QUANTITATIVE SENSORY TESTING IN PATIENTS WITH NEUROPATHIC PAIN DUE TO SMALL FIBER SENSORY POLINEUROPATHY

Ioana MINDRUTA[1,2], Bogdan O. POPESCU[1,2], Mihai VASILE[1,2], Amalia ENE[1], Cristina TIU[1,2], Ana COBZARU[1], Ovidiu BAJENARU[1,2]

[1]Neurology Department, University Emergency Hospital of Bucharest
[2]University of Medicine and Pharmacy "Carol Davila", Bucharest

ABSTRACT

Quantitative sensory testing (QST) is a potentially useful tool for measuring sensory impairment for clinical and research studies but there is still no consensus regarding the place of this evaluation in every day clinical practice.

Our study included 15 patients previously diagnosed with neuropathic pain due to small fiber sensory polyneuropathy based on clinical and electrodiagnostic criteria.Variables were compared with an age matched control group of 7 healthy persons. We looked to pain severity rated on Visual Analog Scale and Pain Detect Questionnaire and we searched for correlations with sensory nerve conduction studies and parameters of quantitative sensory testing – thermotest, limits method.

QST was a sensitive technique for evaluation of patients with small fiber sensory polyneuropathy.

Score on Pain Detect Questionnaire has statistically significant correlation with values recorded for cooling detection threshold on QST, documenting sensory loss and A delta fibers dysfunction in the study group.

Key words: pain, neuropathy, quantitative sensory testing, neurophysiology.

INTRODUCTION

Quantitative sensory testing (QST) started as a clinical method for human subjects 25 years ago. Since then, it has been applied for a large variety of clinical pathology that involve sensory function and also it has been compared with other functional tests as nerve conduction studies and autonomic tests and demonstrated to be highly sensitive for subtle sensory changes. (2)

As major pathology in the peripheral nervous system involve large and small sensory fibers, QST and nerve conduction studies could be considered complementary tests. (1)

Thermic and vibratory modalities are used in clinical settings and provide information about the functionality of the somatosensory system from receptor to cortex, a large spectrum of sensory fibers being tested. (7)

Vibration is initially detected by Pacinian corpuscles and through A-beta large myelinated fibers reach the spinal dorsal columns.

Thermic stimuli and pain are conducted through naked nerve endings and A delta and C small, unmyelinated fibers into the spinothalamic tracts.

But it is important to mention that this technique would not be effective to localize the injury or disfunctionality on a certain level of the somatosensory axis. (2)

Threshold measurements usually represent the most common parameter in QST. Although the

Author for correspondence:
Ioana Mindruta, University Emergency Hospital, Neurology Department, 169 Splaiul Independentei, District 5, Bucharest
email: ioana@signfactor.ro

method is designed to produce quantitative data, results could be biased by poor cooperation of subjects and failure to provide consistent, reproducible answers for every test algorithm. (5)

Hyposensitivity of A delta sensory fibers could be demonstrated using the cooling detection threshold.

If cooling is mediated by small sensory myelinated A delta fibers, warmth and heat pain reflect the activity of unmyelinated C fibers.

Small fiber sensory neuropathies are common disorders of the peripheral nervous system with different etiologies: metabolic – most frequent in diabetes, toxic, inflammatory or paraneoplastic. (9)

Patients are usually very disabled due to pain and abnormal sensation with distal distribution affecting the lower and very frequent the upper limbs associated in some cases with autonomic dysfunction. (4,6)

In contrast with the usually severe symptomatology, the paucity of findings on clinical examination and electrophysiologic studies could be puzzling. (5)

Electrophysiology reflects dysfunction of large myelinated fibers, but has a limited value for following small fiber involvement.

So the use of QST may provide significant data to facilitate the evaluation of this syndrome and neuropathic pain that represents the most disabling symptom. (5, 6)

PATIENTS AND METHOD

Our study included 15 patients previously diagnosed with neuropathic pain due to small fiber sensory polyneuropathy based on clinical and electrodiagnostic criteria.

Variables were compared with an age matched control group of 7 healthy persons.

