Epidemiology and Impact of Neuropathic Pain

Neuropathic pain—“pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” according to the NeuPSIG (Special Interest Group on Neuropathic Pain) definition—is a challenge to health care. This common type of pain is often underdiagnosed and undertreated, and it is associated with suffering, disability, impaired quality of life, and increased cost.

The exact prevalence of neuropathic pain is not known. Two population-based studies from Europe reported the prevalence of pain of predominantly neuropathic origin or pain with neuropathic characteristics to be 8% and 7%, respectively. In both studies neuropathic pain was more severe than other types of pain. A German study reported that 37% of patients with prolonged low back pain had predominantly neuropathic pain. Depression, anxiety, and sleep disorders were significantly more prevalent in patients with neuropathic pain compared to those without such pain. Post-traumatic and postsurgical nerve injuries and postherpetic neuralgia are also common causes of neuropathic pain in the population. For example, herniotomy results in chronic neuropathic pain that affects everyday life in approximately 10% of patients. Pain continues after healing of the rash in 8% of herpes zoster patients. Pain in patients with neuropathic pain compared to those without such pain. Post-traumatic and postsurgical nerve injuries and postherpetic neuralgia are also common causes of neuropathic pain in the population. For example, herniotomy results in chronic neuropathic pain that affects everyday life in approximately 10% of patients. Pain continues after healing of the rash in 8% of herpes zoster patients.

Contrary to nociceptive pain, which results from physiological activation of nociceptors by potential or actual tissue injury, chronic neuropathic pain has no beneficial effect.

The prevalence of painful peripheral neuropathy was 16% in people with diabetes in the United Kingdom, and despite significant disability, one-third of diabetics with pain had never received any treatment for their neuropathic pain. In another population-based sample of diabetes patients, those with painful diabetic neuropathy reported significantly lower global quality of life compared to those without pain and those with non-neuropathic pain. In a U.S. survey, two-thirds of working patients with painful diabetic neuropathy reported absence from work or decreased work productivity due to pain, and only one-fifth of the patients were satisfied with their prescribed pain medication. As the prevalence of diabetes is expected to double over the next two decades, the prevalence of painful diabetic neuropathy is expected to increase. According to an insurance database study, health care charges...
were threefold higher for painful neuropathic disorder patients compared with matched control subjects.\textsuperscript{14}

To meet the challenge, all clinicians should be adequately trained to diagnose and treat neuropathic pain. Future general practitioners need basic knowledge of the neurological evaluation of the patient. Additionally, there should be the opportunity to refer difficult cases to a pain specialist or neurologist. This issue of \textit{Pain: Clinical Updates} focuses on the clinical diagnosis of neuropathic pain and also considers the aims of treatment and assessment of treatment effects in the clinic.

**The Nature and Management of Neuropathic Pain**

Contrary to nociceptive pain, which results from physiological activation of nociceptors by potential or actual tissue injury, chronic neuropathic pain has no beneficial effect. Neuropathic pain can arise from damage to the nerve pathways at any point from the terminals of the peripheral nociceptors to the cortical neurons in the brain. Neuropathic pain is classified as central (originating from damage to the brain or spinal cord) or peripheral (originating from damage to the peripheral nerve, plexus, dorsal root ganglion, or root). Neuropathic pain is also classified on the basis of the etiology of the insult to the nervous system (Table 1). It is not known why the same condition can be painful in some patients and painless in others. Currently a mechanism-based classification of neuropathic pain is not possible, because the detailed pain mechanisms in each individual case cannot be revealed. Furthermore, one mechanism can be responsible for many different symptoms, and the same symptom in two patients can be caused by different mechanisms.\textsuperscript{15} As neuropathic pain can coexist with nociceptive and idiopathic pains, clinicians should try to identify different pain components and treat each of them according to the best available evidence.

Neuropathic pain is characterized by spontaneous and provoked pain (Fig. 1), by other positive symptoms such as paresthesias and dysesthesias, and by negative signs (sensory deficits) reflecting the neural damage (Table 2). It is not possible to determine the etiology of neuropathic pain from the clinical characteristics of the pain.\textsuperscript{16} Additionally, there may be other symptoms and clinical findings (e.g., motor paresis, muscle cramps, and autonomic nervous symptoms), depending on the site of the lesion.

