Can we distinguish between inflammatory and neuropathic pain?

Gary J Bennett PhD

Inflammatory and neuropathic pain were once considered to be distinct entities. However, research over the past decade or so has brought to light many shared mechanisms, and the distinction between the two is no longer clear. Consideration of mechanisms, symptoms and the effects of analgesic drugs does not reveal any definitive or universally applicable differentiating factors. Given the present level of understanding, it may not be possible to distinguish between inflammatory and neuropathic pain in a large number of patients, and a satisfying definition of neuropathic pain may not be possible.

Key Words: Allodynia; Chronic pain; Hyperalgesia; Inflammation; Neuropathy

WHAT CONSTITUTES A NERVE LESION?

If neuropathic pain is defined as being caused by a nerve lesion, then differentiating it from inflammatory pain will depend on our ability to document a nerve lesion. Our ability to do this is not very impressive. Trauma or disease that injured 50% of the axons in the sciatic nerve would be easy to document and would obviously qualify as a nerve injury. But injury to 5% of the axons in the sciatic nerve would not be easy to document. The gold standard electrodiagnostic procedure, the sensory nerve conduction velocity (SNCV) test, is insensitive to partial injuries and to injuries to small A- and C-fibres. A sciatic nerve in which every single C-fibre had died could have a perfectly normal SNCV. Many nerves are small; for example, the knee joint is innervated by several small nerves and it is probable that one of these is sometimes damaged in arthroscopic procedures. Such damage would be difficult to document, because the SNCV tests cannot be performed on small, deep, short nerves. In some circumstances, quantitative sensory testing (QST) may be used to document small or partial nerve injuries, or injuries to just small fibres. But such documentation is accepted only if one allows ‘subjective’ evidence. Moreover, the sensitivity of QST for small nerve injuries has not been documented, and it is not always practical (how would one use QST to detect damage to the knee joint’s innervation?).

As they approach their target tissue, somatosensory nerves divide into smaller and smaller branches; the smallest, most
Inflammation can cause neural damage, and neural damage can cause inflammation. I think it is likely that inflammatory and neuropathic pain mechanisms frequently coexist. This makes the distinction between the two difficult in both the clinical and experimental contexts.

Inflammatory processes damage healthy tissue that surrounds an injury or infection, and this damage includes the tissue's sensory innervation. As noted above, inflammation-evoked damage to even the sensory terminal arbors within the tissue may constitute a lesion capable of producing neuropathic pain. Perhaps the clearest example of this is with bone cancer, where the intramedullary sensory innervation is destroyed by the expanding tumour mass and the inflammatory response to the presence of the tumour (13).

Neural damage from any cause will produce an inflammatory response. Even in a perfectly sterile injury, cellular debris from degenerating nerves, fascicles and terminal arbors is a sufficient stimulus to activate the immune system. This inflammatory response is a necessary component of the healing process; cellular debris must be removed (or at least cordoned off) before tissue regeneration can proceed. Ordinarily, this is an acute process. But one can imagine situations in which it would be chronic, or chronically episodic. For example, nerves have limited elasticity and are generally not attached to surrounding structures; thus, bending the elbow produces a relatively small stretch to the ulnar nerve. A nerve that becomes tethered to adjacent tissue loses much of its elasticity and may suffer excessive stretch every time the surrounding structures moved, resulting in repetitive microdamage that generates cellular debris. This is a likely reason for the pain of patients with ‘tennis elbow’ or carpal tunnel entrapment. Entrapment of the ulnar nerve is easy to detect, but could we document entrapment of an articular nerve in postarthroscopic scar tissue? As another example, consider the distal, symmetrical, dying-back neuropathy that is so common in the diabetic patient. The cause of the axonal degeneration is unknown, but it is clearly a chronic and progressive process, in which new neural debris is constantly produced. It is thus conceivable that the diabetic patient’s nerve is constantly inflamed (and that inflammation itself may contribute to axonal injury).

