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Sensitivity of joint position sense test, tuning fork test, Semmes-Weinstein Monofilament Examination and Michigan Neuropathy Screening Instrument in the diagnosis of diabetic polyneuropathy

Comparação entre o Teste de Senso de Posição Articular (TSPA), Teste do Diapasão (TD), Exame do Monofilamento de Semmes-Weinstein (EMSW) e Instrumento de Rastreio de Neuropatia de Michigan (QMNSI) na sensibilidade do diagnóstico da polineuropatia diabética

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ABSTRACT: Objectives: To compare, in patients with diabetic neuropathy, the prevalence of hallux position perception (joint position sense) test (JPST) abnormalities with tuning fork test (TFT) and Semmes-Weinstein monofilament examination (SWME) abnormalities and with the results of the questionnaire designed for neuropathic symptoms assessment that is part of the Michigan Neuropathy Screening Instrument (QMNSI). Subjects and Methods: This is a retrospective study of 35 ambulatory patients with peripheral diabetic polyneuropathy confirmed by nerve conduction studies. All the patients underwent TFT, SWME, QMNSI and JPST. Severe neuropathy was defined as peripheral neuropathy with no response to the electrical stimulation by any of the motor or sensitive nerves. Results: The prevalence of TFT (63%) and of QMNSI abnormalities (69%) in patients with diabetic neuropathy was significantly greater than JPST abnormalities (25.7%). Prevalence of abnormal JPST and TFT was increased in patients with severe nerve conduction study abnormalities. Concurrent evaluation with TFT, SWME and QMNSI was the most sensitive strategy to diabetic neuropathy diagnosis (sensitivity, 89%). SWME had a particularly low sensitivity (40%). Abnormalities revealed by JPST was significantly more prevalent in patients reporting previous ulcerations (p=0.006). However, JPST did not identify a greater number of patients with prior ulcerations when compared to the other tests. Conclusions: The application of a single test (especially JPST and SWME) in the screening of diabetic neuropathy may lead to a considerably lower sensitivity when compared to the combined use of multiple tests. JPST abnormalities have the potential to indicate a more severe neuropathy and a higher risk of ulcerations.

Keywords: Toe Joint, Proprioception, Position Sense, Diabetic neuropathies, Diagnosis, Foot ulcer, Diabetic foot

RESUMO: Objetivos: Comparar, em uma população com neuropatia diabética, a prevalência de alterações no teste da percepção da posição do hálux (teste do senso de posição articular - TSPA) com o teste do diapasão de 128 Hz (TD), exame do monofilamento de Semmes-Weinstein (EMSW) e os resultados do questionário elaborado para avaliação dos sintomas neuropáticos que faz parte do Instrumento de Rastreio de Neuropatia de Michigan (QMNSI). Casuística e métodos: Estudo retrospectivo de 35 pacientes ambulatoriais com polineuropatia diabética

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periférica confirmada por estudos de condução nervosa. Todos os pacientes foram submetidos à avaliaçao com TD, EMSW, QMNSI e TSPA. Neuropatia grave foi definida como polineuropatia periférica com ausência de resposta à estimulação elétrica por qualquer um dos nervos sensitivos ou motores. Resultados: A prevalência de anormalidade no TD (63%) e no QMNSI (69%) em pacientes com neuropatia diabética foi significativamente maior do que as alterações no TSPA (25,7%). A prevalência de anormalidade do TSPA e do TD foi maior em pacientes com anormalidades graves no estudo da condução nervosa. A avaliação simultânea com TD, EMSW e QMNSI foi a estratégia mais sensível para o diagnóstico de neuropatia diabética (sensibilidade, 89%). EMSW teve uma sensibilidade particularmente baixa (40%). As anormalidades do TSPA foram significativamente mais prevalentes nos pacientes com antecedente de ulcerações (p = 0,006). No entanto, a SPA não identificou um número maior de pacientes com ulcerações prévias quando comparado aos outros testes. Conclusões: O uso de apenas um teste clínico para triagem de neuropatia diabética, especialmente o TSPA e o EMSW, pode levar a uma sensibilidade consideravelmente menor quando comparado ao uso combinado de vários testes. Anormalidades do TSPA têm o potencial de indicar um quadro de neuropatia mais grave e com maior risco de ulcerações.

