

Neuropathic pain: are there distinct subtypes depending on the aetiology or anatomical lesion?

Nadine Attal, Christian Fermanian, Jacques Fermanian, Michel Lantéri-Minet, Haiel Alchaar, Didier Bouhassira

▶ **To cite this version:**

Nadine Attal, Christian Fermanian, Jacques Fermanian, Michel Lantéri-Minet, Haiel Alchaar, et al.. Neuropathic pain: are there distinct subtypes depending on the aetiology or anatomical lesion?. Pain, 2008, 138 (2), pp.343-53. 10.1016/j.pain.2008.01.006 . inserm-00292335

HAL Id: inserm-00292335

https://inserm.hal.science/inserm-00292335

Submitted on 1 Jul 2008

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Neuropathic pain: are there distinct subtypes depending on the aetiology or anatomical lesion?

N Attal[1], MD, PhD, C. Fermanian[2], PhD, J Fermanian[3], MD, PhD, M Lanteri-Minet[4], MD, A. Al Chaar[4] , MD, and D Bouhassira[1], MD, PhD

[1] INSERM U-792, Centre d'Evaluation et de Traitement de la Douleur, Hôpital Ambroise Paré, APHP, Boulogne-Billancourt, F-92100, France; Université Versailles Saint-Quentin, Versailles F-78035, France;

[2] Unité de Recherche Clinique, Hôpital Ambroise Paré, APHP, Boulogne-Billancourt, F-92100,France

[3] Service de biostatistiques, Hôpital Necker, APHP, F-75006 Paris

[4] Centre d'Evaluation et de Traitement de la Douleur, Hôpital Pasteur, F-06100 Nice, France

Corresponding author: Nadine ATTAL, MD, PhD
INSERM U 792
Hôpital Ambroise Paré, AP-HP
9, avenue Charles de Gaulle
92 100 Boulogne-Billancourt
France
Tel: +33 1 49 09 33 34 Fax: +33 1 49 09 44 35
nadine.attal@apr.aphp.fr

ABSTRACT

Neuropathic pain can be caused by a variety of nerve lesions and it is unsettled whether it should be categorised into distinct clinical subtypes depending on aetiology or type of nerve lesion or individualised as a specific group, based on common symptomatology across aetiologies.

In this study, we used a multivariate statistical method (multiple correspondence analyses) to investigate associations between neuropathic positive symptoms (assessed with a specific questionnaire, the Neuropathic Pain Symptom Inventory [NPSI]) and aetiologies, types of nerve lesion and pain localisations. We also examined the internal structure of the NPSI and its relevance to evaluation of symptoms of evoked pains by exploring their relationships with clinician-based quantified measures of allodynia and hyperalgesia.

This study included 482 consecutive patients (53% men; mean age: 58 ± 15 years) with pain associated with peripheral or central lesions. Factor analysis showed that neuropathic symptoms of the NPSI can be categorised into five dimensions. Spearman correlation coefficients indicated that self-reported pain evoked by brush, pressure and cold stimuli strongly correlated to allodynia/hyperalgesia to brush, von Frey hairs and cold stimuli ($p < 0.0001$, $n = 90$). Multiple correspondence analyses indicated few associations between symptoms (or dimensions) and aetiologies, types of lesions, or pain localisations. Exceptions included idiopathic trigeminal neuralgia and postherpetic neuralgia.

We found that there are more similarities than differences in the neuropathic positive symptoms associated with a large variety of peripheral and

central lesions, providing rationale for subgrouping aetiologically diverse neuropathic patients into a specific mulltidimensional category for therapeutic management.

Key words: neuropathic pain; Neuropathic Pain Symptom Inventory; symptoms; multivariate analyses

Word count : abstract 249 ; introduction : 375 ; discussion : 1153.

1- INTRODUCTION

An aetiologically highly heterogeneous group of patients experience neuropathic pain (NP) due to disease or a lesion of the nervous system. NP has many causes, but is characterised by the combination of a relatively small number of core positive symptoms (particularly burning pain, electric shocks, dysaesthesia and allodynia to brush) and negative signs (particularly sensory deficits) distinguishing it from other types of chronic pain (4, 6). We have recently shown that positive symptoms pertained to distinct dimensions (*i.e.* superficial pain, deep pain, paroxysmal pain, evoked pain) (8). However, it is unclear whether the multidimensional nature of NP is related to the aetiology or location of the neurological lesion. In other words, it has not been determined whether the various aetiologies are associated with specific or preferential symptom combinations or, in contrast, whether the clinical expression of NP is similar whatever the underlying cause.

The symptoms probably reflect the pathophysiological mechanisms. Thus, such information may be useful for a mechanism-based approach for selecting therapy for neuropathic pain (3, 6, 7, 8, 19, 37). In particular, identification of sub-syndromes corresponding to various combinations of symptoms (related or not to the aetiology) may contribute to reformation of current therapeutic strategies (7, 8, 19). The traditional aetiology-based categorisation of neuropathic pain still prevails for clinical, experimental (20, 21) and pharmacological studies (1, 11, 14). Pharmacological studies have evaluated neuropathic pain as a global and uniform symptom. This empirical approach may be a main cause of therapeutic failure in these patients (3, 7, 37).

In our study, we used a multivariate statistical method–multiple correspondence analyses (16, 17) to investigate the associations between neuropathic positive symptoms (and dimensions) and aetiologies, types and locations of neurological lesions in a large consecutive sample of patients with neuropathic pain. Negative symptoms or signs (ie, sensory deficits) were not included in these analyses, since they are expected to be more directly associated with nerve lesions. We assessed symptoms and dimensions with the Neuropathic Pain Symptom Inventory (NPSI), a recently validated questionnaire specifically designed for such a purpose (8). We also confirmed the internal structure of the NPSI and determined its relevance to evaluation of symptoms of evoked pain by exploring their relationships with clinician-based quantified measures (*i.e.* quantitative sensory testing) of allodynia and hyperalgesia.

