

REVISIÓN

Phenotypes and diagnosis in neuropathic pain

Fenotipos y diagnóstico en dolor neuropático

ABSTRACT:

Introduction: Although all the clinical pictures of peripheral neuropathic pain have a common denominator as a characteristic, that is; damage or disease of the somatosensory nervous system, we must estimate that the underlying etiologies and pathogenesis of these damages may be different and also the patterns of sensory signs and symptoms that develop after neuropathy vary between different etiologies and even between individual patients with neuropathies of the same etiology.

Objectives: To synthesize and disseminate the studies carried out by Dr. Jan Vollert and his teams in patients with peripheral neuropathic pain using quantitative sensory tests or Quantitative Sensory Testing (QST), in order to classify patients into subgroups

AUTHORS:

Eduardo Marchevsky, Facultad de Medicina, Universidad de Buenos Aires. Coordinador del Grupo de Interés Especial en Dolor Neuropático de la AAED. Buenos Aires, Argentina; **Santiago Guaycochea**, coordinador de Medicina del Dolor Sanatorio Otamendi, Sanatorio Finochietto y Maternidad Suizo Argentina. Director del Centro de Medicina del Dolor Pain Care Center. Buenos Aires, Argentina; **Mariana Bendersky**, profesora Adjunta de Anatomía y Neurología, Facultad de Medicina, Universidad de Buenos Aires. Neurofisióloga del Hospital Italiano de Buenos Aires. Buenos Aires, Argentina. **Susana González**, Facultad de Medicina, Universidad de Buenos Aires. Laboratorio de Nocicepción y Dolor Neuropático IBYME-CONICET. Buenos Aires, Argentina

CORRESPONDENCE:

marchevsky.eduardo@gmail.com

(phenotyping), improving the design of clinical trials and future therapeutic strategies.

Material and methods: The source used to review articles included the *Pain Journal* between 2015 and 2018 inclusive and the PubMed database.

Results: It was possible to synthesize the results that relate the symptoms with possible subgroups of patients and the evolution of that said research.

Conclusion: A feasible algorithm to be used for stratification of patients suffering from secondary pain in peripheral neuropathic disease or in clinical trials has been presented that may indicate more effective treatment strategies in the future. However, the challenge will be to develop with more studies an algorithm that more precisely allocates patients to the groups described in this review.

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Palabras clave: *Pruebas sensoriales cuantitativas, fenotipo sensorial, red alemana de investigación sobre dolor neuropático, polineuropatía, lesión de nervio periférico.*

RESUMEN:

Introducción: Aunque todos los cuadros clínicos de dolor neuropático periférico tienen un común denominador como característica, es decir, el daño o enfermedad del sistema nervioso somatosensorial, debemos estimar que las etiologías subyacentes y la patogénesis de estos daños pueden ser distintas y, además, los patrones de los signos sensoriales y los síntomas que se desarrollan después de la neuropatía varían entre diferentes etiologías e incluso entre pacientes individuales con neuropatías de la misma etiología.

Objetivos: Sintetizar y divulgar los estudios realizados por el Dr. Jan Vollert y sus equipos en pacientes con dolor neuropático periférico, empleando pruebas cuantitativas sensoriales o *Quantitative Sensory Testing* (QST), con la finalidad de clasificar pacientes en subgrupos (fenotipado), mejorando el diseño de ensayos clínicos y las futuras estrategias terapéuticas.

Material y métodos: Las fuentes utilizadas para la revisión de artículos fueron la revista *Pain*, entre los años 2015 y 2018 (ambos inclusive), y la base de datos PubMed.

Resultados: Se pudieron sintetizar los resultados que relacionan los síntomas con posibles subgrupos de pacientes y la evolución de dicha investigación.

Conclusión: Se ha presentado un algoritmo factible de usarse para estratificación de pacientes que padecen dolor secundario en neuropatía periférica, o para ensayos clínicos que puedan indicar en el futuro estrategias de tratamiento más efectivos. No obstante, el desafío será desarrollar con mayor cantidad de estudios un algoritmo que asigne en forma más precisa los pacientes a los grupos descritos en esta revisión.

