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Stress as a trigger of autoimmune disease

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Abstract

The etiology of autoimmune diseases is multifactorial: genetic, environmental, hormonal, and immunological factors are all considered important in their development. Nevertheless, the onset of at least 50% of autoimmune disorders has been attributed to "unknown trigger factors". Physical and psychological stress has been implicated in the development of autoimmune disease, since numerous animal and human studies demonstrated the effect of sundry stressors on immune function. Moreover, many retrospective studies found that a high proportion (up to 80%) of patients reported uncommon emotional stress before disease onset. Unfortunately, not only does stress cause disease, but the disease itself also causes significant stress in the patients, creating a vicious cycle. Recent reviews discuss the possible role of psychological stress, and of the major stress-related hormones, in the pathogenesis of autoimmune disease. It is presumed that the stress-triggered neuroendocrine hormones lead to immune dysregulation, which ultimately results in autoimmune disease, by altering or amplifying cytokine production. The treatment of autoimmune disease should thus include stress management and behavioral intervention to prevent stress-related immune imbalance. Different stress reactions should be discussed with autoimmune patients, and obligatory questionnaires about trigger factors should include psychological stress in addition to infection, trauma, and other common triggers.

Keywords: Physical and psychological stresses; Autoimmune disease; Trigger factors

Contents

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1. Introduction

The etiology of the loss of normal self-tolerance in an autoimmune disease is considered multifactorial. Genetic, environmental, hormonal and immunological factors are all considered important in the development of these disorders [1]. Nevertheless, the onset of at least 50% of autoimmune disorders has been attributed to *unknown trigger factor*s. Physical and psychological stress has been implicated in the development of autoimmune disease, since numerous animal and human studies [2] demonstrate the effect of sundry stressors on immune function [3]. Many retrospective studies found that a high proportion (up to 80%) of patients report uncommon emotional stress before disease onset [4]. Several studies suggest that stress is not only a participating factor, but can in fact cause disease exacerbation. Unfortunately, not only does stress cause disease, but the disease itself also causes significant stress in the patients, creating a vicious cycle. [5,6].

However, although physicians and patients agree that stress plays a role not only in the onset of many disease processes, but also in their exacerbation, there is very little clinical research work demonstrating the mechanisms by which this occurs. One of the reasons for this is that animal models are much easier to control environmentally, and that these models are genetically identical. In humans, factors like the environment, diet, and concomitant medication are difficult variables that need to be controlled.

2. Back to the past

More than 50 years ago Dr. Hans Selye demonstrated how stress diminishes health and leads to glandular disturbances, including autoimmune endocrine disorders [7,8]. 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 one receives good or bad news, whether the impulse is positive or negative. While many natural health enthusiasts, as well as a number of rheumatologists, continued to research the role of stress, the elite fraction of mainstream medicine, particularly the endocrinologists, grew skeptical [9,10]: how could one prove that stress, and not some genetic flaw or predisposition, was responsible for those withered glands Selye offered us? Cause and effect have always been tinted with doubt in medicine. Unless one is hit by a car, how can one prove exactly what caused any medical disorder? This prevailing thought holds the key to a certain lack of progress surrounding *prevention*, not just treatment, of autoimmune diseases.

3. Definition and diagnosis of stress

Hans Selye was the first to define stress as *a nonspecific response of the body to any demand made upon it* [7]. It has been demonstrated that Selye's theory about the effects of stress is applicable to any sort of stress. He called negative stress *distress* and positive stress *eustress*. Some commentators consider him the first to demonstrate the existence of a particular stress disease, the stress syndrome, or the *general adaptation syndrome.* Selye was also the first to describe the system by which the body copes with stress — the hypothalamus–pituitary–adrenal system. However, the word *stress* has been oversimplified and manipulated in public usage [9], with psychiatrists and psychologists mainly responsible for a great overlap and consequent confusion between the definition of stress and its diagnosis. It is worth re-iterating that the stress system orchestrates the response of the body and of the brain to the environment.