Palavras-chave: Articulação do Dedo do Pé, Propriocepção, Senso de posição, Neuropatia Diabética, Diagnóstico, Úlcera do Pé, Pé diabético

INTRODUCTION

Diabetes mellitus is a well-known risk factor for neuropathy and foot complications and its role has been extensively revised[1-6]. Diagnosis of diabetic neuropathy with loss of protective sensitivity allows early interventions to reduce the risk of foot ulceration and amputation[7-9]. Although peripheral neuropathy is the leading cause of diabetic foot, it remains an underdiagnosed complication[10]. One of the main reasons is the lack of recognition by medical teams of the presence of neuropathy.

The employment of validated questionnaires for symptoms assessment, such as the questionnaire of Michigan Neuropathy Screening Instrument (QMNSI), helps in the identification of patients with diabetic polyneuropathy[11]. Since, however, only about 50% of patients with diabetic neuropathy are symptomatic, physical examination of the foot is also important in screening and diagnosis of diabetic neuropathy[2].

At physical examination, two main classical clinical tests can traditionally be used to assess presence of neuropathy and of protective sensation and to predict future risks of foot complications - the 10 g Semmes-Weinstein monofilament examination (SWME) and the 128 Hz tuning fork tests (TFT)[6,9].

Proprioception consists of the sense of position and movement of the limbs and body in the absence of vision. Proprioception includes two components, the sense of stationary position of the limbs (limb position sense) and the sense of limb movement (kinaesthesia)[11]. In the present study, the hallux joint position sense test (JPST) was selected to assess proprioception with regards to the sense of stationary position. To our knowledge, there are no prior studies that evaluated the use of this proprioception clinical test in diabetic neuropathy diagnosis.

OBJECTIVES

This study aims to compare the prevalence of abnormalities of JPST, TFT, SWME and QMNSI in a population with diabetic polyneuropathy.

SUBJECTS AND METHODS

Subjects

In the division of Endocrinology of *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* (FMUSP), ambulatory diabetic patients being followed up were evaluated through a thorough clinical and neurologic examination by at least one of three endocrinologists (F.M.S., P.H.Z. and A.C.R.F.). All these physicians were previously trained together to rigorously evaluate these patients and had performed this evaluation in more than one hundred patients. The present study is a retrospective evaluation of data of patients who had been diagnosed with diabetic polyneuropathy previously confirmed by a complete nerve conduction evaluation within 2 years prior to the clinical evaluation. This study was approved by the Ethical Board of the Hospital das Clínicas da FMUSP, which approved the study without the need of acquisition of informed consent from patients. This retrospective study collected data from patients from 2005 to 2010.

Only patients whose data completely fulfilled all the following criteria, were considered to be included in the study: fulfilling of (a) QMNSI[11], (b) questions about intermittent claudication, (c) a physical examination that included searching for deformities of the foot, palpation of foot pulses and the application of SWME, TFT and JPST.

All patients had their laboratory exams and prior clinical evaluation verified and were excluded from the study if another diagnosis that could lead to neuropathy was suspected. Following this protocol, three patients were excluded – the first previously diagnosed with Hansen's disease, the second testing positive for serology for C hepatitis virus infection and the third with concomitant amyotrophic lateral sclerosis. Consequently, from the 38 initial patients with neuropathy confirmed by a complete nerve conduction, 35 patients were included in the study.

Table 1 describes the demographic profile of the studied population. Nephropathy was defined as the presence of two measurements of microalbuminuria greater than 30mg in 24h or the presence of serum creatinine greater than 1.4 mg/dL. Foot deformity was defined as the presence of hallux valgus, claw toes, hammer toes or high arch (pes cavus).

