
Editorial:

Fibromyalgia and Related Central Sensitivity Syndromes: Twenty-five Years of Progress

Twenty-five years ago, Muhammad Yunus and colleagues published in *Seminars in Arthritis and Rheumatism* the first controlled study of the clinical characteristics of fibromyalgia syndrome and the first data-based criteria for diagnosis, which provided a sensitivity of 96% and a specificity of 100% against healthy control subjects (1). The impact of this seminal article was enormous. Up to this point, the amorphous nature of fibromyalgia and the absence of criteria for diagnosis or any clear distinction from “normal” had severely compromised the place of fibromyalgia in medicine. Mainstream opinion in rheumatology considered fibromyalgia to be more of a concept than a disease, essentially synonymous with psychogenic rheumatism, and unworthy of investigation or clinical interest (“Don’t many in the normal population have pain, fatigue, and poor sleep? Doesn’t everyone have sore muscles and tender insertions if enough pressure is applied?”) (2). The 1981 *Seminars* article answered these important questions. The Yunus criteria were the most frequently used in the literature until the 1990 American College of Rheumatology (ACR) criteria were published (3) and, in certain respects, remain superior to the ACR criteria (4).

In this issue of *Seminars*, which is published on the 25th anniversary of his earlier controlled study of fibromyalgia, Yunus again makes a seminal contribution to the field of chronic pain and fatigue (5). Here he painstakingly synthesizes a huge scientific and clinical literature together with his own deep personal experience with fibromyalgia into the concept of central sensitivity syndromes (CSS). My commentary will attempt to place Muhammad Yunus’ earlier and present contributions into historical context with emphasis on the heuristic impact of his observations and insight. I conclude with several suggestions for future research and clinical practice in this area. Without question, Muhammad Yunus is the father of our modern view of fibromyalgia.

STATUS OF THE FIELD BEFORE 1981

Recognition of diffuse aches and pains as a form of “muscular rheumatism” had occurred ~400 years earlier (6), with clear distinction from deforming articular disease dating at least from the 18th century (7). The British

neurologist Sir William Gowers coined the term “fibrositis” in 1904, based on the erroneous belief that muscular rheumatism was analogous to cellulitis, with “inflammation of the fibrous tissues of the muscles” (8). When it was observed clinically that there is no underlying inflammation, Kahler Hench in 1976 suggested “fibromyalgia” as a more appropriate term for this disorder (9). [The final proof of an absence of inflammation came from a controlled and blinded muscle biopsy article by Yunus and colleagues in 1989 (10).] By this time, Traut had described the female gender association and clinical features (including tender points, poor sleep, fatigue, association with regional pain in the head and gut, and an emphasis on mind–body interaction in its pathogenesis) in a form quite similar to our modern concept of fibromyalgia (11). Hugh Smythe (12) and Harvey Moldofsky and coworkers (13) popularized the concept of fibromyalgia and its associated abnormal stage 3 and stage 4 non-REM sleep that continues to influence clinicians and researchers today. Indeed, as a young faculty member in rheumatology at the University of Virginia in the mid-1970s, I vividly recall reading Smythe and Moldofsky’s article in the *Bulletin of Rheumatic Disease* (14) and thinking (erroneously) that the essence of fibromyalgia pathogenesis had now been clarified.

Another element in the pathogenesis of fibromyalgia also had been recognized after World War II, namely the contribution of psychological factors and stress in soldiers returning from combat (15). The term “psychogenic rheumatism” was introduced (16) in 1943, and for the next 30 years (and, unfortunately, to a significant extent even today), most physicians remained skeptical of fibromyalgia as a valid clinical entity. During the 1960s and most of the 1970s, scant attention was paid to fibromyalgia in the biennial *Rheumatism Reviews* prepared by the Rheumatism Review Subcommittee of the American Rheumatism Association, Section of the Arthritis Foundation. For example, for the years 1963 to 1970, there is nothing on fibromyalgia, and in the 21st *Rheumatism* review (17), the entire summary of information on fibromyalgia published in the years 1971 and 1972 was the following:

“Symptoms were greatly benefited in 85% of a series of patients treated with phenylbutazone or oxyphenylbutazine for primary fibrositis. Long-term management was considered safe and effective. [*Conservatism in the long-term use of these*

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agents in mild, chronic conditions such as fibrositis continues to be appropriate in our judgment. Ed.]

Hats off to the early pioneers in fibromyalgia in the second half of the 20th century: Hugh Smythe, Harvey Moldofsky, Muhammad Yunus, and Alfonse Masi!

