Is Fibromyalgia a Neuropathic Pain Syndrome?

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ABSTRACT. The fibromyalgia syndrome (FM) seems an unlikely candidate for classification as a neuropathic pain. The disorder is diagnosed based on a compatible history and the presence of multiple areas of musculoskeletal tenderness. A consistent pathology in either the peripheral or central nervous system (CNS) has not been demonstrated in patients with FM, and they are not at higher risk for diseases of the CNS such as multiple sclerosis or of the peripheral nervous system such as peripheral neuropathy. A large proportion of FM sufferers have accompanying symptoms and signs of uncertain etiology, such as chronic fatigue, sleep disturbance, and bowel/bladder irritability. With the exception of migraine headaches and possibly irritable bowel syndrome, the accompanying disorders are clearly not neurological in origin. The impetus to classify the FM as a neuropathic pain comes from multiple lines of research suggesting widespread pain and tenderness are associated with chronic sensitization of the CNS. An examination of how the term neuropathic pain is defined reveals a conceptual split into 2 partially overlapping groups of disorders: those with demonstrable pathology in the nervous system and those characterized primarily by enduring dysfunction in the nervous system. Requiring demonstrable pathology in the nervous system in the definition of neuropathic pain is the traditional approach. The expansion of the definition to require only enduring nervous system dysfunction is less palatable because it opens the classification to many disorders of uncertain etiology, including complex regional pain syndrome. As it is uncertain which of the many different chronic pain syndromes include an enduring component of central sensitization, restricting the term "neuropathic pain" to those disorders with a primary etiology clearly related to the peripheral or CNS is prudent and consistent with clinical practice. (J Rheumatol 2005;32 Suppl 75:38-40)

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INTRODUCTION

Fibromyalgia (FM) is a chronic pain syndrome consisting of widespread musculoskeletal pain and tenderness. Can FM be considered a neuropathic pain syndrome? It seems a conceptual leap is needed to bridge the gap between pain accompanying a disorder diagnosed using the criteria of musculoskeletal tenderness on the Manual Tender Point Survey[1] and pains accompanying disorders defined in terms of pathologically verifiable damage to the nervous system. FM is not a new disorder; Gowers wrote about "lumbago" 100 years ago[2]. In the intervening years, fibrositis and muscular rheumatism were used to distinguish the disorder we now call fibromyalgia from inflammatory conditions with objective findings in joints, such as osteoarthritis and rheumatoid arthritis.

A large body of work on the etiology of FM has left the question of nervous system function aside and focused on whether the structure and function of muscle and connective tissue is abnormal. Despite a wide variety of abnormal findings reported to date, there is no consensus[3]. Although a number of studies have demonstrated altered thresholds for pain and abnormal windup to repetitive noxious stimuli, pathological changes in the central or peripheral nervous system have not been identified. Other lines of investigation have focused on abnormalities of the hypothalamic-pituitary-adrenal axis and endocrine dysfunction, including growth hormone deficiency and abnormal thyroid function, all of which can affect function of the nervous system or, in theory, result from pathology in the brain.

Before considering whether FM should be classified as a neuropathic pain, a review of the current taxonomy of neuropathic pain and related terms is in order. Not all neuropathic pain syndromes are alike, and clinicians vary widely in their willingness to describe various chronic pains in neuropathic terms.

HOW IS NEUROPATHIC PAIN DEFINED?

A convenient starting point is the International Association for the Study of Pain (IASP) taxonomy[4] (also available from: http://www.iasp-pain.org/terms-p.html#Neuropathic%20pain). Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system." Neuropathic pain is then broken down into 2 major divisions based on lesion location. Peripheral neuropathic pain occurs "when the lesion or dysfunction affects the peripheral nervous system." Central pain is defined in a manner consistent with the peripheral neuropathic pain definition as "pain initiated or caused by a primary lesion or dysfunction in the central nervous system" (CNS). Further, "central pain may be retained as the term when the lesion or dysfunction affects the central nervous system."

