Stress and autoimmunity

Ljudmila Stojanovich *

"Bezhanijska Kosa", University Medical Center, Belgrade University, Serbia

ABSTRACT

The etiology of autoimmune disease is multifactorial, including genetic, environmental, hormonal, and immunological factors. Nevertheless, the onset of autoimmune disorders remains enigmatic. Physical and psychological stresses have been suggested in the development of autoimmune disease, since numerous animal and human studies demonstrated the effect of stressors on immune function. Moreover, many retrospective studies had found that a high proportion (up to 80%) of patients reported uncommon emotional stress before disease onset. This, however, is not surprising as the disease itself causes significant stress in the patient. Recent reviews discuss the possible role of psychological stress, and of the major stress-related hormones, in the pathogenesis of autoimmune disease and presume that the stress-triggered neuroendocrine hormones lead to immune dysregulation, which ultimately results in autoimmune disease by altering or amplifying cytokine production. However, there is no evidence based research to support this concept. Nonetheless, stress reactions should be discussed with autoimmune patients. Applied implications are discussed, concentrating on the need for multidisciplinary care interventions that target patients’ disease symptoms and help them cope with their illness.

© 2009 Elsevier B.V. All rights reserved.

Contents

1. Introduction .............................................................. A271
2. Back to the past ............................................................ A272
3. Definition of stress ........................................................... A272
4. Pathogenesis of a stress-related disease ................................................. A273
5. The role of stress in immunity ..................................................... A274
6. Stress management and behavioral intervention ............................................. A275
Take-home messages ............................................................ A275
Acknowledgement ............................................................. A275
References ................................................................. A275

1. Introduction

The etiology of the loss of normal self-tolerance in an autoimmune disease is multifactorial. Genetic, environmental, hormonal, and immunological factors are all considered important in the development of these disorders (Table 1) [1]. Physical and psychological stresses have been implicated in the development of autoimmune disease, since numerous animal and human studies demonstrate the effect of various stressors on immune function [2,3]. Many studies had found that a high proportion (up to 80%) of patients reported uncommon emotional stress before disease onset [2,4,5]. However, there is no evidence based research to support this concept and the disease itself causes significant stress in patients [5,6]. Stress itself is not an illness, but rather a state, and long term stress causes serious health problems [2,6]. There are, however, interesting uncontrolled studies that examine whether childhood traumatic stress increases the risk of developing autoimmune diseases in an adult [7]. The authors found that childhood traumatic stress increased the likelihood of hospitalization with a diagnosed autoimmune disease decades into adulthood. These findings are consistent with recent studies on the impact of early life stress and subsequent responses but again are not entirely rigorous [8–10].

However, although physicians and patients agree that stress plays a role in modifying disease processes, few clinical studies demonstrate...
the mechanisms by which this occurs. Studies are conducted on animal models, and their results are not easily generalized to the human population because animal models are genetically identical and are much easier to control environmentally.

In humans, the environment, diet, concomitant medication, and other factors offer different variables that need to be controlled to explain the cause of autoimmune disease (Table 1). A recent theory combines all these factors together with stress into a mosaic that describes the pathogenesis of autoimmune disorders [8]. But we should caution that everyone experiences stress, which may be related to one’s health, work, community, or family. Despite the fact that the existence of stress is widely acknowledged, it is “a reality like love or electricity — unmistakable in experience but hard to define”.

2. Back to the past

More than 50 years ago Dr. Hans Selye demonstrated how stress diminishes health and leads to glandular disturbances [11,12]. His seminal theoretical work focused on the non-specific response of the organism to stress, and studied the impact of stress on the production of corticosteroids. While he did not recognize many aspects of the role of corticosteroids in the body, Selye was aware of their role in stress response. Selye is often considered the first to have demonstrated the existence of a separate stress disease, called “stress syndrome”, or “general adaptation syndrome” (GAS). Philosophically, the concept of adaptation runs through most life activities, from wound response, to language, to literature and beyond. The general adaptation syndrome is one which invokes a systemic response (Fig. 1). The initial inspiration for GAS came from an endocrinological experiment in which mice were injected with extracts of various organs. Selye first believed that he had discovered a new hormone, but was proved wrong when every irritating substance he injected produced the same symptoms — swelling of the adrenal cortex, atrophy of the thymus, gastric and duodenal ulcers. This, paired with his observation that people with different diseases exhibit similar symptoms, led to his description of the effects of the so-called “noxious agents”.

