Redefining Neuropathic Pain: The First Step in Improving Care

The distinction between “neuropathic” and “nociceptive” pain may be outdated and of limited value clinically. Here’s a more sophisticated approach.

Traditionally, neurological research and practice distinguishes between the peripheral and central nervous systems; in many regards, this has served the field well—for example, distinct clinical courses have been mapped for demyelinating disorders of the PNS (e.g., inflammatory demyelinating polyradiculoneuropathy) and the CNS (e.g., demyelinating disorder of multiple sclerosis), even though both can be progressive and include chronic pain as part of their presentation. On the other hand, pain does not respect the PNS/CNS distinction. When pain occurs, each system is activated—from nociception to modulation to perception—leading to the pain experience. Even though neuropathic pain may appear “centralized,” it may still exhibit ongoing nociceptive input from the periphery.

A further conceptual challenge for neuropathic pain: although the clinical course and expression of the disorder are under the influence of the underlying disease process (e.g., idiopathic trigeminal neuralgia versus spinal cord injury), most phenomenological manifestations are frequently similar and overlapping, regardless of whether injury occurs to the PNS or CNS. Simply put, these symptoms and signs do not tell us where the lesion is. The nature and the extent of the injury and the natural course of repair that follows with involvement of inflammatory processes all increase the complexity and dynamic nature of neuropathic pain in each patient.

Some may feel the distinction between inflammatory pain and neuropathic pain is arbitrary, but on a practical level the distinction may have direct implications for diagnosis and therapy in addition to understanding the natural course of the disease for each type of pain. Insult or irritation of nerves may promote inflammation (e.g., neurogenic inflammation) and inflammation may affect neural function.

Conventional, older classifications have divided persistent pain into two mutually exclusive categories: nociceptive and neuropathic. Clinicians later considered persistent pain as neuropathic, non-neuropathic (e.g., nociceptive), or non-neuropathic pain largely with or somewhat with neuropathic features/qualities/characteristics or a neuropathic component. More recently, the distinction has been viewed more as a spectrum with proposals that pain may have degrees of neuropathic components and thus may be viewed on a continuum of “more or less neuropathic.” Bennett coined the term “pain of predominantly neuropathic origin (POPNO),” hoping that the old all-or-nothing labeling of neuropathic pain would wane.1

Neuropathic pain assessment should include mechanical and thermal hyperalgesia/allodynia, as well as a detailed traditional neurological examination. Ideally, a valid specific tool for the physical examination of patients with chronic pain will be developed that will allow the examiner to accurately predict whether or not neuropathic pain is present.

Furthermore, when appropriate this information may be supplemented with various laboratory testing, imaging, electrodiagnostic testing, quantitative sensory testing, as well as specific testing of the skin such as: provocative or challenge testing; assessing whether various agents (e.g., capsaicin) exacerbate, alleviate, or do not affect pre-existing spontaneous pain, and analysis of skin punch biopsies.

Experienced pain assessors (you don’t have to be a pain specialist to assess pain!) with the above information will be better equipped to characterize neuropathic pain and it is hoped that categorization proposed below may be useful in the future:

1. Neuropathic Pain: Pain thought to be purely or largely neuropathic.

2. Pain with Significant Neuropathic Component: Pain which is largely neuropathic in nature but may exhibit a minor non-neuropathic component.

3. Mixed Pain: Pain comprised of roughly equally significant neuropathic and nociceptive components

4. Pain with Significant Non-neuropathic Component: Pain which is largely non-neuropathic in nature but may exhibit a minor neuropathic component.

5. Non-neuropathic Pain: Pain which is thought to be purely or largely nociceptive. This would include pain of predominantly non-neuropathic origin.

A significant problem for clinicians seems to arise when a patient presents with symptoms that seem compatible with neuropathic pain but there is no evidence of neurological injury, such as in the case of complex regional pain syndrome (CRPS) type I (RSD/Reflex Sympathetic Dystrophy) in which minor injuries not routinely detectable by standard tools are present. One approach to aide clinicians in these difficult evaluations is to continue to develop methods that are sensitive enough to detect minor nerve injury, such as the technique of intraepidermal nerve analysis described by Griffin et al. Alternatively, the continued development of compre-
A variety of growth factors help to information becomes available. Model with and self-correction as new information to modify and update the built-in flexibility that would allow new and a working model which should have the establishment of general principles.