Introduction

In the Argentinean Association for the Study of Pain (AAED), member of the international Association for the Study of Pain (IASP), we are committed to the spread of every scientific advance on diagnosis and treatment of pain. With this view, the neuropathic pain research group of AAED, has carried out a revision based on the research and publication of Jan Vollert, who is a researcher of the Department of Surgery and Cancer from the faculty of medicine of the Imperial College London (England), who received for these publications the Ronald Dubner Research award given by the IASP, for the use of Quantitative Sensory Testing (QST) in peripheral neuropathic pain diagnosis.

According to IASP's definition, neuropathic pain develops as a result of an injury or disease affecting the somatosensory nervous system (1). This system is a group of neural networks of the CNS that receives, processes and associates every afferent stimulus which comes from the individuals' sensory nerve endings, including balance, posture and movement through space and time.

Despite the breakthroughs on the understanding of the complex neurobiology of pain, the pharmacological management of these syndromes is still insufficient and several promising medicines have failed even during the last developmental stages, this failure is in some occasions attributed to an inadequate classification of the criteria for inclusion as pain phenotypes were not taken into consideration (2,3).

In current practice, a specific treatment is usually administered to a wide range of patients with the same etiological cause. Therefore, it is presumed that they would all be similar to an "average" patient so as to achieve a unique convergence of the treatment's effect. Nevertheless, from the etiological therapeutic approach, first line treatments are beneficial on less than 50% of patients, as well as the low response rate on clinical trials (4-6).

Currently, it is considered inappropriate and insufficient the approach of grouping neuropathic component expressions of pain according to the etiologies of the causing pathologies, when there is existing research pointing out the need to predict which are going to be the patients that respond to treatment, both for clinical practice and for clinical trials' design (3,7).

First line treatments are beneficial on less than 50% of patients

Even though every clinical picture of neuropathic pain has a common factor as a characteristic, a somatosensory nervous system damage or disease, we should estimate that the underlying etiologies and pathogenesis of these damages may be different and that sensory signs' patterns and the symptoms developed after the neuropathy vary between different etiologies and even between patients with neuropathy with the same etiology (8).

Materials and methods

For this revision, the publications in Pain magazine by Jan Vollert and collaborators between the years 2015 and 2018 were taken into consideration (9-13) as well as the bibliography associated with these articles which support the concepts mentioned in said publications, consulting PubMed database.

These investigations are centred in the implementation of statistical and computational models for pain research, mainly using Quantitative Sensory Testing (QST) on patients suffering from peripheral neuropathic pain.

Brief history

For some time, there has been a search for a diagnosis strategy for neuropathic pain which would allow to gather symptomatic expressions and sensory signs together, so that it leads to a treatment approach based on mechanisms aiming for more effective results. This is why, more than 20 years ago, the physiopathological mechanism-based classification strategy was proposed, which means, grouping the patients' neuropathic component according to the pain generating mechanism and not exclusively due to its etiology.

This hypothesis has been first proposed by Max (15), who claimed that the development of mechanism-based treatments required three coordinated research efforts:

1. preclinical studies on pain mechanisms and drug targets.
2. the development of patients' classification that correspond with underlying mechanisms of pain.
3. clinical trials designed for examining which patients' subgroup best responds to specific treatments.

Subsequently, Fields (16), Von Hehn (17) and Baumgartner (18), identified two main patient subtypes according to the damage of their nerve fibres: patients with "irritable nociceptors" and patients with "deafferentation". This last group, characterized by afferent impulses interruption due to damage to the neural pathway was in turn divided into patients with and without mechanical or dynamic allodynia.

In 2003, Jensen (19) was already categorical: "a completely new strategy has been proposed, in which pain is differentiated based on underlying mechanisms emphasizing the justification of a treatment approach directed at mechanisms rather than at diseases". And in the conclusions he adds: "This can be done once there is consensus about what the content should be in the examination" (19).

This aforementioned concept can be articulated through the stratification of clinical profiles, which has the aim of obtaining subgroups of patients whose utility would be redundant in terms of a higher certainty of diagnosis, prognosis and/or treatments. Lately we count with the necessary tools for the identification of patient subgroups based on the protocols used for the phenotyping of the population affected by a particular syndrome (20).

It has to be said that given the complexity of the clinical profiles, some difficulty may exist to unequivocally classify some patients into a particular subgroup and therefore it will be the doctors' judgement that will take precedence on the patients' classification to the most relevant phenotype for their prognosis and treatment.

