Afterword

The Relationship of Fibromyalgia to Neuropathic Pain Syndromes

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ABSTRACT. The appropriateness and utility of considering fibromyalgia syndrome (FM) and other syndromes without anatomically localized pathology of the nervous system as neuropathic pain syndromes is uncertain. In this afterword, a synthesis of the information presented in these proceedings and opinion as to how FM relates to classical neuropathic pain syndromes is provided. (J Rheumatol 2005;32 Suppl 75:41-45)

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INTRODUCTION

The fibromyalgia syndrome (FM) is characterized by the clinical experience of chronic widespread pain necessarily involving the musculoskeletal system, but frequently associated with cutaneous and visceral pain. Symptoms of distress frequently accompany pain, including fatigue, sleep disruption, cognitive dysfunction, anxiety, and depression. The diagnosis of FM is based on a history of generalized pain and physical findings of tenderness in response to mechanical stimulation in multiple musculotendinous sites throughout the body[1], although it should be emphasized that hyperalgesia and allodynia are not limited to the tender points used for diagnosis.

In the preceding articles, evidence has been presented to suggest that functional alterations of the nervous system are present in patients with FM. However, the appropriateness and utility of considering FM and other syndromes without anatomically localized pathology of the nervous system as neuropathic pain syndromes is uncertain. In this afterword, a synthesis of the information presented and opinion as to how FM relates to classical neuropathic pain syndromes is provided.

PATHOPHYSIOLOGY OF FM SYNDROME

History

Description of FM-like syndromes in the medical literature, including the presence of tender points, goes back more than 150 years, although different appellations have been applied[2]. One of the most enduring, neurasthenia, was put forth by George Beard in the mid-nineteenth century[3]. Beard maintained that neurasthenia, or nervous exhaustion, was caused by subtle and undetectable abnormalities of the nervous system. Since that time, great progress in understanding the anatomy and biochemistry of pain processing has been made, as reviewed by Price and Staud elsewhere in this supplement[4]. The tools available to examine pain processing in human subjects have improved dramatically, allowing for improved evaluation of the dynamic changes in the central nervous system (CNS) after acute exposure to a painful stimulus. The imaging and biochemical analysis of chronic pain as a clinical syndrome in humans remains to be fully defined. Nevertheless, data currently support the conclusion that CNS alterations are indeed present in FM, although it is unclear whether these changes cause the syndrome or result from other pathology.

Family and Genetic Studies

It is now widely appreciated that FM has a genetic component. A family study by Arnold and colleagues demonstrated that the odds ratio for a family member of a patient with FM, as compared with rheumatoid arthritis, to also have FM was 8.5 (95% confidence intervals 2.8 to 26; $p = 0.0002$)[5]. Family members of FM patients had increased pain sensitivity as measured by the total myalgic score, and they had a higher lifetime prevalence of mood disorder. A number of studies emphasize the potential genetic relationship between FM and psychiatric disorders, recognizing that the lifetime prevalence of psychiatric diagnoses, particularly anxiety and depression, in FM patients approaches 60%[5,6]. In discussing the potential common mechanisms shared by FM and pain disorders, it is important to keep in mind that FM may also share pathogenic mechanisms with depression and

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related disorders.

Hudson and colleagues demonstrated familial aggregation of major depressive disorder (MDD) with FM and other disorders they term "affective spectrum disorders" because they improve after treatment with a number of chemically unrelated antidepressant drugs[7,8]. The disorders in their affective spectrum include 10 psychiatric disorders: attention-deficit/hyperactivity disorder, bulimia nervosa, dysthymic disorder, generalized anxiety disorder, major depressive disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social phobia; plus 4 medical disorders: FM, irritable bowel syndrome, migraine, and cataplexy. Other medical disorders that often occur in FM patients are not included since their response to sufficient numbers of different antidepressant drugs has not been studied. A second study was performed by Raphael, *et al*, this time using a community sample, in a 4 by 4 design of MDD alone, FM alone, MDD plus FM, and neither diagnosis[9]. They tested the 2 hypotheses that MDD and FM share genetic risk or that MDD is a consequence of living with FM by assessing the prevalence of MDD and FM in the family members of probands in each group. Their data were consistent with the proposition that FM is a depression spectrum disorder since the risk for MDD and anxiety disorders was similar in family members of FM probands with or without MDD and those with MDD alone. These family studies support the hypothesis that there are shared CNS pathophysiological mechanisms among psychiatric and somatic syndromes as suggested by their response to drugs. Further, this type of approach may help to reveal common genetic vulnerabilities and thereby advance theoretic understanding and clinical treatment.