The hypothalamus–pituitary–adrenal system used by the body to cope with stress was also first described by Selye. Selye points to an alarm state, a resistance state, and an exhaustion state, largely referring to glandular states [12]. Later he developed the idea of two “reservoirs” of stress resistance or, alternatively, of stress energy: a superficial level, which can be restored, and a deeper level, which is permanently depleted when drawn upon. This may be compared with muscular exercise where strength is gained by tension-release, whereas either tension or relaxation by itself is wasteful. According to Selye’s theory, an ill person should do everything to reduce stress, and conserve strength to fight the primary disease.

While many natural health enthusiasts, as well as a number of physicians, continued to research the role of stress [10,13–15], mainstream medicine remains skeptical [16,17]: how could one prove that stress, and not some genetic flaw or predisposition, is responsible for those withered glands Selye offered us? Cause and effect have always been tinted with doubt in medicine. This prevailing theory should be considered in our understanding and future studies of autoimmune diseases. Nonetheless, Selye’s model has been the inspiration for later researchers, and has contributed to the development of understanding. It has, however, the fundamental weakness of being essentially a static model. It assumes that the stressors acting upon an organism must be endured; that the changes which eventually occur, either towards adaptation or towards collapse, occur within the subject organism.

3. Definition of stress

Hans Selye was the first to define stress as a non-specific response of the body to any demand made upon it [11]. Selye claimed to have coined the term stress, which was consequently accepted into the lexicon of various other languages. However, according to Robert Sapolsky [10,15], the term stress should rightly be attributed to Walter Cannon. In the preface to his book “Stress”, Selye acknowledges Cannon’s concept of homeostasis, in which stress is an activating mechanism in all life that is capable of activation. A cell sits content till a stressor, such as danger or appetite, activates mechanisms leading to an adaptation to circumstance. In higher animals this includes activities from blood clotting, fight and flight, etc.

Selye conceptualized the physiology of stress as having two components: the negative, which he called distress, and the positive, which he called eustress (Fig. 2). To grossly oversimplify to the point of a circular argument, Selye discovered and documented that stress differs from other physical responses in that stress is stressful irrespective of whether the body is receiving good or bad news, that is, of whether the impulse is positive or negative. Because there is such a wide range of factors that contribute to the experience of stress, many researchers have sought to categorize them (Table 2).

The term stress has been oversimplified and manipulated in public use with psychiatrists and psychologists mainly responsible for great overlap and consequent confusion between the definition of stress and its diagnosis [13,15]. It is worth re-iterating that the stress system orchestrates the response of the body and of the brain to the environment.

Table 1
Factors contributing to autoimmune disease.

<table>
<thead>
<tr>
<th>Changeable factors</th>
<th>Unchangeable factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infection</td>
<td>• Genetic</td>
</tr>
<tr>
<td>• Vaccination</td>
<td>• Hormonal</td>
</tr>
<tr>
<td>• Smoking</td>
<td>• Immune deficiency states</td>
</tr>
<tr>
<td>• Obesity</td>
<td>• Gender</td>
</tr>
<tr>
<td>• Ultraviolet light exposure</td>
<td></td>
</tr>
<tr>
<td>• Drugs</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. The general adaptation syndrome (GAS) by H. Selye, 1974.