It is particularly noteworthy that the incidence of pain following inflammation and neural injury is clearly different. Any but the most trivial inflammatory condition is accompanied by at least some pain in nearly everyone (the only important exception being when the inflammation is confined to an organ that does not have a sensory innervation, eg, the brain). But neural damage causes pain in only a minority of patients. For example, only approximately 20% of diabetics with peripheral neuropathy have neuropathic pain. The highest incidence is approximately 50% for postherpetic neuralgia patients who have shingles when they are in their 80s or older. Why apparently identical neural lesions cause neuropathic pain in some people but not in others is one of the outstanding questions. I
suspect that differentiating neuropathic and inflammatory pain would be easier if we had the answer.

THE SPECIAL CASE OF PAIN DUE TO NEURITIS

‘Neuritis’ refers to an inflamed nerve, but the importance of the exact location of the inflammation is rarely considered. Inflammation of the nerve’s epineurial sheath will activate and sensitise nociceptors that are part of the sheath’s sensory innervation (ie, the nervi nervorum). The result is likely to be a nerve that is sore and tender to palpation, and the pain is likely to be fairly well localized. If one asks a patient with sciatica to point to his pain, one will often see the patient press his finger into the sciatic notch, drag it across the buttck, press it between the medial and lateral thigh muscles on the back of his leg, and run the finger down between the muscles to the popliteal fossa. I suggest that the patient is tracing the course of his sciatic nerve. His nerve is sore; to be precise, his epineurium is sore. Such pain would be classified as inflammatory pain.

However, an inflammatory process need not be confined to the nerve’s connective tissue sheath – it may also be present in the endoneurial compartment. The sensory axons travelling within a nerve do not express the transduction molecules that are responsible for activation by noxious stimuli. These molecules are expressed only in the membrane of the sensory axon’s terminals (alternatively, they may be expressed in the axonal membrane everywhere, but functional only when inserted into the terminal’s membrane). However, there is evidence that at least some inflammatory mediators can evoke an ectopic activation of the axon itself. For example, normal C-nociceptor axons will discharge when tumour necrosis factor-alpha is applied endoneurally (14). Pain produced in this way will not be localized to the nerve; it will be felt in the tissue innervated by the activated axon. It seems reasonable to classify this as neuropathic pain.

Thus, I propose a distinction between epineurial neuritis and endoneurial neuritis, with the former producing inflammatory pain and the latter producing neuropathic pain. Clinically, one might expect to find either in relative isolation in at least some cases, but one can easily imagine that they commonly coexist. Moreover, there is reason to believe that an epineurial inflammation can evoke an endoneurial inflammation via a mechanism distinct from simple spread across the nerve sheath (15).

SYMPTOMS

Is it possible to differentiate inflammatory and neuropathic pain on the bases of their symptoms? I think the answer is “sometimes, but not very often”. First, we must acknowledge that our knowledge of exactly what kinds of pain abnormality are present in inflammatory and neuropathic pain patients is woefully inadequate. For example, what percentage of patients with painful diabetic peripheral neuropathy have cutaneous mechanoallodynia? Do osteoarthritits patients have heat hyperalgesia in the skin overlying their painful joints? Is an attack of gout accompanied by cutaneous mechanoallodynia? I think the answer to both questions is yes, but little evidence is available (16).

Second, it is important to note that the location of the symptoms usually differs. Cutaneous pain abnormalities are frequent in neuropathic pain patients, but relatively rare in patients with inflammatory pain. The exceptions to this are the relatively rare cases with cutaneous inflammatory disease and the more common cases of cutaneous referred pain secondary to inflammation of some visceral organs. Chronic inflammatory pain is most often localized to musculoskeletal and visceral tissue (eg, osteoarthritis and cystitis). Neuropathic pain patients sometimes report deep tissue pain, usually in muscle and bone, but this deep tissue pain has received far less study than the cutaneous symptoms and its incidence is unknown. Importantly, experimental investigations in both animals and patients have mostly looked only at abnormalities of cutaneous pain. Neuropathic pain referred to a visceral organ is either exceedingly rare or not convincingly documented. This is noteworthy, given that surgical injuries to sensory nerves innervating visceral organs (eg, excision of a gall bladder or uterus) are common.

