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Fibromyalgia: A Stress Disorder?

Piecing the Biopsychosocial Puzzle Together

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Key Words

Fibromyalgia · Chronic fatigue syndrome · Functional somatic syndromes · Biopsychosocial model · Stress-related illnesses

Abstract

Fibromyalgia (FM) is a controversial syndrome, characterised by persistent widespread pain, abnormal pain sensitivity and additional symptoms such as fatigue and sleep disturbance. The syndrome largely overlaps with other functional somatic disorders, particularly chronic fatigue syndrome (CFS). Although the exact aetiology and pathogenesis of FM are still unknown, it has been suggested that stress may play a key role in the syndrome. This article first reviews the function of the stress response system, placing special emphasis on the relationships between adverse life experiences, stress regulation and pain-processing mechanisms, and summarising the evidence for a possible aetiopathogenetic role of stress in FM. Finally, an integrative biopsychosocial model that conceptualises FM as a stress disorder is proposed, and the clinical and research implications of the model are discussed.

Introduction

Fibromyalgia (FM) is a 'medically unexplained' syndrome, mainly consisting of widespread musculoskeletal pain and tenderness, and frequent additional symptoms such as fatigue, effort intolerance, poor sleep quality, concentration difficulties and depression, with a duration of at least 3 months. The diagnosis is based on the presence of at least 11 'tender points' [1] but, during the past decade, this criterion has been strongly debated [2]. Moreover, since FM largely overlaps with other 'functional somatic syndromes' such as irritable bowel syndrome, temporomandibular disorder and multiple chemical sensitivities [3, 4] – and particularly chronic fatigue syndrome (CFS) [5, 6] – its existence as a distinct medical entity has been called into question [7]. Some authoritative rheumatologists have even pleaded for the 'demedicalisation' of FM [8, 9] whereas other authors argue that the syndrome should be considered a challenge for modern medicine [10].

Epidemiological data indicate that FM affects at least 2% of the general population, with women outnumbering men by 6:1 [11]. The syndrome may coexist with other rheumatic diseases [1], its course is chronic [12], and medical or psychological treatments have been found to be rather disappointing [13].

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From a pathogenetic point of view, no clear muscle pathology has been demonstrated in FM [14, 15] but, recently, evidence for an underlying central nervous disturbance is accumulating [16, 17].

Psychological investigations have repeatedly pointed to the frequent occurrence of psychiatric comorbidity (particularly anxiety and depression) in FM, but the nature and direction of this association have long been disputed [10]. However, recent studies suggest that psychological distress or psychopathological factors may play a causal role in the syndrome [18–20], supporting the view that FM is a disorder that should be understood from a biopsychosocial perspective [21].

The purpose of this article is, first, to discuss the interrelationships between stress and pain – particularly in FM – from a psychological as well as a neurobiological point of view, with special emphasis on developmental issues, and second, to propose an integrative biopsychosocial model, conceptualising FM as a stress disorder. Although the model primarily focuses on pain, it may – for reasons mentioned above – largely be applicable to chronic fatigue syndrome (CFS) and possibly other functional somatic syndromes as well.

The Stress Response System: A Brief Outline

'Stress' may be defined as a threat to the organism's homeostasis [22], reflecting the need to maintain stability through change ('allostasis') [23]. This threat – be it a physical assault (biological stress) or emotional burden (psychosocial stress) – activates genetically determined neuronal, hormonal and behavioural programs (the stress response system), aimed at preserving or restoring the equilibrium.