- The first stage is the stage of alarm-reaction, due to a shock (psychological or physiological). The organism responds (enlarged adrenal cortex, shrank thymus, spleen and lymph nodes, and deep and bleeding ulcers in the stomach).
- This stage is followed after a few days by the stage of resistance. The organism seems to adapt to stress and hormone levels return to normal, but in fact, it has no defenses left.
- The stage of exhaustion is the third and final stage. The adaptation is over, and the stress ‘reappears’. The immunology defenses are low, glands and organs have an increased activity.
The stress system orchestrates body and brain responses to the environment. This action is exerted by the mediators of the stress system with two modes of operation. The immediate-response mode is driven by corticotropin-releasing hormone (CRH), which organizes the behavioral, sympathetic and hypothalamic–pituitary–adrenal responses to a stressor via CRH-1 receptors. The slower-response mode, which facilitates behavioral adaptation, is driven by urocortins, acting through CRH-2 receptors. Corticosteroid hormones secreted by the adrenal cortex are implicated in both modes through their high-affinity type 1 mineralocorticoid receptors and lower-affinity type 2 glucocorticoid receptors that are co-localized in limbic neural circuitry. Current data suggests that mineralocorticoid receptors control, in specific afferents, the threshold or sensitivity of the fast CRH-1 driven stress system mode, preventing disturbance of homeostasis. On the other hand, glucocorticoid receptors facilitate the recovery of homeostasis by restraining stress responses and by mobilizing energy resources. In preparation for future events glucocorticoid receptors facilitate behavioral adaptation and promote the storage of energy. The balance in the two stress system modes is thought to be essential for cell homeostasis, mental performance and over-all health. Imbalance induced by genetic modification or by chronic stressors changes specific neural signaling pathways underlying psychic domains of cognition and emotion, anxiety and aggression [20–22].

Adaptation to stressful stimuli, maintenance of homeostasis, and, ultimately, survival require bidirectional feedback communication among components of the stress-response system, and immune and endocrine systems [9,21]. Substantial progress has been made in delineating molecular, cellular, and systemic physiological mechanisms underlying this communication, particularly mechanisms that target the immune system. For example, our understanding of the immunomodulatory activities of numerous neuroendocrine media tors, such as cortisol, estrogen, testosterone, DHEA, catecholamines, corticotropin-releasing hormone, and adrenosine, has advanced substantially. Substantial progress has also been made in defining how abnormalities involving these factors may contribute to the initiation, progression, and severity of autoimmune rheumatic diseases [16,17,20,22], particularly rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). For RA, the available data supports the theory that inflammatory and immune system inhibitory mechanisms that involve the hypothalamic–pituitary–adrenal axis and sympathetic nervous system are deficient. Age, gender, and reproductive status, acting in part through gonad hormonal effects on disease susceptibility genes, are also likely to modulate inhibitory stress-response and immune function. Animal model data also provides direct evidence that many autoimmune disease regulatory genes are gender-influenced. For SLE, a growing body of recent data indicates that estrogens and androgens exert contrasting effects on B lymphocytes. These observations provide potential new insights into SLE pathogenesis and gender differences in prevalence.

Continued investigation will refine our understanding of these observations and will uncover even more extensive interactions of the nervous, immune, and endocrine systems. Moreover, it is highly likely that an improved understanding of these interactions will lead to improved therapy and help patients cope with their rheumatic diseases [22,23].

Epidemiological research increasingly suggests that exposure to traumatic stressors and psychological trauma is related to increased health care utilization, adverse health outcomes, onset of specific diseases, and premature death [19,20]. To date, studies have linked traumatic stress exposures and posttraumatic stress disorder to such conditions as cardiovascular disease, diabetes, gastrointestinal disease, fibromyalgia and chronic fatigue syndrome [14,22,24].

Evidence linking cardiovascular disease and exposure to psychological trauma is particularly strong and has been found consistently across different populations and different stressor events (Table 2). In addition, clinical studies have suggested the biological pathways through which
stressor-induced diseases may be pathologically expressed [10,21]. In particular, recent studies implicate the hypothalamic–pituitary–adrenal and the sympathetic–adrenal–medullary stress axes as key in this pathogenic process, although genetic, behavioral, and psychological risk factors cannot be ruled out [15,24,25].

