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The Role of Gender in Fibromyalgia Syndrome

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Fibromyalgia syndrome (FMS), characterized by widespread pain and tenderness on palpation (tender points), is much more common in women than in men in a proportion of 9:1. Two recent studies have shown important gender differences in various clinical characteristics of FMS. In a community and a clinic sample, women experienced significantly more common fatigue, morning fatigue, hurt all over, total number of symptoms, and irritable bowel syndrome. Women had significantly more tender points. Pain severity, global severity and physical functioning were not significantly different between the sexes, nor were psychologic factors, eg, anxiety, stress, and depression. Gender differences have also been observed in other related syndromes, eg, chronic fatigue syndrome, irritable bowel syndrome, and headaches. The mechanisms of gender differences in these illnesses are not fully understood, but are likely to involve an interaction between biology, psychology, and sociocultural factors.

Introduction

Gender differences in various aspects of diseases have been reported since the middle of the 20th Century [1,2], but only in recent years has the great importance of this sexual dimorphism been recognized. It is now known that men and women vary significantly not only anatomically and physiologically, but also pharmacologically and in most disease states. Gender differences in genetics, pathophysiology, clinical manifestations, diagnosis, management, and prognosis of many illnesses or diseases have been reported. Among rheumatologic disorders, for example, differences between men and women have been reported in rheumatoid arthritis (RA) [3], systemic lupus erythematosus [4], ankylosing spondylitis (AS) [5], and gout [6]. Men have less severe RA with less severe symptoms. AS is less severe among women. Women with gout are older and have greater occurrence of tophi compared with men. Although not well studied, the prognosis is likely to be different between men and women in these diseases.

An exploration of gender differences in any disease is important because such a study may provide important new information on the pathophysiologic mechanism of a disease or illness. In addition, for clinical practice purposes, a physician may find it useful in diagnosing, treating, and prognosticating a particular case based on gender.

Information on gender differences between men and women in fibromyalgia syndrome (FMS) is limited. This review describes the role of gender in FMS and several related overlapping syndromes. Pain is the cardinal feature in FMS; to explain gender differences in pain, the relevant literature on experimental pain in humans and pain responses among animals that may shed some light on the underlying biopathophysiologic mechanisms are discussed. Although a differentiation between sex (the biologically determined differences between men and women) and gender (potentially modifiable behavioral and other traits of masculinity and femininity) has been made by some authors, I use the terms gender and sex interchangeably because the biologic and psychosociocultural aspects of being a man or a woman interact and overlap and cannot be teased out easily in studies of a given illness or disease.

Gender Differences in Fibromyalgia Syndrome

Fibromyalgia syndrome or fibromyalgia is characterized by widespread musculoskeletal pain accompanied by multiple areas of tender points (TP) at many locations [7–11]. Other important symptoms are fatigue, poor sleep, a swollen feeling in the tissues, and paresthesia. Several associated symptoms are also common, such as irritable bowel syndrome, headaches, and restless legs syndrome. However, pain as a symptom or tenderness as a sign is the predominant feature of FMS. Widespread musculoskeletal pain may occur in various diseases besides FMS, but the presence of many TP is a unique component of FMS. The American College of Rheumatology (ACR) criteria for classification of FMS require 11 or more TP among 18 sites in different parts of the body. Because pain and TP are the core features of FMS, any study of gender difference in FMS should evaluate the difference in these features between men and women with this disorder.

Table 1. Selected clinical and psychological characteristics of male and female patients with fibromyalgia*

Clinical features	Male	Female	*P* value
Pain (0–100), *mean ± SD*	60 ± 21	61 ± 20	NS
Fatigue (0–100), *mean ± SD*	56 ± 23	65 ± 19	<0.01
Morning fatigue, %	65	79	<0.01
Hurt all over, %	49	67	<0.002
No. of symptoms, *mean ± SD*	5.5 ± 2.4	6.7 ± 2.2	<0.02
Swollen feeling, %	52	53	NS
Paresthesia, %	45	44	NS
Irritable bowel, %	14	39	<0.001
Tension headaches	51	55	NS
No. of TPs (ACR 18 sites)	13.6 ± 2.3	15.6 ± 2.4	<0.001
Disability and global severity			
Disability by HAQ (0–3)	0.68 ± 0.61	0.75 ± 0.55	NS
Global severity (0–100)	60 ± 22	61 ± 22	NS
Psychological factors			
Anxiety (STAI-1)	45 ± 15	42 ± 11	NS
Depression (ZSDS)	42 ± 11	44 ± 09	NS
Daily stress (DHS)	61 ± 53	53 ± 42	NS

