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Neuropathic pain

Redefinition and a grading system for clinical and research purposes

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ABSTRACT

Pain usually results from activation of nociceptive afferents by actually or potentially tissue-damaging stimuli. Pain may also arise by activity generated within the nervous system without adequate stimulation of its peripheral sensory endings. For this type of pain, the International Association for the Study of Pain introduced the term neuropathic pain, defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system." While this definition has been useful in distinguishing some characteristics of neuropathic and nociceptive types of pain, it lacks defined boundaries. Since the sensitivity of the nociceptive system is modulated by its adequate activation (e.g., by central sensitization), it has been difficult to distinguish neuropathic dysfunction from physiologic neuroplasticity. We present a more precise definition developed by a group of experts from the neurologic and pain community: pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. This revised definition fits into the nosology of neurologic disorders. The reference to the somatosensory system was derived from a wide range of neuropathic pain conditions ranging from painful neuropathy to central poststroke pain. Because of the lack of a specific diagnostic tool for neuropathic pain, a grading system of definite, probable, and possible neuropathic pain is proposed. The grade possible can only be regarded as a working hypothesis, which does not exclude but does not diagnose neuropathic pain. The grades probable and definite require confirmatory evidence from a neurologic examination. This grading system is proposed for clinical and research purposes. *Neurology*® 2008;70:1630–1635

GLOSSARY

IASP = International Association for the Study of Pain; **MS** = multiple sclerosis; **NeuPSIG** = IASP Special Interest Group on Neuropathic Pain.

Pain usually arises as a consequence of activation of primary nociceptive afferents by actually or potentially tissue-damaging stimuli and processing of this activity within the nociceptive system. This type of pain is physiologic. Pain, however, may also arise by activity generated within the nociceptive system without adequate stimulation of its peripheral sensory endings. For these clinical conditions, the term neuropathic pain has been introduced.

The International Association for the Study of Pain (IASP) defines neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction in the nervous system."[1] This definition has been useful to distinguish between neuropathic and other types of pain, but it lacks both diagnostic specificity and anatomic precision.[2-7] Two issues need to be resolved: 1) neuropathic pain needs to be distinguished from pain due to secondary neuroplastic changes in the nociceptive system resulting from sufficiently strong nociceptive

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stimulation, e.g., inflammatory pain[8,9]; 2) neuropathic pain needs to be distinguished from musculoskeletal and other types of pain that arise indirectly in the course of neurologic disorders.[10-12] The lack of precision in the current definition has prevented progress in diagnosis, classification, epidemiology, and treatment.

The aim of this article is to develop a more precise definition of neuropathic pain that will be useful for clinical and research purposes and will fit into the nosology of neurologic disorders. In addition, a grading system is presented that defines the level of certainty as to how likely a given pain condition is neuropathic in nature.

PROCEDURE The objective of this consensus process was to revise the current definition of neuropathic pain according to the major criticisms that had been published since 1994.[2-7,13] Neuropathic pain is a symptom, whose diagnosis indicates a lesion or a disease of the somatosensory system which links symptom and lesion/disease together. It was recognized that at present there is no specific diagnostic tool which permits an unequivocal diagnosis of neuropathic pain to be established. Accordingly, a grading system with different levels of certainty about the presence of neuropathic pain was considered to be a useful way to progress. A similar approach was taken for multiple sclerosis (MS)[14] before the introduction of the current McDonald criteria based on lesions observed on T2-weighted MRI.[15]

A group of neurologists, neuroscientists, clinical neurophysiologists, and neurosurgeons established a task force in collaboration with the IASP Special Interest Group on Neuropathic Pain (NeuPSIG). Through several face-to-face meetings and electronic mail, members of the NeuPSIG task force reviewed several drafts of a revised definition and grading system for neuropathic pain by comparing those definitions with the characteristics of disorders generally accepted to cause neuropathic pain (trigeminal neuralgia, painful diabetic polyneuropathy, postherpetic neuralgia, central poststroke pain) to those of disorders generally accepted to lead to nociceptive pain (postoperative pain, osteoarthritis, musculoskeletal pain). A draft of this article has been reviewed by the NeuPSIG management committee prior to submission. As recommended in the guideline for guidelines,[16] the grading system is intended to be reviewed 5 years after its publication. At that time, a systematic literature review will be performed summarizing its clinical use. A systematic review of the sensitivity and specificity of tests for symptoms and signs of neuropathic pain has been published elsewhere by a task force of the EFNS.[7] These tests are needed to obtain the evidence for the grades probable and definite neuropathic pain.

Revised definition of neuropathic pain. We propose to replace the current definition of neuropathic pain as "pain initiated or caused by a primary lesion or dysfunction in the nervous system" by the following wording: "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."