Propathic pain, with all of its implications, disorders may lead to chronic disability. The puzzle of pain by clinicians, is certainly there are many types of pain, such as visceral pain or migraine headaches, that could not easily be categorized either as inflammatory or as neuropathic pain. Other types, such as cancer pain, may have elements of both in addition to other factors not well described, such as those specific for the type of cancer and its location. In addition, rapid expansion of information regarding basic pain mechanisms and the deluge of possible candidate ligands and receptors as the possible driving forces behind those mechanisms, challenges our traditional concepts about how to categorize and to study pain.

The diversity of many types of pain and an ever-increasing number of pain mechanisms continually challenges the need for conceptual clarity and the establishment of fundamental principals for mechanism-based diagnosis and treatment of pain. The solution to these challenges begins by open debate, ongoing discussions, and developing a definition of neuropathic pain, with all of its implications, and the establishment of general principles and a working model which should have built-in flexibility that would allow new information to modify and update the model with and self-correction as new information becomes available.

**Parsing the Pathophysiology**

The most common consequence of injury to the nervous system is loss of neurological function, and in case of the somatic sensory system it is loss of many modalities of sensation. Although some return of function will likely occur as a part of healing, it is always only partial and incomplete. The chronic nature of neurological disorders may lead to chronic disability related to the sensory system. The puzzle for patients, and at times the source of dismissal of the report of pain by clinicians, is the fact that patients with injury to their thermoneceptive system have pain in the same areas innervated by the nervous system. That is, pain may exist in the absence of sensory or motor impairment. And pain may persist long after healing takes place, such as in traumatic nerve injuries or following shingles. For the majority of these patients, pain is the overwhelming problem, taking precedence over other neurological symptoms.

The implication of this paradoxical phenomenon is the need for a better understanding of the relationship between multiple components of neuropathic pain and its most disturbing component, ongoing pain. Neurological deficits have to be taken into account, assessed and monitored because the course of pain will depend on the natural course of the underlying disease. Under optimal circumstances, one would expect improvement of sensory function would lead to lessening of neuropathic pain; however, thus far that goal has not been able to achieve even with positive findings reviewed by Apfel in preclinical investigations. Fields et al. described three subsets of patients with postherpetic neuralgia:

1. Abnormal sensitization of unmyelinated cutaneous nociceptors (“irritable nociceptors”).
2. Small fiber deafferentation resulting in impaired pain and temperature sensation with allodynia. Oaklander and colleagues have demonstrated this neurite drop-out in PHN patients.
3. Deafferentation of large and small diameter fibers: spontaneous pain most likely largely due to central mechanisms without hyperalgesia or allodynia.

Two other subsets of patients with persistent neuropathic pain may include:

4. Immunomodulatory neuritis/Glial Dysfunction.
5. Dysafferentation.

Smith (in 2005) coined the term “dysafferentation” to refer to conditions in which there is abnormal sensory function of a region without the loss of nerve supply. A variety of growth factors help to maintain the proper mix of skin nerve endings in a delicate equilibrium. Neurological insult may disrupt this harmonious mix, resulting in an imbalance associated with pathologic pain in which some nerve endings are lost or decreased, whereas others may increase.

Another difference that needs to be addressed is the distinction of pain mechanisms from pathological mechanisms due to specific etiological causes. Certainly, specific etiologies result in disorders with specific clinical pictures and the natural course specific for each disorder, such as traumatic neuropathy, most of which are painless. The basis of this distinction between painless and painful traumatic neuralgia is the possibility that pain mechanisms lead to specific symptoms and a natural course which are under direct influence but independent of etiological mechanisms.

An example is diabetic neuropathy, and the question in this case would be: are the pathological mechanisms that lead to diabetic neuropathy the same as or different than those mechanisms that lead to pain in painful diabetic neuropathy? Chronic pain leads to specific comorbidities and disabilities and require specific therapies. This is a circumstance where the symptom becomes the disease, analogous to when seizures which could be resultant symptoms of biochemical imbalance become the disorder of epilepsy.