A recent study by Boscariino [19] assessed the association between chronic posttraumatic stress disorder in a national sample of 2490 Vietnam veterans with the prevalence of common autoimmune diseases, including rheumatoid arthritis, psoriasis, insulin-dependent diabetes, and thyroid disease. This analysis attempted to demonstrate that chronic posttraumatic stress, particularly comorbid posttraumatic stress disorder and complex posttraumatic stress disorder, is associated with all of these conditions. Posttraumatic stress disorder has higher circulating T-cell lymphocytes and lower cortisol levels, placing these patients at risk for autoimmune disease. Patents with comorbid posttraumatic stress disorder are more likely to have hyper-reactive immune responses on standardized delayed cutaneous hypersensitivity tests, clinically higher immunoglobulin-M levels, and clinically lower dehydroepiandrosterone levels, in addition to higher T-cell counts [24,26,27]. However, in the absence of rigorous controls, case definitions and standardization of the conclusions are only theoretical.

5. The role of stress in immunity

The activation of the stress-response system influences the close relationship between the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system, and the immune system. Social factors, such as the quality of the relationship between the patient and his family, are useful prognostic factors in patients with autoimmune rheumatic disease [2,4,22,28]. Coping strategies are important for the daily routine and for the psychological well-being of chronic patients. They enable the patient to adapt to problems and stressors arising from the disease, such as pain, fatigue, limitations in mobility, difficulties in daily life activities, and threats to the patient's self-esteem [17,23,29]. In recent years, clinicians involved in autoimmune rheumatic research proposed a link between the stress-response system and abnormal immune function.

Most interestingly, the release of endogenous glucocorticoids is critical in regulating the severity of disease activity in patients with inflammatory conditions such as rheumatoid arthritis (RA). Blocking of cortisol production results in a flare-up in disease activity in RA patients, while surgical removal of the adrenals in patients with Cushing’s disease has been reported to exacerbate autoimmune disease [10,29].

In adjuvant-induced arthritis (a rat model of RA), there is an activation of the hypothalamic-pituitary-adrenal axis associated with the development of inflammation. In addition, there are profound changes in peptides within the paraventricular nucleus, which are responsible for regulating the hypothalamic-pituitary-adrenal axis. Understanding the regulation of the hypothalamic–pituitary–adrenal axis in health and disease holds out the promise of targeted therapy to alleviate inflammatory conditions [18,30]. The findings indicate the impact of stress on an individual and its susceptibility to inflammation, questioning the idea that stress is “all bad”. Exposure to a single acute stressor can alter the phenotype of a rat, changing it from being susceptible to autoimmune disease – to being resistant to the disease. This alteration in susceptibility takes days to manifest itself, but can last for weeks, suggesting beneficial effects of exposure to an acute stressor [31].

Stojanovich [4] conducted a study in which patients with systemic lupus erythematosus (SLE), RA, and primary antiphospholipid syndrome (PAPS) were asked to complete a questionnaire about different stressors that preceded the onset or exacerbation of their disease. Patients stated that sickness or death in the family, financial problems, loss of a job, and the unstable political situation (e.g., the Serbia bombings and economic sanctions) caused them considerable prolonged anxiety. One or several factors outside of a person's control, many of them persisting for long periods of time, were reported to cause stress. The study included 120 SLE patients, 141 patients with PAPS, and 94 RA patients. SLE patients selected stress in 75.8% of the cases, far more often than other known triggers such as smoking (46.8%) and family history (21.3%). A significant percentage of PAPS patients (44.8%) considered prolonged stress to be the lead cause of their disease, as did a similar number of RA patients (42.5%).

Catastrophic antiphospholipid syndrome (CAPS), also known as Asherson's syndrome, is an accelerated form of the antiphospholipid antibody syndrome (APS) which results in multi-organ failure [32]. Due to the rarity of the condition, and to the diversity of clinical and serological manifestations, an international registry of CAPS patients was created in 2000 under the aegis of the European Forum on Antiphospholipid Antibodies (aPL) held in Taormina, Italy at the Tenth International Congress on aPL. A consensus statement on classification criteria was recently proposed by the Catastrophic Antiphospholipid Syndrome Registry Project Group (European Forum on Antiphospholipid Antibodies) [33]. Clinical and laboratory features are the most important among the criteria for the diagnosis of CAPS.

