Review

Fibromyalgia in women: somatisation or stress-evoked, sex-dimorphic neuropathic pain?

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ABSTRACT

Somatic symptom disorder is excessive anxiety towards persistent symptoms that do not have an identifiable physical origin. Fibromyalgia is a stress-related illness. The overwhelming majority of fibromyalgia patients seeking medical care are women. Most fibromyalgia sufferers fulfil the somatic symptom disorder diagnostic criteria.

The objectives of this article are the following: 1) to examine fibromyalgia and somatic symptom disorder analogy. 2) to discuss stress-evoked neuropathic pain sexual dimorphism, and 3) to propose a neuropathic pathogenesis that may explain how stressed women could develop fibromyalgia.

Recent research demonstrates a clear link between fibromyalgia and small fibre neuropathy. Dorsal root ganglia contain the small nerve fibre nuclei. In rodents, physical, chemical, or environmental stressors lead to dorsal root ganglia phenotypic changes and to hyperalgesia. This phenomenon is much more frequent in females. Prolactin, oestrogens, and progesterone alter dorsal root ganglia physiology, establishing abnormal connections between the stress response system and pain pathways.

Rather than a mental somatic symptom disorder, fibromyalgia patients may have a stress-induced neuropathic pain syndrome. Sexually dimorphic dorsal root ganglia physiology may explain why it is women who more often develop fibromyalgia. Understanding fibromyalgia as a real stress-evoked neuropathic pain syndrome may lead to more compassionate patient care and may open new avenues for gender-related neuropathic pain investigation.

Introduction

Stress can be defined as a state of disharmony, or threatened homeostasis. For human beings a stressor could have a psychological origin (being abused, ongoing anxiety, or depression) but can also originate from a biological insult (an infection, a burn, or a chronic illness). The term stress or stressor should therefore not be restricted to psychological events but, rather, should be viewed in an ample physiological context (1). Fibromyalgia is a stress-related disorder. Physical psychological and other types of environmental stressors are frequent fibromyalgia drivers (1).

The overwhelming majority of fibromyalgia individuals seeking medical care are women (2). Until recently, there was no objective abnormality explaining the multiplicity of fibromyalgia symptoms. Women suffering from fibromyalgia are frequently labelled with mental diagnoses including the "somatisation symptom disorder" (3). Somatisation implies symptoms with no organic basis.

The objectives of this article are the following: 1) to examine fibromyalgia and somatic symptom disorder analogy. 2) to discuss stress-evoked neuropathic pain sexual dimorphism, and 3) to propose a neuropathic pathogenesis explaining how stressed women could develop fibromyalgia.

This proposal is based on the author's group research on fibromyalgia as stress-related neuropathic pain syndrome. Additionally, the PubMed database was searched linking the word "fibromyalgia" to the word "somatisation", and the term "dorsal root ganglia" to "sexual dimorphism". On these bases, a fibromyalgia sex-dimorphic neuropathic pathogenesis is proposed.

History of somatisation as a medical diagnosis

In 1880 the renowned French clinician Jean Martin Charcot proposed the term hysteria (from the Latin Hysterĭcus, relating to the uterus) to diagnose women

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with "functional" symptoms. Hysteria includes symptoms such as anxiety, insomnia, irritability, fainting, and non-epileptic seizures, among others. Charcot proposed that hysteria was due to an unknown disturbance of the women's nervous system. However, Charcot's most famous disciple, Sigmund Freud "psycho-analysed" hysteria and suggested that it is the result of emotional trauma during female development, including the "penis envy" (4).

The "chronic hysteria" concept gave rise to the "somatisation" diagnosis, now classified by the DSM-5 Manual of Mental Disorders as "somatic symptom disorder" (5). A patient is diagnosed as having a somatic symptom disorder (*i.e.* a mental disorder), if he/she had at least 1 severe somatic symptom, usually chronic pain, and excessive anxiety towards the seriousness of persistent symptoms that do not have an identifiable physical origin. It is proposed that, in somatic symptom disorder, internal psychological conflicts are expressed as physical symptoms (3, 5).