2- METHODS

2.1. Patients

Consecutive patients were recruited from the Pain Centre of Ambroise Paré Hospital (Boulogne-Billancourt) and the Pain Centre of Pasteur Hospital (Nice) between November 2004 and November 2006. Patients had pain attributed to a primary lesion of the peripheral or central nervous system confirmed by appropriate clinical examination by an experienced neurologist and/or additional investigations when required (eg, EMG in most cases of peripheral nerve lesions, spinal cord or brain MRI in patients with lesions of the central nervous system or trigeminal neuralgia). Patients were included if they were > 18 years old; had experienced pain for at least three months with a mean pain intensity ≥ 30/100; had the ability to understand, write and read French; and were making their first visit to the pain clinic. Patients were excluded from the study if they had somatic pain that was more severe than the neuropathic pain, pain of unknown aetiology, a severe progressive disease (eg, cancer, AIDS), a severe psychiatric condition (psychosis, severe depression), chronic alcoholism or substance abuse or a nerve injury that was not clearly identified (*e.g.* complex regional pain syndrome [CRPS] type I, stomatodynia and atypical facial pain).

2.2. Study design and recording

All patients underwent standard clinical neurological examination focused on sensory deficits and evoked pain. They were asked to rate the mean intensity of their pain during the last 24 hours on an 11-point (0-10) numerical scale on the neuropathic pain symptom inventory (NPSI) (8). This questionnaire includes ten symptoms most commonly described by neuropathic patients (burning, pressure, squeezing, electric shocks, stabbing; pain evoked by brushing, pressure, or cold;

tingling, pins and needles). On factor analysis, these symptoms were categorised into five distinct dimensions (eg, combination of symptoms), as previously reported (8): superficial burning pain, deep pain, paroxysmal pain, allodynia and paraesthesia/dysaesthesia. The score obtained for each dimension (from 0 to 10) corresponded to the mean score for individual symptoms, as reported previously (*e.g.* deep pain corresponded to the mean score for pressure and squeezing, paroxysmal pain corresponded to the mean score for electric shocks and stabbing).

2.3. Quantitative sensory testing

Ninety patients from the Ambroise Paré hospital (with the exception of patients with amputation pain and trigeminal neuralgia) were randomly selected for a quantitative sensory assessment of allodynia and hyperalgesia by a second experienced investigator – blinded to results of the questionnaire – using a method largely described elsewhere (2, 10). Measurements were systematically taken in the affected area (the area of maximal pain determined on the day of assessment) and in a normal non-painful area. This normal area was usually on the homologous contralateral side, except in ten patients with painful polyneuropathy. In these patients, the control area was the closest area with normal sensitivity (*i.e.* the thigh). Tactile allodynia (dynamic) was tested for by stroking the skin three times with a paintbrush and was considered to be present if this evoked a clear sensation of pain. The intensity of allodynia within the area of maximal pain was recorded according to a visual analogue scale (VAS). The mean of three consecutive VAS scores was determined. Calibrated von Frey hairs (0.057 to 140 g) were used to assess detection and pain thresholds for static (punctate) mechanical stimuli. Thermal detection and pain thresholds were

assessed with a Somedic thermotest (Somedic AB, Stockholm, Sweden) by the method of limits, with baseline temperatures adjusted to the patient's skin temperature (mean 30.9 ± 0.5 °C). A contact thermode of Peltier elements measuring 25 x 50 mm was applied to the skin. Thresholds were calculated as the mean of five successive determinations for detection and three determinations for pain and were expressed ~~as absolute thresholds (degrees C)~~ as the difference between thermode neutral temperature and threshold temperatures. Pain induced by suprathreshold mechanical and cold stimuli applied in a pseudo-random order was rated on a VAS. Selected von Frey hairs (between 6.2 and 140 g) were used for mechanical stimuli. The temperature of the cold stimulus was decreased in steps of 5 °C (between 20 and 5 °C) with a thermal rate of change of 2 °C/sec. The patients were informed that they could stop the stimulus sequence at any time. If a VAS score of 80 or more was reported for one of the intensities, no more stimuli were applied. In such a case, the same VAS score was assigned to all higher stimulus intensities in the series in order to allow analysis of the cumulative group data. This method allowed the construction of mean stimulus/response curves for pain intensity against graded mechanical and thermal stimuli.

2. 4. Statistical analysis

SAS 8.2 software (SAS institute Inc, Cary, NC, USA) was used for data analysis. Quantitative variables were described with means and standard deviations (SD). Qualitative variables were described with proportions and percentages.

2.4.1. Factor analysis using the principal component analysis as the method of extraction was carried out to confirm the factorial structure of the

NPSI, previously described in a smaller group of patients (Bouhassira et al 2004). The Catell scree test was used to determine the number of factors extracted. Independent factors were obtained by the Varimax rotation method.

2.4.2. The Spearman correlation coefficient (Rho) was used to explore relationships between the symptoms of allodynia (to brush, pressure or cold) assessed using the NPSI (scored 0 to 10 on numerical scales) and quantitative measures of allodynia or hyperalgesia. Relationships were measured between: 1) symptoms of pain evoked by brush and allodynia to brush (scored on a VAS); 2) symptoms of pain evoked by pressure and mechanical pain thresholds or pain induced by mechanical suprathreshold stimuli (measured on the painful area or expressed as a difference between the painful and control sites and scored on a VAS); 3) symptoms of pain evoked by contact with cold and cold pain thresholds or pain induced by suprathreshold cold stimuli (measured on the painful area or expressed as a difference between the painful and control sites and scored on a VAS).

