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Neuropathic pain : the clinical syndrome revisited

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Abstract

Neuropathic pains associated with an injury of the peripheral or central nervous system are among the most difficult to treat. One of the reasons for the therapeutic difficulties in these patients is that the pharmacological treatments are used in a uniform fashion whatever the clinical picture, while these syndromes are in fact highly heterogenous. The patients can express various combinations of painful symptoms – spontaneous (continuous and/or paroxysmal) and evoked (allodynia and/or hyperalgesia). Recent pharmacological studies have shown that current treatments of these pains do not induce global and uniform analgesic effects but rather act preferentially or selectively on some of their components. Such data emphasize the necessity of a thorough evaluation of patients presenting with neuropathic pains, notably by using quantitative sensory testing. Following recent advances in the understanding of the pathophysiological mechanisms underlying these painful syndromes, through experimental studies in animals, a "mechanism-based" classification and treatment of neuropathic pains can be envisaged. The main goal for clinicians is to propose new methods and strategies for identifying pathophysiological mechanisms in patients in order to validate such an approach in the clinical context.

Key words : Neuropathic pain ; chronic pain ; pathophysiology ; pharmacology.

A large body of experimental and clinical works have been devoted to neuropathic pains over the last few years. Better recognition and diagnosis of these chronic pain syndromes has been complemented by unprecedented advances in experimental studies, induced over the past 10 years by a massive expansion of studies aiming at a better understanding of the pathophysiological mechanisms sustaining such pains. These works were largely based on the development of numerous animal models. Despite their limitations, these models which are designed to reproduce a symptomatology similar to that observed in human diseases, have allowed a better understanding of the multiplicity and complexity of the peripheral and central modifications responsible for neuropathic pains and the determination of their cellular and molecular basis (Attal and Bouhassira, 1998 ; Costigan and Woolf, 2000 ; Woolf and Salter, 2000). Most of these studies have thus helped to reveal new targets for future pharmacologic agents acting at the peripheral or central level and have led to novel pathophysiological concepts for clinicians, favoring rationalization of the therapeutic approach to the various painful syndromes. At present, the main goal for clinicians is to find methods for identifying the pathophysiological mechanisms in the clinic in order to propose therapies to target these mechanisms.

Definition and general clinical features of neuropathic pains

According to the definition proposed by the International Association for the Study of Pain (IASP), the term neuropathic pains refers to all *pains initiated or caused by a primary lesion or dysfunction of the nervous system*. Such a broad category, including pains associated with peripheral or central lesion, was created to distinguish neuropathic pains from "nociceptive pains", mainly on the basis that the former respond poorly to usual analgesic treatments (most notably opiates), suggesting the involvement of distinct pathophysiological mechanisms. Such a classification appeared to be justified in the first place since the painful syndromes associated with a lesion of the nervous system do share some clinical features.

The clinical picture includes both *positive and negative phenomena*. Positive phenomena correspond to various painful symptoms (see below) as well as *paresthesia* and/or *dysesthesia* which, by definition, are abnormal *nonpainful* sensations. Negative phenomena include neurological sensory deficits as well as other deficits (motor, cognitive, etc.) depending on the localization of the lesion. Other less specific features of neuropathic pains are their persistance after healing of the lesion and the fact that they can appear tardively after the lesion. Such a symptomatology can be observed in a very large number of etiologies. Painful peripheral neuropathies include quite frequent conditions such as diabetic neuropathy, post-herpetic neuralgia,

traumatic nerve injury, AIDS neuropathy, etc. Central pains are not uncommon since they are observed in up to 8% of patients after a stroke, in approximately 30-50% of patients with a spinal cord injury, a large majority of those presenting with a syringomyelia, and up to 20-25% of patients with a multiple sclerosis (Andersen *et al.*, 1995 ; Beric *et al.* 1988 ; Cassignari and Pagni, 1969 ; Yezierski, 1996).

Pharmacological treatments of neuropathic pains mainly rely on antidepressants and anticonvulsants, whose analgesic properties were found fortuitously and which have mostly been used empirically. Indeed, until recently, very few controlled studies had been performed, notably as regards central pains. Other molecules, such as antiarrhythmics, tramadol, local anesthetics, capsaicin, and opiates have also shown some efficacy in controlled studies (Sindrup and Jensen, 2000). However, the effects of these different treatments are *modest and variable* and we are still a long way from satisfactory management of these pains.

