Introduction

Fibromyalgia from the Perspective of Neuropathic Pain

Neuropathic pain has been defined by the International Association for the Study of Pain as pain "initiated or caused by a primary lesion or dysfunction in the nervous system"[1]. Pain is common when illness or injury produces objective pathology in the peripheral or central nervous system (CNS), and there is little uncertainty about the appropriateness of considering pain neuropathic when patients with conditions such as diabetic polyneuropathy or spinal cord injury report pain that is consistent with their diagnosis. There are other patients, however, who have no demonstrable nervous system lesion but whose pain appears to be consistent with "dysfunction" in the nervous system.

The painful conditions that may reflect such dysfunction include complex regional pain syndrome, fibromyalgia (FM), and migraine headache. It has been argued that the concept of "dysfunction" in the nervous system is vague and can hamper research on pathophysiologic mechanisms and treatment response[2,3]. Nevertheless, important advances have been made in developing diagnostic criteria for these syndromes, which is a critical first step in enabling research on such "unexplained clinical conditions"[4].

FM is one of several chronic pain syndromes that are common, poorly understood, and have been proposed to reflect some primary abnormality of the nervous system. For this reason, a symposium was held at the 6th International Conference on the Mechanisms and Treatment of Neuropathic Pain to discuss whether FM should be considered a neuropathic pain syndrome. The articles in this supplement, which are based on the presentations at the symposium, discuss clinical characteristics, pathophysiologic mechanisms, laboratory findings, and treatment approaches in FM. From the different perspectives of rheumatology, neurology, and basic science, the authors consider whether and to what extent FM reflects nervous system dysfunction.

In this introduction, we neither review what the other contributors have said nor address the question of whether FM is a neuropathic pain syndrome. The authors have done an outstanding job and we have little to add to their important contributions. Instead, we present a brief overview of current issues in understanding the mechanisms and treatment of neuropathic pain, and consider how current research on neuropathic pain may inform research on FM.

MULTIPLE PATHOPHYSIOLOGIC MECHANISMS

In the past 15 years, studies of animal models have provided the basis for important advances in understanding the pathophysiologic mechanisms of neuropathic pain. An important discovery is the number of different mechanisms. Identification of multiple mechanisms has been accompanied by growing consensus of their contribution to chronic neuropathic pain syndromes in humans[5,6]. Further, there is now broad agreement that both peripheral and CNS processes contribute to many pain syndromes.

One important implication of this is that a given etiology may produce pain by more than one mechanism. Consequently, patients with neuropathic pain may be both clinically and pathophysiologically heterogeneous[7,8]. A corollary of this is that patients with conditions that are etiologically distinct may share pain states that are identical with respect to their mechanism and that differ from other patients with the same disease etiology. For example, a patient with diabetic neuropathy may share underlying pain mechanisms with a patient with HIV neuropathy but not with another patient with diabetic neuropathy whose pain is caused by a different mechanism.

SYMPTOMS, SIGNS, AND MECHANISMS

If patients with the same disease can have different underlying mechanisms accounting for their pain, it becomes important to develop methods for identifying these mechanisms. Ongoing studies are examining the extent to which pain mechanisms can be identified from patterns of symptoms, signs, sensory testing, and response to pharmacologic challenges[9,10]. Although it is not possible at present to identify patterns of symptoms and signs associated with different specific pain mechanisms, the belief that it will ultimately be possible to do so has led to new strategies for assessment of neuropathic pain. For example, in considering symptoms and signs of neuropathic pain and their relationships with underlying mechanisms, an important distinction is made between stimulus-evoked pain and spontaneous pain that is stimulus-independent. Spontaneous pain is present in the absence of any stimulation and can be either continuous or intermittent. Most patients describe more than one type of spontaneous pain, that is, their pain has several different qualities (e.g., burning, throbbing, shooting). Spontaneous continuous pain is present almost all the time, although patients typically report that it varies in intensity. Spontaneous intermittent pain is episodic

and typically has a relatively short duration. This type of pain is often paroxysmal and described by patients as shooting, stabbing, or electric-like in quality.