Table 1: Demographic profile of the patients with diabetic neuropathy confirmed by nerve conduction study. The patients were evaluated in the ambulatory of endocrinology of Hospital das Clínicas da FMUSP, from 2005 to 2010

	Study group: Number (%)
N	35
Mean age (years) ± SD	54.1 ± 15.7
Sex distribution	M: 23 (65.7%) F: 12 (34.3%)
Mean time since the diagnosis of diabetes (years) ± SD	13.3 ± 7.4
Mean HbA1C ± SD	7.95 ± 1.84
Distribution between diabetes mellitus types	Type 1: 6 (17.1%) Type 2: 23 (65.7%) Others: 6 (17.1%)
Prevalence of Hypertension	18 (51.4%)
Prevalence of Dyslipidemia	19 (54.3%)
Prevalence of Retinopathy	19/30 (63.3%)
Prevalence of Nephropathy	12/31 (38.71%)
Prevalence of Smokers: Current Ex-smokers Never smoked	 3 (8.6%) 16 (45.7%) 16 (45.7%)
Patients with previous limb amputation	1 (2.9%)
Patients with previous foot ulceration	7 (20%)
Patients with alteration in foot pulse palpation	25 (71.4%)
Patients with symptoms of intermittent claudication	11(31.4%)
Patients with foot deformity	11 (31.4%)
Severity of neuropathy according to results of electrophysiological evaluation	Nonsevere: 27 (77.1%) Severe: 8 (22.9%)

Notes to Table 1: SD, standard deviation.

Anamnesis and physical examination

Tools employed in anamnesis and physical examination are described below.

Evaluation of neuropathic symptoms with the Questionnaire of Michigan Neuropathy Screening Instrument (QMNSI):

The Michigan Neuropathy Screening Instrument is designed to screen for the presence of diabetic neuropathy. This screening instrument was developed to be used in an outpatient setting by primary care or other providers. The first part of this instrument consists of 15 self-administered "yes or no" questions on foot sensation including pain, numbness and temperature sensitivity, of which 13 of them score. A score greater than or equal to 4 suggests the presence of painful neuropathy[11]. Higher scores (out of a maximum of 13 points) indicate more severe neuropathic symptoms.

Semmes-Weinstein Monofilament Examination (SWME)

The monofilament examination application was assessed by stimulating six points in each foot with a 10 g Semmes-Weinstein monofilament. The stimulus was first applied to the patient's forearm so the patient could know what to expect. Each point was tested twice and was classified as "not sensitive" if the patient felt nothing when the stimulus was applied. If the results of both tests were not identical, a third stimulus was then applied to the same point. The result of this test was classified as "abnormal" if 2 or more stimuli out of 6 (the plantar surface of the first, third and fifth toes and metatarsals) were classified as "not sensitive" in the same foot of the patient.

128 Hz Tuning Fork Test (TFT)

TFT was first performed in the patient's wrists, so the patient could know what to expect. Next, this test was applied to a bony part on the dorsal side of the distal phalanx of the hallux, with the patient with their eyes closed, as recommended by Gilman[12]. The test consisted of two phases – in the first, the test examined the ability to register tuning fork vibration and. in the second, the ability to register the abrupt discontinuing of the stimulus, as performed by Perkins et al.[13]. This test was performed twice in each hallux, but it was alternated with at least one "sham" application, in which the tuning fork was not vibrating. The tuning fork test was classified as "abnormal" when at least one of the 2 stages of the test, on the same foot, presented an abnormal result twice.

Hallux joint position sense test (JPST)

JPST tests the perception of joint position[12,13]. Testing was performed according to prior descriptions by Haerer[14] and Gilman[12]. In testing, the hallux was passively

moved by lightly touching the medial and lateral part of the interphalangeal joint - each one was positioned twice in maximum plantar flexion and extension. Therefore, the first metatarsophalangeal joint was passively moved to keep the hallux in maximal flexion and extension. The examiner's fingers were applied parallel to the plane of movement to eliminate variations in pressure. The hallux being tested was separated from adjoining toes to eliminate all contact and thus any possible suggestion of the direction of movement of the hallux. The patient was instructed not to attempt any active movement of the toe on his part. The joint position sense was first applied to the patients without closing their eyes, so they could experience an example of the stimulus pattern to follow and could know what type of answers would be expected from them. The test was considered "abnormal" if any two out of the four answers relating to each toe in either foot were wrong.