All the patients signed the informed consent form.

Clinical criteria consisted in presence of pain and sensory abnormalities with distal symmetrical distribution affecting lower limbs and sometimes upper extremities also.

Duration of symptoms at inclusion was over 3 months and intensity of pain was self rated by the patient using Visual Analogue Scale (VAS).

Patients included in the study had appreciated their medium pain scores as being over 4 on 10 cm VAS for the last 4 weeks before inclusion.

Etiology of neuropathic involvement	Number of cases
diabetes	10
toxic	3
paraneoplasia	2

Etiology of neuropathic involvement was diabetes melitus in 10 patients, toxic in 3 patients and paraneoplasia in 2 cases.

Nerve conduction studies excluded motor involvement and a pattern of distribution for sensory changes that suggested predominant involvement of dorsal ganglia (absence of proximo - distal gradient).

Patients included in the study performed:

1. rating of neuropathic component of pain using Pain Detect Scale
2. quantitative sensory testing using MEDOC Thermotest

Pain Detect Scale (3), validated for Romanian language, was completed by the patients themselves after a short instruction.

The maximum score is 38 points. A score over 18 points means that the neuropathic component of pain is probable (over 90%).

A score between 13 and 18 means that the neuropathic component could be present but some other mechanisms for pain are also involved.

A score under 12 makes the neuropathic character of pain unlikely (figure1).

Medoc Thermotest is using thermal stimulation based on Peltier principle – alternating the direction of current through a metal thermocouple, the metallic surface could became alternatively warm or cool. Computer software can generate temperatures throughout the physiologic range (0-50 degree C) or alter the duration of stimulus.

Test algorithm was referred to as the *method of limits* and required patients to press a button when an increasingly strong stimulus was first perceived. In this method the stimulus intensity continues to increase during the reaction time so it is called reaction time – inclusive.

We have tested four parameters:

Cooling detection threshold – first perception of cold.

Warming detection threshold – first perception of warm.

Cold pain detection threshold – first perception of cold as having a painful character

Heat pain detection threshold – first perception of heat as being painful.

painDETECT CHESTIONAR CU PRIVIRE LA DURERE

Data: Pacient: Nume: Prenume:

Cum ați aprecia durererea dvs. **acum**, în acest moment?

0 1 2 3 4 5 6 7 8 9 10

Durere absentă — Durere maximă

Cât de puternică a fost **cea mai puternică** durere pe care ați simțit-o în cursul ultimelor 4 săptămâni?

0 1 2 3 4 5 6 7 8 9 10

Durere absentă — Durere maximă

Cât de puternică a fost durerea **în medie** în cursul ultimelor 4 săptămâni?

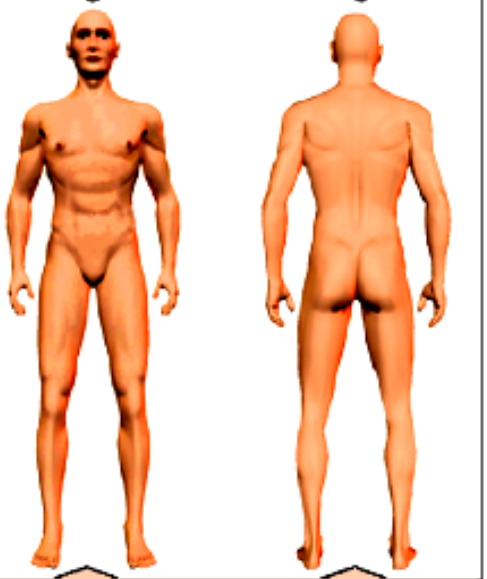
0 1 2 3 4 5 6 7 8 9 10

Durere absentă — Durere maximă

Marcați imaginea care descrie cel mai bine evoluția durerii dvs.:

- **Durere persistentă, cu ușoare variații** ☐
- **Durere persistentă cu atacuri dureroase din când în când** ☐
- **Atacuri dureroase fără durere între acestea** ☐
- **Atacuri dureroase frecvente cu durere persistentă între acestea** ☐

Vă rugăm să indicați **principala zonă dureroasă** prin haşurarea cu pixul a acestei zone



Durerea dvs. iradiază în alte regiuni ale corpului? da ☐ nu ☐

Dacă da, vă rugăm să desenați o săgeată care să arate direcția în care iradiază durerea.