**Clinical Implications**

The challenge for neuropathic pain diagnosis and assessment is the complexity not only of the primary manifestation of symptoms but also the many other manifestations of the neuropathic pain as a disease which crosses more than one domain. For this complexity to be captured and communicated, a model of Multidimensional Pain Assessment (MDPA) has been proposed by Backonja and Argoff.

The clinical implications of neuropathic pain and challenges for the diagnosis
and assessment originate from the fact that the inciting illness or injury may have many consequences in addition to pain. As discussed above, each illness has a specific clinical course and associated comorbidities. Those comorbidities may be medical, such as hypertension and hypothyroidism, or psychiatric such as depression and anxiety. Medical and psychiatric comorbidities may or may not further impact neuropathic pain. Even though many comorbidities do not have direct effects on the clinical manifestations of neuropathic pain, some comorbidities may indirectly affect neuropathic pain, such as hypothyroidism, which if untreated can contribute to worsening of neuropathy and consequently pain.

Psychiatric comorbidities and pain, in general, may pose an even bigger challenge. In this regard, neuropathic pain is perhaps most complicated because of its severity, chronicity and a lack of response to traditional treatments. Ploghaus et al., through recent advances in neuroimaging, elegantly demonstrated a neural basis for the relationship between anxiety and pain in humans. The influence of pain on psychiatric comorbidities and vice-versa is extremely complex and far from clear. The availability of many specific assessment tools for human as well as for bench research provides ample opportunities to study those relationships.

Backonja and Argoff have proposed a framework to assist in obtaining a complete clinical picture about each individual patient. The suggested multidimensional assessment approach provides the means of assessing critical dimensions of chronic pain specifically, and then on the basis of that assessment, rank ordering components that contribute to the patient’s presentation at any given time. It provides for the complexity as well as the dynamic nature of pain. Certainly, use of validated pain intensity rating scales are still considered the “gold standard” for pain intensity assessment, but use of a more comprehensive approach may help to obtain insight into how any particular component of pain including multiple components of neuropathic pain behave in time and respond to treatments.

The most significant implication of applying this approach is the ability to comprehensively assess pain and also to prioritize necessary steps of treatment. Assessment should be made for each dimension, which should be rated as none, mild, moderate or severe, to allow ranking. The severity of items for each particular dimension would determine the order of further diagnostic investigations and treatment steps. Clinical experience points to the fact that most if not all patients with chronic painful disorders have diagnoses on each of these dimensions. It is tempting to concentrate on one component with which the clinician is most comfortable and to ignore others, or to see all of the components as separate and isolated entities. However, it is crucial to remember that these components interact constantly and have to be taken together.

Conclusion

In summary, advances in pain research, including basic science and clinical research have provided ample reason for enthusiasm that progress could be made in the assessment and measurement of pain, leading to improved pain taxonomy and communication. Consequently this would lead to the development of mechanistically-based assessment tools and therapies. At present, a number of conceptual, pathophysiological, and clinical challenges hamper the diagnosis and treatment of neuropathic pain. PN

Note: This month’s column was written based upon work which I have done with Misha Backonja, MD, Professor of Neurology, Anesthesia and Physical Medicine and Rehabilitation at the University of Wisconsin (Madison) and Howard Smith, MD, Associate Professor of Anesthesiology at Albany Medical College.

The Multidimensional Pain Assessment (MDPA)

I. Medical etiology related to pain (e.g., diabetes) and medical comorbidities that could influence manifestation of pain symptoms (e.g., hypothyroidism).
II. Pain mechanisms, such as neuropathic, inflammatory, myofascial, etc.
III. Psychiatric comorbidity (e.g., depression, anxiety and patients’ coping skills, tendency to catastrophize).
IV. Impact of pain on ability to function (with loss of function comes the disabilities) and quality of life.

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<th>Specific Parameters</th>
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<td>I Medical etiology</td>
<td>Specific etiology and medical comorbidities</td>
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<tr>
<td>II Pain Mechanisms</td>
<td>Neuropathic, inflammatory, myofascial, Incidence, other</td>
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<tr>
<td>III Psychiatric comorbidity</td>
<td>Psychiatric comorbidities and coping skills</td>
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<td>IV Function, QOL</td>
<td>Disabilities, impaired QOL</td>
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