Fibromyalgia and somatic symptom disorder

Fibromyalgia is a fairly common illness affecting between 2 and 4% of the general population, and 90% of fibromyalgia patients seeking medical care are women (2). Fibromyalgia is a stress-related condition characterised by generalised chronic pain, profound fatigue and sleep disorders, among other symptoms. Emotional, physical and environmental stressful events are frequent fibromyalgia drivers (1). Fibromyalgia often coexists with post-traumatic stress disorder (6), and autoimmunity is evident in a subgroup of fibromyalgia patients (7, 8). Until recently, there was no structural alteration explaining the patient's symptoms. Women with fibromyalgia go to multiple specialists seeking an explanation and relief of their vexing illness. Fibromyalgia and the mental somatic symptom disorder have overlapping clinical features; several publications corroborate this concordance. In a study of 440 fibromyalgia patients (≈90% female), 90% of the participants met the criteria for somatic symptom disorder (9). Another investigation put this percentage at 82 (10). Therefore, according to the new American Psychiatry Association DSM-5 guidelines (5), the vast majority of women with fibromyalgia could be diagnosed as suffering from a mental disorder.

Stress and fibromyalgia

Fibromyalgia is a stress-related disorder, mainly affecting women; controlled studies have shown that fibromyalgia patients are frequent victims of vexing incidents. These stressful episodes include childhood physical abuse (11, 12), sexual molestation (11, 13), intimate partner violence (14), economic hardship (15), workplace dissatisfaction and monotonous unrewarding labour activities (16), among others. There are other fibromyalgia-related stressors, including physical injuries (17), infectious agents (18) and vaccination (18, 19). Thus, the key issue in fibromyalgia research is to understand how stress becomes chronic pain (20).

Verifiable anatomical damage in fibromyalgia. The role of dorsal root ganglia

Heart rate variability analyses (21), validated questionnaires (22) and genetic investigations (23) have shown stress-response system malfunction in fibromyalgia patients. Two meta-analyses corroborate this maladjustment (24, 25). Stress-response system malfunction would explain insomnia, fatigue, anxiety, bowel and bladder dysfunction, among other fibromyalgia symptoms (26).

We have proposed that the dorsal root ganglia lying along the spinal column play a key role in fibromyalgia pain (27): in this site, stressful events of various kinds could be transformed into chronic pain. Physical (28), chemical (29) or environmental stressors (30, 31) are converted into abnormal biochemical and electric impulses altering the dorsal root ganglia structure. After physical trauma, and other stressful stimuli, there is sympathetic sprouting within the dorsal root ganglia, establishing abnormal connections between the stress response system and the pain-transmitting nerves (28).

Dorsal root ganglia contain the nuclei of the pain-transmitting small nerve fibres. Each nucleus is enveloped by immune-competent glial cells. The small nerve fibres convey painful impulses arising from the body's surface and from different internal organs. The dorsal root ganglia sodium channels, named Nav1.7, play a major role in pain sensitisation (27). Severe fibromyalgia is associated to certain Nav1.7 genotypes (32).

A recent breakthrough in fibromyalgia research has been the objective confirmation of small-fibre neuropathy in many individuals with this condition: specially stained skin biopsies have revealed damage in the skin nerve endings of fibromyalgia patients (33, 34). The eye cornea is the most sensitive, and most richly small fibre innervated part of the human body. Non-invasive confocal microscopy of the eye cornea also shows small nerve fibre pathology in fibromyalgia (35). These new findings confirm the long-standing proposal of fibromyalgia as a neuropathic pain syndrome (36, 37), and the role of dorsal root ganglia in fibromyalgia pathogenesis (27). Furthermore, these recent objective findings corroborate fibromyalgia pain veracity.

The technology to identify small fibre neuropathy is not yet available to clinicians. However, corneal confocal biomicroscopy is a rapidly evolving technique. Automated microscopes will allow complete corneal innervation scan. It is likely that a non-invasive objective fibromyalgia diagnostic tool will be soon available.