Nerve conduction study

Patients underwent nerve conduction study of lower limbs in the neurologic clinic of *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paul*o (FMUSP) and had their exams evaluated by a neurologist with expertise in this field. Nerve conduction study was performed with the electromyography machine Polimedi, model 1110L. Evoked response was measured in the axillar, median, ulnar, radial, sural, peroneal, femoral and tibial nerves. Motor conduction was measured in the axillar, median, ulnar, peroneal, femoral and tibial nerves, and sensory conduction in the median, ulnar, radial and sural nerves. Tests were carried out only after limbs were properly warmed (>34^{o} C). Electrodes were coated with electro conductive gel and held in place with adhesive tape. Amplitude (mV), distal and proximal latencies (ms) were recorded and conduction velocity was calculated. Abnormal values were defined as: velocity <5th percentile; distal latency >95th percentile and amplitude <5th or >95th percentile of the controls. Nerve conduction study was considered abnormal in the presence of abnormalities in two or more nerves, at least one of which in the lower limbs. All patients had symmetrical involvement of nerves in lower limbs, which was compatible with the diagnosis of diabetic polyneuropathy. Velocity of the sensitive nerve conduction and peak of the sensory nerve action potential were used to classify the degree of degeneration of the sensitive neuronal fibers[1,15]. Severe neuropathy was defined as no response to the electrical stimulation by any of the motor or sensitive nerves.

Statistical Analysis

Data are expressed in terms of mean ± Standard Deviation. A computer program (SPSS for Windows; SPSS Inc., Chicago IL) was used for descriptive statistics and 2-tailed statistical analysis. The level of significance was set at 0.05. Analyses were also carried out using Chi-square test, Fisher's exact test and Student's t test, when appropriate, as shown in the results section.

RESULTS

JPST and SWME were particularly insensitive for the diagnosis of diabetic neuropathy when used solely (sensitivity, 26% and 40%, respectively). TFT and QMNSI reached sensitivities respectively of 63% and 69%. The prevalence of abnormalities among the clinical tests was significantly different when a comparison was made between TFT and JPST and between the QMNSI and JPST (Chi-square, p=0.002 and 0.001 respectively). There was a tendency towards a significant difference between TFT and SWMW (Chi-square, p=0.056) and there was no significant difference between SWME and JPST (Chi-square, p=0.2). It should be noted that in the group of patients who had abnormal JPST, none had a normal TFT and only one had a normal SWME. The most sensitive combination of tests to the diagnosis of diabetic neuropathy, as shown in Table 2, was the QMNSI, TFT and SWME (sensitivity, 89%). This sensitivity was statistically greater than performing SWME alone or TFT alone (Fisher's exact test, p=0.001 and 0.02 respectively).

Table 2: Results of clinical tests employed in patients with diabetic neuropathy confirmed by nerve conduction study. The patients were evaluated in the ambulatory of endocrinology of Hospital das Clínicas da FMUSP, from 2005 to 2010

	Number (Percentage)
Number of Patients	35
Patients with Abnormal JPST	9 (25.7%)
Patients with Abnormal SWME	14 (40%)
Patients with Abnormal TFT	22 (62.9%)
Patients with QMNSI ≥ 4	24 (68.6%)
Patients with Abnormal SWME and/or QMNSI ≥ 4	25 (71.4%)
Patients with Abnormal TFT and/or SWME	26 (74.3%)
Patients with Abnormal TFT and/or SWME and/or QMNSI ≥ 4	31 (88.6%)
Patients with abnormal clinical tests	No abnormal test: 9 (25.7%) 1 abnormal test: 15 (42.9%) 2 abnormal tests: 3 (8.6%) 3 abnormal tests: 8 (22.9%)

Notes to Table 2: JPST, hallux joint position sense test. SWME, 10 g Semmes-Weinstein monofilament examination. TFT, 128 Hz tunning fort test. QMNSI, questionnaire of the Michigan Neuropathy Screening Instrument.

