Fibromyalgia 2019: Myths and Realities

Jacob N. Ablin MD

Department of Internal Medicine H, Tel Aviv Sourasky Medical Center, Tel Aviv, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

KEY WORDS: centralized pain, chronic pain, fibromyalgia, patient–physician relationship

IMAJ 2019; 21: 426–428

Fibromyalgia syndrome (FMS), a clinical constellation of symptoms centered on chronic pain and fatigue, epitomizes the concept of pain centralization within the CNS.

While struggling with the challenges of FMS, rheumatologists, as well as physicians in general, have learned a great deal regarding the nature of chronic centralized pain (nociplastic pain) [1]. They have demonstrated how much they can gain when addressing the complaints of their patients, rather than simply assuring them that nothing is wrong because all of the test results are within the normal range. Major progress is being made through a collaboration between clinicians and neuroscientists in the effort to unravel the secrets of FMS and centralized pain in general [2]. Nevertheless, skepticism and mistrust continue to mire the discourse between many clinicians and their FMS patients, and the lack of trust engendered by these attitudes inevitably undermines the therapeutic endeavor.

This article summarizes a presentation given in January 2019, as part of the 7th Italy–Israel 2019 Symposium of Autoimmunity and Rheumatology held at Sheba Medical Center, Tel Hashomer, and the Padeh Medical Center, Poriya, both in Israel. This conference summary addresses some common misconceptions regarding FMS, in an attempt to partially mitigate the negative effects discussed.

MISCONCEPTION 1: FMS IS A WOMEN'S PROBLEM, NO NEED FOR MEN TO WORRY ABOUT IT

Previously, FMS was considered almost exclusively a problem for female patients, and clinicians would tend to ignore the differences in the differential diagnosis of male patients presenting with widespread musculoskeletal pain [3]. This pervasive conception may have had negative consequences regarding the attitude of clinicians toward FMS. Medical issues that disproportionally affect females continue to be taken less seriously in the medical community. While FMS is still considered to be more prevalent in females than in males [4], it is currently recognized that a significant proportion of FMS patients are male. This change in the female–male proportion may in part be the result of the changing criteria used for diagnosing FMS. In the 1990 American College of Rheumatology (ACR) criteria [5], musculoskeletal tenderness was the main criteria for diagnosing FMS; however, the tenderness and pain criteria has subsequently been abandoned in the newer diagnostic criteria [6]. Since women generally experience more musculoskeletal tenderness than men [7], the 1990 criteria tended to underestimate the prevalence among males. On a practical note, physicians encountering a male patient presenting with widespread pain and fatigue should consider FMS in the differential diagnosis, and such patients must be informed that their condition is not uncommon.

MISCONCEPTION 2: IT'S ALL IN THEIR HEAD

Statements such as, "It's all in your head," are frequently offered to FMS patients by their physicians. Sometimes this message will be presented with sympathy and encouragement, for example, implying that the condition can somehow be overcome just by thinking in a more positive way. Other times it will be conveyed in a much more disparaging and even accusatory tone, such as, "Time to snap out of it!" Thus, most patients feel great frustration and are reluctant to establish a therapeutic relationship.

Ironically, evolving evidence indicates that FMS really is all in the head of the patient, or at least within their central nervous system, but in ways that are very different from what has previously been implied. As mentioned earlier, FMS is considered to be a classic centralized pain condition, also characterized as representing a condition of central sensitization [8]; that is, a condition in which there is pain amplification in addition to reduced pain inhibition throughout the central nervous system. Altered patterns of connectivity are being studied to understand the pathogenesis of pain centralization, and such patterns may serve in the future to enable precision medicine and to predict the response to treatment. These areas of research are leading toward the development of a specific FMS–pain neurophysiological signature [9]. Thus, FMS really does appear to be connected to the central nervous system, a finding that obviously does not make the problem any less real or credulous.

MISCONCEPTION 3: THESE PATIENTS ARE SIMPLY DEPRESSED; THEY NEED A GOOD PSYCHIATRIST AND AN ANTI-DEPRESSANT

In fact, a significant number of FMS patients do present with co-morbid psychiatric disorders, mainly anxiety and depres-

sion (as do many patients presenting with other chronic illnesses). Nonetheless, a surprisingly significant number of FMS patients are highly resilient despite their chronic symptoms and do not show clinically significant psychiatric symptoms [10]. Moreover, while patients experiencing major depression may have pain symptoms, they do not universally fulfill FMS criteria. On a practical note, the suggestion that FMS patients should regularly be managed by psychiatrists appears blatantly unacceptable. Psychiatrists are not trained to differentiate between musculoskeletal tenderness and peripheral synovitis (as must be assessed when diagnosing FMS). Ruling out alternative causes of musculoskeletal pain, such as an underlying seronegative spondyloarthropathy (a common FMS lookalike) [11], would also hardly be expected from psychiatrists. Treating FMS as a co-morbidity of an inflammatory joint disease such as rheumatoid arthritis [12] would also be extremely challenging. Of course, there is no logical reason to send FMS patients exhibiting no psychopathology to the realm of psychiatry. Thus, while psychiatric co-morbidity among FMS patients is important to identify, and expert referral must be available when necessary, relegating all FMS patients to the field of psychiatry simply is wrong.

