The Role of Life Stress in Fibromyalgia

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This paper focuses on recent evidence of etiopathogenetic links between fibromyalgia and life stress. From an etiologic point of view, studies concerning the role of adverse life events, personality and lifestyle factors, post-traumatic stress, and negative childhood experiences are reviewed. From a pathogenetic point of view, neurobiologic links between stress and fibromyalgia symptoms, notably chronic pain and fatigue are highlighted. Finally, several methodologic issues with regard to stress research on fibromyalgia, as well as the clinical relevance of the stress concept for fibromyalgia are discussed.

Introduction

Fibromyalgia refers to a cluster of symptoms mainly consisting of chronic widespread musculoskeletal pain and allodynia/hyperalgesia, accompanied by physical and mental fatigue, effort intolerance, non-restorative sleep, and other functional (eg, gastrointestinal) complaints. Fibromyalgia largely overlaps with other 'functional somatic syndromes'—particularly chronic fatigue syndrome (CFS)—and is far more common in women [1]. Although the very existence of the syndrome has recently been debated among rheumatologists, most clinicians still consider fibromyalgia as a recognizable diagnostic entity [2,3•].

Furthermore, there is increasing agreement about the role of disturbed central pain processing in the syndrome [4], and intrinsic links between these disturbances and physical or psychosocial stress have been postulated (see Fig. 1 for a comprehensive biopsychosocial model) [5•]. Recent literature about the etiopathogenetic role of life stress in fibromyalgia will be reviewed in this paper.

Stress as an Etiologic Factor in Chronic Pain and Fatigue

What is stress?

In general terms, "stress" may be defined as a threat (or perceived threat) to the organisms' homeostasis, caused by a physical assault or a psychosocial burden (a stressor). This threat activates genetically determined neuronal, hormonal and behavioral programs—the 'stress response system'—aimed at preserving or restoring the equilibrium.

From a neurohormonal point of view, the stress response is mainly processed by the sympathetic (or locus coeruleus/norepinephrin [LC-NE]) axis producing norepinephrin and epinephrin, and acting in close connection with the hypothalamus-pituitary-adrenal (HPA) axis producing glucocorticoids. Both axes are stimulated by corticotropin-releasing hormone (CRH), secreted by the amygdala, the hypothalamus, and other brain structures. Once the threat has subsided, the stress response is adequately dampened by a negative feedback system [reviewed in 6••].

Life stress during adulthood

Although most clinicians agree that fibromyalgia patients' history is typically characterized by (often multiple) physical and/or emotional stressors [7], evidence for the precipitating and/or predisposing role of stress in the condition is scarce and rather conflicting. This may be a result of various methodologic problems inherent of human stress research.

Recently, a few prospective studies have been carried out that led to negative results. Williams *et al.* [8] and Raphael *et al.* [9] could not demonstrate any effect of the New York terrorist attacks on the prevalence of fibromyalgia complaints. With regard to fatiguing (CFS-like), even a decrease in prevalence was observed [10]. Although these findings may be explained by a general rise of solidarity and social support in the American population—which could have had a "stress-buffering" effect—it may also mean that only "idiosyncratic" stressors with a strong personal significance may play an etiopathogenic role in these disorders [11–13].

Most recently, Kivimäki *et al.* [14••] examined the prospective association between occupational stress and the incidence of newly diagnosed fibromyalgia. After adjustment for covariates, it was found that high workload, low decision latitude, and particularly the experience of being bullied at work were associated with a two- to fourfold risk for fibromyalgia.