2.4.3. Several multiple correspondence analyses (MCA) were used for simultaneous investigation of the relationships among neuropathic symptoms (or dimensions) and clinical characteristics of the patients (age, duration of pain, sex, localisation of pain, aetiology, type of the lesion, anatomical location of lesion).

i- MCA with symptoms as dichotomous categories

The ten neuropathic symptoms of the NPSI were classified into two dichotomous categories (0: absent; ≥1: present). Each category was considered a separate variable. The clinical characteristics of the patients were categorised in the following manner: by age, including seven categories of ten years each

(from 20-30 years to 80-90 years); by duration of pain (in months), without normal distribution, including four categories corresponding to the interquartile intervals (3 to 7.4 months, 7.4 to 33.1 months, 33.1 to 148.4 months, 148 to 480 months); by anatomical location of the lesion (central or peripheral); by pain localisation, including six categories (superior limb, inferior limb, 4 limbs, trunk, hemibody, face/neck); by lesion type, including seven categories (mononeuropathy, polyneuropathy, plexopathy, radiculopathy, amputation, spinal cord, brain); and by aetiology of the lesion, including ten categories (peripheral trauma, diabetic polyneuropathy, non-diabetic polyneuropathy, postherpetic neuralgia (PHN), idiopathic trigeminal neuralgia, stroke, spinal cord trauma, syringomyelia, spinal cord tumour, multiple sclerosis).

In factor analysis (a similar method to MCA), the proportion of variance explained by each axis was calculated and the number of retained axes was chosen to obtain a total percentage of (acceptable) variance. The contribution of each category to each axis was calculated to determine the set of symptoms with maximal contribution to a given axis. The clinical characteristics of the patients and their symptoms were projected on several two dimensional spaces formed by the main axes (*e.g.* axes 1 and 2, axes 1 and 3, axes 2 and 3) in order to visualize their proximity (*i.e.* their association). This graphic representation (example in Fig. 2) aids visualisation of the associations between symptoms and clinical characteristics. Associations are detected only by the proximity of categories within the multidimensional space (which cannot be properly illustrated in a plane). Visually detected associations between symptoms and clinical characteristics were confirmed by using the coordinates of each variable on the retained axes to calculate the exact algebraic proximity (associations).

ii- MCA with dimensions of the NPSI as dichotomous categories

The symptoms explored by the NPSI were categorised into five dimensions (eg, combination of symptoms, see methods), as confirmed in the present sample. Thus, we also used MCA (as described above) to examine possible associations (absent = 0 and present ≥ 1) between these five dimensions and the clinical characteristics of the patients.

iii- MCA with symptoms and dimensions as trichotomous categories

Coding of variables may influence the results of multivariate analyses (14); thus, the two previous MCAs were carried out again as described above, with symptoms and dimensions coded according to their score on a 0 to 10 numerical scale: 1 (mild) = score of 0 to 2; 2 (moderate) = score of 3 to 7; 3 (severe) = score of 8 to 10.

2.4.4 Confirmation of bivariate associations

The chi square test was used to confirm associations between symptoms and clinical characteristics identified by MCA.

For all tests, p values < 0.05 were considered significant.

3- RESULTS

This study included 482 consecutive patients. Demographic and clinical characteristics are indicated in Table 1. Mean pain intensity was 64 ± 19 and was similar across all the neuropathic entities. The proportion of patients reporting each neuropathic symptom is shown in Table 2.

3.1. Factor analysis of the NPSI

Factor analysis clearly confirmed the existence of a five-factor solution, which accounted for 78% of the total variance (Table 3). Factor 1 included the three items associated with evoked pain. Factor 2 included two items corresponding to paraesthesia/dysaesthesia. Factor 3 included two items associated with the deep component of spontaneous ongoing pain. Factor 4 included two items related to paroxysmal pain. Factor 5 included one item ("burning") corresponding to the superficial component of pain. This analysis, based on a large sample of patients, identified the same five factors as our previous study based on a smaller group.

3.2. Relationships between self-reported evoked pain and allodynia/hyperalgesia assessed by quantitative sensory testing

The 90 patients who underwent quantitative sensory tests were matched to the entire group for age (57 ± 14 years), sex (53% men, 46% women), duration of pain (77 ± 64 months) and aetiologies of pain (traumatic/post-surgical nerve lesion being the most common, followed by painful polyneuropathies, postherpetic neuralgia, syringomyelia, post-stroke pain, multiple sclerosis and spinal cord trauma). Most patients (93%) had clinically detectable mechanical and/or thermal deficits identified by a standard neurological examination.

Most patients (68 patients, *i.e.* 76% of the sample) reported at least one

type of evoked pain on the NPSI (score ≥ 1/10) (Table 2). The symptoms of brush-evoked pain (scored from 0 to 10) significantly correlated with the magnitude of allodynia to brush (Fig 1A). Similarly, symptoms of pressure-evoked pain correlated with pain evoked by suprathreshold mechanical stimulation on the painful side (Fig 1B) and were inversely correlated, although to a lesser degree, with mechanical pain thresholds on the painful side (Rho: -0.67; $p < 0.001$). Symptoms of cold-evoked pain correlated with pain evoked by suprathreshold cold stimulation on the painful side (Fig 1C) and, although to a lesser extent, with cold-evoked pain thresholds (expressed as the difference betweeen the neutral temperature and absolute thresholds) on the painful side (Rho: 0.66, $p < 0.0001$).