MISCONCEPTION 4: THERE IS NO WAY TO HELP THESE PATIENTS ANYWAY

FMS is a chronic condition. Response to treatment is often incomplete and slow, and moreover, treating FMS patients is time-consuming and difficult. Thus, physicians may become frustrated and develop a kind of therapeutic nihilism when dealing with these patients. Nonetheless, it is not true that patients never get better. In fact, recent evidence indicates that when looking at patients previously diagnosed with FMS, many patients no longer meet FMS criteria [13]. While some of these findings may be the result of an original misdiagnosis, it seems reasonable that some patients do, in fact, improve to the degree of no longer meeting FMS criteria. The personal experience of physicians may be skewed because patients who really get better are not likely to come for follow-up, while patients who remain static or deteriorate will continue to return for treatment. Physicians, like others, are prone to use the so-called availability heuristic as described by Tversky and Kahneman [14]. In this cognitive shortcut, the ease with which a person remembers relevant examples (the availability) influences the perceived frequency of the event, thus creating an predictable cognitive bias. Based on this bias, it is easy to understand the highly negative prognostic attitude toward FMS patients.

Considerable progress has been made in formulating guidelines, including in Israel [15], for the rational management of FMS. These guidelines emphasize the implementation of non-pharmacological modes of treatment, such as exercise, movement and meditative treatments, hydrotherapy, and cognitive behavioral treatment (CBT) [16]. If these treatments, which are at least moderately evidence-based, become more accessible to FMS patients, we might see more favorable outcomes.

MISCONCEPTION 5: THESE PATIENTS ARE SIMPLY MALINGERING; ANYONE CAN GO ONLINE AND MEMORIZE THE SYMPTOMS OF FMS

Currently, the diagnosis of FMS is based entirely on clinical criteria, as is the assessment of severity and FMS-related disability. This unfortunate situation obviously raises difficulties and increases a lack of trust toward FMS patients, particularly in the medico-legal arena. The introduction of objective biomarkers would certainly be very useful and as previously mentioned, a true specific neurophysiological FMS-pain signature would be a tremendous step forward in this aspect. Still, most clinicians seem capable of identifying secondary pain issues when they emerge and distinguish FMS from malingering. However, it would be unethical for physicians to treat all FMS patients with disbelief because of the occasional malingerer.

MISCONCEPTION 6: BUT COME ON, THIS IS ONLY FIBROMYALGIA WE ARE TALKING ABOUT, NOTHING SERIOUS

Discussions about FMS are often conducted in a less than serious tone. Students and young doctors can easily understand from role models the unstated message that FMS is not serious or may even be worthy of ridicule. This attitude is counterproductive toward patient care. It may seem unnecessary to state this approach because it is not defensible in writing, but in actual medical practice, ranging from doctors informal discussions to social media, the disparaging attitude toward patients with FMS continues. Thus, we must do more to educate medical personnel.

MISCONCEPTION 7: FIBROMYALGIA DOES NOT REALLY EXIST

This last point continues to epitomize FMS misconceptions. Quite obviously, if a problem does not exist, we do not need to solve it. Thus, by throwing the very existence of FMS into doubt, "fibro-skeptics" can avoid either treating their patients or investing effort in developing better future solutions. This strategy appears to correspond with the legendary Turkish admiral, who when charged with the mission of conquering the island of Malta, after woefully failing to even find the island in the Mediterranean Sea, simply reported "Malta Yok!" which translates to: *there is no Malta* [17].

It is somewhat perplexing to argue against this misconception. Based on the evidence, about 2.4% of the Israeli population is estimated to fulfill FMS criteria [18], and similar numbers have been obtained across many other countries. So, even if FMS does not exist, there are millions of individuals presenting with the precise constellation of symptoms, including widespread pain and fatigue, which we associate with FMS. These individuals certainly do exist, and whoever disagrees with the concept of FMS is welcome to come forward and suggest alternative or better terminology, classification, and patho-

genesis to deal with these patients. Until that happens, FMS is the best definition medicine has expressed for dealing with this immense problem and we, as physicians, have the responsibility to treat our patients with both good will and respect while doing our best to understand what FMS is. Looking the other way is not going to solve anything.