Importantly, however, these data do not necessarily imply that FM is somatisized depression, only that shared biologic pathways could be involved in certain clinical manifestations of the syndrome. Relevant to the latter is the finding that elevated rates of MDD in patients with myogenous temporomandibular disorder (TMD), a pain disorder that commonly co-occurs with FM, are due to reactive depression rather than shared vulnerability. Further, rates of widespread pain were not increased in probands with MDD in the study of Raphael, *et al*, although methodologic concerns prohibited definitive conclusions[9]. One could speculate that the pain component of FM and the non-pain distress symptoms of the disorder may be related to different vulnerabilities.

The results of several candidate gene studies have suggested association with neurochemical pathway polymorphisms, including genes involved in serotonergic and adrenergic pathways[10-15]. It has been proposed that polymorphisms in these pathways may lead individuals to respond to stressful or traumatic events with symptoms of pain or distress[9]. It was reported that a functional polymorphism in the promoter region of the serotonin transporter gene affects the influence of stressful life events on depression, and the same region has been reported as associated with FM[11,15,16]. One of the genes perhaps associated with FM, catecholamine-*O*-methyltransferase (*COMT*), was shown to be involved in regulation of pain sensitivity in humans[17,18]. This gene was also reported to play a major role in the vulnerability to developing myogenous temporomandibular joint disorder[18]. The genotype associated with increased activity of *COMT* was associated with a diminished risk for developing new TMD. *COMT* is a key enzyme for metabolizing catecholamines, thereby affecting dopaminergic and adrenergic/noradrenergic neurotransmission and influencing functions regulated by these neurotransmitters. However, the precise mechanism accounting for the relationship between *COMT* and chronic pain states remains unclear.

The finding of a shared biological pathway involved in FM, other somatic syndromes characterized by pain and distress symptoms, and psychiatric disorders in the spectrum of depressive and anxiety disorders would point squarely to the CNS as key to their understanding. A major question remains as to the relationship between the putative common CNS factor and pain processing, particularly since many of these syndromes either do not manifest hyperalgesia and allodynia, or these have not been rigorously assessed.

Biochemical Findings

One of the first and perhaps most robust and repeatable findings in patients with FM is elevated cerebrospinal fluid (CSF) substance P[19-21]. There is no evidence of increased substance P in patients with chronic fatigue syndrome, suggesting that this feature may be related to chronic pain rather than other FM symptoms[22]. Supporting this hypothesis, elevated levels of CSF substance P have been seen in other conditions characterized by chronic pain, such as low back pain, and the levels are associated with the degree of self-reported pain[23]. However, substance P antagonism with neurokinin-1 receptor antagonists results in changes of serotonergic and adrenergic pathways and shows promise in the treatment of depression, relating substance P to pathways that are broadly involved in CNS function[24]. Measurements of other neuropeptides and neurochemicals have been more variable, although altered levels of certain monoamines and amino acids have been reported[25-28]. Again, the biochemical studies implicate nervous system pathways in FM.

Neuroendocrine and Autonomic Alterations

As reviewed by Levine and Reichling in this supplement, many studies have demonstrated alterations in neuroen-

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docrine and autonomic stress response systems[29]. It appears that reduced heart rate variability may be quite reproducible as a feature of FM[30-32]. Although most studies demonstrate alterations of hypothalamic-pituitary-adrenal (HPA) axis function, there is wide variability in the methodology used to assess the HPA axis, and the interpretation of the results has been variable[33]. Further, altered neuroendocrine and autonomic activity is a hallmark of depression, and stress has been widely believed to contribute to the experience of symptoms associated with FM[34,35]. The relationship of altered pain processing with altered HPA and autonomic function remains unclear, although there is no question that nociceptive modulatory pathways are influenced by these systems.

Pain Processing

The first thing to emphasize about pain processing in FM is that patient report accurately reflects the central representation of pain. This is clearly demonstrated in studies by Gracely, *et al*, whereby a patient report of pain corresponds with increased blood flow in regions of the brain typically activated by noxious stimuli[36]. Other objective demonstrations that patients with FM are more sensitive to noxious stimulation used laser evoked potentials[37]. Psychophysical testing has demonstrated that patients are more sensitive to sensory afferent stimulation by a number of different modalities and that there is an association of this sensitivity with cognitive variables such as pain catastrophizing[38,39].