THE 1981 SEMINARS ARTICLE (1)

This study compared 50 consecutive patients referred by other physicians and diagnosed as having primary fibromyalgia by criteria similar to those of Smythe (12) in an academic rheumatology clinic with 50 age-, sex-, and race-matched normal control subjects. The observations and distinctions made in this article are a compendium of "firsts" with respect to our present view of fibromyalgia. A correct distinction was made between "trigger points" and more precise "tender points" in fibromyalgia, the description of which has guided all subsequent work in this area. Although "primary fibromyalgia" was considered to be different from "secondary fibrositis" (a syndrome produced by other inflammatory conditions), Yunus, to his credit, later determined that there was no basis for considering fibromyalgia as primary or secondary, rather that there simply is fibromyalgia alone or coexisting with some other illness (18). Actually, this issue deserves revisiting given the extraordinarily high prevalence of fibromyalgia in inflammatory disorders, such as systemic lupus erythematosus or rheumatoid arthritis.

In the Introduction of their 1981 article (1), Yunus and colleagues list what is missing in the field at that time, ie, poor recognition and acceptance by clinicians, precise criteria for research, and detailed quantization of clinical data (symptoms, tender points, fatigue, anxiety) in patients versus normal controls. Their data and interpretation immediately moved this area of medicine forward with an unparalleled series of "firsts": (1) Fibromyalgia was clearly distinguished from normal controls with respect to 9 symptoms and the presence of >5 tender points, answering the question of what is normal and what is not. Persistent fatigue was shown to be essentially universal in fibromyalgia. The careful analysis of symptoms and tender points characterized, for the first time, fibromyalgia syndrome as a recognizable entity that is distinctly not normal. (2) The special role of female gender in fibromyalgia was emphasized by the finding of a female-to-male ratio of ~6:1 in the 50 consecutive patients studied. (3) Insight into a possible continuum of chronic pain and fatigue in the general population was provided by their detection of 4 or fewer tender points in 48% of the control subjects, all females. Conversely, it was recognized that some fibromyalgia patients have only a few tender points, which until recently (4) was largely forgotten after publication of the ACR classification criteria that required a minimum of 11/18 painful tender points. (4) The laboratory evaluation used by Yunus and colleagues in this study is entirely consistent with the currently recommended panel of screening laboratory tests to

define other illnesses that can present with symptoms of fibromyalgia (19). (5) The observation that the onset of fibromyalgia symptoms had occurred at <15 years of age in 20% of patients led to the first description of juvenile fibromyalgia 5 years later (20). (6) Various modulating factors that ameliorate or exacerbate fibromyalgia symptoms were identified, many of which are now recognized as elements in pathogenesis or treatment. For example, their identification of the association of fibromyalgia with stress and anxiety formed the basis for much subsequent research on the psychological determinants of chronic pain and fatigue (21). Similarly, their insight into the benefit of moderate physical activity (ie, aerobic exercise) and diversional activities (ie, stress reduction techniques) provided the basis for the now well-established efficacy of nonpharmacologic approaches to therapy. Taken together, Yunus and colleagues outlined an approach to management entailing validation, reassurance, education, stress reduction, exercise, and physical modalities that has proven its worth in many subsequent randomized controlled clinical trials. (7) Important correlations were defined, eg, anxiety with headaches and poor sleep, longer duration of fibromyalgia with the presence of >12 painful tender points, and improvement of symptoms with vacation and nap. (8) Most importantly, the strong association of fibromyalgia with irritable bowel syndrome was recognized. Three years later, Yunus depicted the interrelationships of tension headache syndromes, irritable bowel syndromes, primary dysmenorrhea syndromes, and primary fibromyalgia in a Venn diagram (22), which impelled the current wide acceptance of overlap of fibromyalgia with many structurally functional syndromes and their current classification as CSS. He also recognized that multiple overlapping syndromes could be present in the same patient.

CENTRAL SENSITIVITY SYNDROMES

The synthesis achieved by Yunus and his clear exposition of the biological mechanisms underlying so-called idiopathic chronic pain disorders deserves the thoughtful attention of *all* physicians, regardless of specialty or type of practice. I say "all physicians" because CSS, in aggregate, constitute a huge burden of illness in our society that will be encountered daily in essentially all types of medical practice. Unfortunately, the prevailing view of fibromyalgia and other CSS today is not significantly different from the view we had 30 years ago, ie, these are "functional" disorders stemming from psychological illness (depression, anxiety, personality disorders, etc.) that are unworthy of serious clinical attention. Indeed, it is my personal experience that many (most?) rheumatologists will not accept people with fibromyalgia into their practices and fail to recognize, or do not appropriately treat, fibromyalgia that so frequently coexists with rheumatoid arthritis, systemic lupus erythematosus, and other "real" rheumatologic disorders. Many of my patients, especially nurses,

are embarrassed to have a diagnosis of fibromyalgia. Medical school curricula still give "short shrift" to this group of illnesses, and the medical house staff continues to adopt the outdated opinions of their professors. It is as if the huge body of scientific literature on the central mechanisms underlying chronic pain and fatigue had been published only in Sanskrit. I hope that the appellation "CSS" for fibromyalgia and related syndromes will redirect our attention to the fact that these are neurosensory disorders analogous to, but infinitely more complex than, disorders of sight and hearing.