![Fig. 1. Components of neuropathic pain.](image-url)

**Table 1**

Classifications of neuropathic pain

<table>
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<tr>
<th>Location:</th>
<th>peripheral (nerve, plexus, dorsal root ganglion, root) central (spinal, brainstem, thalamus, cortex)</th>
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<tbody>
<tr>
<td>Etiology:</td>
<td>trauma ischemia or hemorrhage inflammation neurotoxic neurodegeneration paraneoplastic metabolic vitamin deficiency cancer</td>
</tr>
<tr>
<td>Symptoms and Signs:</td>
<td>pain quality sensory loss sensory gain</td>
</tr>
<tr>
<td>Mechanisms:</td>
<td>ectopic discharges loss of inhibition peripheral sensitization central sensitization</td>
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</table>

Neuropathic pain tends to be long-lasting. However, some patients can recover from their pain completely, and others may find relief with pharmacotherapy and learn to cope with their symptoms. Neuropathic pain is treated mainly with antidepressants and antiepileptics, whereas simple analgesics have not shown efficacy for this type of pain. Management of pain should be tailored to the individual patient on the basis of pain type(s), the causative disease(s), and psychosocial aspects. Evidence-based symptomatic pharmacotherapy is the mainstay of the treatment of neuropathic pain, and it should be titrated individually according to the efficacy and possible contraindications or side effects.\textsuperscript{17,18} The causative disease may warrant specific treatment (e.g., medication to support normoglycemia for diabetics to prevent progression of neuropathy and other complications, or immunomodulatory treatment of multiple sclerosis) or secondary prevention (e.g., commencement of antithrombotic medication and control of risk factors for atherosclerosis after a stroke). Relevant treatment is possible only if the differential diagnosis of the condition is performed adequately. As in other chronic conditions, a sound doctor-patient relationship, patient counseling, and psychosocial support are needed.

**Aims of Assessment of Neuropathic Pain**

Assessment of a pain patient with suspected neuropathic pain aims at (i) recognizing neuropathic pain, (ii) localizing the lesion (whether it is peripheral or central and whether it is in the brain, brainstem, spinal cord, nerve root, plexus, or the peripheral nerve...
or its branch), (iii) diagnosing the causative disease or event, and (iv) assessing the functional limitations that result from pain. In addition, assessment of psychosocial aspects is necessary for an individually tailored management strategy. Possible comorbidities should be taken into account, such as impaired sleep, anxiety, depression, and disability, as well as secondary impairment in work, family, and social life.

**Recognition of Neuropathic Pain: History and Clinical Examination**

Recognition of neuropathic pain is based on careful clinical examination. The history should include questions about the location, intensity, character, and temporal profile of the pain, along with possible exacerbating factors. Concomitant symptoms should also be queried. The process of diagnosing of neuropathic pain is summarized in Fig. 2.

<table>
<thead>
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<th>Table 2</th>
<th>Definitions of common features suggestive of neuropathic pain</th>
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<tr>
<td>Paresthesia</td>
<td>An abnormal sensation, whether spontaneous or evoked</td>
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<tr>
<td>Dysesthesia</td>
<td>An unpleasant sensation, whether spontaneous or evoked</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>Decreased sensitivity to stimulation (tactile or thermal; both are frequent)</td>
</tr>
<tr>
<td>Hyperesthesia</td>
<td>Increased sensitivity to stimulation (tactile or thermal; both are rare)</td>
</tr>
<tr>
<td>Hypoalgesia</td>
<td>Diminished pain response to a normally painful stimulus</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>An increased response to a stimulus that is normally painful</td>
</tr>
<tr>
<td>Allodynia</td>
<td>Pain due to a stimulus that does not normally activate the nociceptive system</td>
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The location of neuropathic pain is neuroanatomically logical. All neuropathic pains are projected—that is, they are perceived within the innervation territory of the damaged nerve, root, or pathway due to the somatotopic organization of the primary somatosensory cortex. Pain drawings are a good tool to document the location of pain (Fig. 3).

The intensity of pain can be assessed verbally (mild–moderate–severe–excruciating), numerically (on a 0–10 scale), or with a visual analogue scale (VAS). If there are several components of pain (e.g., continuous ongoing pain and superimposed lancinating pain), the intensity of both components should be assessed separately.

Although neuropathic pain is often described as burning, no single feature of pain is diagnostic for neuropathic pain. However, combinations of certain symptoms, pain descriptors, and bedside findings increase the likelihood of neuropathic pain. Screening tools, i.e., simple questionnaires, either patient- or clinician-completed, can be used to alert a clinician to the need for a careful examination in search of neuropathic pain (Table 3). A screening tool must not replace careful clinical examination.

Clinical examination tests the hypothesis of possible neuropathic pain based on the history.

