Rastreio de Polineuropatia Diabética Periférica em Doentes Internados

Screening of Distal Symmetric Polyneuropathy in Hospitalized Diabetic Patients

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Resumo:

Introdução: A polineuropatia simétrica distal (PNSD) é uma complicação frequente e catastrófica da diabetes *mellitus*, mas subdiagnosticada. Os autores colocam a hipótese de o internamento ser uma oportunidade de rastreio da PNSD e pretendem comparar dois métodos de diagnóstico.

Material e Métodos: Estudo prospetivo e multicêntrico, que incluiu doentes diabéticos internados nos serviços de medicina interna de dois hospitais, entre maio e outubro de 2015. Foi aplicada a escala MNSI (*Michigan Neuropathy Screening Instrument*) e o teste SWME (*Monofilamento de 10 g-Semmes-Weinstein exam*) para despiste de PNSD. Uma pontuação > 2 no exame clínico da MNSI ou ≤ 7 respostas positivas em 10 no teste SWME, foram consideradas diagnósticas de DSPN.

Resultados: Foram incluídos 88 pacientes com idade mediana de 77 (13) anos e 45% homens; a maioria com diabetes tipo 2 e 7% tinham diagnóstico prévio de PNSD. A prevalência de PNSD foi de 75% utilizando o MNSI; o teste SWME foi anormal em 38% destes pacientes. A taxa de concordância entre os testes foi de 44,3%. Dos pacientes, 92,4% com diagnóstico de PNSD no estudo não tinham diagnóstico prévio.

Discussão: O número de subdiagnósticos de PNSD neste estudo é alarmante. A percentagem de casos subdiagnosticada pode representar um problema de registo ou de escassez de rastreio.

Conclusão: Neste estudo concluímos que a PNSD é altamente prevalente entre os pacientes hospitalizados, mas profundamente subdiagnosticada. A escala MNSI poderá ser um instrumento adequado para o rastreio, enquanto o teste SWME não deve ser utilizada isoladamente para este propósito.

Palavras-chave: Diabetes Mellitus; Hospitalização; Neuropatias Diabéticas; Polineuropatias.

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Abstract:

Introduction: *Distal symmetric polyneuropathy (DSPN) is a frequent, catastrophic and underdiagnosed complication of diabetes mellitus. The authors have hypothesized that hospitalization could be an opportunity to screen DSPN and also pretend to compare two different diagnostic methods.*

Material and Methods: *This was a prospective and multicentre study that enrolled diabetic patients admitted consecutively to internal medicine wards, between May and October 2015. Patients were evaluated using the MNSI (Michigan Neuropathy Screening Instrument) and the SWME (10 g-Semmes-Weinstein monofilament examination). A score > 2 in the clinical examination of MNSI or ≤ 7 positive answers in a total of 10 in SWME were considered diagnostic of DSPN.*

Results: *Eighty-eight patients were included; average age was 77 (13) years and 45% were males; most were type 2 diabetic patients, 7% had a previous diagnosis of DSPN. DSPN prevalence was 75% using MNSI, SWME was abnormal in 38% of these patients. The agreement rate between MNSI and SWME was 44.3%. A percentage of 92.4% of the patients with a diagnosis of DSPN in the study did not have a previous diagnose.*

Discussion: *The number of underdiagnosed cases in this study is alarming but had been previously detected in studies regarding outpatient; it might represent a problem of registry or an omission in the screening of neuropathy.*

Conclusion: *We have concluded that DSPN is a high prevalent disease in hospitalized patients in Portugal, which remains underdiagnosed. MNSI can be a good instrument to screen neuropathy and SWME should not be used exclusively for this purpose.*

Keywords: *Diabetes Mellitus; Diabetic Neuropathies; Hospitalization; Polyneuropathies.*

Introduction

Distal symmetric polyneuropathy (DSPN) is one of the most frequent complications of diabetes; it can affect up to 50% of patients with type 2 diabetes mellitus (T2DM), and 60% of patients

with type 1 diabetes mellitus (T1DM).[1] The pathogenesis of this condition is still unclear, however, both metabolic and ischemic alterations are thought to contribute to the pathogenesis of this condition.[2,3] The duration and severity of hyperglycaemia seems to be the major risk factor, but glycaemia variability, age, dyslipidemia, hypertension and smoking have also been pointed as risk factors.[4]