4. Pathogenesis of a stress-related disease

The possible role of psychological stress and of the major stress-related hormones as etiological factors in the pathogenesis of autoimmune disease was discussed in recent reviews [2,12,13,14]. It is presumed that neuroendocrine hormones triggered during stress lead to immune dysregulation and altered or amplified cytokine production, resulting in atopic autoimmune diseases or in decreased host defense. Various types of transmitter substances of the neuroendocrine-immune network include epinephrine, norepinephrine, acetylcholine, substance P, vasoactive intestinal peptide, glucagon, insulin, cytokines, growth factors, and numerous other mediators. In addition, the multiple roles of Th2 cells in maintaining allergic inflammation and altering the balance between Th1 and Th2 responses are important mechanisms for allergic inflammation and tissue damage.

5. The role of stress in autoimmune disease

It was presumed that repeated episodes of acute or chronic psychological stress might induce an acute phase response, triggering a subsequent chronic inflammatory process, such as atherosclerosis and certain metabolic diseases [10,14]. There is evidence that the liver, the endothelium, and fat cell depots are the

primary sources of cytokines, particularly of IL-6. IL-6 and the acute phase protein C-reactive protein are strongly associated with, and likely play a dominant role in, the development of such inflammatory process, which leads to insulin resistance, non-insulin dependent diabetes mellitus type II, and Metabolic syndrome X [10]. The fact that psychological stress can activate an acute phase response, which is part of the innate immune inflammatory response, is evidence that the inflammatory response is contained within the stress response, and that stress can induce an inflammatory response [11].

5.1. Association of stress and immune dysregulation

Epidemiological research increasingly suggests that exposure to traumatic stressors and psychological trauma is related to increased health care utilization, adverse health outcomes, the onset of specific diseases, and premature death [15,16]. To date, studies have linked traumatic stress exposures and posttraumatic stress disorder to such conditions as cardiovascular disease, diabetes, gastrointestinal disease, fibromyalgia, chronic fatigue syndrome, and musculoskeletal disorders [10]. Recent finding indicate that victims of posttraumatic stress disorder (PTSD) have higher circulating T-cell lymphocytes and lower cortisol levels, suggesting that chronic sufferers of PTSD may be at risk for autoimmune diseases. In addition, patients with comorbid PTSD were more likely to have clinically higher T-cell counts, hyper-reactive immune responses on standardized delayed cutaneous hypersensitivity tests, clinically higher immunoglobulin-M levels, and clinically lower dehydroepiandrosterone levels. The latter clinical evidence confirms the presence of biological markers consistent with a broad range of inflammatory disorders, including both cardiovascular and autoimmune diseases [15].

5.2. Rheumatoid arthritis as an example of a stress-related disease

Stress is now recognized as an important risk factor in the pathogenesis of autoimmune rheumatic diseases, including. rheumatoid arthritis (RA). 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 [17]. The quality of the relationship between the patient and his family, along with other social factors, were found to be useful prognostic factors in patients with RA [18]. Coping strategies are important for the daily routine and for the psychological well-being of chronic patients. They enable the patient to adapt to the 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 [13,17,18].

Table 1
Factors predicting autoimmune disease

Changeable factors	Unchangeable factors
Psychological stress	
Infection	Genetic
Vaccination	Hormonal
Smoking	Immune deficiency state
Obesity	Gender
Ultraviolet light exposure	
Drugs	

6. Stress management and behavioral intervention

New disciplines like neuroendocrinoimmunology aim to better understand the role of stress in disease pathogenesis, and to develop improved treatment methods for autoimmune diseases [14]. 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 [16,19]. 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 (Table 1).