3-3 MCA: Multivariate associations between symptoms (as dichotomous categories) and clinical characteristics

Four main axes were retained after MCA, accounting for 64.3% of the total variance. The proportion of total variance accounted for by each axis was 24.5% for axis 1, 15.8% for axis 2, 13.5% for axis 3 and 10.5% for axis 4.

Fig 2 shows the projection of symptoms and clinical characteristics in the plane formed by axes 1 and 2. The absence of tingling and pins and needles was associated with PHN, trigeminal neuralgia and localisation to the face/neck. We observed no other association between painful symptoms and clinical characteristics.

Fig 3 shows the projection of symptoms and clinical characteristics in the plane formed by axes 1 and 3. The absence of squeezing and pressure was associated with PHN. This was the only association we observed.

Finally, the presence of the symptoms electric shocks and stabbing was associated with amputation pain and plexopathy (*eg* plexus avulsion) in the plane

formed by axes 1 and 4 (not shown). Calculation of exact algebraic proximity confirmed all the previously detected visual associations.

3.4. MCA: Multivariate associations between dimensions of the NPSI (as dichotomous categories) and clinical characteristics

We carried out the same analysis after replacing the symptoms with the dimensions of the NPSI. We observed associations between the absence of burning and the absence of paraesthesia and trigeminal neuralgia (Fig 4); between the presence of burning, the absence of deep pain and PHN; and between the presence of paroxysmal pain and amputation (Fig 4) and plexopathy.

The absence of paraesthesia was also associated with PHN and trigeminal neuralgia, whereas the presence of evoked pain was associated with PHN in the plane formed by axes 1 and 2 (not shown).

3.5. MCA: Multivariate associations between symptoms (and dimensions) as trichotomous variables and clinical characteristics

We observed similar results when neuropathic symptoms (and dimensions) were categorised as trichotomous variables. Thus, *mild* tingling, pins and needles, squeezing and pressure pain were associated with PHN, trigeminal neuralgia and localisation to the face/neck and *severe* brush-evoked pain was associated with PHN (not shown).

3.6 *MCA: Multivariate associations between dimensions of the NPSI as trichotomous variables and clinical characteristics*

We also observed associations for mild paraesthesia, moderate and severe burning and PHN; and for mild burning, severe paroxysmal pain and trigeminal neuralgia.

3.7 Summary

The only associations indicated by MCA were for PHN and moderate to severe burning pain, brush-evoked pain and the absence of deep pain and paraesthesia/dysaesthesia; trigeminal neuralgia and severe paroxysmal pain and the absence of the three dimensions burning pain, deep pain and paraesthesia/dysaesthesia; localisation to the face/neck (in which PHN and trigeminal neuralgia were highly predominant) and the absence of deep pain and paresthesia/dysesthesia ; and plexus avulsion, amputation and paroxysmal pain.

3.8. Results of univariate analyses

The frequency of dimensions (determined from NPSI) for various aetiologies is indicated in Table 4. Univariate analyses confirmed all the associations between dimensions and aetiologies identified by MCA. Thus, the absence of burning was significantly associated with trigeminal neuralgia (chi square : 19.3; $p < 0.0001$). The absence of deep pain was associated with trigeminal neuralgia (chi square 8.7; $p < 0.01$) and PHN (chi square 16.8; $p < 0.0001$). The presence of paroxysmal pain was associated with amputation pain (chi square: 5.2; $p < 0.05$), plexus avulsion (chi square: 5.5; $p < 0.05$) and trigeminal neuralgia (chi square : 4.2; $p < 0.05$). The presence of burning pain and allodynia was associated with PHN (chi square : 14.3 for burning pain; $p < 0.001$; chi square : 14.8 for allodynia, $p < 0.0001$). The absence of paraesthesia/dysaesthesia was associated with trigeminal neuralgia (chi square 21.7) and PHN (chi square 49.8) ($p < 0.0001$).

Univariate analyses identified similar associations between the symptoms (squeezing, pressure, stabbing, electric shocks, tingling, pins and needles and

brush-evoked pain) and aetiologies. In particular, brush-evoked pain was observed in 93% of patients with PHN and in only 37 to 58% of the other patients (chi square 39.7; $p < 0.0001$).

4. DISCUSSION

We investigated the relationships between positive symptoms, aetiologies and locations of neurological lesions in a large consecutive sample of patients with NP, representative of those seen in pain centres or neurology departments. We confirmed that NP symptoms that were self-reported on the NPSI pertain to distinct dimensions, corresponding to relevant clinical components (*i.e.* superficial pain, deep pain, paroxysmal pain, evoked pain, dysaesthesia/paraesthesia). However, NP clinical expression was "trans-aetiological", as MCA identified only a few associations between the presence (or absence) of various symptoms and specific aetiologies. Overall, our findings suggest that there are more similarities than differences in the neuropathic symptoms associated with a large variety of peripheral and central lesions.

Assessment of NP symptoms in this study was based on the NPSI, which allows evaluation of core neuropathic symptoms, including burning pain, electric shocks, brush-evoked pain (8) and paraesthesia/dysaesthesia (*i.e.* tingling and pins and needles). We confirmed the internal structure of the questionnaire by factor analysis before it was used for multivariate analyses. Factor analysis indicated that neuropathic symptoms were categorised into five independent dimensions formed by specific combinations of symptoms that were identical to those reported in our previous study (8).