*Clinical features, disability and global severity (male n = 67, female n = 469) are based on ref [15]; psychological characteristics (male n = 37, female n = 218) are based on ref [16].
ACR—American College of Rheumatology; DHS—Daily Hassles Scale; HAQ—Health Assessment Questionaire; NS—not significant; STAI—Spielberger State and Trait Anxiety Inventory; ZSDS—Zung Self-Rating Depression Scale.

Sex differences in occurrence of FMS in clinic and community populations

In the early data-based investigative years [7], we learned that FMS is much more common in women than in men. Subsequent studies of patients in clinics [8–11] across various cultures and ethnicity have confirmed that approximately 90% (range 85%–95%) of patients with FMS are women. Population studies have also demonstrated a female preponderance in the prevalence of FMS [12,13], although the female:male ratio is somewhat lower, *ie*, 3.0:6.8, probably because women tend to consult a physician more often than men and are more likely to be seen in a clinic.

Comparison of clinical and psychological features among men and women with FMS

In a population study conducted in Wichita, KS, clinical and psychological parameters were compared among male and female patients with FMS [14••]. Female patients had significantly more frequent fatigue, irritable bowel syndrome, sleep difficulties (assessed by morning fatigue), and pain all over. The number of total TP among the 18 ACR sites was significantly higher among women than men; women were 10 times more likely to have 11 or more TP than men. Interestingly, dolorimetry was more strongly correlated with gender, whereas TP by manual palpation were greater indicators of general distress [14••]. No significant differences were found between men and women in functional disability as measured by the Health Assessment Questionnaire (HAQ), pain by visual analog scale, and paresthesia.

The question remained whether there was a gender difference in FMS among the clinic patients. Because individuals identified as having fibromyalgia in a population study usually are not patients, they satisfy the criteria for FMS but do not have symptoms significant enough to consult a physician for treatment. Thus, it was important to find out if men and women were different in their clinical and psychological manifestations in the patient care setting. Moreover, the sex differences will have a greater reliability and validity if they are found to be similar in general and clinic populations.

Our group studied 67 male and 469 female patients with FMS seen consecutively as new patients in a rheumatology outpatient clinic with the specific goal of determining sex difference in the clinical and functional aspects of FMS [15••]. All patients were studied by a protocol. The important results of this study are shown in Table 1. As may be noted, these findings are strikingly similar to those found in a general population [14••]. To summarize the concordant findings of these two studies [14••,15••], the major features of FMS (*eg*, fatigue, morning fatigue, hurt all over, and number of TP) were significantly more frequent or greater among women than men. Irritable bowel syndrome was also much more common in women than men. Interestingly, pain, functional disability, and global severity were similar in the male and female groups, as was the frequency of paresthesia, in both the studies. In our study, women had more symptoms than men and reported more frequent modulating factors, such as weather and physical activities. However, the frequency of swollen feeling and headaches were similar in both sexes

(Table 1). We had also included a healthy male control group in our study; all features were significantly more common in men with FMS than in the normal, healthy controls.

In a logistic regression analysis, number of TP, irritable bowel syndrome, hurt all over, and global anxiety were found to be the most significant variables that accounted for the differences between women and men; global mental stress, global depression, number of symptom sites, fatigue, sleep disturbance, and morning fatigue did not enter into the equation.

There were no significant differences between men and women in the psychological aspects of FMS, as measured by validated questionnaires, in the general population [14••] or among the clinic patients [16]. Anxiety and depression evaluated by Arthritis Impact Measurement Scales (AIMS) in the study of Wolfe *et al.* [14••] were similar between men and women with FMS, as they were in our clinic population [16]. We had assessed anxiety by Spielberger State and Trait Inventory and depression by Zung Self-Rating Depression Scale. In addition, daily stress measured by Daily Hassles Scale was also similar between the men and women with FMS seen in our clinic [16].