Several non-randomized small-scale studies suggest that autoimmune disease could be prevented if treated aggressively prior to manifestations of symptoms [2,5]. However, in order to better understand the utility of preventive treatment, patient selection criteria must be normalized: only patients who are relatively more likely to develop clinical disease should be treated while still asymptomatic. Individuals who are at risk to develop an autoimmune disease should be advised to refrain from lifestyle and activities that endanger their future health and quality of life [5,16]. Different stress reactions should be discussed with autoimmune patients, and obligatory questionnaires about trigger factors should include psychological stress in addition the usual suspects such as infection and trauma. We refer to a variety of additional works on other autoimmune diseases which reflect the concept of the Mosaic [20–40].

Take-home messages

- Stress is considered to be a risk factor of several diseases. It is very important to both understanding the effects of stress on our body, and to develop effective stress management techniques.
- The exact role of stress in the pathogenesis of autoimmune diseases should be clarified by prospective studies with both clinical and immunoserological focus.
- Rheumatoid arthritis has been identified as an example of a stress-related illness. Like other stress-induced or stress-aggravated illnesses, rheumatoid arthritis and some other autoimmune diseases often can be contained through a program of stress management.
- Stress affects the immune system. Different stress reactions should be discussed with autoimmune patients, and obligatory questionnaires about trigger factors should include psychological stress in addition to other common triggers.