An adequate neurohormonal stress response is mainly processed by two interconnected systems: the locus coeruleus-norepinephrin (LC-NE) axis, and the hypothalamus-pituitary-adrenal (HPA) axis. Both axes are stimulated by corticotropin-releasing hormone (CRH) secreted by the hypothalamus, the amygdala, and other brain structures. Whereas the LC-NE axis primarily mediates the immediate stress reaction and provokes general arousal and vigilance, preparing the organism for 'fight or flight', the HPA axis particularly comes into play when long-term coping and perseverance is needed, and particularly when there is (at least a perceived) loss of control [24, 25]. The stimulation of both systems mainly results in increased cardiorespiratory and metabolic activity, while at the same time the digestive, the reproductive and the immune system are temporarily 'turned off'. After the threat has subsided, an adequate dampening of the stress response is necessary to avoid possible overshooting which may produce harmful effects [22].

Effects of Early Stressors

These phylogenetically determined neurohormonal programs may be ontologically influenced by early stress experiences, and this has convincingly been demonstrated by animal as well as human research.

For example, behavioural and physiological stress responses in rat pups were definitively changed as a consequence of their mothers' 'licking behaviour' and neonatal handling during a critical period of their development [26]. Similar results have been obtained in experiments with differential early rearing in primates [27]. Even minor parenting deficits may have persistent effects on neurobiological and behavioural development in the offspring [28].

Human studies also suggest that the cumulative effects of physical or psychosocial burden may increase susceptibility to stress in later life, either through sensitisation or failed inhibition of the HPA-axis [29, 30], possibly due to glucocorticoid-related hippocampal damage [31]. For example, retrospective studies have shown that emotional, physical or sexual abuse during childhood may not only increase future risks for anxiety, depression and somatisation [32, 33], but even organic diseases such as coronary disorders, CVA, diabetes, COPD and viral infections [34–36] – which may be related to lifelong hyperreactivity of the LC-NE and HPA axes. This hypothesis was supported by a recent prospective study showing that long-term exposure to maternal stress during early infancy resulted in higher salivary cortisol levels at age 4.5 [37]. By contrast, secure attachment in new-borns and adequate maternal responsiveness appear to facilitate adequate dampening of both LC-NE and HPA axes, leading to a higher stress threshold and lifelong better cognitive and affective stress coping [38–40].

Finally, it should not be overlooked that childhood psychosocial stressors could interact with a 'stressing' physical environment (such as early inflammation processes or infections) in programming neuroendocrinoimmune axes [41].

Thus, stress – and particularly traumatic stress – early in human development may alter the set point of the stress response system, rendering these individuals particularly prone to stress and stress-related disorders during later life [42–44].

Stress and Pain

An Intimate Relationship

Although, from a phylogenetic point of view, stress and pain seem to be closely connected, the relationships between the two phenomena have only recently become a topic of increased interest [45]. Particularly Melzack [46] has called for more studies in this domain and formulated a 'neuromatrix' theory of pain in which CRH, cortisol and catecholamines – in conjunction with the immune system and the endogenous opioid system – are thought to play a pivotal role.

Within this context, it has been suggested that while acute stress is known to produce analgesia, chronic stress may have the opposite effect, and both may be mediated by CRH [47]. On the other hand, an inverse relationship has been demonstrated between pain sensitivity and sympathetic reactivity [48].

There is also growing recognition of the role of neuroinflammation and neuroimmune activation in the pathogenesis of pain, involving pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α, which may be stress induced [49]. This could shed new light on various painful neuropathies and other badly understood painful conditions [50, 51].

Early Life Stress and Pain

Physical and psychological stress, as is the case in neonatal pain, may have long-term effects on developing nociceptive systems [52]. For example, young boys circumcised without adequate anaesthesia showed more pronounced pain responses during later life than their anaesthetised peers [53], and early maternal deprivation as well as childhood sexual trauma have been found to result in lower pain thresholds [54, 55].

These data may be explained by increased receptor binding of CRH in the nucleus raphe [56], leading to decreased activity of serotonergic neurons [57] and lack of inhibition of nociceptive stimuli by descending pain-controlling mechanisms [58]. Moreover, due to limbic connections between stress-regulating and pain-processing mechanisms, memories of childhood pain may in later life be triggered by physical as well as psychological stressors, without the presence of a specific nociceptive stimulus [59–61].