Buskila *et al.* [17••] studied the gender differences in FMS in an Israeli population. In contrast to the US population, the Israeli men had greater pain, fatigue, functional disability (measured by Fibromyalgia Impact Questionnaire), and worse quality of life. Considering that women in North America and Europe generally have worse symptoms, not only in FMS but in related overlapping syndromes (to be discussed later), the findings of Buskila *et al.* [17••] are interesting and underscore the complex and multiple interacting facets of the gender difference in many diseases.

Gender Differences in Fibromyalgia: Related Syndromes

It is recognized that many chronic illnesses, such as irritable bowel syndrome (IBS), tension-type headaches, migraine, chronic fatigue syndrome (CFS), temporomandibular disorders (TMD), restless legs syndrome, and multiple chemical sensitivity, are related to FMS with overlapping features and a common neuroendocrine mechanism [7,18–21]. They are called stress-related syndromes [22], affective spectrum syndromes [19], dysfunctional spectrum syndromes [20], and central sensitivity syndromes (CSS) [21•]. These syndromes share a common biopathophysiologic mechanism of neuroendocrine dysfunction, rather than a classic anatomic pathology [21•]. An important aspect of the common mechanism of these overlapping syndromes is most likely to be central sensitivity [21•,23]. These illnesses are characterized by a hypersensitivity to many sensory stimuli, for example, mechanical, chemical, noise, and smell. Thus, an amplified pain response is found in FMS, headaches, IBS, temporomandibular disorder, myofascial pain syndrome, and multiple chemical sensitivity (MCS); MCS is characterized by hypersensitivity to many chemicals and smell. Gender differences in a few selected members of these FMS-related syndromes (central sensitivity syndromes) are described later.

Irritable bowel syndrome

Like FMS, IBS is more common in women than in men, both among non-patients [24] and those who seek medical help [25]. Interestingly, Gwee [26] recently reported equal male: female occurrence of acute gastroenteritis, but subsequently more female (77%) than male (36%) developed IBS.

Two studies reported more IBS symptoms among women than men [27,28]. Smith *et al.* [27] reported that Manning criteria for IBS significantly correlated with the female gender, whereas such correlation was not significant among men. Manning criteria are composed of six symptoms: abdominal pain, abdominal distension, pain relief by bowel movement, loose and more frequent stools, mucus in stools, and an incomplete sense of evacuation; the more these symptoms occur, the greater the likelihood of a diagnosis of IBS [27]. Thompson [28] reported that women were more likely to fulfill the Manning or the Rome criteria, and that abdominal pain was similar in both genders. Thus, akin to FMS [15], female patients with IBS have more symptoms, but the severity of pain is not different from that in men.

Headaches

Headaches are more common in women than in men, with the exception of cluster headaches, which are more common in men [29]. Women are more likely than men to suffer from chronic tension-type headaches [30] and migraine [31]. Women with migraine also miss more work than men [32]. Celentano *et al.* [32] investigated several aspects of gender differences in migraine. Women were more likely to report nausea/vomiting, scalp soreness, headaches awakening the respondent from sleep, and visual scotoma before headache onset. Females also consistently reported a longer duration of headaches and many associated symptoms, such as numbness/tingling, nausea/vomiting, ocular symptoms, and soreness of scalp. Moreover, females reported more disability and more health care-seeking behavior. Fourteen percent of women, compared to 8% of men, restricted their activities of daily life for at least half a day. Fifteen percent of women consulted a physician for headaches in the previous 12 months, compared to 6.5% of men; the female:male ratio being 2.3, even after adjusting for pain severity, age, and duration of headache by logistic regression analysis [33].

Panconesi *et al.* [34] studied gender differences in migraine headaches in response to Hand Arm Vein Distension (HAVD) test. This test was perceived to be painful significantly more often in women (65%) than men (14%), with no significant difference between headache and headache-free periods. Thus, females were more sensitive than males to an extracephalic nociceptive stimulus.

