Is stress a factor in the pathogenesis of autoimmune rheumatic diseases?

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Stress and autoimmune rheumatic diseases

Rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and Sjögren’s syndrome (SS) are inflammatory chronic diseases with an autoimmune pathogenesis whose aetiology and progression is multifactorial, including a range of immune, genetic, neuroendocrine, environmental and psychosocial factors (1). How these variables interact with one another and how they ultimately influence the disease process in these conditions is only partially known. Nonetheless, research clearly demonstrates links between the stress system and alterations in disease activity, and associated outcomes (e.g., pain, disability) in rheumatic conditions (2-9).

In particular, stressors and the stress response system are pivotal in rheumatic conditions, since living with a painful, chronic, and somewhat unpredictable disease can be a significant source of stress in itself (10).

The stress response system is made up of psychological and neuroendocrine components that can be activated by a range of physical and psychological stressors. Stressors are any events that activate the stress-response system which, in turn, attempts to return the organism to a homeostatic state (1, 11, 12). Research indicates that psychological and physical stressors may affect disease activity in rheumatic conditions by disturbing the homeostasis of the neuroendocrine and immune systems (11, 13-15) (see Figure 1). In fact, studies have clearly demonstrated that hypothalamic-pituitary-adrenocortical axis (HPA) and hypothalamic-pituitary-gonadal axis (HPG) functioning are altered in RA patients, and both are major components of the stress response system (16). For example, cortisol levels are often inappropriately low for the inflammatory status of RA, and low levels of gonadal and adrenal androgens have been found in premenopausal RA patients (1, 17).

Hence, stressors and the components of the stress response seem to be inextricably involved in the disease process of rheumatic autoimmune conditions.

Rheumatoid arthritis

There are a number of dimensions along which psychosocial stressors can be defined, with major and minor life events being an important category. Major life stressors tend to be defined as severe stressors of great intensity and are often acute in nature. Previous findings regarding the impact of major life events on RA are conflicting, with a number of studies reporting no relationship between major stressors and RA disease onset and outcome (9, 18). Nonetheless, other studies indicate that major life events may be implicated in the onset and exacerbation of RA, as well as in higher levels of distress, and changes in functional disability (5, 6, 19, 20). A few studies suggest that major life events might represent one of the factors involved in the pathogenesis of RA (6, 21, 22). Therefore, it has been hypothesised that severe life events may disturb the homeostatic balance between neuroendocrine and immune mechanisms to the extent that a substantial subgroup of individuals may be susceptible to developing RA (3-6, 23).

A recent study investigated the relationship between the number of objective stressful life events at the time of onset of illness in RA patients compared to matched OA controls using self-report questionnaires (5). A high-stress-at-onset subgroup of RA patients was found which corresponded to a personality frequency distribution subgroup and which had a worse disease prognosis (5).

In a recent study, 40% of a series of RA patients were found to show an obsessive-compulsive personality and 40% a borderline personality disorder (6). The results indicated that RA patients had significantly more stress at disease onset compared to OA controls. Furthermore, confirming the findings of Latman & Wallis, a subgroup of high-stress-at-onset RA subjects experienced more severe disease and a worse prognosis than RA patients with no stress at onset.

Minor life events, such as interpersonal stressors (24), are low intensity events that are typically ongoing sources of strain for individuals with RA, which may precipitate further RA flare-ups (6, 25-27). The greater occurrence of minor
stressors has been shown to be related to increased disease activity, joint tenderness and pain in RA (21, 28-30) and associated alterations in neuroendocrine and immune functioning (13-15, 31, 32). A recent study examined the relationships between minor life events, interpersonal stressors, depression, coping efficacy, neuroendocrine function, and disease status in women with RA and in OA controls (14). The results indicated that changes in prolactin (PRL) levels in RA patients were correlated with levels of depression, interpersonal conflict, coping inefficacy, and the clinician’s ratings of disease activity, while no significant relationships were found between PRL levels, and psychosocial and disease variables for OA (14).

A prospective study also investigated the relationships between interpersonal stress, spouse support, sIL-2R, total T cell activation, and disease activity in married women with RA (15). Results showed significant elevations in disease activity from baseline values (including immune markers) after a highly stressful week. These studies seem to provide evidence for the role of psychosocial stressors and related psychosocial variables in RA disease activity.