References

[1] Shoenfeld Y, Isenberg D. The Mosaic of Autoimmunity. Research Monographs in ImmunologyAmsterdam. The Netherlands: Elsevier Science Publishers; 1989.
[2] Herrmann M, Sholmerich J, Straub RH. Stress and rheumatic disease. Rheum Dis Clin North Am 2000;26:4.
[3] Brickman CM, Shoenfeld Y. The mosaic of autoimmunity. Scand J Clin Lab Invest 2001;61(Suppl 235):3–15.
[4] Stojanovich L. Stress as a trigger of autoimmune disease. Abstracts book: 5th International Congress on Autoimmunity, Sorrento, Italy. Autoimmun Rev 2006:355.
[5] Shepshelovich D, Shoenfeld Y. Prediction and prevention of autoimmune diseases: additional aspects of the mosaic of autoimmunity. Lupus 2006;15:183–90.
[6] Huerta PT, Kowal C, DeGiorgio L, et al. Immunity and behavior: antibodies alter emotion. PNAS 2006;103:678–83.
[7] Selye H. The story of the Adaptation Syndrome. Montreal: Acta Inc.; 1952.
[8] Selye H. The Stress of life. New York: McGraw-Hill; 1956.
[9] Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. BMJ 2006;332:521–4.
[10] Black PH. The inflammatory response is an integral part of the stress response: implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. Brain Behav Immun 2003;17(5):350–64.
[11] Chida Y, Sudo N, Kubo C. Social isolation stress exacerbates autoimmune disease in MRL/lpr mice. J Neuroimmunol 2005;158(1–2):138–44 Jan.
[12] Wolfe F. Psychological distress and rheumatic disease. Scand J Rheumatol 1999;28(3):131–6.
[13] Persson LO, Berglund K, Sahlberg D. Psychological factors in chronic rheumatic diseases-a review. The case of rheumatoid arthritis, current research and some problems. Scand J Rheumatol 1999;28(3):137–44.
[14] Frieri M. Neuroimmunology and inflammation: implications for therapy of allergic and autoimmune diseases. Ann Allergy, Asthma, & Immun 2003;90(6 Suppl 3):34–40.
[15] Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Ann N Y Acad Sci 2004;1032:141–53.
[16] Kozora E, Ellison MC, Waxmonsky JA, Wamboldt FS, Patterson TL. Major life stress, coping styles, and social support in relation to psychological distress in patients with systemic lupus erythematosus. Lupus 2005;14(5):363–72.
[17] Cuolo M, Straub RH. Stress as a risk factor in the pathogenesis of rheumatoid arthritis. Neuroimmunomodulation 2006;13(5-6):277–82.
[18] Hutchins J, Erkan D, Yazici Y, Robbins L. Patients' perspective of autoimmune diseases» in Abstract book from 7th Intern Congress of SLE, NY; 2004. M 14A.
[19] Herrmann M, Scholmerich J, Straub RH. Stress and rheumatic diseases. Rheum Dis Clin North Am 2000;26(4):737–63 Nov.
[20] Adamus G, Webb S, Shiraga S, Duvoisin RM. Anti-recoverin antibodies induce an increase in intracellular calcium, leading to apoptosis in retinal cells. J Autoimmun 2006;26:146–53.
[21] Alper CA, Husain Z, Larsen CE, Dubey DP, Stein R, Day C, Baker A, Beyan H, Hawa M, Ola TO, Leslie RD. Incomplete penetrance of susceptibility genes for MHC-determined immunoglobulin deficiencies in monozygotic twins discordant for type 1 diabetes. J Autoimmun 2006;27:89–95.
[22] Alvarado-Sanchez B, Hernandez-Castro B, Portales-Perez D, Baranda L, Layseca-Espinosa E, Abud-Mendoza C, et al. Regulatory T cells in patients with systemic lupus erythematosus. J Autoimmun 2006;27:110–8.
[23] Anaya JM, Castiblanco J, Tobon GJ, Garcia J, Abad V, Cuervo H, et al. Familial clustering of autoimmune diseases in patients with type 1 diabetes mellitus. J Autoimmun 2006;26:208–14.
[24] Aoki CA, Roifman CM, Lian ZX, Bowlus CL, Norman GL, Shoenfeld Y, et al. IL-2 receptor alpha deficiency and features of primary biliary cirrhosis. J Autoimmun 2006;27:50–3.
[25] Asherson RA. New subsets of the antiphospholipid syndrome in 2006: "PRE-APS" (probable APS) and microangiopathic antiphospholipid syndromes ("MAPS"). Autoimmun Rev 2006;6:76–80.
[26] Barral AM, Thomas HE, Ling EM, Darwiche R, Rodrigo E, Christen U, et al. SOCS-1 protects from virally-induced CD8 T cell mediated type 1 diabetes. J Autoimmun 2006;27:166–73.
[27] Chuang YH, Lian ZX, Tsuneyama K, Chiang BL, Ansari AA, Coppel RL, et al. Increased killing activity and decreased cytokine production in NK cells in patients with primary biliary cirrhosis. J Autoimmun 2006;26:232–40.
[28] Eisenlohr LC, Rothstein JL. Oncogenic inflammation and autoimmune disease. Autoimmun Rev 2006;6:107–14.
[29] Erkan D. Therapeutic and prognostic considerations in catastrophic antiphospholipid syndrome. Autoimmun Rev 2006;6:98–103.
[30] Konttinen YT, Porola P, Konttinen L, Laine M, Poduval P. Immunohistopathology of Sjogren's syndrome. Autoimmun Rev 2006;6:16–20.
[31] Mandler RN. Neuromyelitis optica — Devic's syndrome, update. Autoimmun Rev 2006;5:537–43.
[32] Mosca M, Tani C, Neri C, Baldini C, Bombardieri S. Undifferentiated connective tissue diseases (UCTD). Autoimmun Rev 2006;6:1–4.
[33] Oyarbide-Valencia K, van den Boorn JG, Denman CJ, Li M, Carlson JM, Hernandez C, et al. Therapeutic implications of autoimmune vitiligo T cells. Autoimmun Rev 2006;5:486–92.