Abnormal results of the JPST and the TFT were more frequent in patients whose neuropathy was severe when compared to patients with non-severe neuropathy, in studies of nerve conduction velocity (Fisher's Exact test, p=0.015 for both comparisons). Abnormalities in the SWME, on the other hand, were not more frequent in patients with severe neuropathy (Fisher's Exact test, p=0.22). When analyzing patients with abnormal JPST results, 55% had severe neuropathy as defined by the nerve conduction studies. On the other hand, only 36% of patients with abnormalities of SWME had severe neuropathy and 36% of patients with abnormalities of TFT had severe neuropathy (Table 3). Abnormalities in JPST were not related to presence of abnormalities in foot pulse palpation (Fisher's Exact test, p=0.24) nor to the presence of any deformity in the feet (Fisher's Exact test, p=0.42).

Table 3: Number of patients with diabetic neuropathy with abnormal clinical tests, according to the severity of abnormalities found in nerve conduction study. Patients were evaluated in ambulatory of *Hospital das Clínicas da FMUSP*, from 2005 to 2010

	JPST	TFT	SWME	QMNSI
Severe (n=8)	5	8	5	7
Non-severe (n=27)	4	14	9	17

Notes to Table 3: JPST, hallux joint position sense test. TFT, 128 Hz tuning fork test, SWME, 10 g Semmes-Weinstein monofilament examination. QMNSI, questionnaire designed for neuropathic symptoms assessment that is part of the Michigan Neuropathy Screening Instrument.

There was a higher prevalence of abnormalities in the JPST in patients with a history of foot ulcers than in those without this history (Fisher's Exact test, p=0.006). The same association was not found with abnormal TFT (Fisher's Exact test, p=0.22) or SWME (Fisher's Exact test, p=0.09). The percentage of patients who had previously experienced an ulceration of the foot was 56% (5 of 9 patients) among patients with abnormal JPST, 36% (5 of 14 patients) among those with an abnormal SWME, 27% (6 of 22 patients) among those with abnormal TFT and 25% (6 of 24 patients) among those with an abnormal QMNSI. Out of 7 patients with a history of foot ulcers, TFT and QMNSI were each abnormal in 6 patients while JPST and SWME were each abnormal in 5 patients.

DISCUSSION

Diabetic polyneuropathy represents an insidious and progressive disorder, in which the pathological severity is poorly linked with the development of symptoms. The detection of this diabetic complication, which is so prevalent, is important, since interventions in high-risk patients have been shown to decrease the ulceration rate by up to 60% and the amputation rate by 50%[8,16].

Additionally, the rate of diabetic neuropathy detection by clinicians remains low[10]. The use of isolated or multiple simple tests in clinical practice to increase the detection rate of this complication and to find patients at greater risk for ulceration could significantly improve the management of this complication.

In patients suffering from diabetic neuropathy, according to nerve conduction evaluation analysis, the prevalence of abnormalities revealed by JPST was lower than by TFT and the clinical questionnaire score (QMNSI). The low number of patients studied may have prevented this difference from reaching a level of statistical significance when comparing the frequency of SWME abnormality with that of JPST abnormality. This low prevalence of abnormal JPST in relation to TFT, QMNSI and SWME indicates that JPST should not be used as a screening test for diabetic neuropathy in clinical practice. The absence of patients with abnormal JPST and both normal TFT and SWME shows that this test does not add to the traditional clinical screening methods in the screening of neuropathy in diabetic patients.

It is important to attempt to stratify patients with known neuropathy at different risk levels, as the patients at greater risk of complications need more frequent evaluations and more intensive prevention[3] There is a trend in searching for fast screening methods for diabetic foot that does not employ any instruments[17,18,19]. Hallux JPST is a very simple and fast test that does not require any instrument and that would have potential to predict foot at risk. The usefulness of testing joint position sense to identify patients with neuropathy at a higher risk of developing complications, such as ulceration or amputation, can be inferred from the following two findings. Patients with abnormal JPST had significantly more severe neuropathy according to nerve conduction evaluation and had more chances of reporting previous foot ulceration than patients with normal JPST. These findings were not exposed by SWME and the latter was not observed with TFT. This suggests that JPST could possibly be used as a prognostic factor in patients known to have neuropathy. The major limitation of this finding is that the sample size was small and that the multiple tests to detect foot ulcers were performed in individuals who had already had ulcers, whereas the real issue is how the tests are able to predict the future development of ulcers.