One of the reasons for the therapeutic difficulties in these patients is that treatments are used in a uniform fashion whatever the clinical picture, while these syndromes are in fact *highly heterogeneous*. Such a heterogeneity is apparent from the clinical examination of the patients. They generally present with various painful symptoms including *spontaneous pain,* either *continuous* (mostly described as burning) or *paroxysmal* and evoked pains (see figure 1). The latter, which can be more distressing than spontaneous pains, are termed *allodynia* when they are triggered by normally non-noxious stimuli and *hyperalgesia* when they correspond to an exaggerated response to a normally noxious stimulus. Evoked pains can be triggered by mechanical or thermal stimuli. Mechanical allodynia can be preferentially triggered by moving stimuli, i.e. *dynamic* mechano-allodynia*,* or by pressure or punctate stimuli, i.e. *static* mechano-allodynia. Evoked pains can also be triggered by thermal — either heat or cold — stimuli, although cold allodynia/hyperalgesia is much more frequent than heat allodynia/hyperalgesia in these patients.

Thus, the term neuropathic pains in fact refers to a very large number of symptoms and syndromes. All of these symptoms are not present in a single patient, but the fact that patients can present with various combinations of such symptoms suggests, by itself, that these different components of neuropathic pains are sustained by different pathophysiological mechanisms and should respond differentially to the treatment. In accordance with this hypothesis, our previous works (Attal *et al.*, 1998, 1999, 2000) corroborated by those of other groups