In clinical practice, DSPN is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after exclusion of other causes. The diagnosis of DSPN is predominantly clinical. A combination of typical symptomatology and symmetrical distal sensory loss or typical signs in the absence of symptoms in a patient with diabetes is highly suggestive of DSPN and may not require additional evaluation. As up to half of the patients may be asymptomatic, a diagnosis may only be made on examination or, in some cases, when the patient presents with a painless foot ulcer.[5] The American Diabetes Association (ADA) recommends the use of more than one test, with 10 g- Semmes-Weinstein monofilament examination (SWME) being add to at least one of three: pinprick, temperature or vibration sensation using 128 Hz tuning fork.[5] In DSPN, small and large fibbers are affected, producing different signs and symptoms. SWME is worldwide used and in Portugal is recommended to identify feet in risk to ulceration.[6] It tests large fibbers lesions, which explains some lack of accuracy to diagnose earlier stages of neuropathy.[5,7] Scales like *Michigan Neuropathy Screening Instrument* (MNSI), *United Kingdom Screening Test* (UKST), *Neuropathy Symptoms Score* (NSS) or *Diabetic Neuropathy Score* (DNS), which combine some of the tests, have been developed to facilitate the diagnosis of DSPN.[8-11]

MNSI has been recently validated to the Portuguese population; it is an easy scale with a sensitivity/specificity of 86%/61% and a positive predictive value of 73% / 79%.[12]

The early diagnosis of this condition allows the proper education of patients to prevent its catastrophic complication, like diabetic foot lesions and subsequent amputation.[5,13]

Diabetes is a prevalent condition in Portugal, especially in hospitalized patients, where it affects 10% to 43% of the inpatients.[14-16] Hospitalization could be an opportunity to screen diabetic neuropathy and a window to education of these patients in an attempt to reduce the burden of foot lesions and amputations.

The authors have hypothesized that hospitalization of diabetic patients could be an opportunity to screen DSPN and to educate patients. Authors also intended to compare SMWE and MNSI performance.

Material and Methods

STUDY DESIGN AND PATIENT POPULATION

This was a prospective and multicentre study that enrolled diabetic patients admitted consecutively to internal medicine wards, between May and October 2015. Patients were enrolled in two central hospitals: Hospital de Santo Antonio (HSA) and Hospital de Vila Real (HVR). HSA is also a teaching hospital. Patients were enrolled in the study if they had a diagnosis of diabetes previous to admission. Other causes of peripheral polyneuropathy were excluded through patients interview and electronic medical records query (hospital and national electronic health records: SClinico® and RSE®, respectively), including alcohol, HIV infection, hypothyroidism, vitamin B12 deficiency, renal chronic failure, paraproteinemias, malignant disease, personal or familial neurological disease and use of neuropathy-inducing drugs (Appendices 1). Demographic variables (sex, age) and data regarding the medical history of diabetes mellitus (type, years of evolution and HbA1c value) were also obtained by patients interview and consulting electronic medical records. Vascular complications (neuropathy, retinopathy, cerebrovascular disease, coronary heart disease

Appendice 1: Exclusion criteria definition.

Exclusion Criteria	Definition
Non cooperative patients	Patients who refused to participate in the study, patient with dementia or other condition that did not permit his/her active participation in the study.
Alcohol consumption	(> 40 g/day for men and > 20 g/day women).
Hypothyroidism	TSH > 10 µUI/mL on the last 6 month or clinical hypothyroidism under levothyroxine less than 1 year.
HIV infection	Evidence in the electronic process.
B12 Deficit	B12 < 200 pg/mL on the last 6 months.
Renal chronic failure	GFR < 30 mL/mint/1.73 m (calculated using CDK- EPI formula, using a creatinine value out of acute phase, available on the previous 6 months).
Autoimmune disease	Including: vasculitis, connective tissue diseases, other immuno-mediated diseases.
Paraproteinemias	Including: Multiple myeloma, Waldenström's macroglobulinemia, primary amyloidosis, cryoglobulinemia.
Oncological disease	Submitted to systemic chemotherapy and / or without cure criteria at the time of the evaluation.
Personal and / or family history of neurological disease	Including: chronic inflammatory demyelinating neuropathy, hereditary neuropathy (hereditary motor and sensory neuropathy, hereditary sensory and autonomic neuropathy, familial amyloid neuropathy).
Neuropathy-inducing drugs	Use of the following drugs within 6 months prior to admission and / or during hospitalization: amiodarone, reverse transcriptase inhibitors, dapsone, perexilin, phenytoin, metronidazole, nitrofurantoin, ethambutol, isoniazid.