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NEUROGENIC PAIN CAUSED BY A TRANSITORY PERTURBATION IN THE NERVOUS SYSTEM

Neurogenic pain, defined as "pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system," also appears in the IASP taxonomy. This term is easily confused with neuropathic pain, and should probably not be perpetuated. It is here that terminology begins to blur between "normal" pain, as might occur after simple trauma or surgery, and pathological pain. Depending on how broadly a "transitory perturbation in the nervous system" is interpreted, this category may include any somatic pain in which an area of transient secondary hyperalgesia surrounds an area of intense primary afferent stimulation. More than a century ago, Henry Head meticulously documented patterns of cutaneous sensory dysfunction (Head's zones) accompanying visceral disorders of the heart, ureters, and prostate[5], as did Fields[6]. Studies by Dahl and others have mapped and quantitated the time course of secondary hyperalgesia after surgery[7]. Therefore, some aspects of postoperative pain, or for that matter, any pain associated with prolonged activation of primary afferent nociceptors and either central or peripheral sensitization, would fall into this category, and the term is meant more for short-term pain problems rather than disorders notable for their unremitting and chronic nature, like FM. However, given Head's observations, the widespread pain of FM and frequent co-occurrence of irritable bowel syndrome (IBS) and FM is noteworthy.

NEUROPATHIC PAIN DUE TO A PRIMARY LESION OF THE NERVOUS SYSTEM

The term "primary lesion" presents no conceptual difficulties. The term "lesion" has various definitions, including, as a typical example, Dorland's: "pathological or traumatic discontinuity of tissue or loss of function of a part"[8]. Many definitions include the requirement of a physical change (see http://www.google.com/search?q=define:lesion), implying that the lesion can be visualized or precisely characterized in anatomical terms. Thus defined, there is no disagreement about including as neuropathic pain the chronic pain syndromes in which a "primary lesion" in the peripheral or CNS can be confirmed using objective tests or direct pathological examination. In these disorders, pain is in an area of sensory abnormality. The sensory abnormality is most often a reduction in sensation, with diabetic neuropathy an excellent example. Patients with central pain due to spinal cord injury, stroke, or focal brain lesion present even less of a problem to the clinical neurologist. The primary lesion can usually be easily visualized by an imaging study such as magnetic resonance imaging (MRI), and the accompanying non-sensory neurological deficits serve as markers of the location of the primary lesion within the CNS.

In some patients with injury to the nervous system, allodynia is the most prominent sensory abnormality. For example, some patients with postherpetic neuralgia (PHN) have such severe allodynia that examining for a more elemental underlying sensory dysfunction (touch threshold, thermal threshold, pin prick perception) becomes difficult if not impossible. Although uncommon, some patients with post-stroke pain have few or no non-sensory findings on neurological examination to help locate lesions by clinical examination. In these patients, an MRI study confirming a lesion in sensory pathways in the CNS is crucial. However, there is one accepted example of neuropathic pain with prominent touch-evoked pain, no underlying sensory deficit, and diagnostic imaging studies that are usually normal: trigeminal neuralgia. The neuropathic origin of the pain can be confirmed at surgery because the majority of patients are found to have a vascular abnormality affecting the trigeminal ganglion.

Progression of a regional myofascial pain syndrome to widespread pain, thereby meeting criteria for FM, is a widely appreciated phenomenon. Similarly, development of widespread musculoskeletal pain and other FM symptoms is observed in some patients with nervous system pathology and a clearly defined regional neuropathic pain syndrome [including complex regional pain syndrome (CRPS II)]. Eventually, the patient appears to have FM, although the initial regional neuropathic pain should still be evident. How involvement of the nervous system in these cases of "secondary" FM differs from typical cases of neuropathic pain remains uncertain.

Clinical neurologists tend to think in terms of a primary lesion in the nervous system in patients with chronic pain and symptoms that appear referable to the nervous system, such as burning sensations, numbness, easy fatigability, weakness, and lack of coordination. When no primary lesion in the nervous system is found at neurological examination and diagnostic testing, symptoms may be viewed as "non-organic." This is especially likely if the clinician doubts the authenticity of the patient's suffering, suspects significant underlying psychological issues such as secondary gain, or suspects malingering. Alternatively, especially if the patient's suffering is viewed as genuine, the symptoms can be attributed to "dysfunction" in the nervous system. Examples of intermittent neurological dysfunction that may have somatic manifestations include migraine, trigeminal neuralgia, or certain types of seizure disorder.