From a psychosocial point of view, early adversities and trauma may lead to attachment problems, preparing the ground for increased susceptibility to pain and disability via several pathways, notably higher susceptibility to stress, disturbed affect regulation and dysfunctional health-care-seeking behaviour [62–64].

Possible Role of Stress in the Aetiology of FM

Predisposing Role

Genetic/Environmental Interactions. Clinical observations suggest that genetic factors may be involved in FM, particularly in the case of first-degree female relatives [65], and this is probably due to an interaction of genetic and environmental (e.g. social learning) factors determining pain and stress sensitivity. More specifically, a genetically based disturbance in the serotonin transporter gene may exist in some FM patients, which may negatively impact on susceptibility to stress and affective disorders and result in less effective descending pain inhibitory mechanisms, as mentioned above [66].

Early Adversities. FM patients report a history of emotional neglect or abuse, physical and/or sexual abuse during childhood as well as re-victimisation during adulthood more often than healthy or medical controls [67, 68].

Certainly, evidence for a traumatic history is not found in all FM patients, suggesting that this factor may have variable aetiological weight and may also be buffered by protective factors determining a person's future well-being [67–69]. Moreover, the aetiological relevance of victimisation has not been confirmed by a recent prospective study in a non-selected population, though this could be due to the fact that neither 'subtle' emotional stressors (e.g. chronic parental disharmony or parental depression) nor protective factors had been taken into account [70, 71]. (Thorough methodological discussions can be found in the articles of Lampe et al. [72] and Hardt and Rutter [73]).

Personality. A substantial subgroup of FM patients seems to be characterised by problematic self-esteem and immature defence mechanisms with a tendency to anxiety, depression, and lack of emotional openness [74]. This may lead to compensatory overactive lifestyles [75], excessive striving for high achievement and recognition [76] as well as aggression inhibition and harm avoidance [77]. Such personality factors and behavioural styles may in the long run become an important source of chronic (physical and/or psychosocial) stress.

Precipitating Role

From a clinical perspective, there is little doubt that FM is often initiated by physical stress such as painful injury, infection or chronic physical overuse [78]. In many cases, psychosocial stress accompanied by lack of support seems to play a role as well, including critical life events [77, 79–81], psychotraumatic experiences [20] and daily hassles [82], particularly when the latter have high

personal relevance and refer to core themes of the patient's illness experience [83].

These etiological findings are clearly similar to those in CFS [83, 84] and in keeping with various psychosomatic studies [85, 86] but, nonetheless, conclusive proof of life stress predicting the onset or exacerbation of FM has not yet been established [87, 88].

Perpetuating Role

Comorbid Depression. Although FM has been hypothesised – along with other functional somatic syndromes – to be part of an affective spectrum disorder [89] and lifetime depression appears to be strikingly high in these patients [90], pain in FM should not be considered a mere expression of depression [91].

On the other hand, the stress of the illness may lead to frequent depressive comorbidities, contributing to symptom persistence via chronic sleep problems, less adaptive coping, physical and mental dysfunction, and decreased quality of life [92].

Comorbid Anxiety. FM frequently causes anxiety and worrying, for example about the uncertain prognosis, which may be an important reason for health care seeking [93]. Anxiety may play a perpetuating role in FM since it gives rise to increased arousal, irritability, muscle tension, hyperventilation and – in the case of pain-related fear – avoidance behaviour [94], resulting in higher pain intensity, more tender points, more severe functional limitations, and more fatigue and exhaustion [90, 94–98].

Cognitive-Perceptual Factors and Illness Behaviour. FM patients with high levels of stress and negative affectivity are more somatically focused [99, 100] and some may show pain-related hypervigilance, particularly those with catastrophising thoughts and more severe pain ratings [101, 102]. This may lead to hypochondriacal concerns [74] and low self-efficacy [103], promoting dysfunctional health care utilisation and further chronification.