We also verified the relevance of the assessment of symptoms of evoked pains with this questionnaire by showing clear correlations between self-reported evoked pain and allodynia/hyperalgesia assessed by the investigator using quantified sensory tests. These tests are the method of choice for quantification of allodynia and hyperalgesia (9). However, they are difficult to use in large

samples (18, 34, 39), despite their significant advantages for pathophysiological studies (3, 9, 13, 18). Additionally, normative values (30) are not relevant to elderly patients, are limited to some pain areas and do not include responses to suprathreshold stimulation, which may be less reliable on repeated examination (38). Our data demonstrate the validity of NPSI-based self-assessment of evoked pains, making it suitable for our study and for clinical practice and therapeutic trials.

Multiple correspondence analyses are the most appropriate multivariate (multifactorial) methods to estimate associations between categorised variables (16, 17). These analyses indicated that idiopathic trigeminal neuralgia was strongly associated with electric shocks only. From a therapeutic perspective, only trigeminal neuralgia responds particularly well to sodium channel blockers, including carbamazepine, oxcarbazepine and lamotrigine (1, 25), which are more modestly effective for other neuropathic pain (1, 5, 36). Our data emphasize the relevance of distinct definitions, diagnostic and therapeutic algorithms for neuropathic pain and idiopathic trigeminal neuralgia (1, 35).

Unexpectedly, PHN was different from other aetiologies on the basis of its symptom profile. PHN was characterised by a high prevalence (*i.e.* more than 90% of the patients) of burning pain and allodynia (particularly brush-evoked pain) and the absence of deep pain and paraesthesia/dysaesthesia. Previous psychophysical studies have also reported brush-evoked allodynia in 78 to 100% of patients (24, 26, 31). From a therapeutic perspective, the response of PHN to the major drugs used for neuropathic pain — including gabapentin, pregabalin, tricyclics and opioids — does not seem specific (1, 14). However, this condition has particular symptomatic characteristics that may account, in part, for its

response to treatment. For instance, the NMDA antagonist dextromethorphan and the anti-epileptic lacosamide have no effect on this condition, whereas they have been found effective for other neuropathic pain syndromes (22, 29, 32). Conversely the topical agent capsaicin is effective for PHN, but has been reported to have minimal effect for painful polyneuropathies (1, 14). Our data challenge the relevance of using PHN as a model of neuropathic pain in pharmacological studies. Our findings also emphasize the need for large-scale studies to better investigate response profiles for PHN in comparison with those for other neuropathic conditions.

Plexus avulsion and amputation pain were also different from other aetiologies in that they were closely associated with pain paroxysms (electric shocks, stabbing), which were present in 90% of patients with plexus avulsion and 100% of patients with amputation pain. These data are consistent with classic observations (23, 27) and may account for some of their therapeutic specificities, particularly the good efficacy of surgical procedures (*e.g.* dorsal root entry zone lesions) for pain paroxysms in plexus avulsion (33).

Multiple correspondence analysis did not show associations between neuropathic symptoms (or dimensions) and the other aetiologies, types or locations of lesions or pain localisations (with the exception of the localisation “face/neck”, which shared common characteristics with PHN and trigeminal neuralgia, probably because both aetiologies were predominant in this pain area). In contrast, symptoms and dimensions were very similar for various aetiologies, without evidence for specific characteristics. Thus, symptoms alone are not discriminant enough to indicate specific aetiologies. Identifying neurological deficits and analysing their topography (both of which are directly

related to the nerve lesion itself) is essential for such a purpose (20, 28). The absence of associations between symptoms and almost all pain localisations suggests that lesion topography does not influence neuropathic characteristics of pain and should not determine the response to therapy. Symptoms were also not associated with duration of pain, sex or age. For example, symptoms were not more severe in patients with very long duration of pain than in those with pain for less than one year.

Our data indicate that the clinical entity neuropathic pain has strong clinical consistency, although heterogeneous regarding aetiologies and types of nerve lesions. From a therapeutic perspective, our findings suggest that the current way of selecting patients on the basis of the disease or topography of the lesion might not be the most appropriate or rational approach (19). This is illustrated by pharmacological trials showing similar efficacy of most treatments of neuropathic pain due to various aetiologies, including painful polyneuropathies and central pain (1, 11, 14). The multidimensional nature of neuropathic symptoms supports the relevance of subgrouping patients on the basis of symptoms or dimensions in therapeutic trials. This categorisation, which has been used in only a few studies (9), should contribute to improved therapeutic response to treatments, compared to the current therapeutic approach (1, 14).

In the present study, only positive neuropathic symptoms – either painful or non painful - but not negative ones (ie, sensory deficits), were considered for multivariate analyses. The latter are the hallmark of neuropathies and strongly related to the nature and severity of the nerve lesion, while they are not simply or directly correlated to the magnitude or characteristics of neuropathic pain (10, 12, 15). However we cannot rule out the possibility that particular combinations of

positive and negative symptoms or signs would be associated with specific aetiologies or nerve lesions. Studies remain necessary to further investigate the relationships between positive symptoms, sensory deficits and aetiologies or nerve lesions.

In conclusion, our findings indicate that there is a need for better assessment of positive symptoms and dimensions in large-scale pharmacological studies of neuropathic pain (19). This is a first step towards establishing a mechanism-based approach (3, 13, 37) for selecting therapy and should contribute to improvement of our current therapeutic strategies for these difficult-to-treat pains.