Chronic fatigue syndrome

Gender differences in CFS has been reported by Buchwald *et al.* [35•]. Morning stiffness, sore throat, painful lymph nodes (by physical examination), IBS, total TPs, and associated FMS were found to be significantly more common among women than men; frequency of severe fatigue was similar between men and women. In addition, physical functioning was significantly worse among women than men. Similar to our questionnaire study of gender differences in psychological aspects in FMS [16], psychiatric diagnoses were similar between men and women with no significant difference in the occurrence of anxiety disorders, major depression, and dysthymia by Diagnostic and Statistical Manual of Mental Disorder (DSM) - III Revised.

Why the Gender Difference?

While the gender difference is obvious in fibromyalgia and other related conditions, the cause or the mechanism for such a difference is not. The debate has centered around whether the gender difference is caused by biologic mechanisms, psychological contributions, or sociocultural influences. However, it seems likely that the difference is caused by an interaction between all three, as proposed by Fillingim [36] in the case of pain; their relative influence would vary depending on a particular individual, disease, or illness.

It is known that given the same intensity of stimulus, females report greater pain [37••]. With the same subjective severity of pain, women are more likely to seek medical help, use more resources, and report greater disability [33]. Biology and psychosociocultural factors most probably determine such differences.

Biologic factors of gender differences include genetics, physiology, and pathology; psychological factors involve anxiety, depression, stress, behavioral aspects, and cognitive factors; and sociocultural aspects encompass ethnicity, childhood influences and events, cultural milieu in which one lives, gender roles, occupation, and health behaviors, *eg*, physical exercise.

Because fibromyalgia and most members of the central sensitivity syndromes (overlapping syndromes) are predominantly pain syndromes, the following discussion regarding the mechanisms of gender differences is based on studies on pain.

Biological aspects

Genetics

Genetic contribution to pain varies between 10% and 50% [38]. Several pain-related genes have been isolated, as has been well reviewed by Mogil [38]. A mutation of the NTRK1 gene has been isolated in anhydrosis, which is characterized by congenital insensitivity to pain; this gene encodes the nerve growth factor receptor that is involved in pain. The CACNL1A4 gene has been linked with the familial hemiplegic migraine. It has also been determined that the CYP2D6 gene that encodes a neuronal cytochrome P450 enzyme influences the analgesic property of codeine. Although much work needs to be done on the influence of genetics on gender difference, animal experiments suggest that the degree of inheritance of a particular pain-related gene may be different among males and females.

Physiologic mechanisms

Studies of experimental pain among pain-free, healthy persons as well as some chronic pain conditions have shown greater sensitivity among women than men, more consistently to mechanical, electrical, ischemic, and cold pressure than to thermal stimuli [37••]. The responses vary considerably, however, among individuals of the same sex. Response differences also depend on various modes of stimuli (*eg*, phasic *vs* tonic, pricking *vs* aching, brief *vs* prolonged, and cutaneous *vs* deep). Gender differences also depend on some clinical determinants, such as the diagnosis of the pain condition and patient status, (*eg*, nonpatients, community samples, and tertiary care patients). Studies of temporal summation (progressive increase in pain response with repeated stimuli) have also shown that healthy women have lower pain threshold and pain tolerance threshold when subjected to heat pain stimulus [39].

It has been observed that the gender difference in healthy experimental subjects is more marked when stimuli causing deep and tonic pain are involved, *ie*, mechanical, cold pressor, and ischemic. Such pain sensation is akin to chronic pain states [37••]. However, data on gender difference in experimental pain in various chronic pain illnesses (such as FMS) are limited. As stated earlier, women with FMS have decreased pain threshold [14••,15••] and female patients with migraine demonstrate greater sensitivity to peripheral venous distension by Hand Arm Vein Distension test [34]. With regard to some explanation for the gender difference in pain, it has been reported that the rate of serotonin synthesis in the human brain is 52% higher among men than women [40].

Animal studies in general have shown greater sensitivity to noxious stimuli in females compared with females [41]. However there is a great deal of variation depending on many factors, *eg*, the nature of stimuli, animal species and strains, phasic (brief noxious stimulus, escapable) versus tonic (stimulus of longer duration, inescapable) pain models used, the phase of the estrous cycle, or even the time of the day. Female rats show greater sensitivity to electric shock [42] and in formalin test [43], but no gender difference was found in mice in hot plate test [44]. More consistent results are obtained in opioid analgesia, showing that males are more sensitive than females [45]. Greater sensitivity to cold water swim stress-induced analgesia modulated by endogenous opioids have also been observed in male rodents [41].