Sensory testing, i.e., testing of the function of different sensory fibers with simple tools, is the most important part of the clinical examination (Table 4). The findings in the painful area are compared with findings in the contralateral area in unilateral pain and in other sites on the proximal-distal axis in bilateral pain. The relation between a stimulus and the perceived sensation may be changed quantitatively (hypo- or hyperphenomena), qualitatively, spatially, and temporally, and in an individual patient the somatosensory findings are a mosaic of aberrant responses to different modalities. Sensory loss should be specified with respect to the somatosensory submodalities involved—tactile, thermoreceptive, or nociceptive—in order
specified with respect to the stimulus modality to which the patient exhibits an exaggerated pain response (heat, cold, pinprick, or blunt pressure). In addition, dynamic mechanical allodynia to moving light tactile stimuli may occur. Of note, allodynia can be found also in nociceptive pain, and so the diagnosis of neuropathic pain cannot be made purely on the basis of finding allodynia.

Table 5

<table>
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<th>Sensory abnormalities found in patients with neuropathic pain</th>
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<tr>
<td><strong>Quantitative</strong></td>
</tr>
<tr>
<td>Hypoesthesia</td>
</tr>
<tr>
<td>Hyperesthesia</td>
</tr>
<tr>
<td>Hypoalgesia</td>
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<tr>
<td>Hyperalgesia</td>
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Source: Modified from Hansson.30

Localizing the Lesion: Neurological Examination

Identifying a neurological disease or a nervous system lesion is based on a systematic search for neurological abnormalities in clinical examination. In a neurological examination, the signs are repeatable, and the location of the lesion is determined on the basis of the neurological signs. In addition to a sensory examination, which reveals any abnormal somatosensory function, the physician will perform a motor assessment (muscle strength, tendon reflexes and cranial nerves) and an examination of tendon reflexes and cranial nerves. Assessment of peripheral autonomic nervous function (warmth and color of skin, sudomotor function) is important, especially when small-fiber neuropathy or complex regional pain syndrome is suspected. On the basis of clinical examination, it is possible to hypothesize the location of the lesion.

Fig. 3. Examples of pain drawings of neuropathic pain patients with (A) radicular pain of the right C6 dermatome and (B) painful polyneuropathy.
Diagnosis of the Causative Disease: Additional Investigations May Be Needed

Sometimes the diagnosis is straightforward, as in the case of neuropathic pain after a known surgical nerve lesion or posttherapeutic neuralgia after shingles. In these cases no additional tests are needed. If a patient has a stocking-and-glove pain location (Fig. 3A), polyneuropathy is documented with electroneuromyography (EMNG), and the cause of polyneuropathy is determined by laboratory tests including full blood count, sedimentation rate, glucose, creatinine, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), vitamin B₁₂, serum protein immunoelectrophoresis, and thyroid function.²³ If EMNG results are normal, the patient may have pure small-fiber neuropathy, which can be diagnosed using quantitative somatosensory testing, laser-evoked potentials, and skin biopsy to assess small-caliber (C and Aδ) sensory fibers.¹⁹,²⁴ The most common cause of thin-fiber painful polyneuropathy is impaired glucose tolerance.

Guidelines for diagnosis and treatment are available for many common neuropathic pain conditions such as low back pain (including cases with radicular pain)²⁵ and suspected carpal tunnel syndrome.²⁶ In many cases, there is complete recovery after surgical decompression of a nerve or nerve root.

Assessment of overall satisfaction and quality of life summarizes the therapeutic effects of treatment and any side effects

In general, decisions about consultation should be individualized and based on assessments of the patient’s symptoms, the experience and training of the clinician, and the availability of specialists with relevant expertise. Patients considered to have neuropathic pain are usually referred to a neurological clinic for further assessment. Tests in a specialized center may include conventional electrophysiological procedures, quantitative somatosensory testing,²⁷ neuroimaging, blood and cerebrospinal fluid samples, and less conventional laboratory tools to assess the nociceptive pathways in the peripheral and central nervous system.¹⁹

Assessment of Treatment Effects in the Clinic

The aim of pain treatment is pain relief and functional rehabilitation, which are assessed with repeated requests to rate pain intensity. Reduction of pain by at least 30% is clinically relevant.²⁸ If a patient has allodynia or hyperalgesia, relief can be assessed with repeated sensory testing at follow-up visits. Possible side effects of medication need to be noted. Improvement of sleep, mood, and functional deficits should also be noted in the follow-up visit, and if the treatment does not relieve these problems, they should be treated separately. People with chronic pain consider functioning and well-being to be appropriate targets of treatment. Assessment of overall satisfaction and quality of life summarizes the therapeutic effects of treatment and any side effects.¹⁹

Treatment of a patient with neuropathic pain is a long-term process. In the beginning, the diagnostic procedures are most important. History and clinical findings should be documented clearly in the medical charts to facilitate the assessment of treatment effects at follow-up visits. After a diagnosis has been made, more attention is paid to the assessment of treatment effects. Because depression, disturbed sleep, and functional impairment are common in patients with chronic pain, these problems should also be assessed in addition to pain relief.

References

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