Aveți senzație de arsură (de ex., senzație de urzicare) la nivelul zonei dureroase?

deloc ☐ foarte puțin ☐ puțin ☐ moderat ☐ mult ☐ foarte mult ☐

Aveți senzație de mâncărime sau înțepături la nivelul zonei dureroase (cum ar fi furnicături sau senzație de curentare ușoară)?

deloc ☐ foarte puțin ☐ puțin ☐ moderat ☐ mult ☐ foarte mult ☐

Atingerile ușoare (prin îmbrăcăminte, pătură) vă provoacă durere la nivelul zonei dureroase?

deloc ☐ foarte puțin ☐ puțin ☐ moderat ☐ mult ☐ foarte mult ☐

Suferiți de atacuri dureroase fulgerătoare, ca niște șocuri electrice, la nivelul zonei dureroase?

deloc ☐ foarte puțin ☐ puțin ☐ moderat ☐ mult ☐ foarte mult ☐

Simțiți uneori durere la rece sau la cald (apa de baie) la nivelul zonei dureroase?

deloc ☐ foarte puțin ☐ puțin ☐ moderat ☐ mult ☐ foarte mult ☐

Aveți senzație de amorțeală la nivelul zonei dureroase?

deloc ☐ foarte puțin ☐ puțin ☐ moderat ☐ mult ☐ foarte mult ☐

Aplicarea unei presiuni ușoare la nivelul zonei dureroase, de ex., prin apăsarea degetului, declanşează durere?

deloc ☐ foarte puțin ☐ puțin ☐ moderat ☐ mult ☐ foarte mult ☐

(A se completa de către medic)

deloc	foarte puțin	puțin	moderat	mult	foarte mult
x 0 = 0	x 1 =	x 2 =	x 3 =	x 4 =	x 5 =

Scor total ___ **din 35**

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Figure 1. *Questionnaire in Romanian*

painDETECT

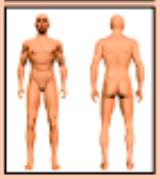
Calcularea scorului chestionarului cu privire la durere

Data: Pacient: Nume: Prenume:

Vă rugăm să transcrieţi scorul total din chestionarul cu privire la durere:

Scor total ☐☐

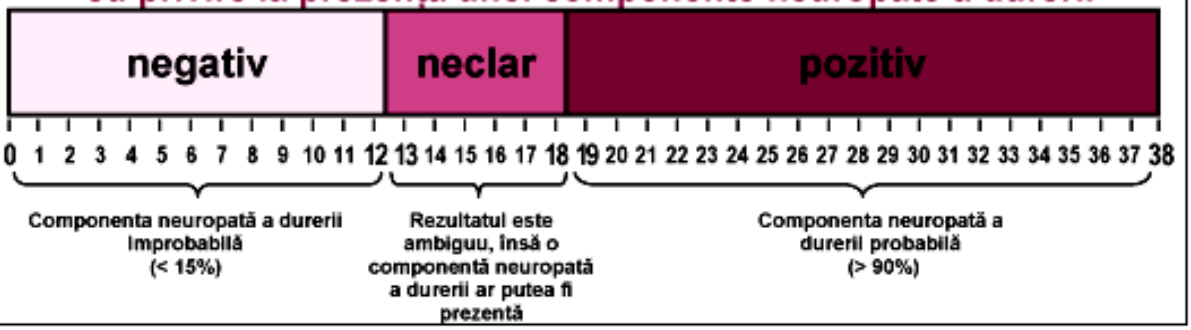
Vă rugăm să adunaţi următoarele cifre, în funcţie de modelul de evoluţie a durerii marcat şi de iradierea durerii. Apoi calculaţi scorul final:

	Durere persistentă, cu uşoare variaţii	0
	Durere persistentă cu atacuri dureroase din când în când	-1 dacă a fost marcat, sau
	Atacuri dureroase fără durere între acestea	+1 dacă a fost marcat, sau
	Atacuri dureroase frecvente cu durere persistentă între acestea	+1 dacă a fost marcat
	Dureri care iradiază?	+2 dacă da

Scor final ☐☐

Rezultatul screening-ului

cu privire la prezenţa unei componente neuropate a durerii



Acest formular nu înlocuieşte diagnosticul medical!
El este utilizat în screening-ul prezenţei unei componente neuropate a durerii.