Conflicts of interest : The authors declare no conflicts of interest

REFERENCES

1. Attal N, Cruccu G, Haanpaa M, Hansson P et al EFNS Task Force. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol. 2006 ;13 :1153-69.
2. Attal N, Rouaud J, Brasseur L, Chauvin M, Bouhassira D Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. Neurology, 2004; 27: 219-226.
3. Baron R. Mechanisms of disease: neuropathic pain--a clinical perspective. Nat Clin Pract Neurol. 2006 ;2 :95-106.
4. Bennett MJ, Attal N, Backonja M et alUsing screening tools to identify neuropathic pain. Pain 2007 ; 127 : 199-203.
5. Beydoun A, Shaibani A, Hopwood M, Wan Y. Oxcarbazepine in painful diabetic neuropathy: results of a dose-ranging study. Acta Neurol Scand. 2006;113:395-404.
6. Bouhassira D, Attal N, Alchaar H et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114 : 29-36.
7. Bouhassira D, Attal N. Novel strategies for neuropathic pains. *In :* Villanueva L, Dickenson AE, Ollat H, eds. The pain system in normal and pathological states. Seattle : IASP Press, 2004, pp. 299-310.
8. Bouhassira D, Attal N, Fermanian J et al. Development and validation of the Neuropathic Pain Symptom Inventory. Pain. 2004;108 :248-57.
9. Cruccu G, Anand P, Attal N, Garcia-Larrea L et al. EFNS guidelines on neuropathic pain assessment. Eur J Neurol. 2004 ;11 :153-62.
10. Ducreux D, Attal N, Parker F, Bouhassira D. Mechanisms of central neuropathic pain: a combined psychophysical and fMRI study in syringomyelia. Brain. 2006 ;129:963-76.
11. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007 ;132 :237-51.

12. Fields HL, Rowbotham M, Baron R. Postherpetic neuralgia: irritable nociceptors and deafferentation. Neurobiol Dis. 1998 ;5 :209-27.

13. Finnerup NB, Jensen TS. Mechanisms of disease: mechanism-based classification of neuropathic pain-a critical analysis. Nat Clin Pract Neurol. 2006;2 :107-15

14. Finnerup NB, Otto M, McQuay HJ, et al. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118:289-305.

15. Finnerup NB, Sorensen L, Biering-Sorensen F, Johannesen IL, Jensen TS. Segmental hypersensitivity and spinothalamic function in spinal cord injury pain.Exp Neurol. 2007 ;207 :139-49.

16. Greenacre M, Blazius Y Multiple correspondence analysis and related methods. Statistics in the social and behavioral science series, Chapman and Hall (eds), CRC press, vol. 1, 2006, 581 pages.

17. Greenacre M, Hastie T The Geometric Interpretation of Correspondence Analysis Journal of the American Statistical Association, 1987, 82 : 437-447.

18. Hansson PT, Backonja M, Bouhassira D Usefulness and limitations of quantitative sensory testing: Clinical and research application in neuropathic pain states. Pain. 2007 ; 129 : 256-259.

19. Hansson PT, Dickenson AH Pharmacological treatment of peripheral neuropathic pain conditions based on shared commonalities despite multiple etiologies. Pain. 2005 ;113 :251-4.

20. Jensen TS, Baron R. Translation of symptoms and signs into mechanisms in neuropathic pain. Pain. 2003, 102: 1-8.

21. Jensen TS, Cervero F Handbook of clinical neurology, vol 81, Pain, Elsevier 2006, 911 p.

22. Nelson KA, Park KM, Robinovitz E, Tsigos C, Max MB. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. Neurology. 1997 ;48:1212-8.

23. Nikolajsen L, Brandsborg B Postamputation pain. In : Handbook of clinical neurology, vol 81., Pain, F Cervero and TS Jensen (eds), Elsevier 2006, pp. 679-686.

24. Nurmikko T, Bowsher D Somatosensory findings in postherpetic neuralgia. J Neurol Neurosurg Psychiatry 1990, 53: 135-141.
25. Nurmikko TJ Trigeminal neuralgia and other facial neuralgias. In : Handbook of clinical neurology, vol 81, Pain, F Cervero and TS Jensen (eds), Elsevier 2006, pp 573-596.
26. Pappagallo M, Oaklander AL, Quatrano-Piacentini AL, Clark Heterogenous patterns of sensory dysfunction in postherpetic neuralgia suggest multiple pathophysiologic mechanisms. Anesthesiol 2000, 92: 691-698.
27. Parry CB. Pain in avulsion of the brachial plexus. Neurosurgery. 1984 ;15 :960-5.
28. Rasmussen PV, Sindrup SH, Jensen TS, Bach FW. Symptoms and signs in patients with suspected neuropathic pain. Pain. 2004 ;110 :461-9.
29. Rauck RL, Shaibani A, Biton V, Simpson J, Koch B. Lacosamide in painful diabetic peripheral neuropathy: a phase 2 double-blind placebo-controlled study. Clin J Pain. 2007;23 :150-8.
30. Rölke R, Baron R, Maier C et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain. 2006 ;123 :231-43.
31. Rowbotham MC, Fields HL. The relationship of pain, allodynia and thermal sensation in post-herpetic neuralgia. Brain. 1996 ;119 :347-54.
32. Sang CN, Booher S, Gilron I, Parada S, Max MB. Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. Anesthesiology. 2002 ;96:1053-61.
33. Sindou MP, Blondet E, Emery E, Mertens P. Microsurgical lesioning in the dorsal root entry zone for pain due to brachial plexus avulsion: a prospective series of 55 patients. J Neurosurg. 2005 ;102 :1018-28.
34. Shy ME, Frohman EM, So YT et al Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2003 ;60 :898-904.

35. Treede R-D Pain and hyperalgesia : definitions and theories. In : Handbook of clinical neurology, vol 81, Pain, F Cervero and TS Jensen (eds), Elsevier 2006, pp 3-10.