Appendice 2: Exclusion criteria population frequencies.

Exclusion Criteria	Frequency
HIV infection	1
Neurological disease	3
Hypothyroidism	4
Neuropathy-inducing drugs	8
B12 Deficit	17
Autoimmune disease	17
Alcohol	26
Oncological disease	33
Renal chronic failure	38
Non cooperative patients	106
Total	**255**

and/or peripheral arterial disease) were considered if reliably described in electronic medical records (yes or no answers). In concern to diabetic nephropathy, it was taken into account if described in electronic medical records or microalbuminuria results in the past year.[17] Laboratory results (HbA1c and microalbuminuria) were also analysed if undone in the previous three months prior to hospitalization.

DSPN SCALES

The SWME and the MNSI were applied to each patient by one of two neurology residents in each centre in order to reduce interobserver variability. A 10 g-monofilament was used to press 10 different points in each foot as proposed by the practical guideline from Michigan Diabetes Research and Training Center.[18] A normal response corresponded to 8 or more correct answers, 7 or less correct answers was considered an abnormal response predictive of DSPN. MNSI includes two separate assessments: a 15-item questionnaire (Section A) and a lower extremity examination (Section B). Section A is self-administered by the patient and assesses the clinical symptoms through 15 "yes" or "no" questions, regarding foot sensations, numbness, temperature alterations, general asthenia, and peripheral vascular disease. In the original version, "yes" responses to items 1 to 3, 5 to 6, 8 and 9, 11 and 12, 14 to 15 count as 1 point each. For items 7 and 13 a "no" response counts as 1 point. Items 4 (a circulation assessment) and 10 (a general status measurement) are excluded in the original scale. Section B includes (1) the inspection of both feet (for dry skin, calluses, fissures or deformities); (2) the assessment of ulcerations; (3) the examination and grading of the muscle stretch reflexes as either normal, reduced, or absent (if necessary, the ankle reflex [AR] may be elicited using the Jendrassik maneuver, which is defined as "presence with reinforcement"); and (4) the determination of vibration sensation (VS) at the interphalangeal joint of the hallux, using a 128-Hz tuning fork. A score > 2 in this section defined neuropathy.[10] The prevalence of DSPN was calculated through results of Section B. The validation of MSNI for Portuguese population occurred after this study was performed, so we applied the cut offs suggested by *Feldman et al.* in the original article.[19]

STATISTICAL ANALYSIS

The data study was analysed using SPSS version 24.0.0. Shapiro-Wilk test was used to test normality. Duration of diabetes (years), HbA1c (%) and age were not normally distributed and so described as median ± interquartile amplitude. Mann-Whitney test was used to compare median of continuous variables. Chi -square test and Fisher test were performed to determine the significance of categorical variables. The global agreement rate between MNSI and SWME was based on positivity or negativity for both tests in the same patient. A p-value < 0.05 was considered significant.

ETHICAL STATEMENT

This study was reviewed and approved by both institutional and ethics committee. All patients signed informed consent. Information about diabetic neuropathy and how to prevent amputation was given to all patients with a probable diagnosis of DSPN.

Results

During the study period, 343 diabetic patients were evaluated (225 in HVR and 117 in HSA); of these, 88 patients (65 in HVR and 23 in HSA) were included in this study. The median (interquartile amplitude) age of patients was 7713 years and 45% were males. Most were type 2 diabetic patients (93.2%) and the median duration of diabetes was 10[11] years; populations from both hospitals had similar demographic and clinical characteristics (Table 1). Macrovascular complications were present in 40% of the patients and 26% had at least one microvascular complication; of these, 7% had a previous diagnosis of diabetic neuropathy (Table 2).