Correspondence
Dr. J.N. Ablin
Dept. of Internal Medicine H, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel
Phone: (972-3) 697-4000
email: jacobab@tlvmc.gov.il

References

1. Treede R-D, Rief W, Barke A, et al. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the: International Classification of Diseases: (ICD-11:). *Pain* 2019, 160 (1): 19-27.
2. Sluka KA, Clauw DJ. Neurobiology of fibromyalgia and chronic widespread pain. *Neuroscience* 2016, 338: 114-29.
3. Wolfe F, Ross K, Anderson J, Russell IJ. Aspects of fibromyalgia in the general population: sex, pain threshold, and fibromyalgia symptoms. *J Rheumatol* 1995; 22 (1): 151-6.
4. Queiroz LP. Worldwide epidemiology of fibromyalgia. *Curr Pain Headache Rep* 2013; 17 (8): 356.
5. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum* 1990; 33 (2): 160-72.
6. Wolfe F, Clauw DJ, Fitzcharles M-A, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum* 2016; 46 (3): 319-29.
7. LeResche L. Defining gender disparities in pain management. *Clin Orthop Relat Res* 2011, 469 (7): 1871-7.
8. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. *Semin Arthritis Rheum* 2007; 36 (6): 339-56.
9. López-Solà M, Woo C-W, Pujol J, et al. Towards a neurophysiological signature for fibromyalgia. *Pain* 2017, 158 (1): 34.
10. Hassett AL, Finan PH. The role of resilience in the clinical management of chronic pain. *Curr Pain Headache Rep* 2016, 20 (6): 39.
11. Ablin JN, Eshed I, Berman M, et al. Prevalence of axial spondyloarthritis among patients with fibromyalgia: a magnetic resonance imaging study with application of the Assessment of Spondyloarthritis International Society classification criteria. *Arthritis Care Res (Hoboken)* 2017, 69 (5): 724-9.
12. Gist AC, Guymer EK, Eades LE, Leech M, Littlejohn GO. Fibromyalgia remains a significant burden in rheumatoid arthritis patients in Australia. *Int J Rheum Dis* 2018, 21 (3): 639-46.
13. Walitt B, Katz RS, Bergman MJ, Wolfe F. Three-quarters of persons in the US population reporting a clinical diagnosis of fibromyalgia do not satisfy fibromyalgia criteria: the 2012 National Health Interview Survey. *PLoS One* 2016, 11 (6): e0157235.
14. Tversky A, Kahneman D. Availability: a heuristic for judging frequency and probability. *Cognitive Psychology* 1973, 5 (2): 207-32.
15. Ablin J, Amital H, Ehrenfeld M, et al. Guidelines for the diagnosis and treatment of the fibromyalgia syndrome. *Harefuah* 2013, 152 (12): 742-7, 751, 750.
16. Dramsdahl E, Gundersen DS, Harari M. Multidisciplinary biopsychosocial program for chronic musculoskeletal pain at the Dead Sea. *IMAJ* 2019, 21 (4): 255-9.
17. Felsenstein D, Portnov BA. Regional disparities in small countries: Heidelberg: Springer Science & Business Media; 2006.
18. Ablin J, Oren A, Cohen S, et al. Prevalence of fibromyalgia in the Israeli population: a population-based study to estimate the prevalence of fibromyalgia in the Israeli population using the London Fibromyalgia Epidemiology Study Screening Questionnaire (LFESSQ). *Clin Exp Rheumatol* 2012, 30 (6 Suppl 74): 39-43.

Capsule

Vectors in stealth mode

Gene therapy using adeno-associated virus (AAV) vectors has shown safety and efficacy in hemophilia. However, AAV vectors have limitations hindering their efficacy in some patients. The use of lentiviral vectors (LVs) has been explored as a possible alternative; however, preclinical data reported low transduction efficacy, possibly owing to fast clearance by phagocytes. **Milani** et al. developed a shielded LV able to escape phagocytosis by expressing the phagocytosis inhibitor CD47 on its surface. With intravenous administration in monkeys, the LVs showed high transduction efficacy without signs of toxicity. Thus, LV-mediated gene therapy might be an effective strategy for treating hemophilia.

Sci Transl Med 2019; 11: eaav7325

Eitan Israeli

Capsule

Citrobacter rodentium alters the mouse colonic miRNome

Citrobacter rodentium is a murine pathogen that causes transmissible colonic hyperplasia and colitis with a pathogenic mechanism similar to foodborne enterohaemorrhagic *Escherichia coli* in humans. Mechanisms underlying intestinal responses to *C. rodentium* infection not completely understood. **Wen** et al. identified 24 colonic microRNAs (miRNAs) as significantly deregulated in response to *C. rodentium*, including miR-7a, -17, -19a, -20a, -20b, -92a, -106a, -132, -200a, and -2137. Most of these miRNAs belong to the oncogenic miR-17-92 clusters. Pathways involved in cell cycle, cancers, and immune responses were enriched among the predicted targets of these miRNAs. The authors further demonstrated that an apoptosis facilitator, *Bim*, is a candidate gene target of miRNA-mediated host response to the infection. These findings suggest that host miRNAs participate in *C. rodentium* pathogenesis and may represent novel treatment targets.

Genes & Immunity 2019; 20: 207

Eitan Israeli