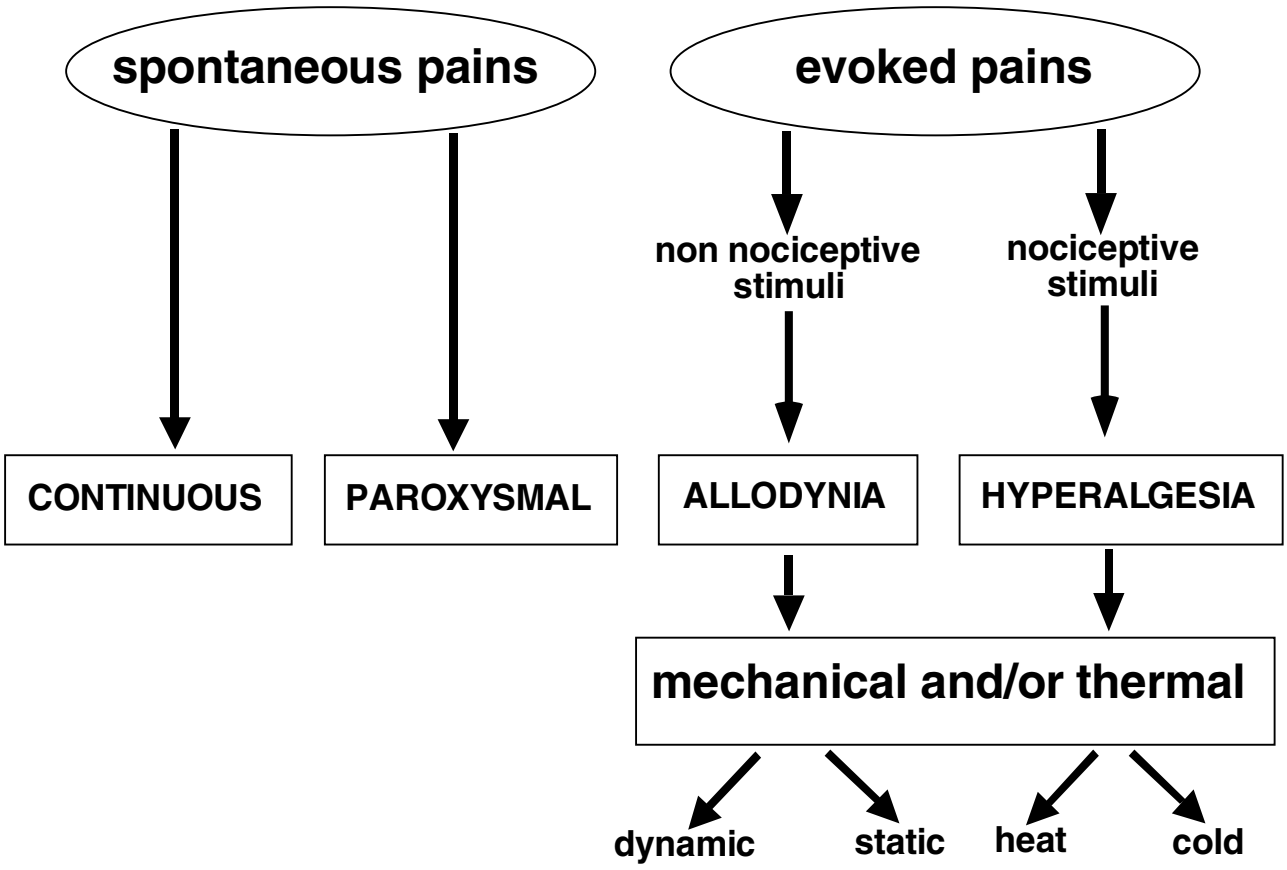

FIG. 1. — Clinical features of neuropathic pains

(Vestergaard *et al.*, 2001 ; Wallace *et al.*, 2000) have contributed to show that current treatments of these pains do not induce global and uniform analgesic effects but rather act preferentially or selectively on some of their components.

Evaluation of neuropathic pains

Evaluation of neuropathic pains should be considered as a crucial step. Besides the standard clinical examination, it is important to assess and, as far as possible, to quantify all the components of these painful syndromes (i.e., spontaneous and evoked pains) as well as sensory deficits.

Categorical, numerical, or visual analog scales (VAS) are used to evaluate spontaneous ongoing pain. Paroxysmal pains can be evaluated by simply counting the daily number of paroxysms and measuring their intensity on a VAS. As regards dynamic mechanical allodynia (i.e., brush-induced allodynia), it can easily be evaluated with a coton swab or a brush. *Quantitative sensory tests* (QST) currently seem to be the best tool for the evaluation of evoked pains (Hansson and Lindblom, 1992). These methods, derived from psychophysics, are used to measure detection and pain thresholds in response to various thermal (heat or cold) and mechanical stimuli and to quantify sensations evoked by suprathreshold stimuli. Thus, these methods are particularly suitable for the quantification not only of evoked pains but also of sensory deficits. Owing to major technical progress, presently available equipment allows application of controlled intensity stimulation and may easily be used in clinics.

In practice, the testing is usually performed in the painful area and compared to a nonpainful, if possible, homologous area. Measurements of pain thresholds are important for the diagnosis and quantification of allodynia which, by definition, corresponds to a decreased pain threshold. Several algorithms have been proposed for such measurements (Yarnitzky, 1997). The method of limits which consists in applying ascending or descending stimulus intensity until the subject stops it as soon as he perceives a painful sensation, is by far the easiest and the most rapid and therefore is generally preferred in spite of several limitations. The evaluation of hyperalgesia, which by definition corresponds to an increased response to normally noxious stimuli, necessitates the application of suprathreshold stimuli. The response to each stimulus is measured on a VAS. It is thus possible to build stimulus-response curves. Hyperalgesia corresponds to an increase of the slope of the curve as compared to the normal side, while the threshold can be normal, decreased, or increased.

The applications of QST are quite wide. These methods are important for the semiological characterization of the patients. They can also be used for the pharmacological evaluation. In particular, they helped to demonstrate that several currently used treatments for neuropathic pain do not have a general analgesic effect but rather act as antihyperalgesic agents (Attal *et al.*, 1998, 1999, 2000). Finally, these methods are of interest for pathophysiological studies.

Application of these methods is illustrated by a study in which we compared the results of QST in patients with a painful or not painful distal sensory polyneuropathy due to HIV (Bouhassira *et al.*, 1999). In pain patients, we showed a decrease of pain threshold and an increase of the slope of the stimulus-response curve to pressure mechanical stimuli, suggestive of a static mechanical allodynia/hyperalgesia (see figure 2A). This abnormality was modality selective since the heat and cold pain threshold as well as the stimulus-response curves to heat or cold stimuli were similar in the two groups of patients. Thus, these data suggested a specific dysfunction in the processing of mechanical stimuli in pain patients. Interestingly, we also observed a correlation between the intensity of mechanical hyperalgesia and the intensity of spontaneous pain in these patients, suggesting that these two symptoms share some pathophysiological mechanisms (figure 2B). Another example concerns postherpetic neuralgia (PHN) in which brush-induced allodynia (i.e., dynamic subtype of mechano-allodynia) is a prominent symptom. On the basis of a thorough clinical evaluation including QST as well as pharmacological tests using topical capsaicin and local anaesthetic infiltration, it has been proposed that PHN patients fall into at least three subgroups (Fields *et al.*, 1998 ; Petersen *et al.*, 2000). The first group is characterized by the presence of a severe dynamic mechanical allodynia associated with minor heat deficit. In these patients, painful symptoms were reduced by local anesthetics and increased by capsaicin, suggesting the involvement of peripheral mechanisms (i.e., nociceptor sensitization). In the second group of patients, brush-induced allodynia was associated with a profound sensory heat deficit and inconsistent response to local infiltration of anesthetics and application of capsaicin, suggesting that central mechanisms were prevalent in these patients (e.g., structural plasticity with a reorganization spinal nociceptive afferent terminals). Finally, the third group was characterized by an absence of allodynia and profound sensory heat deficit. The lack of effects of local anaesthetic and capsaicin in these patients also suggest the involvement of central mechanisms (e.g., central disinhibition).