The term disease replaces the previous term dysfunction, which is an ill-defined term and may erroneously be interpreted as including the normal plasticity of the nociceptive system.[5] In contrast, the term disease refers to identifiable disease processes such as inflammatory, autoimmune conditions, or channelopathies, while lesion refers to macro- or microscopically identifiable damage. The restriction to the somatosensory system is necessary because diseases and lesions of other parts of the nervous system may cause other types of pain that should not be confused with neuropathic pain, such as the pain associated with spasticity and rigidity that is mediated by activation of nociceptive afferents from muscles. These two changes with respect to the old definition reflect the concept that in neuropathic pain an aberrant somatosensory processing is inferred that goes beyond the normal plasticity of the undamaged nociceptive system.[17]

Where possible, neuropathic pain should be divided into peripheral or central neuropathic pain based on the anatomic location of the lesion or disease.[6,18,19] This distinction is clinically important, as lesions or diseases of the CNS and PNS are distinct in terms of clinical manifestations and underlying pathophysiology. For that reason the terms peripheral neuropathic pain and central neuropathic pain are proposed to refer to lesions/diseases in the PNS and CNS.

Grading system for neuropathic pain. The neuropathic pain grading system is intended to be used to decide on the level of certainty with which the presence or absence of neuropathic pain can be determined in an individual patient (table). The levels definite and probable indicate that the presence of this condition has been established. The level possible indicates that the presence of this condition has not yet been established, which

Table Grading system for neuropathic pain

Criteria to be evaluated for each patient
1. Pain with a distinct neuroanatomically plausible distribution*
2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system†
3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test‡
4. Demonstration of the relevant lesion or disease by at least one confirmatory test§

Grading of certainty for the presence of neuropathic pain: definite neuropathic pain: all (1 to 4); probable neuropathic pain: 1 and 2, plus either 3 or 4; possible neuropathic pain: 1 and 2, without confirmatory evidence from 3 or 4.

*A region corresponding to a peripheral innervation territory or to the topographic representation of a body part in the CNS.

†The suspected lesion or disease is reported to be associated with pain, including a temporal relationship typical for the condition.

‡As part of the neurologic examination, these tests confirm the presence of negative or positive neurologic signs concordant with the distribution of pain. Clinical sensory examination may be supplemented by laboratory and objective tests to uncover subclinical abnormalities.

§As part of the neurologic examination, these tests confirm the diagnosis of the suspected lesion or disease. These confirmatory tests depend on which lesion or disease is causing neuropathic pain.

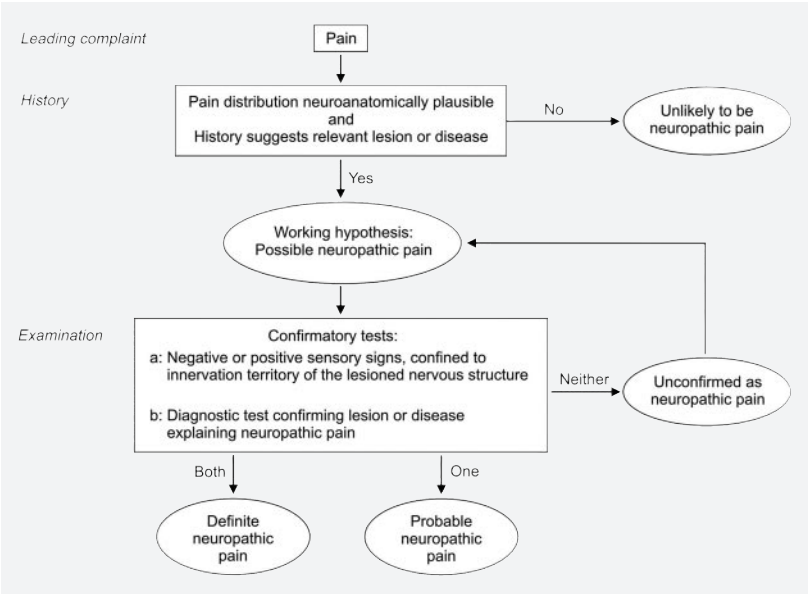
should instigate additional investigations in this patient, either immediately or during follow-up (figure). If a patient does not fulfill the criteria for any of these three levels, it is considered unlikely that this patient has neuropathic pain.

