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EDITORIAL

Fibromyalgia: A Never-Ending Story of Central and Peripheral Pain Mechanisms

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Fibromyalgia (FM) is a complex of peripheral and central pain mechanisms that cause and maintain the wide range of symptoms characterizing the clinical history of patients with FM (1,2). The disease is easy to diagnose, but it is surprisingly difficult to explain its underlying pathophysiologic mechanisms. Many pain clinicians still believe that unexplained benign chronic pain is a disease in itself that does not require an explanation, and therefore they concentrate simply on trying to treat it successfully regardless of what it may be called: chronic widespread pain, FM, or a type of psychoaffective or somatoform disorder (2,3).

The pathophysiologic basis of FM remains a matter of debate, partially because it is usually claimed that although FM is severe and widespread in nature, it is not associated with any identifiable lesion of peripheral and/or central tissue. Furthermore, patients with FM describe their pain mainly in "neuropathic" terms, i.e., verbal descriptors of the type used by patients with peripheral neuropathic lesions. Many investigators continue to report peripheral tissue abnormalities, including anomalies in muscle tissue, the autonomic nervous system, and immunity.

Several years ago, Caro et al (4) reported a significant association between FM and electrodiagnostic and clinical signs of a demyelinating peripheral nervous system injury similar to that seen in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). In this issue of *Arthritis & Rheumatology*, Caro and colleagues (5) show that the loss of epidermal nerve fiber density (ENFD) is a diffuse proximal and distal process in patients with FM, and that nerve fiber length may also be important, with distal sites being at greater risk. A reduction in ENFD is often (but not always) associated with significant neuropathic pain (hence the name small fiber neuropathy [SFN]), and it can reasonably be expected to give rise to a clinically detectable loss of skin sensation (so-called negative sensory phenomena) rather than painful peripheral symptoms (positive sensory phenomena) (5). However, SFN is associated with both, and it is thought that the painful peripheral symptoms of SFN are attributable to the disproportionate hyperexcitability of lesioned (but still functioning) primary small nerve fibers surrounded by a structurally normal but physiologically hyperexcitable group of secondary small nerve fibers that respond collaterally. The strength of the current study by Caro et al is that they demonstrate that the peripheral nervous system is an important contributor to the symptoms and chronicity of FM, which also implies the significant contribution of small fiber neuropathy. The limitation of the study by Caro and colleagues is that, after excluding certain metabolic and congenital lesions that are known to reduce ENFD, we are left with a heterogeneous group of disorders with a final common pathway that is probably immune mediated.

The demonstration of an association between FM and SFN may therefore support the view held by several investigators that FM has an immunopathogenic component that functionally affects the skin and sympathetic nervous system. It is at least theoretically possible that FM is characterized by a cytokine-related lesion, as indicated by the inverse correlation between serum interleukin-2 receptor (IL-2R) levels and calf ENFD. It

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is well known that cytokines play a role in rheumatic diseases, and it has often been suggested that they mediate injury in FM. Bazzichi et al (6) observed high IL-10, IL-8, and tumor necrosis factor α levels in patients with FM, and intravenous infusion of IL-2 can give rise to a clinical picture that is similar to FM in some patients with cancer (7). Furthermore, it is interesting to note that proinflammatory cytokines may also be among the most likely causes of SFN, especially "idiopathic" SFN.

However, there are other ideas concerning the pathophysiologic mechanisms inducing pain and the constellation of symptoms characterizing FM. FM appears to involve disordered central afferent processing, and although its major symptoms are multifocal pain, fatigue, sleep disturbances, and cognitive or memory disorders, other symptoms may include psychologic distress, impaired functioning, and sexual dysfunction. The pathophysiology of FM is still unknown, but it is believed to be largely central in nature, i.e., central mechanisms enhance the perception of pain or modulate it differentially between individuals (1,2). The common biologic hallmark of such "centrally driven" conditions is that the central nervous system of most patients is affected by widespread hyperalgesia that can be quantified by means of sensory testing and corroborated by functional neuroimaging studies (8).

Certain genes seem to be involved in turning up the "gain" of pain processing and identify one cause of a "chronic pain–prone phenotype." Another hallmark of chronic pain is hypersensitivity to nonpainful stimuli in sensitized patients, and recent evidence suggests that genetic factors may contribute to individual differences in pain sensitivity, the risk of developing painful clinical conditions, and the efficacy of pain treatments. Consistent with previous findings, Martinez-Jauand et al (9) showed that haplotypes of the catechol-*O*-methyltransferase (*COMT*) and genotypes of the Val158Met polymorphism play a key role in pain sensitivity in patients with FM. Finally, it has been claimed that FM symptoms may be related to stress or may simply be an expression of a pain-related syndrome associated with anxiety or depression (10).

In conclusion, the condition that we call FM may be at the crossroads of different pathophysiologic situations with a common clinical background phenotype, and the development of FM and other centralized pain states may be triggered by a familial or genetic predisposition or environmental factors.

Where does FM originate? Is it attributable to a genetic and/or familial predisposition, a stress-related personality disorder, a psychoaffective disorder, or a posttraumatic stress disorder? FM may be associated with all or none of these factors, or just one may reflect and affect the nociceptive system. All we can do is continue to look for tissue abnormalities and central processing alterations in an attempt to discover which come first and then develop the best therapeutic (or, even better, preventive) strategy for the 2–3% of the population with this disease.

AUTHOR CONTRIBUTIONS

Drs. Sarzi-Puttini and Atzeni drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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