Quantitative sensory testing presents some limitations due to long duration, to the difficulties of the test-retest, and the fact that tests must be conducted by trained investigators (Yarnitzky, 1997). Therefore, they are still difficult to apply for multicenter studies including large cohorts of

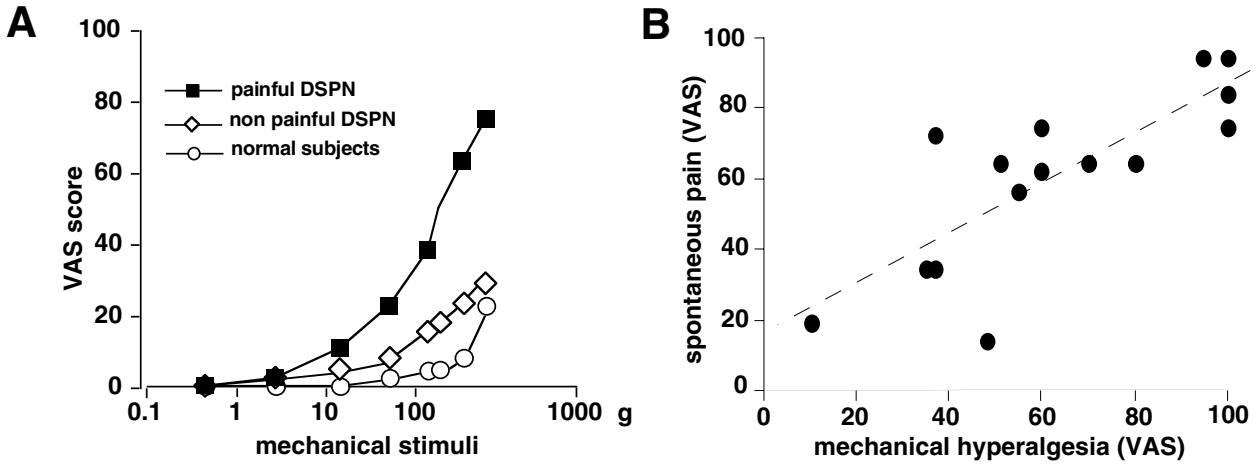

FIG. 2. — A : Intensity/response curves for mechanical stimuli (produced by Von Frey filaments) in patients presenting with a painful or non painful distal sensory polyneuropathy (DSPN) and in normal subjects. The responses to mechanical stimuli (i.e., VAS score) were significantly and selectively increased in patients with a painful DSPN as compared with both the normal control subjects and the patients with a non painful form of DSPN.
B : The intensity of spontaneous pain (ordinate : maximum VAS score during the last 24 h) was positively correlated with mechanical hyperalgesia, suggesting that these symptoms share some pathophysiological mechanisms.

patients. Specific assessments of neuropathic pains would be greatly facilitated by the development of a sensitive and specific questionnaire, that would give information comparable to that provided by quantitative evaluation, as regards the nature and importance of the various painful symptoms. Indeed, the self-questionnaires or multidimensional questionnaires such as the McGill Pain Questionnaires (Melzack, 1975) are not specific for neuropathic pains. In 1997, a questionnaire which aimed to be specific for neuropathic pain, the Neuropathic Pain Scale, was developed but it lacks content validity, since several items specific for neuropathic pains are missing and validation was only preliminary (Galer and Jensen, 1997).