36. Vinik AI, Tuchman M, Safirstein B et al. Lamotrigine for treatment of pain associated with diabetic neuropathy: Results of two randomized, double-blind, placebo-controlled studies. Pain. 2007 ; 128 :169-79.

37. Woolf CJ. Dissecting out mechanisms responsible for peripheral neuropathic pain: implications for diagnosis and therapy. Life Sci. 2004 ;74 :2605-10.

38. Yarnitsky D., Sprecher E, Zaslansky R, Hemli JA. Multiple session experimental pain measurement. Pain. 1996;67 :327-33.

39. Yarnitsky D. Quantitative sensory testing. Muscle Nerve 1997, 20: 198-204.

Table 1. Clinical and demographic characteristics of the patients included in the study (n = 482 patients)

Clinical and demographic data	
Mean age ± SD (range)	57.7 ± 15.1 (20 - 90)
Sex: % men / % women (N)	53.5/46.4 (258/224)
Mean duration of pain (months ± SD) (range)	65 ± 80 (3 - 665)
Mean pain intensity: VAS (range)	64 ± 19 (30 - 100)
Site of injury/anatomical location of lesion	***% (N)***
Peripheral	**72.4 (349)**
- Mononeuropathy[1]	38.6 (186)
- Radiculopathy	8.9 (43)
- Plexopathy	4.8 (23)
- Polyneuropathy	18 (87)
- Amputation	2.1 (10)
Central	**27.6 (133)**
- Spinal cord	16.1 (78)
- Brain	11.4 (55)
Aetiologies of neuropathic pain	***% (N)***
Peripheral trauma	38.4 (185)
- Traumatic nerve lesion	8 (39)
- Post-surgical nerve lesion[2]	14.7 (71)
- Plexus avulsion[3]	4.8 (23)
- Amputation pain with stump neuroma	2.1 (10)
- Post-surgical radiculopathy[4]	8.9 (43)
- Post-surgical trigeminal neuralgia[5]	1.5 (7)
Diabetic painful polyneuropathy	7.3 (35)
Non diabetic painful polyneuropathy[6]	11 (53)
Postherpetic neuralgia	10.2 (49)
Syringomyelia	8.3 (40)
Multiple sclerosis	6.5 (32)
Central post-stroke pain[7]	6.4 (31)
Spinal cord trauma	5.1 (25)
Trigeminal neuralgia	3.7 (18)
Spinal tumour[8]	1.2 (6)
Topography of pain	***% (N)***
Inferior limb	40 (193)
Superior limb	29 (140)
Four limbs	6.2 (30)
Trunk	10.4 (50)
Hemibody	5.6 (27)
Face/neck	8.7 (42)

[1] Postherpetic neuralgia was classified as mononeuropathy. It generally involved the trunk (n = 27) or the face (n = 14), less commonly the upper or lower limb.

[2] Post-surgical nerve lesion always concerned a major nerve: median, ulnar, radial, intercostobrachial or thoracic nerve of the upper limb; genitofemoral, femoral, sural or saphenous nerve of the lower limb.

[3] Plexus avulsion was the only cause of plexopathy. It was generally incomplete with partial deficit.

[4] These patients had post-surgical lumbar radiculopathy in most cases (n = 40) and four had post-surgical cervicobrachial neuralgia. The diagnosis of radiculopathy was based on a documented history of root compression, typical clinical symptoms and signs (ie, pain radiating beyond the knee and evoked by straight leg raising in lumbar radiculopathy, motor/sensory or reflex deficits) and sometimes additional tests (eg EMG).

[5] Symptomatic trigeminal neuralgia referred to post-thermocoagulation trigeminal neuralgia in all cases

[6] Non-diabetic polyneuropathy was predominantly idiopathic (n = 23) and more rarely due to immune disease (n = 12), drugs (n = 7), critical illness (n = 6), hereditary conditions (n = 3) or gammopathy (n = 2).

[7] Central post-stroke pain was associated with ischemia (n = 18), hemorrhage (12) or lacunar infarction (1). It concerned the rolandic or parietal areas (n = 17), the thalamus (n = 8) or the brainstem (n = 6).

[8] Spinal tumour included ependymoma, schwannoma, cavernoma, neurinoma or angioma.

Table 2. Proportion of patients reporting symptoms (NPSI score ≥ 1/10) and mean intensity of symptoms (scored 0 to 10 on a numerical scale) in the 482 patients included in the study.

Symptoms	**% *(N)***	***Mean intensity ± SD***
Burning	65.4 (315)	4.3 ± 3.6
Squeezing	49.6 (239)	3.1 ± 3.6
Pressure	47 (227)	3.0 ± 3.5
Electric shocks	57 (275)	4.1 ± 3.9
Stabbing	36.3 (175)	2.7 ± 3.6
Brush evoked pain	54.9 (265)	3.8 ± 3.8
Pressure evoked pain	52.3 (252)	3.6 ± 3.8
Cold evoked pain	31.3 (151)	2.1 ± 3.4
Tingling	68.9 (332)	4.5 ± 3.7
Pins and needles	65.7 (317)	4.6 ± 3.7

Table 3. Factor analysis with loadings for the ten items on the five-factor solution accounting for 78% of the total variance

