.001
>2.5	0.440	<0.001

Discussion

In this study, we evaluated the diagnostic capabilities of NSC, NIS and MNSI in the diagnosis of DPN in patients with type II DM, with EMG/NCV as reference standard. The correlations of the 3 clinical scoring systems

Table 4. Diagnostic accuracy of different tests compared with EMG/NCV test

	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %	κ value
NSC score	85.96	77.03	74.24	87.69	80.92	0.61
NIS score	59.65	98.65	97.14	76.04	81.68	0.61
MNSI score						
>1.0	70.18	81.08	74.07	77.92	76.34	0.52
>1.5	57.89	97.30	94.29	75.00	80.15	0.58
>2.0	49.12	97.30	93.33	71.29	76.34	0.49
>2.5	36.84	98.65	95.45	66.97	71.76	0.38

with EMG/NCV were analyzed, as well as the performance characteristics, including sensitivity, specificity, PPV, NPV, accuracy and κ value.

This study indicated a high prevalence (43.5%) of DPN in this population with type II DM according to the EMG/NCV findings, in accordance with the results of previous study on MNSI in patients with type II DM [14]. It had been reported that DPN of the limbs usually developed with age and DM duration, and it seemed more frequent in a population with obesity [21, 22]. Conversely, patients in this study with DPN had lower BMI compared with those without DPN. Similarly, Xu et al. [23] also showed lower BMI was a new potential independent risk factor for DPN. Hence, the differences compared with western countries could be explained by ethnic background or other environmental factors.

The NSC and NIS scores were simple clinical scores useful to diagnose DPN [12], as evidenced by the high accuracies compared with EMG/NCV test (80.92 and 81.68%, respectively). Despite a significant positive correlation of the EMG/NCV test with NSC score and NIS score ($p < 0.001$), the analysis showed NSC was sensitive but not very specific to confirm the diagnosis of DPN. It might be due to the reason that NSC was sensitive and specific but that nerve conduction studies were not specific enough for diabetic neuropathy. Fortunately, the combined application of NSC and NIS would be better in DPN diagnosis as the NIS was less sensitive but very specific.

Light touch and vibration sensation can evaluate the functions of big medullated nerve fibers, temperature sensation for the functions of small medullated or non-medullated nerve fibers, and pain sensation for hyperalgesia and hypesthesia [24]. Therefore, NSC/NIS scoring could assess more functions of nerves compared with EMG/NCV test, apart from their convenient and faster diagnosis.

As to MNSI scoring, sensitivity was decreased from a cutoff value of >1.0 to a cutoff value >2.5, and the increasing false negative results was responsible for the decrease in sensitivity [14]. Previous researches reported a sensitivity of 80% and a specificity of 95% at a cutoff value of ≥2.0, with good repeatability [10, 25]. In this study, MNSI score at a cutoff value of >1.5 showed the greatest correlation with EMG/NCV test ($r = 0.618$, $p < 0.001$). However, because of the high specificity but low sensitivity, MNSI was not limited for the early diagnosis of DPN. The other limitation was its inadequacy to screen the involvement of the autonomic nervous system [26].

Some limitations should be addressed in this study. First, pain and other positive sensory symptoms are a prominent presentation of diabetic neuropathy at its very beginning, and most of the patients with this condition have an early involvement of small fibers. In these patients, NCS is frequently normal for years. Hence in this study, one single EMG/NCV test as gold standard may give false negative results as patients may have normal, but decreasing over time, sensory nerve action potentials. Second, for the inter-examiner reliability between the 2 assistant physicians, formal statistics were not performed. Third, our patients cannot represent all DM patients as this study was performed in one center. Hence, a multicentric study would be better in evaluating the true prevalence of DPN.

In conclusion, both NSC and NIS were accurate and reliable diagnostic methods for DPN. The combined application of NSC and NIS was recommended in DPN diagnosis.

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Disclosure Statement

All authors have no conflict of interest to state.

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