Stress-induced neuropathic pain sexual dimorphism. Focus on dorsal root ganglia

Different studies in mice and in humans demonstrate a clear female predominance in stress-evoked neuropathic pain. Dorsal root ganglia seem to play a major role in this phenomenon. Chronic stress increases circulating prolactin levels. There is marked sexual dimorphism in prolactin receptor expression in the dorsal root ganglia. The prolactin receptor long isoform regulates pain sensitisation and opioid-induced hyperalgesia selectively in female mice (38). Paclitaxel is a member of the taxane

family used in cancer chemotherapy. Painful neuropathy is a frequent drug side effect, Paclitaxel is used to generate neuropathic pain in animal models and is concentrated in the dorsal root ganglia (39). Dorsal root ganglia sodium channel Nav1.7 is upregulated in paclitaxel-induced neuropathy in rats and in humans (40). A recent study evaluated the impact of acoustic stress on paclitaxel-induced neuropathy in male and female rats. Paclitaxel hyperalgesia was enhanced in male and female rats previously exposed to unpredictable sound stress. In adrenalectomised rats, paclitaxel did not produce hyperalgesia. Intrathecal administration of antisense oligodeoxynucleotides reduced expression of β_2-adrenergic receptors on nociceptors, and paclitaxel-induced hyperalgesia was slightly attenuated in males, but markedly diminished in females. The authors concluded that stress enhancement of paclitaxel-induced peripheral hyperalgesia is sexual dimorphic and dependent on stress axis mediators, acting at their cognate receptors on nociceptors (39).

In another paclitaxel-induced neuropathic pain model, removal of the ovaries decreases circulating levels of oestradiol and progesterone. This hormonal suppression attenuates dorsal root ganglia inflammation and diminishes female mice painful behaviour (41).

Oestradiol up-regulates the pain-promoting acid-sensing ion channels in dorsal root ganglia. There are sex differences in acid-sensing ion channel expression in rat dorsal root ganglia with higher protein expression in females than in males. Acid-sensing ion channel expression in dorsal root ganglia decreases significantly after ovariectomy, but not after orchiectomy (29).

Ostradiol increases hyperalgesia by upregulating the expression of the pain-promoting sodium channel Nav1.7 in the trigeminal ganglion in response to physical stressor (42). After physical trauma, female mice activate microglial cells leading to neuropathic pain. This microglial activation is not seen in male mice (43).

Epigenetic (environmental) factors may sensitise the pain pathways in women. The transient receptor potential ankyrin 1 (TRPA1) channel is highly expressed in a subset of sensory neurons in the dorsal root ganglia. Childhood traumatisation is associated with differences in TRPA1 promoter methylation in female patients with multi-somatoform disorder with pain as the leading bodily symptom (44).

This body of evidence demonstrates that in females, physical trauma and other types of stressors can lead to neuropathic pain.

Sexual dimorphism in autoimmune diseases associated with fibromyalgia

There is a clear sexual dimorphism in most autoimmune disorders; this marked difference is probably related to the influence of female hormones and the duplication of the X chromosome on the functioning of the immune system (45). Fibromyalgia coexists with several autoimmune diseases including autoimmune thyroiditis and Sjögren's syndrome (SS). Up to 62% of patients with autoimmune thyroiditis have concomitant fibromyalgia (46). More than 90% of individuals with autoimmune thyroiditis are women; similarly, more than 90% of individuals suffering from SS are female. Many patients with fibromyalgia complain of dry eyes and mouth, and many SS patients also complain of fibromyalgia symptoms. Novel tissue specific autoantibodies (SP-1, CA6, and PSP), observed in the early stages of SS are also present in one third of fibromyalgia patients (47).

Autoimmunity is frequently seen in small fibre neuropathy, and autoimmune dysautonomia is a new concept applied to the presence of stimulating autonomic receptor antibodies evident in various painful autoimmune disorders (48).

Conclusion

The somatic symptom disorder is a death-end alley diagnosis revealing limited knowledge in contemporary medicine. Somatisation implies imaginary symptoms, and male paradigms cannot be used to explain female diseases. Rather than a mental somatic symptom disorder, fibromyalgia patients may have a stress-induced neuropathic pain syndrome. Stress-evoked, sexually dimorphic dorsal root ganglia inflammation explain why women more often develop fibromyalgia. Understanding fibromyalgia as a real stress-evoked neuropathic pain illness may lead to more compassionate patient care and may favour novel gender-related pain investigations.

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