The neurologic diagnosis depends on the answers to two questions: "Where is the lesion?" (anatomy) and "What type of lesion?" (pathology, including pathophysiology). These principles also apply to neuropathic pain and hence form the basis of the proposed grading system (table, figure). Ideally, it should be possible to diagnose and classify neuropathic pain solely on the basis of history, but as in other neurologic conditions, a clinical examination is mandatory. Based on the history, there are two requirements: 1) a pain distribution consistent with the principles of topographic diagnosis in neurology, i.e., it must correspond to a peripheral innervation territory (nerves, fascicles, roots) or to the topographic representation of a body part in the CNS; 2) clinical suspicion of a relevant lesion or disease that affects the peripheral or central somatosensory system and with a temporal link between the lesion or disease causing the pain. Although the onset of pain following nerve lesions can be delayed for weeks up to a few months, a careful history and examination will often indicate links between the initial damage and the subsequent development of pain. It is not possible to give exact temporal criteria for the development of pain, but in neuropathic pain conditions, pain onset is usually immediate or within the first weeks after the injury.[20,21] When these requirements are fulfilled, the pain complaint may be termed possible neuropathic pain. Higher levels of certainty about the presence of neuropathic pain require confirmatory evidence from a neurologic examination and diagnostic tests to reach a level of probable or definite neuropathic pain.

The first criterion of the grading system (table) relates to pain distribution. In peripheral neuropathic pain the distribution has to conform to the innervation territories of peripheral nerves, branches of the brachial or lumbar plexus, or spinal segments. However, the distribution of pain or hyperalgesia does not necessarily need to be identical to the innervation territory of a peripheral nerve or root, but it should be in a distribution that is typical for the underlying disorder. For example, in carpal tunnel syndrome it is not unusual for patients to describe proximal painful symptoms because of referred pain, and in postherpetic neuralgia brush-evoked pain may extend outside the primarily affected dermatome due to central sensitization. In central neuropathic pain, the pain distribution needs to conform to the somatotopic representation of the body within the CNS. Since central sensitization is one of the mechanisms that contribute to neuropathic pain, expansions of receptive and projected fields should be taken into account when making this judgment. The burden of proof is on the clinician to show that a sensory or pain pattern is the result of a lesion or disease of the somatosensory system. A diagnostic manual for neuropathic pain conditions containing a list of sensory patterns will be of value in the future. Detailed analysis of pain distribution is a standard part of taking the medical history of a patient, and is also represented as a pain drawing in many pain questionnaires.

The second criterion of the grading system (table) relates to establishing a link between history and the pain distribution. Following the general diagnostic principles of neurology, causality is assumed if spatial and temporal congruence can be shown for the signs and symptoms of the patient and the location of the underlying lesion or disease process. To qualify for causing neuropathic pain, the lesion or disease should be capable of affecting the somatosensory system. This requirement is fulfilled by many classic neuropathic pain

Figure Flow chart of grading system for neuropathic pain



disorders such as painful neuropathies, syringomyelia, and central poststroke pain. However, for less well-defined disorders, such as fibromyalgia, the evidence for a lesion or primary disease of the somatosensory system is not established so these conditions cannot be characterized as neuropathic. Therefore, in the well-defined neuropathic pain disorders it will be sufficient to establish the diagnosis of the underlying disorder (evidence for the disease), whereas for the less well-defined disorders it is essential to demonstrate in the individual patient that this disorder does affect the somatosensory system (evidence for neural damage).

The third criterion of the grading system (table) relies on a clinical examination with demonstration of neurologic signs (negative or positive sensory signs) that support the presence of a lesion or disease consistent with the distribution of pain. Some tests can serve a dual purpose, i.e., determine the distribution of pain (criterion 3) and document a relevant lesion (criterion 4), e.g., the use of a von Frey hair to delineate an area with cutaneous hyperalgesia/allodynia or the demonstration of a loss of sensitivity to pinprick stimuli. These sensory signs may or may not be accompanied by motor or autonomic signs in the same distribution. For many clinical conditions such as distal symmetric polyneuropathy,[22] signs and objective tests carry more weight than subjective symptoms. Questionnaires with verbal descriptors are useful in suggesting a neuropathic pain disorder,[23-25] and symptoms have in some,[24,25] but not all,[13] studies proven to be useful in classifying neuropathic pain. The relative merits of questionnaires, quantitative sensory testing, electrophysiology, biopsies, and neuroimaging were recently reviewed systematically by an EFNS task force.[7] With a level B of strength of recommendation, the following tests were considered as validated as confirmatory tests for the anatomically plausible distribution: nerve conduction studies, electromyography, laser-evoked potentials, blink reflex, masseter inhibitory reflex, RIII component of the withdrawal reflex, and skin biopsy.[7] More work is needed to establish the sensitivity and specificity of these or other tests. The availability of a grading system will greatly facilitate the validation of confirmatory tests. In turn, the grading system can be validated according to the interobserver reliability that is obtained when two or more experts apply the grading system to representative patients based on findings from these confirmatory tests.