Yunus, who took a rather more biological approach to fibromyalgia in the past, now emphasizes a biopsychosocial perspective. In my view, this is tremendously important because it is the only way to synthesize the disparate contributions of such variables as genes (23,24), adverse childhood experiences (25), life stress and distress (26), posttraumatic stress disorder, mood disorders, self-efficacy for pain control, catastrophizing, coping style, and social support into the evolving picture of central nervous system dysfunction vis-a-vis chronic pain and fatigue. Mapping of areas of the brain by functional magnetic resonance imaging is graphically revealing the interplay of heretofore strictly psychological variables in central nociceptive processing (27,28). Patients with fibromyalgia can now be subgrouped by pressure pain thresholds and levels of anxiety/depression, catastrophizing/control over pain, and degree of tenderness (29). "Unexplained" pain syndromes are rapidly being clarified by sophisticated brain imaging techniques, by the interdisciplinary sciences of psychoneuroendocrinology and psychoneuroimmunology (30), by high throughput genotyping methods (31), and by studies of the biology of emotion. Dualism between psyche and soma is obsolete.

Yunus concludes with a listing of reasons the concept of central sensitization is significant. I concur entirely and offer a few suggestions for improved medical practice and for future research.

Suggestion 1

Integrate a biopsychosocial perspective of illness and an appreciation of the relevance of CSS to everyday medical care into curricula of medical schools and residency training programs. At present, organized medicine is doing a terrible job in the care of people with CSS, particularly fibromyalgia. In addition to serving as a perpetuator of illness in individual patients, if not an outright barrier to recovery, much time, effort, and money are being wasted on inappropriate diagnostic testing and treatment, eg, to rule out multiple sclerosis or to apply expensive invasive procedures in a patient with fibromyalgia. CSS transcend most specialty boundaries and, in aggregate, constitute half of outpatient medicine. Yet people with CSS are so frustrated with the care they receive from practitioners of traditional medicine that they spend billions of dollars on complementary and alternative medicine.

Suggestion 2

Promulgate the concept of central sensitivity (CS) and the interwoven biological bases that underlie depression, anxiety, and pain to the medical profession and the general public. For example, we now understand why antidepressant medications, such as dual reuptake inhibitors of serotonin and norepinephrine, have efficacy in chronic pain independently of the presence or absence of clinical depression. It is not because depression underlies pain in fibromyalgia, it is because descending pathways of pain control in the spinal cord require serotonin and norepinephrine. People with fibromyalgia and other CSS need not feel ashamed of their diagnosis. It is not biological or psychological. It is all biological!

Suggestion 3

Emphasize in future research the delineation of similarities and differences among the various CSS members and also within an individual CSS. The Yunus paradigm for CSS is (1) mutual associations between the members and (2) demonstration of CS to various sensory stimuli. How much more do they have in common and why? Why is overlap of fibromyalgia and irritable bowel syndrome so high, yet overlap of fibromyalgia and temporomandibular disorders is relatively low? Why do most patients with fibromyalgia also have chronic fatigue, yet some patients with chronic fatigue syndrome have no pain? Conversely, it will be extremely important for both treatment and research to further subgroup patients within a given syndrome (32).

Suggestion 4

Incorporate the very significant methodological and theoretical advances in life stress research into pain research, as has been suggested by Van Houdenhove and Luyten (30). Now available are sophisticated interview-based strategies (33) and experience sampling methods (34) that provide insights totally missed by the superficial self-report questionnaires most commonly used. It is now recognized that individuals generate, in part, their own life stress (35). It has been known for some time that the psychological and physiological responses to stress may depend on the "fit" between the nature of the stressor and personality (36).

CONCLUSIONS

There are 2 principal elements in CSS. First, all overlap to greater or lesser degrees and all share CS. Second, all derive from a combination of genetic and environmental influences that render an individual *vulnerable* to the development of clinically apparent CSS, particularly in settings of persistent stress/distress. Science and medicine now have a rational scaffolding for understanding and treating chronic pain syndromes previously considered to be "functional" or "unexplained." As one example, recognition of individual polymorphic variations in genes en-

coding regulatory molecules in pain amplification pathways can help identify individuals at risk for CS and should provide insight into potential targets for pharmacological therapy. Neuroscience research will continue to reveal the mechanisms of CS, but only if informed through a biopsychosocial perspective and with the interdisciplinary collaboration of basic scientists, psychologists, sociologists, epidemiologists, and clinicians.

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