Towards mechanism-based classification and treatment of neuropathic pains

An optimal therapeutic approach to neuropathic pains would rely on identification of the mechanisms presumably responsible for the pain (ultimately in individual patients) and aim to select treatments targeting these mechanisms. However, although several authors now agree on the utility of this approach in clinical practice, there is still little data confirming its real benefit in patients with neuropathic pains (Baron, 2000 ; Woolf and Decosterd, 1999).

Such a mechanism-based approach to neuropathic pain was undertaken on the basis of the major advances made in the last decade concerning the pathophysiology of neuropathic pains following studies in various animal models. Thus, there is now general agreement to consider that both peripheral (ectopic discharges, crossed excitation or multiplication of impulses) and central mechanism (central sensitization, structural plasticity with reorganization of nociceptive terminals in the spinal cord) are involved in these painful syndromes (Attal and Bouhassira, 1999 ; Woolf and Manion, 1999 ; Woolf and Salter, 2000). However, direct transposition of the animal data in a clinical context remains difficult. Most animal models (e.g., constriction of the sciatic nerve) do not correspond to clinical lesions and therefore should only be condidered as “symptomatic” models. Another problem with animal studies is that they do not specifically adress the problem of the relationships between the different peripheral and central mechanisms and the nociceptive behaviors observed in animals. Thus, it is not possible on the basis of these studies to determine whether each symptom (i.e., mechanical allodynia, cold allodynia, heat hyperalgesia, etc.) is sustained by a specific mechanism, whether a single mechanism can explain several symptoms or whether a single symptom can be sustained by several mechanisms. Although there is some evidence in support of the latter two hypotheses, this still needs to be clarified.

Thus, it appears necessary to adress these questions in the clinical context and develop new strategies and methodologies that may provide relevant pathophysiological information for therapeutic decisions.

Future clinical studies should aim notably at clarifying the role of aetiological factors and/or localization of the lesion in the nervous system (peripheral or central) in the therapeutic response and, indirectly, in the pathophysiology of the various symptoms. For this purpose, it would be of interest to compare the effects of various pharmacological agents (antiepileptics, antidepressants,

and antiarrhythmics) by using quantitative sensory tests in several populations of patients : i) patients with similar symptoms (cold allodynia, brush-induced allodynia, heat-induced hyperalgesia, etc.), although related to distinct aetiologies (diabetic neuropathies, traumatic neuropathies, stroke, spinal cord lesions, etc.) ; ii) patients with distinct symptoms related to similar aetiology. The results of such studies should help to determine whether a particular symptom (e.g., cold allodynia) is induced by similar mechanisms whatever the aetiology or localisation of the lesion or whether, conversely, a single symptom may be produced by distinct mechanisms.

To further analyze the role of peripheral and central mechanisms, it should be possible to use systematic pharmacological tests to dissociate the various peripheral and central mechanisms. As this has already been proposed (Fields *et al.* 1998 ; Petersen *et al.*, 2000), the general objectives of these studies would consist in comparing in a single patient the effects of several pharmacological agents selected according to their action mechanisms. The role of peripheral mechanisms (ectopic discharges, nociceptor sensitization) could be tested in patients with painful peripheral nerve injury by analyzing the effects of local anesthetic agents (nerve blocks), such as lidocaine, that block voltage dependent sodium channels and by comparing the effects of cutaneous applications of capsaicin in normal and painful areas. Capsaicin is a neurotoxin that selectively interacts with C nociceptive fibers, whose action is mediated by specific receptors that induce nociceptor activation (Caterina *et al.*, 1997, 2000). The role of central mechanisms (i.e., central sensitization) could be tested by studying the effects of the administration of NMDA receptor antagonists, such as ketamine, in patients with peripheral or central neuropathic pains. Experimental data have emphasized the role of NMDA receptors in the persistent hyperexcitability of central nociceptive neurons (central sensitization), a major central mechanism of neuropathic pains.

These studies should allow the definition of new categories of patients on the basis of the mechanisms demonstrated by these tests. They should also allow clarification of the interrelations between the aetiology, the localization of the lesion (peripheral, central), the underlying mechanisms, and the therapeutic response.

In conclusion, neuropathic pains should no longer be considered as a single entity. More clinical research and interactions between clinicans and basic scientists are necessary to define new criteria for a better categorization of these syndromes. Indeed, although clinical research depends on basic results, it is worth pointing out that, in return, it provides essential information for identifying the true medical problems, formulating new scientific questions, adapting the experimental models, and finally, for validating or refuting pathophysiological hypotheses and concepts.

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