Symptoms	*Factor 1 Evoked pain*	*Factor 2 Paresthesia/ dysesthesia*	*Factor 3 Deep pain*	*Factor 4 Paroxysmal Pain*	*Factor 5 Burning pain*
Burning	0.02	0.07	0.00	0.00	**0.94**
Pins and needles	0.09	**0.87**	-0.06	0.02	0.01
Tingling	0.02	**0.89**	0.08	-0.03	-0.03
Electric shocks	0.00	0.08	-0.11	**0.79**	0.03
Stabbing	0.00	-0.10	0.12	**0.72**	0.05
Pressure	0.01	-0.09	**0.89**	-0.05	-0.07
Squeezing	-0.03	-0.05	**0.87**	0.05	0.06
Evoked by brushing	**0.78**	-0.00	-0.11	0.07	0.05
Evoked by pressure	**0.80**	-0.06	0.04	-0.03	-0.11
Evoked by cold stimuli	**0.62**	0.17	0.04	-0.04	0.04

Table 4. Frequency of dimensions of the NPSI (in %) for the most common aetiologies of neuropathic pain included in the study (n ≥ 10 patients). Univariate analyses confirmed all the associations between dimensions and aetiologies identified by MCA (proportions in bold type).

	PHN	*Diabetic PPN*	*Nondiabetic PPN*	*Nerve trauma*[1]	*Plexus avulsion*	*Amputa-tion*	*Radiculo-pathy*	*Trigeminal neuralgia*	*Spinal trauma*	*MS*	*Syrinx*	*Stroke*
	N =49	*N=35*	*N= 53*	*N =110*	*N=15*	*N=10*	*N=43*	*N=18*	*N=25*	*N=26*	*N=40*	*N=31*
Burning pain	**89.8**	62.8	58.5	51.1	66.7	60	65.1	**16.7**	76	57.7	75	74.2
Deep pain	**28.5**	68.6	62.3	58	66,7	70	51.2	**22.2**	74	61.6	60	64.5
Paroxysmal pain	63.2	62.8	62.3	66.3	**89.7**	**100**	72	**89.9**	72	65.3	65	58
Evoked pain	**91.9**	51.5	64.1	76	46.7	70	44.2	61.1	70	73	62.5	74
Paresthesia/dysesthesia	**30**	82.9	84.9	86	93.3	70	81.4	**33**	80	84.6	87.5	83.9

Abbreviations : PHN : postherpetic neuralgia ; PPN : painful polyneuropathy ; MS : multiple sclerosis

[1] Nerve trauma included surgical trauma

Figure 1.

Correlations between symptoms of evoked pains (assessed using the NPSI) and signs of allodynia or hyperalgesia (evaluated using quantitative sensory testing on the painful side).

A) Correlation between symptoms of brush-evoked pain (scored from 0 to 10 on a numerical scale) and allodynia to brush (scored from 0 to 100 on a VAS). Rho: 0.83; $p < 0.0001$.

B) Correlation between symptoms of pressure-evoked pain (scored from 0 to 10 on a numerical scale) and pain induced by suprathreshold (140 g) von Frey hairs on the painful side (scored from 0 to 100 on a VAS). Rho: 0.79; $p < 0.0001$.

C) Correlation between symptoms of cold-evoked pain (scored from 0 to 10 on a numerical scale) and pain induced by 5 °C stimulation on the painful side (scored from 0 to 100 on a VAS). Rho: 0.75; $p < 0.0001$.

Similar relationships were found when the values obtained for pressure and cold were expressed as a difference between the painful and control sides (not shown). Significant relationships were also obtained when lower suprathreshold mechanical and cold stimuli were used (not shown).

Figure 2.

Multiple correspondence analysis (MCA) showing the associations between symptoms (blue squares), categorized as absent (0) or present (1) and clinical characteristics of the patients (red triangles), *eg* aetiologies, pain localisation, type of nerve lesion and location of the lesion in the plane formed by axes 1 and 2 (see Methods for the categories of the clinical characteristics). All the categories are located in a Euclidian space. The closer the values, the more highly associated they are. For clarity of the presentation, age, sex and pain duration are not indicated.

The bottom right quadrant of the figure shows that the categories postherpetic neuralgia, trigeminal neuralgia and localisation of pain to the face/neck are associated with absent tingling and pins and needles.

Abbreviations : DPN: diabetic polyneuropathy; PPN: painful non-diabetic polyneuropathy; PHN: postherpetic neuralgia; TN: trigeminal neuralgia.

Figure 3

Multiple correspondence analysis (MCA) showing the associations between symptoms (blue squares) categorized as absent (0) or present (1) and clinical characteristics of the patients (red triangles) in the plane formed by axes 1 and 3 (see the legend of figure 2 for further details).

The bottom right quadrant of the figure shows that the categories postherpetic neuralgia, trigeminal neuralgia and localisation of pain to the face/neck are associated with absent squeezing and pressure.

Abbreviations : DPN: diabetic polyneuropathy; PPN: painful non-diabetic polyneuropathy; PHN: postherpetic neuralgia; TN: trigeminal neuralgia.

Figure 4

Multiple correspondence analysis (MCA) showing the associations between dimensions (*eg,* combination of symptoms) (blue squares) categorized as absent (0) or present (1) and clinical characteristics of the patients (red triangles) in the plane formed by axes 1 and 3 (see the legend of figure 2 for further details).

The bottom of the figure shows that trigeminal neuralgia is associated with absent burning pain and paresthesia. The bottom left of the figure shows that amputation pain is associated with presence of paroxysmal pain. Although not obvious in the bidimensional space, there was also an association between postherpetic neuralgia, presence of burning pain and absence of deep pain, and between plexopathy (*eg* plexus avulsion) and presence of paroxysmal pain.

Abbreviations : DPN: diabetic polyneuropathy; PPN: painful non-diabetic polyneuropathy; PHN: postherpetic neuralgia; TN: trigeminal neuralgia.