[34] Rahbar A, Bostrom L, Soderberg-Naucler C. Detection of cytotoxic CD13-specific autoantibodies in sera from patients with ulcerative colitis and Crohn's disease. J Autoimmun 2006;26:155–64.
[35] Rieger R, Leung PS, Jeddeloh MR, Kurth MJ, Nantz MH, Lam KS, et al. Identification of 2-nonynoic acid, a cosmetic component, as a potential trigger of primary biliary cirrhosis. J Autoimmun 2006;27:7–16.
[36] Rivadeneyra-Espinoza L, Ruiz-Arguelles A. Cell-penetrating anti-native DNA antibodies trigger apoptosis through both the neglect and programmed pathways. J Autoimmun 2006;26:52–6.
[37] Rotstein Z, Hazan R, Barak Y, Achiron A. Perspectives in multiple sclerosis health care: special focus on the costs of multiple sclerosis. Autoimmun Rev 2006;5:511–6.
[38] Rovensky J. Asherson's syndrome — catastrophic antiphospholipid syndrome. Autoimmun Rev 2006;6:61–3.
[39] Rovensky J. Rheumatic diseases and Klinefelter's syndrome. Autoimmun Rev 2006;6:33–6.
[40] Sisto M, Lisi S, Castellana D, Scagliusi P, D'Amore M, Caprio S, et al. Autoantibodies from Sjogren's syndrome induce activation of both the intrinsic and extrinsic apoptotic pathways in human salivary gland cell line A-253. J Autoimmun 2006;27:38–49.

CD8+ T cell-mediated suppression of autoimmunity in a murine lupus model of peptide-induced immune tolerance depends on Foxp3 expression

Systemic lupus erythematosus (SLE) is an autoimmune disease caused by autoantibodies, including IgG anti-DNA. New Zealand Black/New Zealand White F(1) female mice, a model of spontaneous polygenic SLE, tolerized with artificial peptide (p Consensus) based on anti-DNA IgG sequences containing MHC class I and class II T cell determinants, develop regulatory CD4+CD25+ T cells and CD8+ inhibitory T cells (CD8+ Ti), both of which suppress autoantibody production. CD8+ Ti inhibit primarily via secretion of TGF-beta. In the present study, Singh RP. et al. (J Immunol 2007; 178: 7649-57) show that the inhibitory function of CD8+ T cells from tolerized mice is sustained for up to 8 wk and at all times depends on expression of Foxp3. Both CD28-positive and CD28-negative CD8+ T cells contain inhibitory cells, but the expression of mRNA for Foxp3 and for TGF-beta is higher and lasts longer in the CD28-subset. In vitro addition of TGF-beta (in the presence of IL-2) induces Foxp3 expression in a dose-response manner. Gene inhibition or blockade with small interfering RNA of Foxp3 abrogates the ability of CD8+ Ti to inhibit anti-DNA production and proliferation of CD4+ Th cells. Moreover, a significant correlation between expression of Foxp3 and ability of CD8+ Ti to secrete TGF-beta is observed. Therefore, CD8+ Ti in this system of tolerance are similar to CD4+CD25+ regulatory T cells in their dependence on expression of Foxp3, and there may be a bidirectional Foxp3/TGF-beta autocrine loop that determines the ability of CD8+ T cells to control autoimmunity.

TLR9 stimulation drives naïve B cells to proliferate and to attain enhanced antigen presenting function

Mechanisms that regulate naïve B cell proliferation and function are incompletely defined. In this study, Jiang W. et al. (Eur J Immunol 2007; 37: 2205-13) test the hypothesis that naïve B cell expansion, survival and ability to present antigen to T lymphocytes can be directly modulated by Toll-like receptor (TLR) agonists. In the absence of B cell receptor stimulation, CpG oligonucleotide, a TLR9 agonist, was particularly efficient in inducing naïve B cell proliferation and survival. Although the expanded naïve B cells did not mature into CD27+ or IgG+ memory B cells, these cells did differentiate into IgM-secreting cells with increased surface expression of HLA-DR and CD40 and CD8. This was associated with an increased potential for these B cells to activate allogenic T cells. Thus, it is proposed that the activation and expansion of naïve B cells induced by TLR9 agonist could enhance the potential of these cells to interact with cognate antigens and facilitate cell-mediated immune responses.