Price and Staud have reviewed the evidence that patients with FM exhibit alteration in temporal summation of pain and prolonged after-sensations of pain following repetitive thermal or mechanical stimulation[4]. These investigators suggest that central sensitization at the level of the dorsal horn is likely to reflect a deep-tissue peripheral pain generator that evokes and maintains FM-related pain. These studies have renewed the debate as to the role of peripheral tissues in the development and maintenance of FM pain. It may be that there are many triggers for FM that involve musculoskeletal damage, including such diverse causes as joint hypermobility, accidental injury, particularly whiplash, and degenerative or inflammatory arthritis. Bennett suggested that muscle microtrauma in patients who were deconditioned or had low levels of growth hormone/insulin-like growth factor-1 contributed to FM pain[40]. Metabolic abnormalities have been demonstrated in the muscles of patients with FM using magnetic resonance spectroscopy[41,42]. Altered autonomic activity controlling the muscle microcirculation has been demonstrated and could allow accumulation of factors that would sensitize muscle nociceptors[43]. Taken together, it is likely that peripheral factors contribute to central sensitization and the symptom of pain in FM.

INTEGRATING PERIPHERAL AND CENTRAL FACTORS IN THE PATHOGENESIS OF FM

There are compelling data suggesting that both peripheral musculoskeletal and CNS factors play a role in FM. Genetic factors appear to increase vulnerability to develop FM, but there is insufficient data on at-risk individuals to determine what specific factors contribute to clinical expression of the syndrome. Discrete triggering events are identified for some, but not all, patients and other environmental exposures or adverse health behaviors have not been fully explored. Whether these necessarily involve a peripheral pain generator within deep muscle tissues that leads to central sensitization is not certain.

Levine and Reichling discuss an animal model linking peripheral afferent input with changes in central modulatory pathways for pain processing that may also have clinical relevance for some patients with FM[29]. Their model is based on the hypothesis that signals from the viscera rather than muscle could be involved in initiating and maintaining sensitization. In an animal model, disruption of vagal afferent input to the CNS led to downstream events that included reduced mechanical nociceptive threshold and enhanced bradykinin-induced hyperalgesia. These animals also developed hyperactivity of the sympathoadrenal axis and removal of the adrenal medulla reverses hyperalgesia. Of great interest and similar to patients with FM, these animals also develop hypersensitivity to sensory stimulation from noise. These authors speculate that dysfunction of vagal afferents in humans may also lead to long-lasting changes in sensitivity to sensory stimuli, and perhaps it links irritability of the viscera to musculoskeletal hyperalgesia. Finally, they point out sexual dimorphism in the response to vagotomy that could shed light on the gender difference in prevalence of FM.

THE RELATIONSHIP BETWEEN FM AND NEUROPATHIC PAIN SYNDROMES

Neuropathic pain is defined as arising from a primary lesion or dysfunction in the nervous system, as discussed by Rowbotham[44]. There is a requirement that a lesion be demonstrable in anatomical terms, or that there be evidence of persistent dysfunction. There is no evidence for an anatomically definable nervous system lesion in FM. Although there is altered function of the CNS in FM, at the level of both the spinal cord and the brain, the evidence that these changes are necessary for FM as the syndrome is presently defined is lacking. Further, there is little specificity in the CNS findings observed thus far in FM. For these reasons, referring to FM as a neuropathic pain syndrome is speculative at the present time.

It may be, however, that thinking of FM in the spectrum of neuropathic pain syndromes is reasonable. It is particularly important that the practicing clinician understand that the pathogenesis of FM has more in common with affective spectrum disorders and neuro-

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pathic pain than the typical inflammatory or degenerative musculoskeletal pain disorders, and that treatments should be directed towards CNS mechanisms. Evidence is accumulating that FM and classical neuropathic pain syndromes respond similarly to drugs of several different chemical classes with different mechanisms of action consistent with, while not providing direct evidence of, shared pathogenic mechanisms. Similar to the rationale used by Hudson and others for grouping psychiatric and medical syndromes based on response to intervention, FM could be grouped with neuropathic pain syndromes based on this common response to drugs that act by modulating central pain pathways. For example, pregabalin and gabapentin are agents that bind to the alpha-2-delta subunit of subtypes 1 and 2 voltage-gated calcium channels in neurons, and alter the kinetics and voltage dependence of calcium currents[45-50]. As a result, release of substance P, norepinephrine, and glutamate is reduced[51-53]. Pregabalin has been found effective in the treatment of diabetic neuropathy, post-herpetic neuralgia, and FM[54-56]. Similarly, tricyclic antidepressants that alter norepinephrine and serotonin reuptake are effective treatments for FM and neuropathic pain syndromes[57,58]. Response to treatment is by its nature very nonspecific with these agents that affect multiple different central pathways. Development of new drugs with actions that more specifically probe central pathways may be helpful in further refining our understanding of the similarities and differences between FM and neuropathic pain syndromes. Should there continue to be evidence of common pathogenic mechanisms that cause or sustain FM and classical neuropathic pain syndromes, terminology that indicates a mechanistic link may be appropriate.

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