NEUROPATHIC PAIN CAUSED BY DYSFUNCTION OF THE NERVOUS SYSTEM

By this definition, no anatomically verifiable lesion of the nervous system is required. Dysfunction of the nervous system is implied, but not proven, as the etiology of continued pain. Part of the problem lies in the phrase "anatomically verifiable." Electromyography and nerve conduction studies cannot be applied to all parts of the nervous system, and are insensitive to small-caliber afferents. Herpes zoster and PHN are an instructive example. In some cases the rash is mild, the skin heals without any visible change, and cutaneous sensation may appear nor-

mal to bedside and quantitative thermal sensory testing with the exception of allodynia. Electromyography and nerve conduction studies can't be performed on the trunk. Even skin biopsy may not show a difference in cutaneous epidermal fiber counts. Yet, these patients are routinely accepted as having neuropathic pain as long as a zoster rash was initially present based on what is known of the biology of the viral reactivation and its effect on the nervous system.

There do not seem to be any noncontroversial examples of neuropathic pain with only "dysfunction" and no lesion. CRPS type II is accepted as neuropathic pain because of the requirement for a primary lesion in the peripheral nervous system. Assigning a neuropathic pain label to CRPS I is controversial. The diagnosis of CRPS I does not require evidence of nervous system injury, although many patients have suffered traumatic injuries that could easily have produced an initial injury to nerves inaccessible to conventional electrophysiological testing. A taxonomic debate about the wisdom of including CRPS as a neuropathic pain has been published, in which it was proposed by Mitchell Max that the IASP taxonomy[4] eliminate the term "dysfunction"[9-11].

Although the Manual Tender Point Survey[1] as a diagnostic tool implies multiple discrete foci, FM is best considered a generalized pain disorder. What is the dysfunction in the nervous system that maintains pain in the absence of obvious injury to the nervous system? If the primary afferent endings are spontaneously active because of a tissue-altering process in the area (infection, inflammation, tumor), then the etiology of the pain is the etiology of the process that has altered the non-neural tissues. When primary afferent endings from an area of pain are spontaneously active, maintenance of pain and hyperalgesia in the region of pain is to be expected as a normal function of the CNS. While it is possible that a process that primarily affects the peripheral terminals of primary afferent nociceptors is a contributing factor, for FM it is the role of the CNS that has been emphasized.

DOES THE UNDERLYING CAUSE OF FM RESIDE IN THE CNS?

Disordered sensory processing at a central level is a more recent theory for the origin and maintenance of FM symptoms. Most of the evidence comes from studies showing differences between FM patients and pain-free controls in pain thresholds, pain modulation in response to repeated noxious stimuli, and secondary hyperalgesia areas following capsaicin application or injection of hypertonic saline. A weakness in this line of evidence is the lack of studies using patients with chronic pain of a known etiology (neuropathic or non-neuropathic) as the comparison group. For example, Price and colleagues have gathered important evidence, presented elsewhere in this issue, that patients with inflammatory bowel syndrome also show evidence of chronic sensitization of the nervous system. It is important in this regard that studies in patients with chronic sleep disorders and those experimentally sleep-deprived have also demonstrated widespread musculoskeletal symptoms. Clinically, some patients with severe chronic low back pain or atypical facial pain also demonstrate widespread tenderness on examination, and may or may not have obvious depressive symptoms. The question of whether chronic central sensitization is a primary process that is a necessary and selective component of FM remains open.

SUMMARY AND CONCLUSIONS

It seems premature to classify the fibromyalgia syndrome (FM) as a neuropathic pain. No consistent pathology in either the peripheral or CNS has been identified, and the diagnostic criteria are relatively nonspecific. Therefore, to consider FM a neuropathic pain would require either new observations or a substantial change in the definition of what constitutes a primary neurological syndrome. Although multiple lines of research suggest that the widespread pain and tenderness of FM is associated with sensitization of pain-transmitting pathways in the CNS, it has not been proven that this is a necessary component of the disorder or that it is specific to FM.

From a taxonomy perspective, how the term neuropathic pain is defined reveals a conceptual split into 2 partially overlapping groups of disorders: those with demonstrable pathology in the nervous system and those characterized primarily by enduring dysfunction in the nervous system. For the time being, restricting the term "neuropathic pain" to those disorders with a primary etiology clearly related to the peripheral or CNS is prudent and consistent with actual clinical neurology practice.

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