The clinical examination of MNSI (section B) was positive in 66 patients (52 patients in HVR and 14 patients in HSA) reflecting a global prevalence of DSPN of 75% without significant differences between centres (Table 3); of these, 49 patients (55.7%) had a score ≥ 4 in the questionnaire (section A) and 82 patients (93.2%) had at least one symptom of neuropathy.

Most patients (92.4%) with a diagnosis of DSPN done during hospitalization did not have their condition diagnosed previously. Six patients had a previous diagnosis of DSPN; of these, 4 (66.7%) had a positive MNSI and 2 (33.3%) had a negative one. One of these patients had 11 points in Section A and the other had 3 points.

SWME was abnormal in 25 of the DSPN patients (38%);

Table 1: Population demographic and clinical characteristics.

	Total n = 88	Vila Real Hospital (HVR) n = 65	Santo António Hospital (HSA) n = 23	*p- value*
Age (years) Average +/- SD (min. – max.) Median + interquartile amplitude (IQ)	74.7 ± 13,2 (20 - 97) 77.0 13	74.4 ± 13.1 (20-97) 77.0 12	75.6 ± 13,7 (30-93) 79.5 15	0.571*
Sex (%)	45% males 55% females	41,5 % males 58,5% females	56,5% males 43,5% females	0.233***
Type of diabetes	93.2% T2DM 6.8% other types of DM	92.3% T2DM 7.7% other types of DM	95.7% T2DM 4.3% other types of DM	1.000***
Duration of diabetes (years) Average +/- SD (min.- max.) Median + IQ	12.0 ± 8.8 (1-40) 10.0 11	12.6 ± 9.3 (1-40) 10.0 14	9.9 ± 6.2 (2-30) 9.5 4	0.507*
HbA1c (%) Average +/- SD (min.- max.) Median + IQ	7.6 ± 1.8 (5.3-17.4) 7.0 1.7	7.7 ± 1.9 (5.5-17.4) 7.0 1.9	7.3 ± 1.3 (5.3- 10.6) 7.2 1.7	0.637*

*Mann-Whitney test **Chi-square test *** Fisher test

Table 2: Vascular complications.

	Total % (N)	Vila Real Hospital (HVR) % (N)	Santo António Hospital (HSA) % (N)	*p- value*
> 1 Microvascular complications	26% (23/87)	25% (16/64)	30% (7/23)	0.595***
Diabetic neuropathy	7% (6/87)	6% (4/64)	9% (2/23)	0.653***
Diabetic retinopathy	17% (15/87)	17% (11/64)	17% (4/23)	1.000***
Diabetic nephropathy	16% (14/87)	16% (10/64)	17% (4/23)	1.000***
>1 Macrovascular complication	40% (35/87)	39% (25/64)	43% (10/23)	0.806***
Cerebrovascular disease	20% (17/87)	17% (11/64)	26% (6/23)	0.370***
Coronary heart disease	20% (17/87)	16% (10/64)	30% (7/23)	0.137***
Peripheral arterial disease	11% (10/87)	14% (9/64)	4% (1/23)	0.279***

*** Fisher test

Table 3: MNSI results.

DSPN positive	All n = 88	HVR n = 65	HSA n = 23	*p-value***
MNSI part B > 2 points	66 (75.0%)	52 (80.0%)	14 (60.9%)	0.093
MNSI part A ≥ 4 points	49 (55.7%)	39 (60%)	10 (43.5%)	NS

more patients in HSA presented a positive SWME (71% *vs* 29%, $p = 0.005$) (Table 4). One of these 25 patients had a previous diagnosis of DSPN.

The global agreement rate between MNSI and SWME was weak (44.3%). We identified that 25 (28.4%) out of 88 patients had both tests positive (MNSI and SWME), and 14 (15.9%) had both tests negative (Table 5). This agreement rate was significantly higher in HSA than in HVR (61% vs 39%). MNSI score was significantly higher in SWME positive patients, in global group and in HSA (Table 6).

Discussion

This study found that 75% of the hospitalized diabetic patients had DSPN and 92% of these patients were not previously diagnosed.

In Portugal this is the first study to estimate the prevalence of diabetic neuropathy in hospitalized patients. This is a higher percentage than has been described in the outpatient's studies.[20,21] For instance, Barbosa AP *et al* reported a prevalence of 32.3% of DSPN, based on signs and symptoms, among outpatients in the north side of the country.[20,21]

Table 4: MNSI and SWME results: differences between centers.