Third, the complaints of patients with inflammatory pain are relatively uniform (arthritis patients have aching pain in their joints, low-back pain patients have aching pain in their backs, regardless of whether they have sciatica) and their pain seems well localized to the area of inflammation. In contrast, neuropathic pain patients present with a bewildering mix of symptoms such as burning pain, aching pain, stabbing pain, mechanoallodynia, cold allodynia and heat hyperalgesia, alone or in multiple combinations. Moreover, neuropathic pain is frequently not well localized and may spread to the territories of multiple nerves and dermatomes (17). However, localization of pain is unlikely to be a key differentiating factor for inflammatory and neuropathic pain.

There are some differences in the symptoms. Cold allodynia is a frequent (although far from invariant) symptom in at least some kinds of neuropathic pain. The cold-pain threshold depends strongly on the size of the area stimulated, but is generally in the range of 0°C to 10°C in normal persons. Neuropathic pain patients with cold allodynia report pain with stimuli of 15°C to 20°C, and it is important to note that the pain that is evoked has an abnormal quality – ‘burning’, rather than the ‘aching’ pain that cold normally evokes. I am not aware of any demonstration that cold allodynia exists in patients with inflammatory pain. Indeed, cold relieves inflammatory pain. It is thus possible that the presence of cold allodynia is an unequivocal marker for neuropathic pain, although its absence clearly does not preclude the presence of neuropathic pain.

Some neuropathic pain patients report shooting, electric shock-like pains. I have argued elsewhere (18) that such paroxysmal pains are literally like those produced by an electric shock, because they are both due to the simultaneous activation of large numbers of sensory axons. I am not aware of any purely inflammatory condition where the patient reports electric shock-like pain. It is thus possible that the presence of electric shock-like pain is an unequivocal marker for neuropathic pain, although here again its absence clearly does not preclude the presence of neuropathic pain.

Neuropathic pain is frequently (although not invariably) associated with a partial loss of sensory acuity in the area of the pain. This is probably a correlate of the inciting event – damage to sensory neurons. However, a partial loss of sensory acuity has also been reported for inflammatory pain conditions, where it has been hypothesized as being due to changes in central processing (16). Thus, it seems that the presence or absence of a decrease in sensory acuity will not be a clear differentiating factor.
Dysesthetic sensations are commonly reported by neuropathic pain patients. By definition, these are not pain. Patients frequently volunteer that dysesthetic sensations are difficult to describe. The word 'numb' is often used, not in the doctor's sense of 'insensate', but in the common usage of the word to describe the positive sensations arising from an ischemic limb. The presence of dysesthetic sensations may be an excellent differentiating factor for neuropathic versus inflammatory pain (19), but its absence will not exclude the presence of neuropathic pain.

**TREATMENT RESPONSES**

Is it possible to differentiate inflammatory and neuropathic pain on the bases of their responses to drugs? I think the answer is probably not.

Until recently, one might have asserted that pain that was resistant to opioids was neuropathic pain by definition. This is no longer tenable – neuropathic pain can be relieved by opioids, although it is very likely that relief is obtained only with doses larger than those commonly used for the relief of inflammatory pain and that their efficacy against stimulus-evoked neuropathic pain may be limited (20,21).

Tricyclic antidepressants (TCAs) are a mainstay in the treatment of neuropathic pain and it is clear that their efficacy is separable from their effects on mood (22). Accumulating evidence suggests that the efficacy of TCAs against neuropathic pain may result at least in part from their ability to block voltage-gated sodium channels (23). But animal studies suggest that TCAs may have at least some efficacy against inflammatory pain and open-label trials suggest that sodium channel blockers may also be effective in patients with osteoarthritis and low-back pain (24,25). It is noteworthy that at least some of the changes in sodium channel expression in primary afferent neurons that were first found in neuropathic pain models are now known to also occur in chronic inflammatory pain conditions (26). Thus, analgesic effects from TCAs and sodium channel blockers will probably not be a clear differentiating factor for neuropathic and inflammatory pain.

Several of the new generation of antiepileptic drugs have efficacy in at least some neuropathic pain patients. The best-characterized drugs in this group are gabapentin and pregabalin (gabapentinoids). Gabapentinoids have little or no analgesic activity in patients with inflammatory pain (it may simply be that no one has looked). However, very recent reports suggest that gabapentinoids may have efficacy in preventing and reducing at least some types of postoperative pain (27,28).

**REFERENCES**

Inflammatory versus neuropathic pain

COPYRIGHT PULSUS GROUP INC. - DO NOT COPY