Possible Pathophysiological Mechanisms

LC-NE Axis

A dysregulation of the sympathetic nervous system seems to be very probable in FM but the nature of this dysregulation remains unclear. Most evidence found concerns a blunted sympathetic response (LC-NE hyporeactivity) to stressors by demonstrating, for example, disturbed skin microcirculation [104], reduced orthostatic pulse [105] and decreased neuropeptide Y – a parameter for adrenergic output [48].

HPA Axis

Several authors have found relatively low basal cortisol secretion in FM [106, 107]. In a recent investigation, however, FM patients showed a delayed ACTH plasma peak on CRH stimulation by IL-6, while cortisol was normal [108]. Likewise, patients with CFS showed decreased ACTH production in response to psychological, physiological or pharmacological stressors, whereas cortisol output was within normal range [109].

These findings suggest that FM (and CFS) may be characterised by an impaired ability to activate the HPA axis (particularly at the pituitary level), which does not result in impaired basal cortisol levels but leads to an inadequate cortisol response to applied stress or normal activities of daily living [110].

Discrepancies and Unresolved Questions

In apparent contrast to the above, some authors have demonstrated basal LC-NE hyperfunction [111] and increased central CRH release [112] in FM patients. Such discrepant findings might be due to associated anxiety, depression, sleep disturbances, level of physical activity/deconditioning, diet factors such as caffeine consumption, variation of LC-NE/HPA axis functioning over time, and heterogeneity of FM subgroups [48, 113, 114].

Sympathetic hyperfunction may be related to the clinical observation of a whole range of neurovegetative symptoms in FM and experimental findings of NE-evoked pain in these patients [111].

On the other hand, LC-NE/HPA axis hypofunction has been found in various other stress-related bodily disorders [115, 116] as well as in posttraumatic stress disorder [117] and atypical depression [118], all showing marked clinical overlap with FM and CFS.

Nonetheless, whether LC-NE/HPA axis impairment – and particularly hypofunction – is actually a causal factor or should be considered an epiphenomenon, and whether these disturbances are based on central CRH deficiency, pituitary receptor down-regulation or dysregulated glucocorticoid feedback remains a matter of controversy [114, 115, 119].

Other Hormonal Axes

Some research has been carried out on growth hormone/IGF-1, and thyroid and gonadal axes in FM, but no firm conclusions can be derived from these studies [112, 114]. Interestingly, stress-related disturbances of oxytocin levels [120] and a marked variation of symptoms during the menstrual cycle [121] have also been demonstrated in FM patients.

Neuronal Mechanisms

Animal and human research suggests that descending antinociceptive systems may be deficient in FM, implying a lack of inhibition of peripheral nociceptive impulses (especially from deeper structures) and consequently fostering spontaneous pain, mechanical allodynia and hyperalgesia [122, 123].

Increased central sensitivity for peripheral stimuli may be mediated by biogenic amines (particularly serotonin), excitatory amino acids (such as glutamate) and neuropeptides (such as substance P and nerve growth factor) [17], and has been demonstrated by brain-imaging techniques [124, 125].

Neuroimmunological Mechanisms

Recent findings of neuroglial involvement in chronic pain make it plausible that pro-inflammatory cytokines, prostaglandines, leucotrienes and nitric oxide may be implicated in the pathophysiology of FM [17, 126]. Indeed, typical FM symptoms such as widespread pain, lethargia, flu-like symptoms, social withdrawal and concentration/memory difficulties may be linked to immune activation and have been described as 'sickness response' [49–51].

Although this (mild) immune activation could be due to the above-mentioned relative inability of FM patients to mount adequate levels of cortisol, the exact nature of neuroimmune disturbances in FM and, particularly, cause-and-effect relationships, are still unclear [5, 114].