**Systemic lupus erythematosus**

A number of studies have found that a high proportion of individuals with SLE report that major stressful life events and daily hassles exacerbate their SLE symptoms; they complained of greater levels of disease activity and severity, joint pain, abdominal distress, rash, and disability (33-38). In fact, a recent investigation found that the majority of individuals with SLE believe that stress plays a role in the onset and flare-up of their condition (39).

One study has examined the link between major and minor stressors, disease activity and damage variables, and changes in functional disability in women with SLE over an eight-month period (35). Hierarchical multiple regression indicated that major negative life events occurring in the six months preceding the baseline measurements were predictive of changes (13% of the variance) in disability in SLE, even after accounting for the baseline disability scores and depression. However, minor daily sources of stress were not found to be related to changes in disability levels over time. The authors concluded that various forms of stress may play different roles in SLE-related outcomes (35).

Another study examined the role of disease-related and psychosocial variables, including self-reported distress and the severity of daily stress, in the overall health of individuals with SLE (36). The results indicated that the severity of daily stresses and SLE disease were the best predictors of the individual’s perception of his/her global physical health. In addition, psychological distress accounted for a significant proportion of variance in both disease activity and damage. In other words, individuals who experienced greater levels of distress and severity of daily stresses reported poorer global physical health and had higher levels of SLE disease activity and damage, thus further supporting the role of stress in both the etiology and exacerbation of SLE.

**Sjögren’s syndrome and systemic sclerosis**

There are few studies investigating the role of psychosocial and physical stressors and the stress response in SS and SSc (40-42), making it difficult to draw general conclusions about their role in the pathogenesis and exacerbation of these rheumatic conditions. Nonetheless, a recent study examined the functional
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The role of increased cortisol release is hypothesized to be a stressor to which the immune system may respond (14). On the other hand, chronic exposure to stressors seems to have the greatest effect on the physiologic and immunologic levels (47, 48). Further studies are needed to definitively identify the locus of the defects and assess the significance of the pattern of neuroendocrine perturbations and the role of psychosocial and physical stressors in the pathogenesis and expression of SS and SSc.

Activation of the stress system

As stated above, the immune system seems to be directly linked to the stress system, and is profoundly influenced by the effects of the stress response. The stress response is associated with the activation of several neuroendocrine systems, including the HPA and HPG axes and the sympathetic nervous system (45). Activation of the HPA axis may occur when the patient is confronted by a psychosocial stressor which, if perceived as threatening, can result in associated affective and behavioural (i.e. coping) responses, as well as elevated serum levels of cortisol (Fig. 1). Therefore, the HPA axis provides an essential interface between the internal and external environments and enables the individual to adapt to diverse noxious stimuli, whether they be psychological, physical or other (46).

The role of increased cortisol release is adaptive in nature and attempts to counteract the effects of stressors in order to re-establish homeostasis. However, failure to mount an appropriate HPA axis response to a stress trigger, as can happen following chronic exposure to stressors, may be detrimental and could represent a significant contributory factor in the aetiology of a variety of disease processes, including autoimmune and inflammatory autoimmune diseases. Indeed, evidence from in vitro, animal and human studies demonstrates that activation of the immune system may constitute per se a stressor to which the HPA-axis responds (14). On the other hand, interpersonal stressors may have the greatest effect on the physiologic and psychologic functioning of individuals with autoimmune diseases, at least in RA (14).

As noted above, major versus minor stressors appear to have differential effects, and these differences may be mediated by disparate physiological mechanisms involving the HPA and the sympathetic-adrenal-medullary systems (SAM) which can influence the immune system. The length and intensity of exposure to stressors may also play a critical role. Short-term, acute stressors tend to elicit immediate but relatively transient changes in physiologic parameters, whereas chronic stressors may lead to relatively stable changes in baseline physiologic levels (47, 48).

The patient’s prior stress history also plays an important role in determining how he or she will respond to subsequent stressors. For example, in animal models, chronic intermittent exposure to a stressor of low intensity may lead to decreased sympathetic activity, whereas frequent exposure to a stressor of high intensity increases sympathetic activity (49). Therefore, a number of physiologic stress systems (e.g., HPA and SAM) are associated with autoimmune diseases and appear to mediate the relationship between environmental stressors and the disease pathophysiology (50). In particular, chronic exposure to stressors seems to reduce the efficacy of the stress system response and increase the risk of an altered immune response to antigenic stimuli.

In conclusion, the altered psychologic and physiologic profile of responses to different types of stressors in autoimmune rheumatic diseases suggests that stress is an important factor in their pathogenesis. The research to date has only revealed the tip of the iceberg (3).

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