From a totally different perspective, Wentz *et al.* [15] focused on fibromyalgia patients' life stress by using qualitative research strategies based on "grounded theory". The authors concluded that their fibromyalgia patients were pre-morbidly characterized by the core feature of "an unprotected self," which they overcompensated by intense

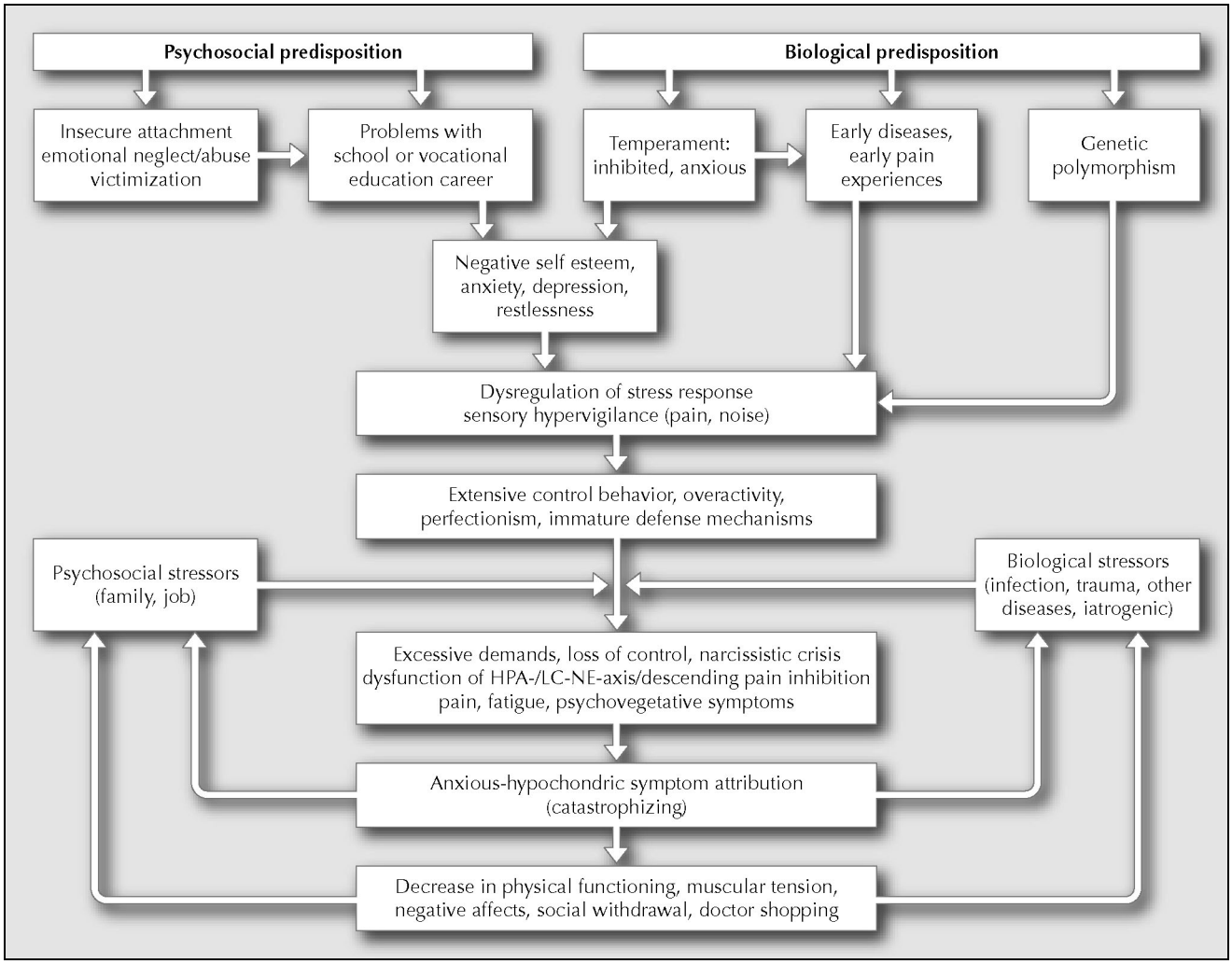

Figure 1. Biopsychosocial illness model of fibromyalgia.

activity or hypomanic helpfulness. When these individuals were subsequently exposed to increased mental load or emotional burden, they lost their previous physical and mental energy, and fell prey to generalized pain.