Stress and FM: A Biopsychosocial Model

The above-discussed data suggest that susceptibility to FM may be based, at least in some patients, on genetically determined hyperresponsiveness to stress. This genetic predisposition may interact with unfavourable environmental and developmental factors (such as insecure attachment resulting from early adverse experiences), leading to further sensitisation of the stress response system. Negative affectivity, inner unrest, labile self-esteem, immature defence mechanisms and inadequate stress coping may follow, increasing the risk of unhealthy behaviours, dysfunctional lifestyles and unsatisfying relationships.

Accumulating physical and/or psychosocial stress (e.g. due to excessive physical activity, exhausting care giving, persisting sleep problems, familial conflicts, job dissatisfaction) seems to precipitate the illness. In fact – as the patients' histories show [127, 128] – FM symptoms often start in the aftermath of a protracted period of overburdening, and are triggered by painful injury, infection, or a traumatic experience. This would suggest that the illness onset might be facilitated by a shift within the stress system from chronic hyperfunction to hypofunction, implying an inability to adequately respond to new stressors and, eventually, giving rise to long-term disturbances in stress-regulating, pain-processing and immune mechanisms [5, 115–118, 129–132].

Several stress-related factors may contribute to the perpetuation of symptoms and disability in FM, such as the burden of continuing pain, ongoing anxiety, depression, irritability, worrying, catastrophic thinking, somatic hypervigilance, non-restorative sleep and inadequate health-care-seeking behaviour. Moreover – as in all functional somatic syndromes – physical deconditioning, social withdrawal, secondary gain and medico-legal disputes may favour the chronic course of the illness [130].

The model also predicts that different FM subgroups should be distinguished due to the relative weight of predisposing, precipitating and perpetuating factors and subtle variations in pathophysiological mechanisms. The exact nature of subgroups, however, including differential therapeutic implications, remains to be elucidated [114, 133, 134].

Clinical Implications

Conceptualising FM as a stress disorder may have important therapeutic value. First, referring to the – highly recognisable and non-stigmatising – concept of stress is acceptable for most patients and may lower the threshold for discussing psychosocial problems [45].

Second, the model can be used as an illness theory with high 'face validity', providing an excellent starting point for an individualised, person-centred therapeutic approach [135]. Symptomatic measures to manage pain and stress, correct sleep problems and treat anxious or depressive comorbidities (e.g. using relaxation therapy or antidepressants) should be complemented by physical rehabilitation and psychotherapeutic strategies. Cognitive behavioural therapy has proven to be particularly helpful in optimising coping, implementing adaptive lifestyle changes and encouraging long-term self-management and self-care [136, 137].

Third, the model may give rise to practical therapeutic guidelines, such as carefully tailoring low-intensity aerobic exercises to the patient's neurobiologically-determined vulnerabilities and physical limitations [138].

Future Research

Several aspects of this model may have heuristic value. For example, the potential role of a victimisation history and related attachment problems as a subgrouping criterion could be further clarified. Temporal relationships between stress and the onset or worsening of the illness could be examined in detail, retrospectively as well as longitudinally [139].

On the biological domain, prospective neuro-hormonal (e.g. HPA axis) and neuroimmune (e.g. glucocorticoid receptor and cytokine) studies could be undertaken in populations at risk, for example in victims of whiplash injury or in persons having experienced a prolonged period of severe emotional stress. Similar investigations could be performed in those who are recovered from FM in order to determine whether pathophysiological findings have to be considered trait or state markers [140].

Finally, the model presented here is compatible with recent pharmacotherapeutic developments in FM [141] and may open exciting new research avenues, e.g. on possible benefits of experimental substances such as CRH agonists/antagonists [142] and cytokine receptor blockers [143]. Hopefully, this will lead to novel medications aimed at complementing current symptomatic, psychotherapeutic and rehabilitation strategies by correcting – and possibly preventing – stress-related pathophysiological processes underlying FM and other functional somatic disorders.

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