The second broad type of neuropathic pain is stimulus-evoked pain (also termed stimulus-dependent pain). Stimulus-evoked pain includes allodynia, which is pain in response to a normally nonpainful stimulus, and hyperalgesia, which is an enhanced pain report in response to a normally painful stimulus. The stimuli that have been used in evaluating stimulus-evoked pain are of many types, including thermal, vibratory, dynamic, and static (punctate or blunt). Dynamic allodynia can be elicited by lightly moving a paint brush or a cotton swab across the skin, static allodynia and hyperalgesia can be elicited by blunt pressure with a finger or punctate pressure with a von Frey filament, and thermal allodynia and hyperalgesia can be assessed by heating or cooling with a metal probe (or by applying ice).

Distinguishing between spontaneous and stimulus-evoked pain is valuable for characterizing differences between patients with different diseases and among patients with the same disease. For example, allodynia is present in approximately three-quarters of patients with postherpetic neuralgia but only one-quarter of patients with painful diabetic neuropathy. Patients with prominent allodynia, who often have less sensory loss than patients with continuous pain, can report pain relief following application of local anesthesia[7-9]. These data suggest that one important pathophysiologic mechanism of allodynia is a persisting state of central sensitization that causes input from mechanoreceptors to be experienced as painful and that is maintained by continuing activity from damaged primary afferent nociceptors[5-10].

In contrast to patients with prominent allodynia, patients with spontaneous pain and minimal allodynia can have marked sensory deficits in the areas where they have the most pain[7-9]. The contribution of primary afferent nociceptors to pain in these patients appears to be minimal, and their spontaneous pain may be caused by destruction of primary afferent fibers and central changes associated with deafferentation. These central abnormalities may involve a loss of inhibition in the dorsal horn of the spinal cord, especially inhibitory currents mediated by GABA (gamma-aminobutyric acid), and such disinhibition may contribute to central hyperexcitability and provide a mechanism for spontaneous neuropathic pain[6,7].

Differences in symptoms and signs among patients reflect complex relationships between the qualitatively different types of pain and their underlying mechanisms. Although there may be one-to-one correspondences between symptoms and mechanisms, the process is frequently complex: multiple mechanisms can contribute to the same symptom within a patient, the same symptom in different patients can be caused by different mechanisms, and different symptoms can share the same mechanism.

Interest in accurate assessment of specific qualities of neuropathic pain has increased not only because symptoms and signs may allow identification of underlying mechanisms, but also because there may be better measures of treatment effects than ratings of overall pain intensity[11,12]. However, it remains to be determined whether measures of specific symptoms and signs better differentiate neuropathic pains that have different mechanisms.

TREATMENT

Given the multiple mechanisms of neuropathic pain, clinicians would ideally first identify the specific pathophysiologic mechanisms of a patient's pain and then target treatment to these mechanisms. Results of recent randomized controlled clinical trials provide a basis for an evidence-based treatment approach. Drugs that have demonstrated efficacy in multiple randomized controlled trials include gabapentin, lidocaine patch 5%, opioid analgesics, pregabalin, and tramadol, as well as tricyclic antidepressants and selective serotonin and norepinephrine reuptake inhibitors (i.e., venlafaxine and duloxetine)[13-16].

Under some circumstances neuropathic pains having different underlying mechanisms would be expected to respond differently to medications with different mechanisms of action[6,17]. Despite the numerous studies on treatment of neuropathic pain, however, specific relationships between pain mechanisms and treatment response have not yet been identified. An important objective for future research is to go beyond the determination of whether a treatment is effective to the identification of specific patient characteristics that predict good response[18], an area that will be informed by the developing field of pharmacogenomics. It is essential to note that there may be patient variables (both genetic and environmental) unrelated to pathophysiology of pain that have robust effects on responses to different drugs (e.g., pharmacokinetics and metabolism of drug). Other genetic factors may mediate risk for certain types of pain mechanisms; thus careful correlation of patient pain characteristics including the genetic makeup will provide an important avenue for future research.