The fourth criterion of the grading system (table) relates to diagnostic tests for the presence of a relevant disease or lesion affecting the somatosensory system. Examples of such tests include MRI or CT confirmation of stroke, surgical or radiologic confirmation of nerve compression, laboratory confirmation of diabetes or MS, or nerve biopsy confirmation of neuropathy. An etiology of the underlying lesion or disease does not have to be found in order to reach the level definite neuropathic pain. Peripheral neuropathies can be idiopathic but the pain is clearly neuropathic. The characterization of pain as neuropathic or not depends on the application of the usual, careful neurologic diagnostic process. In this respect, the presence of a single positive finding on investigation is often not diagnostic. Take the simple case of a painful foot drop, where the differential diagnosis may be an L5 radiculopathy or a peroneal nerve lesion. Neurophysiologic and other (e.g., imaging) investigations are carried out to confirm a diagnosis that has been made on history and examination. While this provides a certain probability about the anatomic location, it does not necessarily indicate a pathologic diagnosis. The proposed redefinition of neuropathic pain reflects this well-established clinical approach in neurology. Any suggestion that neuropathic pain might be recognized and treated without a thorough diagnostic assessment of the underlying lesion or disease must be resisted.

DISCUSSION The revised definition of neuropathic pain replaces the term dysfunction by the term disease. In this way, diagnostic criteria for neuropathic pain are linked to generally accepted

principles in neurology. The revised definition specifies that the underlying lesion or disease must involve the somatosensory system, which includes the nociceptive system and its ascending and descending pathways. This revision serves to distinguish neuropathic pain from, e.g., musculoskeletal pain that arises indirectly from disorders of the motor system.

It is important to note that neuropathic and other types of pains are often present in the same patient (e.g., degenerative spine disease). Even in cases of definite neuropathic pain, a coexisting inflammatory pain may be clinically more important. The word primary has been omitted in the definition because of the difficulty in distinguishing between primary and secondary causes.

The proposed grading system relies entirely on positive criteria and can be used both for clinical and research purposes. It is intended to be used to decide on the level of certainty with which painful symptoms can be attributed to an underlying neurologic disease. Identification of the presence of neuropathic pain requires evidence for a disease process or lesion affecting a neuroanatomically identifiable part of the peripheral or central somatosensory system, which is concordant with the distribution of the pain. The neuropathic nature of a pain complaint cannot be determined without a physical examination of the patient, because the concept of neuropathic pain implies pathology of the nervous system, more precisely the somatosensory system. If neuropathic pain could be defined on symptoms only, such information should be included in the grading system. However, there is not (yet) agreement about the validity of symptoms.[16] Research criteria can only be guidelines. In drug trials more stringent criteria may be necessary than those used, for example, in epidemiologic studies. Explanatory trials investigating possible pathophysiologic mechanisms must rely on selective recruitment of cases with definite neuropathic pain,[26] whereas in pragmatic trials investigating treatment efficacy in daily practice inclusive recruitment at the level of probable neuropathic pain may be appropriate.[27] Inclusion in trials of patients with possible neuropathic pain would usually be inappropriate.

Because no grading system for neuropathic pain has existed so far, this system is initially designed to be conservative and restrictive. The lack of a gold standard for neuropathic pain requires a grading system based on judgment. Future studies will determine the utility of the present grading and the possible necessity for revision, for example, by including symptoms in the grading. A similar strategy was used in the classification of headache done by the International Headache Society.[28] Note that this grading system is for communication among clinicians and researchers, not for medico-legal purposes. The level of definite neuropathic pain should only be reached by those cases where there is no reasonable doubt about the presence of a lesion/disease of the somatosensory system and that the pain is directly due to such disorder. It needs to be stressed that patients with somatosensory deficits do not necessarily have pain.[20]

Controversy over whether diseases such as complex regional pain syndrome type I or fibromyalgia constitute neuropathic pain cannot be resolved by the process of formulating a definition. These issues must be decided on the basis of evidence from scientific research into the pathophysiology of these clinical entities. A definition of neuropathic pain, however, should include a set of rules on how such new scientific findings will lead to a decision one way or the other. We believe that the proposed definition and grading system provide such a set of rules, both for individual cases and for clinical entities.

The present grading system includes two levels of established neuropathic pain. For many conditions it is not possible to obtain these levels of evidence although the pain may have neuropathic features or a neuropathic component. This may be the case for certain types of low back pain where it is impossible with currently available investigations to distinguish neuropathic from nociceptive pain with confidence, particularly when they coexist. A large proportion of patients with chronic pain may only fulfill the first two criteria of the grading system and could as such be termed possible neuropathic pain. The present grading system makes it possible to test groups of patients with different pain types, as defined by the criteria proposed here, and test whether they differ, for example in terms of underlying pathophysiology or response to treatment. The figure presents a flow chart for practical use of the grading system.

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