Definition

We define phenotype as "the set of observable characteristics shown by an organism". Even though some phenotype considerations are objective and do include genetic data evaluation (e.g., the functional genetic variation SCN9A related to sodium channels alteration), the research that we will mention is mainly focused on phenotypes formed by the study of patient informed symptoms (psychosocial factors, symptoms characteristics, sleeping patterns) or the response to accurately calibrated standardized somatosensory stimuli provocation (QST) (21, 22).

Grouping the patients' neuropathic component according to the pain generating mechanism and not exclusively due to its etiology

Nowadays, phenotypes are already being used in different specialties. For example, on the cardiovascular field (23), on pneumology (24), in sleep medicine (25), etc.

In pain medicine, the neuropathic pain applied phenotype concept has resulted in the ensemble of different kinds of patients with a prognostic and therapeutic relevance.

“Sensory phenotype”, “sensory profile” or “individual somatosensory profile” are some names that can be found in different publications and is a terminology which refers to the neuropathic pain generation mechanisms that reflect on the signs and sensory symptoms the patient shows individually.

Therefore, the new concepts propose the patient stratification according to the pain mechanisms expressed in their sensory profile. This would promote an upgrade on the design of clinical trials with the aim of leading to a stratified treatment approach and finally to a customized treatment (26,27).

Based on Campbell’s work (28), Baron (9) describes “Individual Somatosensory profile” as the assortment of hyperalgesia, allodynia and sensory loss, since these reflect the physiopathological mechanisms that affect the damaged and surviving nerve fibres, which the most frequent consequence is the presence of afferent nerve fibres with conduction blockade, the generation of ectopic impulses, and peripheral and central sensitization.

Research

In order to maintain this research direction and to develop reliable phenotyping, the authors on which this revision is based assembled different stages with concrete results according to a different neuropathic pain classification for its treatment. The focus of this research involves establishing if there are groups of patients with a higher response probability (or better tolerance) when a specific treatment is administered (29,30).

This development came in different stages:

- In 2015, the results were published for the assessment of the use of QST and its reliability degree using the dollee DFNS protocol (German Research Network on Neuropathic Pain) (10).
- After this, in 2016, QST trials were assessed according to DFNS

protocol, comparing it against the results of other European countries (11). A conclusion is drawn where QST, both in healthy individuals and in patients with peripheral neuropathic pain, was homogeneous to a great extent within the European centres, being this an essential previous requirement for the conduction of multi-centred studies based on QST (11).

- In 2017, through its Committee for Medicinal Products for Human Use, the European Medicines Agency (EMA), recommended: a) the sensory phenotypes stratification on patients for trials on neuropathic pain, b) the determination of eligible sensory phenotypes on patients for trials on neuropathic pain, and c) the incorporation of the new indicator on the clinical development of new pain treatments guide (31).

Based on these recommendations, in the year 2017 a statistical study started which main purpose was to identify subgroups from a big sample of peripheral neuropathic pain patients. As a result, three subgroups or profiles of patients with pain were identified which could be related with the physiopathological mechanisms and therefore, they could be potentially useful for the design of clinical trials that may increase the study population in the search for treatment responders (9).

Since then, different studies published in Pain magazine (9, 12, 13), proposed reasons to consider these three fundamental phenotypes, namely: 1) sensitivity loss, 2) thermal hyperalgesia, 3) mechanical hyperalgesia (Figure 1).

As previously clarified, not every patient met the necessary criteria to classify them unequivocally into the subgroups, and the doctors’ clinical judgement will be what defines which phenotype best suits the patient according to their prognosis. In this direction, the clinical examination will classify the patient independently of their base pathology. Therefore, we should be able to identify, given the patients signs and symptoms, the subgroup they belong to and be guided to the best treatment possible.

The interest on predictive phenotyping means advancing with the goal of adapting personalized treatments, and a future where patients are phenotyped in a comprehensive way (besides being diagnosed on their base pathology), and the professional can operate consistently with algorithms that match with the patient’s

The assortment of hyperalgesia, allodynia and sensory loss, reflect the physiopathological mechanisms that affect the damaged and surviving nerve fibres

profiles for the optimal treatment combination, as an intermediate step towards a more “profound” phenotype (22).

So, the new concepts suggest the stratification of the patient according to their pain mechanism. The challenge presented is to identify the phenotypic characteristics which are measurable on the patient, and that these are as predictive as possible for the analgesic treatment’s results, as well as having the adequate measurement tools to test these characteristics.