Despite limitations, the idea of multiple mechanisms accounting for neuropathic pain and/or drug efficacy has clear treatment implications because it provides a rationale for both sequential and combination treatment. Patients who do not respond to one medication may respond to another, especially one with a different mechanism of action; and combination treatment should be considered when patients show only partial response. Unfortunately, there have been few clinical trials in which treatments have been compared directly. Such comparison studies would not only assess whether treatments vary in efficacy, safety, and tolerability, but also when

conducted in the same patients would determine the extent treatment response to one medication predicts response to another[19].

Systematic evaluation of combination treatment is also needed. Although a large percentage of patients with neuropathic pain are currently treated with 2 or more medications, little is known about which patients will likely benefit from combination treatment. There are also no studies in neuropathic pain that have compared pharmacologic and nonpharmacologic treatments alone and together. It is therefore unknown, for example, whether physical therapy or psychosocial interventions provide an additional benefit beyond that obtained from pharmacologic management. This is an important question because the pharmacologic treatments that are currently available are rarely associated with the complete elimination of pain, and evidence of their beneficial effects on daily functioning and overall quality of life is limited.

As many as one-half of patients with neuropathic pain are refractory to treatment, and failure to provide relief for many patients has stimulated interest in prevention. Examples of efforts to prevent neuropathic pain include clinical trials immunizing elderly individuals with the varicella vaccine to prevent herpes zoster and treating herpes zoster patients preemptively with medications demonstrated to be efficacious in postherpetic neuralgia to potentially prevent it[20]. In addition, improved glycemic control in patients with diabetes can delay onset and progression of diabetic neuropathy[21], thus promising to prevent development of painful diabetic neuropathy in many patients. In addition, more effective strategies for administering perioperative analgesia may prevent the development of postmastectomy pain as well as other postsurgical neuropathic pain syndromes[22-24].

In evaluating patients and treatments in FM, there are more general issues that must be considered. Some patient variables have not been tied to particular pain-generating mechanisms and pharmacogenomics. Such variables may include CNS mechanisms that relate to pain transmission and modulation. For example, a damaged peripheral nerve may contain sensitized nociceptors[5-10]. Such nociceptor input causes a variable degree of central sensitization. In this case, the cause of spontaneous and stimulus-evoked pain is identical to what occurs under normal physiological conditions, for example, non-neural tissue damage. However, among a normal human population there may be variability in either the firing of the nociceptor or the mechanisms contributing to central sensitization such that a large component of the patient's pain is due to a "physiologic" rather than pathophysiologic process. This type of pain should respond just like non-neuropathic pain to a range of analgesics. Whatever the cause of FM, much of the disability and pain might be due to such a normal physiologic process.

IMPLICATIONS FOR FIBROMYALGIA

Progress in understanding the mechanisms and treatment of neuropathic pain can inform research on FM, even if FM is not considered a neuropathic pain syndrome. The most important implication of research on neuropathic pain involves heterogeneity of mechanisms. As the authors of the articles in this supplement and others have noted[25,26] it is likely that multiple processes also contribute to the pathogenesis of FM, which is a pathophysiologically and psychologically heterogeneous syndrome.

The role of psychosocial factors in development and maintenance of disease appears to be greater in FM than in neuropathic pain syndromes such as diabetic neuropathy and central post-stroke pain. There is considerable comorbidity of chronic pain and depression, and it has been argued that this may be a result of shared biological pathways and neurotransmitters[27]. While the extent of this comorbidity may vary among different specific pain syndromes, it appears to be greater for FM and depression[28]. This makes FM research into mechanisms more difficult than it is for neuropathic pain. In FM, attention must be paid not only to the contribution of multiple pathophysiologic mechanisms but also to the possibility that these mechanisms interact in complex ways with psychosocial processes like depression and anxiety.