DFNS

pain

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Figure 2. *Questionnaire in Romanian*

RESULTS AND DISCUSSION

Age of patients included in the study ranged from 43 to 77 (mean 60.8, ± 9.9 SD)

Disease duration was highly variable in the study group from 6 month to 10 years (median duration was 16.5 month).

Assessment of pain intensity on 10 cm VAS ranged from 4 to 9 and had a symmetrical distribution – mean score was 6.9 (±1.5 SD).

Evaluation of neuropathic component of pain using Pain Detect Questionnaire:

- 25% of patients rated their pain between 12 and 18 (first quartile Q1= score 18)
- 75% of patients scored their pain as clearly neuropathic – over 18 (Q2 = 21, Q3 = 26) mean value of PD score was 21.4 (±5.1, quotient of variation CV= 23.8%).

Amplitude of sural nerve sensory action potential (SNAP) ranged from 1 microV to 15 microV – mean 6.96 microV and high dispersion (±3.8 microV, QV=54.6%), median value of amplitude 7.25microV.

Amplitude of peroneal nerve SNAP ranged from 2.9 microV to 11 microV – mean amplitude 6.37 microV (±2.3 microV, QV=36.1%), median value for amplitude 6.65 microV would characterize better the distribution.

Sural nerve sensory conduction velocity varied between 24.6 m/s and 54.8 m/s – mean 36.8m/s (±8.9m/s, QV = 24.2%). Q1=30.8m/s, Q2=34.7m/s, Q3=41.6m/s.

Peronier nerve conduction velocity varied between 28 m/s and 51.8 m/s – mean conduction velocity was 38.7 m/s (±6.3m/s, QV=16.4%)

Parameters evaluated with QST

Distribution of values recorded for cooling and warming detection threshold:

	Cooling detection threshold (degreeC)	Warming detection threshold (degreeC)
Interval of variation	18 - 30.8	35.2 - 48.4
Q1	21	37.7
Q2	24.7	39.9
Q3	26.2	44.3
mean	24.3	41.2
SD	±3.9	±4.3
QV	16.3%	10.4%

Distribution of values recorded for cold and heat pain thresholds:

	Cold pain threshold (degreeC)	Heat pain threshold (degreeC)
Interval of variation	0-27.4	43.8-50.0
Q1	7.8	47.9
Q2	14	48.85
Q3	21	50.0
mean	13.95	48.3
SD	±7.98	±2.2
QV	16.3%	10.4%

Comments

We noticed a large dispersion of values recorded for cold pain threshold and a low dispersion for values of heat pain threshold.

Correlation analisis between parameters of nerve conduction studies and the rating of pain intensity on VAS:

	Correlation coefficient (r)	Coefficient β	Statistical significance (p<0.05)
Score on VAS – amplitude of sural SNAP	- 0.35	- 0.14	n.s.
Score on VAS – amplitude of peronier SNAP	- 0.24	- 0.16	n.s.
Score on VAS – SCV on sural	- 0.43	- 0.07	n.s.
Score on VAS – SCV on peronier	- 0.32	- 0.08	n.s.

Comments

Values obtained for variation coefficients did not indicate a statistical significant correlation between the rating of pain intensity on VAS and amplitude of SNAP on peroneal and sural nerves, a parameter that express the loss of large myelinated sensory fibers as a consequence of polineuropathic involvement.