A common factor in these types of analysis has been the QST implementation as a reliable measurement resource, given that it is a psychophysical tool which assesses the sensory perception evoked as a response to a certain sensory stimulus (32).

The goal of the research regarding this matter published between 2017 and 2018 by IASP was to provide the scientific and medical community with an algorithm based on previous works, to classify sensory phenotypes and to create a stratification which allows to perform: a) clinical trials, b) efficient for hospitalized patients.

Materials and methods on the works published by Jan Vollert and his team

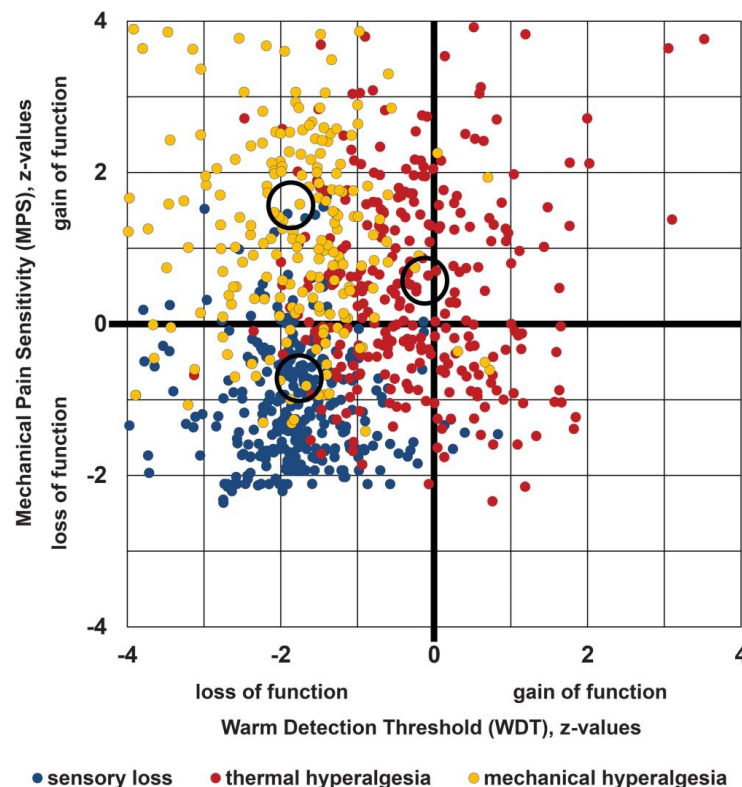
Cluster analyses were performed in order to identify and cross-validate three subgroups of patients with peripheral neuropathic pain. Patients were assigned to each of the three aforementioned phenotypes.

The research was based on patients recruited by the DFNS consortium (10 centres from the German Research Network on Neuropathic Pain), IMI (Innovative Medicines Initiative, European pharmaceutical consortium), Europain (academic group from Germany, Denmark, United Kingdom, and Spain that researches pain), Neuropain (neuropathic pain experts group sponsored by Pfizer Ltd), and Pain in Neuropathy Study PiNS (observational cross-sectional multicentre study).

The standardized QST protocol, developed and validated by DFNS, includes 13 sensory function parameters (32,33).

These are:

- Cool detection threshold.
- Warm detection threshold.



Blue: sensory loss. Red: thermal hyperalgesia.

Yellow: mechanic hyperalgesia.

Authorship by Baron et al. (9). Publication authorized.

- Paradoxical heat sensation (alternating cool and warm stimuli).
- Cold pain threshold.
- Heat pain threshold.
- Tactile and vibration detection threshold.
- Mechanical pain sensitivity.
- Mechanical pain threshold including pinprick stimuli.
- Intense pressure induced pain threshold.
- Stimulus-response for pinprick-evoked pain.
- Dynamic mechanical allodynia.
- Repetitive pinprick stimuli.
- Negative for every parameter (function loss).

Figure 1.
This figure illustrates the distinction between the 3 subgroups, sorted out by colour in a 2-D scattering plot. One axis for heat detecting threshold in order to assess function loss degree (horizontal axis) and another index to express mechanical pain sensitivity intensity (vertical index).

Cluster analyses were performed in order to identify and cross-validate three subgroups of patients with peripheral neuropathic pain

Four pathologies that usually develop a neuropathic component were chosen, namely: *diabetic polyneuropathy, peripheral nerve lesion, radiculopathies and postherpetic neuralgia*, providing the phenotypic frequencies and suggesting minimum sample sizes for stratified phenotype assays.