	All n = 66	HVR = 52	HSA = 14	*p- value*
Deformity	42 (64%)	35 (67%)	7 (50%)	NS**
Foot ulcers	5 (8%)	4 (8%)	1 (7%)	NS**
Reflexes ↓ or abolished	52 (79%)	39 (75%)	13 (93%)	0.007**
Vibration sensitivity ↑ or abolished	53 (80%)	43 (83%)	10 (71%)	NS**
SWME	25 (38%)	15 (29%)	10 (71%)	0.005***

Chi-square test * Fisher test

Table 5: MNSI and SWME agreement rate.

	SWME / MSNI	Positive	Negative	*p- value***
VRH (n = 65)	Positive	23.1% (15)	56.9% (37)	NS
	Negative	4.6% (3)	15.4% (10)	
HAS (n = 23)	Positive	43.5% (10)	17.4% (4)	NS
	Negative	21.7 % (5)	17.4% (4)	

**Chi-square test

Table 6: MNSI score between centers in SWME positive and negative patients.

	SWME / MSNI	Positive	Negative	*p- value**
Total (n = 88)	MNSI part A	3.0 ± 5.0	2.0 ± 3.0	NS
	MNSI part B	3.5 ±3.3	2.5 ± 2.5	0.028
VRH (n = 65)	MNSI part A	5.0 ± 4.0	3.0 ± 2.0	NS
	MNSI part B	3.8 ±2.8	3.0 ± 2.0	0.013
HSA (n = 23)	MNSI part A	2.0 ± 4.0	1.5 ± 4.0	NS
	MNSI part B	3.0 ± 2.5	1.5 ± 2.1	0.027

* Mann-Whitney test

Our result reflects a bias towards older patients, with longer duration of diabetes and with more associated comorbidities in inpatients. However, the inclusion of two different centres in the north of Portugal, with similar inpatient population and with the same prevalence of DSPN in both centres when using MNSI criteria, is a positive aspect of this study.

The number of underdiagnosed cases of neuropathy in this study is alarming. Silva AM *et al* have already noticed that most inpatients electronic clinic registries lack documentation of vascular complications, particularly microvascular ones.[20] Our percentage of underdiagnosed neuropathy, 92% of the cases, can represent either a problem of registry or an omission in the screening of neuropathy in diabetic patients. This study reinforces that hospitalization can be a window of opportunity to screen the neuropathy in the diabetic population and also to educate these patients in order to reduce the number of amputations.

Another aspect that can contribute to our results is the diagnostic tests used to detect DSPN. Abraham et al postulated that ankle reflex in addition to vibration or pinprick sensation is a sensitive combination for diagnosing polyneuropathy.[22] In our study, we verify that reflexes and vibration sensation were the tests that contributed mostly to the positivity of MNSI. We also verify that there was a higher proportion of patients with reduced or abolished reflexes in one centre; however, the number of cases of DSPN using MNSI was not significantly different between the two centres, suggesting that this can be a good tool to screen neuropathy in hospitalized patients. One of the limitations of this work is absence of electrophysiological tests to confirm the MNSI results.

We found a high variability in DSPN detection when we used SMWE, with a significantly higher percentage of detected cases in one centre. This result suggests that there is an important interobserver variability in monofilament examination, which can limit the use of this test in the diagnosis of neuropathy and reinforces that this test should not be used isolated in the diagnosis of DSPN. This difference in monofilament test results also contributes to agreement rate of MNSI and SMWE in HSA.

The cut-off point of MNSI has been an issue of debate.[19,23] In this study, the cut-off point of 2 was considered but our results suggest that higher cut-off points could contribute to higher agreement between tests. However, the ROC results (unpublished data) don't confirm an alternative cut-off point.

Conclusion

In this study we conclude that DSPN is a high prevalent disease in hospitalized diabetic patients in Portugal but remains mostly underdiagnosed. This reinforces that hospitalization is an opportunity to screen neuropathy in diabetic patients and to educate these patients. Our result suggests that MNSI can be a good instrument to screen neuropathy and that SWME should not be used exclusively for this purpose. The validation of the MNSI for Portuguese population, after our work, reinforces the possibility of using this scale as a screening test. ■

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

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