The latter study is in accordance with previous data showing that many fibromyalgia patients created (or at least contributed to) their own life stress by engaging in a "hard driving," perfectionistic, or self-sacrificing lifestyle. Van Houdenhove *et al*. [16] operationalized these premorbid features in terms of high "action-proneness" and found that CFS/fibromyalgia patients described themselves as significantly more "action-prone" than a medical and psychiatric control group; moreover, the patients' self-descriptions were largely confirmed by their significant others.

Finally, a discussion of the etiologic role of life stress in fibromyalgia would be incomplete without mentioning the contribution of genetic factors (eg, polymorphism in the serotonin transporter gene regulatory region) since these factors may co-determine the programming of the stress system and, consequently, have a major influence on the susceptibility for various kinds of stress-related disorders [3•].

Post-traumatic stress

Whether fibromyalgia may be precipitated by post-traumatic stress disorder (PTSD) still remains a controversial issue, although evidence for the co-morbidity of both conditions is increasing. Cohen *et al*. [17] found PTSD symptoms in 57% of a sample of fibromyalgia patients, nearly identical to the 56% rate previously reported by Sherman *et al*. [18]. Raphael *et al*. [19] carried out a methodologically sophisticated study in a community sample before and after the World Trade Center terrorist attacks, and found that the odds of probable PTSD were more than three times greater in women with fibromyalgia-like symptoms.

In a reaction to the Cohen *et al*. [17] article, Van Houdenhove [20] drew attention to the fact that traumatic stressors in fibromyalgia are mostly superimposed upon a long history of chronic physical and/or psychosocial burden. Other authors underlined the importance of post-

event worry, catastrophizing, and inactivity in fibromyaglia development [21] or found a major role for dysfunctional positive affect regulation [22].

Nonetheless, the nature of the link between fibromyaglia and PTSD is still a matter of speculation. Some authors have discussed this link in terms of mutual maintainance [23], or found evidence for the mediating role of depression [24], but the hypothesis that fibromyalgia and PTSD share common psychobiologic risk factors is plausible as well [19].

Childhood victimization

Early adversities, and traumatic experiences during childhood, may play an important role in the etiopathogenesis of (at least a subgroup of) fibromyalgia patients. In Table 1 controlled retrospective research data with regard to this topic are summarized, and two recent studies are discussed here in more detail.

Van Houdenhove *et al*. [25•] found in 48% of patients suffering from fibromyalgia and/or CFS emotional neglect or abuse, and in 23% physical maltreatment, while reports of sexual abuse (10%) did not differ significantly from organic and healthy control groups. In this study most patients reported multiple types of victimization, and 39% were (re)victimized during adulthood, suggesting that these persons remained entangled in burdening and threatening relationships throughout life. In a similar retrospective study, Imbierowicz and Egle [26] compared fibromyalgia patients with somatoform and organic chronic pain patients, and found that the fibromyalgia group had the highest scores on 14 childhood adversities. In addition to emotional neglect, physical maltreatment, and sexual abuse, fibromyalgia patients reported more household disharmony, frequent physical violence between the parents, addictive behavior in the mother, and a poor financial situation. The same research group found adverse childhood experiences to be linked with predominantly immature defense mechanisms in adulthood, resulting in stronger stress experiences from negative life events and daily hassles [27].

On the other hand, the etiologic relevance of physical and sexual victimization for fibromyalgia was not confirmed in a study comparing retrospective reports with prospective follow-up data from a non-selected cohort relying on court-documented childhood abuse [28]. However, this discrepancy could be because of the fact that neither subtle emotional stressors (such as parental disharmony), nor the protective role of court-documentation were taken into account in this study [29].