Even though idiopathic trigeminal neuralgia appears amongst the pathologies previously mentioned in the ICD 11 from new classification of the International Statistical Classification of Diseases and Related Health Problems (ICD) (34), it wasn't included in this research in the peripheral nerve damage group due to its unclear origin and its distance from what a classic peripheral neuropathy is.

This selection allowed the use of statistical segmentation methods. This enabled the exploration of the intrinsic pattern of the sensory profiles in a wide representative range of patients suffering from peripheral neuropathic pain.

A standardized protocol was implemented, using QST as a tool on patients with peripheral neuropathic pain from the different, previously described, etiologies with the following aims:

1. Describe and analyse typical patterns of sensory signs on more than 900 patients, with a validation cohort of more than 200 patients.
2. Gather patients into subgroups based on characteristic sensory profiles.
3. Establish an organizational principle for neuropathic pain based on the sensory profile.
4. Replicate the results in a second, independent cohort consisting of more than 200 patients.

The QST assesses the sensory function of A-beta myelinated fibres and, C and A delta unmyelinated fibres, both for function loss (hypoesthesia) or gain in function (hyperalgesia, allodynia) and altered temporal summation (33).

Peripheral neuropathic pain is induced by partial damage on the neural pathway. This can, as previously said, aggravate two kinds of nociceptors candidates for producing pain: damaged nociceptors and surviving nociceptors without damage to their basic structure. The latter may be peripherally sensitized by inflammatory processes related to denervation and reinnervation being the cause for hyperalgesia. Damaged nociceptors are responsible

for denervation induced sensory loss, but they are as well responsible for continuous pain due to ectopic activity that arises from the periphery or second-order neurons with denervation.

Both types of nociceptors may, in turn, lead to the sensitization of neural pathways causing hyperalgesia and/or allodynia. So, we have four possible mechanisms for peripheral neuropathic pain: denervation, ectopic activity, peripheral sensitization and central sensitization. Despite the ectopic activity being related to spontaneous pain, the remaining three mechanisms are linked to evoked pain altered perception and consequently registered by QST (13).

These profiles coincide with the ones generated by substitute human models with well-defined mechanisms, meaning that evidence exists sustaining that these phenotypes are linked to neuropathy mechanisms or neuropathic pain (13).

Results

The aforementioned studies confirmed three different predominant phenotypes, that are mainly characterized by:

1. Mechanical sensory loss and thermal alteration, afterwards called "*sensory loss*" and identified in these works with the colour blue. About 52 % of patients suffering from polyneuropathies were included in this category that indicates degeneration and death of almost all kinds of fibre. The sensory profile is similar to that of a nerve compression or blockade. The paradoxical heat feeling sensation was more frequent (43 %), which suggests that this is a positive sensory sign possibly related to a central uninhibitedness process. It is possible that it represents the so-called painful hypoesthesia. Spontaneous pain could be caused by ectopic action potentials originated in sites close to damaged nociceptors, for example, in the dorsal root ganglion. Denervation and loss of function of nerve fibres may appear. They are better opioid respondents. Some diabetic patients have responded better to duloxetine.
2. Sensory function of unmodified small fibres, associated with hyperalgesia produced by warm or cool and mild dynamic mechanical allodynia, afterwards named "*thermal hyperalgesia*"

The QST assesses the sensory function of A-beta myelinated fibres and, C and A delta unmyelinated fibres

shown in red in this research. 33 % of patients from all the chosen pathologies, maintained their functions preserved despite evident nerve fibres damage, which indicates that peripheral neuropathic pain may be associated with an effective axonal regeneration and with sensitized nociceptors. This subgroup could be linked to “irritable nociceptor” cases described by other authors.

Sensitized nociceptors are generally associated with channel overexpression and receptors that lead to a spontaneous discharge and a reduced activation threshold for warm, cool and mechanical stimuli. Surviving nociceptors may be responsible for continuous pain due to constant hyperactivity.