Despite early diagnosis and an improved understanding of the underlying pathophysiological mechanisms that lead to CAPS, its mortality rate remains unacceptably high (48%), especially in SLE patients with cardiac, pulmonary, renal, spleen, and adrenal involvement. Fortunately, CAPS accounts for less than 1% of APS cases [33]. The first results from the Serbian National APS Registry demonstrate an over four times higher incidence of CAPS in the population of APS patients (4.7%), compared to other studies [34]. This project started in January 2006, and currently records information about 256 patients in its database. Of these, 162 patients are diagnosed with PAPS and 94 are SLE patients with secondary APS. 12 patients in the project presented with CAPS. Analysis of precipitating factors for CAPS identified infection in 50% of the patients. Stress was also proposed in 33% of the cases.

Stress may affect the immune system either directly or indirectly through the nervous and endocrine systems [21,25,35]. Interdisciplinary psychoneuro-immunological research increasingly demonstrates clinically relevant interrelations between psychological stressors and the onset and progression of chronic diseases. Disturbances of the bi-directional interaction between the nervous system, the immune system and the endocrine system have been hypothesized to be implicated in several endocrinological autoimmune diseases [1,3,8,21,23].

The possible role of psychological stress and of the major stress-related hormones as etiological factors in the pathogenesis of metabolic diseases such as atherosclerosis is discussed in [3,13,14]. The metabolic syndrome is a cluster of risk factors that increases the risk of heart disease and type 2 diabetes. Characteristics of the metabolic syndrome are abdominal obesity, atherogenic dyslipidemia, raised triglycerides, low levels of low-density lipoprotein particles, and low concentrations of high-density lipoprotein cholesterol, high blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states.

Cross-sectional studies found a social gradient in work-related stress and in the metabolic syndrome, suggesting that heart disease could in part be explained by greater exposure to stress among disadvantaged social groups [13,36]. However, subsequent studies develop a hypothesis that stress can induce an acute phase response and inflammation, including a chronic inflammatory process [1,14,18]. Such processes are characterized by the presence of cytokines and acute phase reactants, which are associated with certain metabolic diseases. The loci of origin of these cytokines, particularly interleukin 6 (IL-6), and their induction, have been considered. Evidence is presented that the liver, the endothelium, and fat cell depots are the primary sources of cytokines, particularly of IL-6. IL-6, the acute phase protein (APP), and C-reactive protein (CRP)
are strongly associated with, and likely play a dominant role in the development of this inflammatory process, leading to insulin resistance, non-insulin-dependent diabetes mellitus type II, and metabolic syndrome X. Stress can activate an acute phase response, which is a part of the innate immune inflammatory response. This provides evidence that the inflammatory response is contained within the stress response, or that stress can induce inflammation [18]. The fact that the stress, inflammatory, and immune systems all evolved from a single cell, the phagocyte, is further evidence of their intimate relationship which almost certainly was maintained throughout evolution.

Autoimmunity may occur in all endocrine tissues, with a particular prevalence in thyroid and pancreatic islets. The most demonstrative clinical expressions of this autoimmunity are Graves’ disease and insulin-dependent diabetes. In the former, extensive data is available about autoimmune immunological involvement of peripheral blood vessels and of the thyroid itself. The genetic susceptibility profiles of such diseases are well-delineated, and there are known genetic markers of the HLA system.

Clinical observation registers frequent stressful life events just before the onset of these diseases, but there is little convincing data in the literature. Recent findings on the close relations between the immune system and the central nervous system lead to conceive an actual psychoneuroendocrine-immune axis. This axis may explain the eventual priming effect of stress in patients predisposed to an organ-specific autoimmune response [16,23].

A paper by Leclère and Weryha [37] reviews the interaction between stress and Graves’ disease, which is induced by thyroid-stimulating autoantibodies. Psychological stress suggested as a risk factor for Graves’ disease, although the mechanism by which stress induces disease remains unknown. Moreover, the authors found that other stressors, such as delivery, could induce the onset of Graves’ disease. Immune rebound after delivery and the overproduction of Th2-derived cytokines might help produce thyroid-stimulating autoantibodies. During stress, activation of the hypothalamic–pituitary–adrenal axis and of the sympathoadrenal system leads to an increased secretion of glucocorticoids and catecholamines, respectively, in order to maintain homeostasis. This study suggests that stress hormones, acting on antigen-presenting immune cells, may influence the differentiation of bipotential helper T-cells away from a Th1 phenotype and towards a Th2 phenotype. This results in suppression of cellular immunity and in potentiating of humoral immunity. Thyroid autoimmunity is clinically expressed as Hashimoto’s thyroiditis or as Graves’ disease. The different phenotypic expressions of thyroid autoimmunity are largely dependent on the balance of Th1 versus Th2 immune response.