As described above for neuropathic pain, patients with different diseases may have more in common with respect to pain mechanisms than do patients with the same disease. It would therefore be valuable to compare different pain groups: patients with FM, patients with pain caused by lesions of the nervous system, and patients with other pain syndromes caused by "abnormal responsiveness or function of the nervous system, in which heightened gain or sensitivity of the sensory apparatus amplifies symptoms"[6]. The latter syndromes include irritable bowel syndrome, some forms of noncardiac chest pain, and tension-type headache[6,29].

Such comparisons could involve comprehensive assessments of symptoms, signs, and sensory abnormalities as well as response to pharmacologic challenges such as intradermal capsaicin or intravenous lidocaine. For example, it would be interesting to determine the extent to which profiles of symptoms reported by patients with FM are similar (or not) to the profiles of patients with neuropathic, inflammatory, and pain conditions associated with "abnormal responsiveness or function of the nervous system"[11,12]. As in patients with neuropathic pain, the distinction between spontaneous and stimulus-evoked pain is also central in FM, and comparisons between FM and neuropathic and non-neuropathic pain syndromes can also be conducted for pain evoked by various sorts of stimuli[30,31].

As emphasized for neuropathic pain, the existence of multiple mechanisms also has important implications for

research on the treatment of FM. To the extent that a pattern of symptoms or signs reflects a specific underlying mechanism, measures of these symptoms and signs would be expected to be more responsive than overall ratings of pain intensity to the effects of a treatment that targets that mechanism. Turk and colleagues found that FM patients with different profiles of psychosocial functioning respond differently to interdisciplinary treatment, and they suggest that customizing treatment based on these profiles would lead to enhanced treatment efficacy[32]. The evidence that there are multiple mechanisms of pain in FM that include both physiologic and psychosocial abnormalities suggests that future research should attempt to identify and then target treatment to both types of mechanisms considered in tandem[6,18].

It would not be surprising if such combinations of mechanism-based pharmacologic and psychosocial treatments were to prove more efficacious than the nonspecific treatments for FM that are currently available[33-35]. Tension-type headache, which is common in patients with FM and has also been considered a type of pain that involves nervous system dysfunction[6], responds better to a combination of tricyclic antidepressant and stress management intervention than to either as monotherapy[36].

As noted elsewhere in these proceedings, treatments that have demonstrated efficacy in patients with FM overlap with treatments that have demonstrated efficacy in patients with neuropathic pain[13,33-35]. While this overlap does not prove FM is a neuropathic pain syndrome, it would not be unreasonable to investigate treatments that have shown efficacy for neuropathic pain in patients with FM. For example, venlafaxine recently demonstrated efficacy in 3 placebo-controlled clinical trials of patients with different types of neuropathic pain[15,37,38]. To date, however, there are no published controlled trials of venlafaxine in FM. In studying venlafaxine in patients with FM it would be important to examine higher dosages because efficacy appears to be greater in neuropathic pain patients administered these dosages of venlafaxine, which block reuptake of both serotonin and norepinephrine (lower dosages primarily block the reuptake of serotonin)[15,37,38]. Conversely, it would be worthwhile to consider investigating, in patients with neuropathic pain, treatments that appear to be efficacious in FM, for example, tropisetron and other 5-HT3 antagonists[39-41].

Because many patients with FM have pain refractory to all available treatments, prevention is an important research objective (as important as in neuropathic pain syndromes). Forty percent of patients report that surgery or an injury caused by an accident preceded the onset of their FM[42]. If risk factors for the development of FM in such patients can be identified, then it would be possible to administer interventions to high-risk individuals to prevent development of FM. Interventions that can be hypothesized to reduce the risk of FM include the pharmacologic and psychosocial interventions that have been found to be efficacious in patients with established FM[33-35].

We have discussed several implications of current research on neuropathic pain for research on FM. But we do not mean to suggest that research on FM has no implications for research on neuropathic pain. For example, FM research on important methodological and measurement issues in clinical trial design has been largely neglected by those investigating treatments for neuropathic pain[43-45]. Just as research on mechanisms of neuropathic pain provides a valuable context for research on FM, research on neuropathic pain can also benefit from greater attention to research on FM.

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