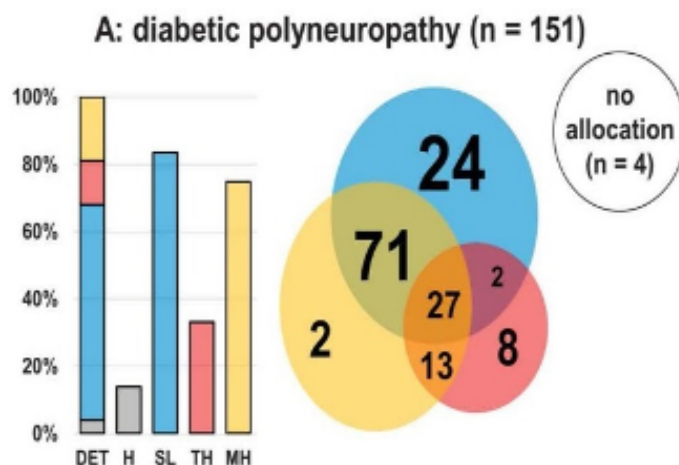
It may provoke central sensitization on the spinal cord dorsal horn, in a way that tactile stimuli transported by A fibres may activate C nociceptor neurons, giving place to hyperalgesia and/or allodynia 12.

Nevertheless, hyperalgesia occurred only in 20 % of the cases, which shows that the peripheral nociceptors’ unit does not always induce central sensitization. This group responds better to carbamazepine.

3. Loss of thermal sensation. This group was characterized by function loss on the small fibre to cool-warm in combination with pressure hyperalgesia and dynamic mechanical allodynia. Afterwards referred to as “mechanical hyperalgesia” it is represented in yellow in these works. This subgroup is associated in 47 % of the cases to postherpetic neuralgia and burning pain predominates. Probably this subgroup is equivalent and described by other authors as “neurogenic hyperalgesia” or “central sensitization”, it responds best to pregabalin, topical or intravenous lidocaine and lamotrigine.

The most common phenotype for diabetic polyneuropathy was sensory loss (83 %) shown in blue, followed by mechanical hyperalgesia (75 %) in yellow and thermal hyperalgesia (34 %) in red (Figure 2).

As it may seem evident, *the same patient may be assigned to more than one phenotype*. It will be the doctor’s decision to take into consideration all the elements gathered in the medical history, screening tests, physical exam, etc. and then choose which subgroup will be ideal for a more effective treatment for the patient.



H: healthy. SL: sensory loss (blue). TH: thermal hyperalgesia (red).

MH: mechanical hyperalgesia (yellow).

DET: deterministic algorithm.

Authorship by Vollert et al. (12). Publication authorized.

Conclusion

Based on the results of Jan Vollert’s works revision, we show the validation of the mechanistic profiles, demonstrated by the assignation precision of approximately 80 %.

In these analyses, models do not explicitly cover endogenous pain modulatory systems, nor ectopic activity. Moreover, small differences in inclusion criteria may exist between the consortiums. Short term follow up is another limitation given that some patients could swap groups in a longer period of time. Therefore, it is not clear enough how stable these phenotypes are and they should be taken as a guide to suggest possible medication that should be prioritized for given patients.

The challenge will be to develop an algorithm that assigns patients in a more precise way to the groups described in this study.

To summarize, an algorithm has been presented that may be used for stratifications of patients suffering from secondary pain in peripheral neuropathy or in clinical trials that may indicate

Figure 2.
Is a Venn diagram where percentages are not additive. Overlappings can be assigned to more than one phenotype in circles that are not to scale, or it may be divided in patients with neuropathic pain and healthy patients (sensitivity: 78 %, specificity: 94 %). Bars are scaled.

The most common phenotype for diabetic polyneuropathy was sensory loss

more effective treatment strategies in the future. Even though the 3 phenotypes are present in diabetic polyneuropathy, peripheral nerve damage and postherpetic neuralgia, frequencies differ, which should affect the number of patients selected for clinical trials (27).

Undoubtedly, in the last years problems related to the design, results and reports about this subject have contributed to the necessity of change, but the implementation of this approach must be accessible for the majority of doctors, and therefore is up to the research community to investigate further the concept of pain therapy based on mechanisms, needing time and cost-efficiency, as well as effective and easy to standardize stratification tools.

Even though nowadays in the majority of pain units there is a lack of these precision instruments, it is important to be informed about the breakthroughs made worldwide on what concerns neuropathic pain diagnosis and believing that in a not so far future we could replicate this research in a multicentred work in our country.

Conflict of interest

Authors declare not to have any conflict of interests.

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Problems related to the design, results and reports about this subject have contributed to the necessity of change

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