As such, our results regarding hallux JPST should be interpreted with caution and the hypothesis that it may be used as a new tool in the prediction of risk of ulceration in patients known to have diabetic neuropathy should be tested by prospective studies.

There is, however, some evidence supporting that abnormalities in proprioception of lower legs may increase the risks of foot ulceration. Bloem et al.[20] studied highly selected patients with exclusive proprioception loss and showed that lower leg proprioception is important to trigger reflexes in ankle muscles. This helps to shape automatic postural responses within a given postural strategy, once this has been triggered by knee or trunk movement. Balance is markedly impaired in patients with severe loss of leg proprioception[20-22] and this may explain why patients with impaired lower leg proprioception have higher incidence of recurrent or accidental falls[23-27], which may precipitate injuries to lower limbs. Lower leg incoordination derived from proprioception loss may also lead to walking pattern abnormalities which may increase plantar pressure in some areas. These areas are acknowledged to be at risk for ulceration[3]. An increased risk of ulcers due to trauma may be also related to decreased reaction time and difficulty in obstacle crossing due to proprioception deficits[28]. Ettinger et al.[29] recently found that patients with diabetes had an abnormal stationary proprioception in the knee, which was presumably associated with peripheral neuropathy. It should be noted that diabetic peripheral neuropathy classically compromises at first the distal extremities, such as the toes, before affecting more proximal parts of the legs[1,2,9]. Therefore, it is assumed that changes in the proprioception of the hallux may occur earlier than in the knees.

As pointed out by Gilman[11], normal subjects can generally correctly identify movements of three degrees at the toes. Therefore, the degree of passive movement we provided to the hallux is much greater than that usually required by a person without neuropathy to correctly identify it. Considering this, it is possible that performing a test with less movement of the metatarsophalangeal joint could increase the sensitivity of joint position sense to the diagnosis of diabetic neuropathy. There would be, however, difficulty to standardize tests without maximal movement in clinical practice.

An important finding of this trial was a tendency toward a higher prevalence of abnormality in TFT when compared to SWME. Indeed, some studies found that TFT may be more sensitive than SWME for diabetic neuropathy diagnosis[30] and that SWME may not be the optimal methodology for identifying individuals at risk for foot ulcers[31]. Moreover, in our study the most appropriate screening strategy was the concurrent testing with TFT, SWME and the clinical questionnaire (QMNSI), which reached a sensitivity of 89%. The reason for this finding is that a significant percentage of patients with neuropathy may have abnormalities only in one of these three clinical tests (Table 2). None of these tests, when applied solely, reached this high sensitivity, and SWME had a particularly poor sensitivity of 40%. It has been already found that examination with as many questionnaires and tests as possible is important for early diabetic neuropathy detection[32].

CONCLUSIONS

In conclusion, hallux JPST does not add to the traditional screening of diabetic neuropathy because of its poor sensitivity. Abnormality in JPST seems to be positively correlated with more severe neuropathies and possibly is a clinical marker of increased ulceration risk in patients with known diabetic neuropathy, although further studies should be carried out to test this hypothesis. The employment of only one clinical test to screen for diabetic neuropathy may lead to a considerably lower sensitivity when compared to the combined use of SWME, TFT and QMNSI. Therefore, a screening strategy for diabetic neuropathy based solely on one clinical test, especially JPST or SWME, should be considered suboptimal.

Author's participation: *Fernando Moreno Sebastianes* - idealized the study, attended the patients in the outpatient clinic, collected and analyzed research data and wrote the manuscript. *Patrícia Helena Zanoni* and *Alina Coutinho Rodrigues* - attended the patients in the outpatient clinic and helped with the writing of the manuscript. *Márcia Nery* and *Maria Cândida Parisi* - guided patient care, structured the care protocol and revised the manuscript.

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