Methodologic Considerations

Assessing life stress

The stress concept is rather vaguely defined and difficult to operationalize [30], which undoubtedly hampers its application in research. However, fibromyalgia researchers should be aware of recent methodologic advances in the area of life stress research, such as the use of sophisticated interview-based strategies that may reveal subtle "inner stressors" associated with personality features and life history [15], as well as "ecologic momentary assessment," "experience sampling" methods, and "multivariate time series" that allow a detailed longitudinal view on the impact of daily life stressors on symptoms [31,32].

Stress: a causal factor?

In a critical commentary on the Kivimäki *et al*. [14••] study, Cleare [33•] rightly warned against all too rash conclusions about a possible etiologic link between stress and fibromyalgia—even when data are prospectively gathered. For example, a fibromyalgia diagnosis after stress may be a reflection of a change in illness perception, illness behavior, or physician behavior; there may be a reverse causation (ie, fibromyalgia symptoms leading to increased stress rather than vice versa); and the relationship may be based on a third variable, such as depression, or sleep disturbances [34]. Thus, future studies should always take these possible confounds into account.

Moreover, a causal relationship between fibromyalgia and stress is probably not linear, but recursive. On the one hand, since fibromyaglia patients seem to deal with emotion and conflict in maladaptive ways [22,27], this could partly explain the role of stress in the onset of their condition; on the other hand, since symptoms—and particularly chronic pain—in turn lead to increased stress, many patients become trapped in a vicious cycle. Hence, future researchers should move away from simple linear etiopathogenetic models—as most of the reviewed studies have assumed. Instead, they should use "multiwave" data to investigate recursive interactions between (pre- and post-morbid) stressors and personality aspects, and the role these interactions play in precipitating and/or perpetuating the condition.

Pitfalls in childhood victimization research

Childhood abuse studies may be affected by multiple biases, (eg, reflected in the disparate rates of sexual abuse), as summarized in Table 1. Moreover, Raphael *et al*. [35] concluded that a causal relationship between childhood abuse and various kinds of chronic pain in adulthood is not supported when current methodologic standards used in epidemiologic research are taken into account. Notably, most data are based on retrospective investigations in tertiary care settings—a well-known selection bias that limits the relevance of findings. The authors formulated several recommendations to enhance our knowledge in this domain, especially by undertaking longitudinal, community-based studies.

On the other hand, Kendall-Tackett and Becker-Blease [36] made a strong plea for continuing retrospective research in the field of long-term health effects of early life stress and trauma, since prospective designs may miss a

Table 1. Childhood victimization in fibromyalgia patients (controlled retrospective studies)

Study	Year	*n*	Rate, %	*P*
Emotional abuse/neglect				
Van Houdenhove *et al.* [25•]	2001	242	48	< 0.01
Imbierowicz and Egle [26]	2003	152	52	< 0.01
Physical maltreatment				
Boisset-Pioro *et al.* [56]	1995	244	13	< 0.01
Alexander et al. [57]	1998	123	28	< 0.01
Van Houdenhove *et al.* [25•]	2001	242	23	< 0.01
Imbierowicz and Egle [26]	2003	152	31	< 0.01
Sexual abuse				
Boisset-Pioro *et al.* [56]	1995	244	37	< 0.01
Taylor *et al.* [58]	1995	82	33	< 0.01
Alexander *et al.* [57]	1998	123	57	< 0.01
Goldberg *et al.* [59]	1999	91	65	< 0.01
Van Houdenhove *et al.* [25•]	2001	242	10	–
Imbierowicz and Egle [26]	2003	152	11	< 0.05

substantial number of cases, and unreported abuse may have even been more severe. Nonetheless, conclusions from retrospective studies should be interpreted with caution, complemented by prospective research, and if possible corroborated by neurobiologic evidence [37].