The role of gonads in pain processing has been reviewed [46]. Estrogen has significant direct effects on the vascular system, causing vasodilation (as occurs in migraine) through stimulation of nitric oxide and prostacyclin; vessel walls contain high-affinity estrogen receptors that are regu-

lated by plasma estrogen levels. Estrogen-induced sensitivity of arterioles to norepinephrine and an increased number of alpha-adrenergic receptors in the myometrium has been demonstrated. In addition, a diminished pain threshold to pressure has been observed 48 hours after administration of beta-estradiol in rats and humans. Estrogen may also exert its effect on pain by modulating serotonergic neural functions, cognitive functions and by its effect on mood—all in a complex way, as reviewed by Bethea *et al.* [47]. Studies of experimental pain across the menstrual cycle phases in healthy volunteers and among patients with dysmenorrhea have given variable results partly as a result of the different nature of stimuli used. Hapidou and Rollman [48] have reported a higher tender point count in follicular versus luteal phase among 66 normal volunteers.

The role of androgens in pain has not been well studied, but in a recent study of female patients with fibromyalgia, adrenal androgens (testosterone and dehydroepiandrosterone) were found to be low in premenopausal and postmenopausal women compared with healthy controls [49]. These low levels were more marked among obese patients and correlated with poor health status. The authors suggest that androgens are protective for FMS.

With regard to pain mechanisms, Fillingim and Maixner [37••] proposed a heuristic model that suggests possible gender differences in peripheral physiologic response to noxious stimuli, primary afferent input to central nervous system (CNS), CNS processing of nociceptive information, and activation of pain modulation system. Because pain physiology involves a complex neuroendocrine mechanism, gender differences are also likely to exist in the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and individual hormones, including gonadal hormones.

Psychological factors

It is known that pain is modulated by psychological factors. Recent studies have demonstrated that gender is a risk factor for psychological distress. In studies of headaches, for example, women endorsed more psychosomatic symptoms than men and reported greater dys-function in daily life [50]. Women also checked more symptoms in measures of depression and somatization [51]. In the general population, women report greater psychological distress than men [52]. In general, women use more coping avenues (problem solving, positive thinking, seeking social support, using more palliative measures) than men [53].

Sociocultural factors

Pain and other symptoms are likely to be influenced by cultural background, upbringing, gender role, ethnicity, religion, education, and socioeconomic status. Sociocultural stereotypes influence gender role. Pain behavior and pain response to a stimulus have been reported to be influenced by gender. Males tend to demonstrate more tolerance to pain, in case they appear "feminine." Mechanic [54] studied the role of gender among fourth and eighth grade children in their attitude toward risk taking and denial of pain. In keeping with societal expectation, younger and older boys were more likely than girls to express a lack of fear in getting hurt and also paid less attention to pain. Thus, attitude toward pain develops at an early stage in life and remains a trait throughout the adult life. However, girls conform to the societal stereotyping role in describing their pain. In a study by Savedra [55], girls used more affective words in expressing their pain perception.

The gender of the examiner or a caregiver also affects a patient's attitude and tolerance to pain. In one study, males reported less pain during a cold pressor test when the experimenter was an attractive, young woman [56]. Other gender difference may be influenced by pain beliefs and health concerns. In general, women tend to catastrophize pain more than men. They tend to think that pain is more serious with worse consequences and feel a general lack of control. Several studies looked at the difference between men and women in catastrophizing chronic pain. Jensen *et al.* [57] found that such greater catastrophizing by women persisted even after controlling for pain severity and subjective health status.

Conclusions

The gender difference in FMS and related syndromes exists. While the actual mechanisms for this difference are not fully understood, they most likely involve an interplay of biology, psychology, and sociocultural factors. In a given patient or disease, the relative contribution of these elements will vary. Further research will be needed in each of these areas for a better understanding of the gender difference in many illnesses or diseases, including FMS. Besides gaining an insight into the biopathophysiologic mechanisms, an awareness of gender differences in these illnesses is also of clinical importance.

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