A predominantly Th1-mediated immune activity may promote apoptotic pathways on thyroid follicular cells, leading to thyroid cell destruction and Hashimoto’s thyroiditis (HT). Conversely, predominance of Th2-mediated immune response may induce antigen-specific B lymphocytes to produce anti-TSH receptor (TSHr) antibodies, causing Graves’ disease.

A different opinion is expressed by Martin-du Pan [38], where 98 patients with Graves’ disease are compared to 95 patients with Hashimoto’s thyroiditis, and to a control group of 97 patients with benign thyroid nodules. The study evaluates the triggering role of major stressors and pregnancy in the occurrence of autoimmune thyroid diseases. A stress factor is encountered in 11% of the cases of Graves’ disease, in 6% of Hashimoto’s, and in 6% of thyroid nodules. Graves’ was triggered by pregnancy in 25% of the women of child-bearing age versus 10% of the cases of Hashimoto’s (p<0.05), and 13% of the thyroid nodules. The role of stressors, if any, in triggering Graves’ disease seems to be weak compared to the role of pregnancy and postpartum. The authors assume that the decrease of immunosuppressive hormones occurring after stress or delivery could induce a rebound autoimmune reaction responsible for the thyroid disease.

In Hashimoto’s thyroiditis, stress and pregnancy do not seem to have any triggering role.

Mizokami et al. [39] suggest that the best circumstantial evidence for the effect of stress on autoimmune thyroid disease is the well-known relationship between the onset of Graves’ hyperthyroidism and major stress. Furthermore, most of the recent case–control studies support stress as a factor in the onset and clinical course of Graves’ disease.

Most evidence for stress contributing to the onset and the course of autoimmune disease remains circumstantial, and the mechanisms by which stress affects autoimmune disease are not fully understood. However, evidence is accumulating on the negative effects of stress on health, suggesting that chronic stress may intensify inflammation and increase a person’s risk for developing infections and other inflammatory diseases [8,9,24,26].

There is also some data suggesting an association between stressful life events and an increased risk for Multiple Sclerosis (MS) exacerbations. Mitsonis et al. [40] summarized the psychological and biological mechanisms by which stress may impact the progression of MS. Their findings indicate the impact of a number of factors, including duration, frequency, severity and the type of stress, as well as the patient’s optimism, perceived social support, and coping strategies. Applied implications are discussed, concentrating on the need for multidisciplinary care interventions that target the patient’s primary disease symptoms.

6. Stress management and behavioral intervention

The treatment of autoimmune diseases should include stress management and behavioral intervention to prevent stress-related immune imbalances. Interventions such as weight management, stress reduction, appropriate diet, and a healthy home environment may be very important in the prevention of flares and in slowing the progression of arthritis [17,22,28]. Unlike hereditary and genetic etiological factors that cannot be changed, many lifestyle and environmental factors can be modified in order to better manage autoimmune disease. Stress reactions should be discussed with autoimmune patients. Finally, it should be noted that the issue of environment and autoimmune diseases remains one of the “hot” areas in autoimmunity and frequently discussed not only with respect to susceptibility, but also found in the majority of epidemiologic analyses. We expect further data on this issue in the future; space does not permit individual discussion but the following references reflect this issue [41–51]. The treatment of autoimmune diseases should consider stress management and behavioral intervention.

Take-home messages

• Stress is a component of diseases. It is very important both to understand the effects of stress on the body, and to develop effective stress management techniques.

• The role of stress in the pathogenesis of autoimmune disease is controversial and not currently accepted as an etiologic factor.

• Stress affects the immune system and different stress reactions should be discussed with autoimmune patients.

Acknowledgement

This work was supported by research grant number 145020 for 2006–2010, issued by the Ministry of Science of the Republic of Serbia.

References

Stress as a trigger of autoimmune disease