The neurobiology of stress-related pain and fatigue

Research data concerning integrated HPA axis and autonomous nervous system function in fibromyalgia have recently been reviewed by several authors [38–40]. They concluded that fibromyalgia is generally characterized by hyporeactivity to physical and mental stressors. This altered neuroendocrine responsiveness seems to be a result of changes in hypothalamic function, not to a primary adrenal defect. However, the precise nature of this "loss of resilience" of the stress system [41] remains an open question, and multiple forms of dysregulation, on different levels of the axis, may play a role: stress-induced CRH receptor down-regulation, increased sensitivity of the HPA axis to negative feedback, and/or glucocorticoid resistance [42].

Thus, the available evidence seems to confirm Clauw and Chrousos' [43••] original hypothesis that the stress response system of patients with chronic pain and fatigue may be impaired after a period of overburdening by physical and/or emotional stressors. This may imply a neurobiologic "switch" from hyperactivity to hypoactivity of the system, associated with functional or even structural receptor changes, and followed-up by a cascade of disturbances in immunologic, neurotransmitter, and central pain processing mechanisms [5•].

Alternatively, stress system hypoactivity might be considered a preceding "trait" factor in some patients. In this context, Glass *et al*. [44•] recently observed that a subset of healthy, regularly exercising individuals developed typical fibromyalgia/CFS symptoms after brief exercise cessation; when neurobiologic parameters at baseline between non-symptomatic and symptomatic individuals were compared, the latter showed lower HPA axis, immune, and autonomic function. The authors speculated that some individuals unknowingly exercise regularly to augment the function of their hypoactive stress system to suppress symptoms. However, these remarkable findings could also be interpreted within the dynamics of fibromyalgia patients' pre-morbid "overactive" lifestyle, as discussed above [6••,45].

Finally, although the above data suggest that neuroendocrine disturbances in fibromyalgia may cause pain and fatigue, it is still possible that these disturbances are (at least partly) the consequence of long lasting pain, sleep disturbances or inactivity [46,47].

Clinical Implications

The concept of stress has the advantage of being "non-psychiatric"—it is devoid from stigma and may be used as a metaphor providing patients with a plausible and acceptable "illness theory," to help them understand the contribution of psychosocial and lifestyle factors in their symptoms. One could say, for example: "Your stress system is out of balance—like a spring that has lost its elasticity; consequently, whenever you exceed your physical limits, your immune system gets activated, and this in turn 'sensitizes' your pain mechanisms and interferes negatively with your effort tolerance".

Moreover, the concept of stress provides multiple handles for managing symptoms and optimizing the patient's chances of regaining physical and mental resilience. One could say, for example: "When you carefully pace your activities, avoid all kinds of overload, and at the same time engage in a gentle aerobic exercise program, your effort tolerance may progressively increase while your symptoms diminish" [5•].

Future Directions

Several new theoretic concepts may advance our understanding of the etiopathogenesis of stress-related psychiatric and somatic syndromes. Excellent examples are the concepts of "stress system disorders" [6••,48••], "allostasis/allostatic load" [49••] and "cognitive activation theory of stress" [50] that have recently been formulated within the "bridging" sciences of psychoneuro-endocrinology and psychoneuroimmunology [51••]. Furthermore, the importance of gene and person-environment correlations [52] and psychobiologic aspects of stress resilience [53] is increasingly recognized in life stress research and will open exciting heuristic avenues to study recursive interactions between life stress, personality, and genetic dispositions. These promising new developments will hopefully lead to better treatments for fibromyalgia, for example new classes of drugs that may correct dysregulated pain and stress mechanisms, and may

complement present cognitive-behavioral and rehabilitative strategies [54,55].

Conclusions

During the past years, evidence has accumulated that fibromyalgia can only be understood psychologically as well as neurobiologically against the background of modern stress research and the implications of the latter for abnormal pain and fatigue. Nonetheless, our knowledge of the exact conditions under which stress may play a predisposing, precipitating, and/or perpetuating role in fibromyalgia, as well as the interference of stress in the pathophysiology of fibromyalgia remain fragmentary, and should be clarified by further research.

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