Correlation analysis for intensity of pain scored on VAS versus parameters tested on QST:

	Correlation coefficient (r)	Coefficient β	Statistical significance (p<0.05)
Score on VAS – coolin detection threshold	- 0.05	- 0.01	n.s.
Score on VAS – warming detection threshold	- 0.09	- 0.03	n.s.
Score on VAS – cold pain threshold	- 0.03	- 0.006	n.s.
Score on VAS – heat pain threshold	- 0.05	- 0.03	n.s.

Comments

Low values for correlation coefficients indicated a low correlation, statisticaly not significant for intensity of pain on VAS and thermal thresholds evaluated on QST, parameters that express the loss of small sensory fibers.

Correlation analysis for PD score – neuropathic component of pain and sensory nerve conduction parameters:

	Correlation coefficient (r)	Coefficient β	Statistical significance (p<0.05)
Score on PD – amplitude of sural SNAP	- 0.32	- 0.43	n.s.
Score on PD – amplitude of peronier SNAP	- 0.30	- 0.66	n.s.
Score on PD – SCV on sural nerve	- 0.48	- 0.27	n.s.
Score on PD – SCV on peroneal nerve	- 0.27	- 0.21	n.s.

Comments:

Low values of correlation coefficients indicated a low correlation for score on PD and sensory nerve conduction parameters that failed to reach statistical significance for a threshold of 5%.

Correlation analysis for score obtained on PD scale and parameters evaluated with QST:

	Correlation coefficient (r)	Coefficient β	Statistical significance (p<0.05)
Score on PD – cooling detection threshold	- 0.72	- 0.91	significant
Score on PD – warming detection threshold	- 0.24	- 0.28	n.s.
Score on PD – cold pain threshold	- 0.03	0.01	n.s.
Score on PD – heat pain threshold	- 0.34	- 0.79	n.s.

Comments:

We noticed a high indirect correlation, statistically significant for score on PD that express the neuropathic component of pain and cooling detection threshold associated with the hypoactivity of A delta small myelinated fibers.

Comparative distribution of values obtained for sensory nerve conduction studies and QST versus control group:

Parameter	Mean values for patients	Mean values for control group	Statistical significance
Amplitude of sural SNAP	6.96 microV	11.2 microV	s (t_c=2.58, p=0.01)
Amplitude of peroneal SNAP	6.37 microV	12.18 microV	s (t_c=4.65, p<0.001)
SCV for sural nerve	36.78 m/s	58.08 m/s	s (t_c=5.47, p<0.001)
SCV for peroneal nerve	38.65 m/s	52.27	s (t_c=4.40, p<0.001)
Cooling detection threshold	24.28 C^0	29.17 C^0	s (t_c=3.01, p<0.001)
Warming detection threshold	41.08 C^0	40.55 C^0	n.s. (t_c=0.27, p>0.05)
Cold pain threshold	13.95 C^0	26.94 C^0	s (t_c=4.18, p<0.001)
Heat pain threshold	48.34 C^0	44.72 C^0	s (t_c=2.72, p=0.01)

Comparative analysis for sensory nerve conduction studies in the group of patients diagnosed with small fiber sensory polyneuropathy and control group revealed significant lower values for nerve conduction studies in patients diagnosed with small fiber sensory polyneuropathy suggesting involvement of large myelinated sensory fibers also.

Concerning parameters assessed on QST, excepting warming detection threshold, all the tested variables were altered statistically significant in the patient group suggestive for sensory loss due to injuries of small sensory fibers conducting pain and thermal sensation.

CONCLUSIONS

Quantitative sensory testing for thermal stimuli using the thermotest-limits method was a sensitive technique for evaluation of patients with small fiber sensory polyneuropathy.

QST was as helpful in confirming the clinical impression of sensory abnormalities related to this pathological process as routine nerve conduction studies is.

Regarding the neuropathic pain severity we could not find any positive correlation with alterations of nerve conduction studies, but the score on Pain Detect Questionnaire had statistically significant correlation with values recorded for cooling detection threshold on QST, documenting sensory loss and A delta fibers dysfunction.

Further studies and larger samples are needed to evaluate the place of QST in the diagnosis work-up for small fiber sensory polyneuropathy with severe pain but only minimal objective clinical abnormalities and normal nerve conduction studies.

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