

Stress as an environmental risk factor for autoimmune diseases

Stres jako środowiskowy czynnik ryzyka chorób autoimmunologicznych

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ABSTRACT

Stress is considered to be both a trigger of autoimmune diseases and a factor which contributes to disease exacerbation. Emotional stress before the disease onset is reported by up to 80% of patients suffering from autoaggressive diseases. A significant increase in the prevalence of autoimmune diseases in recent years and the growing number of stressors in our daily lives, including the work environment, raise a question about a link between psychological stress and autoimmune disorders. Therefore, the objective of this paper is to highlight the potential role of stress in both development and exacerbation of autoimmune diseases. The potential mechanisms by which stress can affect autoimmunity are characterised. In particular, the focus is on rheumatic diseases, autoimmune endocrine disorders, multiple sclerosis, and psoriasis. In addition, the role of post-traumatic stress disorder is underlined, as well as the possible association between stress present in the work environment and the development of autoimmune diseases among employees.

Key words: autoimmune diseases, psychological stress, risk factor

STRESZCZENIE

Stres jest uważany zarówno za czynnik spustowy dla chorób autoimmunologicznych jak i przyczyniający się do ich zaostrzenia. Stres emocjonalny, występujący przed pojawieniem się choroby, zgłasza nawet do 80% pacjentów cierpiących na choroby z autoagresji. Znaczący wzrost zachorowalności na choroby autoimmunologiczne oraz rosnąca liczba czynników stresogennych w naszym codziennym życiu, w tym w środowisku pracy, stawia pytanie o związek pomiędzy stresem psychicznym a chorobami autoimmunologicznymi. Dlatego też celem artykułu jest naświetlenie możliwej roli stresu w rozwoju i zaostrzeniach chorób autoimmunologicznych. Scharakteryzowano potencjalne mechanizmy, za pomocą których stres może oddziaływać na autoimmunizację. W szczególności skupiono się na chorobach reumatologicznych, zaburzeniach endokrynologicznych, stwardnieniu rozsianym oraz łuszczycy. Dodatkowo podkreślono rolę stresu pourazowego jak i możliwych związków pomiędzy stresem w środowisku pracy a rozwojem chorób autoimmunologicznych wśród pracowników.

Słowa kluczowe: choroby autoimmunologiczne, stres psychologiczny, czynnik ryzyka

INTRODUCTION

A significant increase in the incidence of autoimmune diseases in recent years and the simultaneously growing number of stressors in our daily lives raise a question about a link between psychological stress and autoimmune disorders [1]. The exposure to stressors in the surrounding environment is undeniable, and is connected with a wide range of factors present in home and work environments. Several retrospective studies have found that up to 80% of patients report uncommon emotional stress before the disease onset [2]. Stress is considered to be not only a trigger of autoimmune diseases but also a factor which contributes to disease exacerbation [3].

The term *stress* was defined for the first time by Hans Selye in 1936 as a *nonspecific response of the body to any demand made upon it*. Selye also described the role of the hypothalamus-pituitary-adrenal system in coping with stress [3]. Although many studies have focused on the mechanisms by which stress affects autoimmune diseases, they still remain not fully understood. So far, it is believed that two main stress-related mediators – glucocorticoid hormones and catecholamines – may interfere with the function of the immune system and, as a result, lead to autoimmune disease development. Noteworthy are the results of studies showing that probably there is an association between early childhood stressors and the development of autoimmune diseases in adulthood [4]. These findings suggest that childhood stressful life events may increase the risk of autoimmunity independently or amplify the effect of other environmental factors [4].

The objective of this paper is to highlight the role of psychological stress in both triggering and exacerbating autoimmune response and to discuss the potential mechanisms by which stress can affect autoimmunity. Suggested correlation between stressors and autoimmunity calls for improving the ways of stress prevention and management in patients with autoimmune disorders.

MECHANISMS

The adaptive response of the organism to stressors of any kind focuses on maintaining physiological homeostasis. Several studies on animal and human models have demonstrated that stress affects the immune system both directly and indirectly by the activation of the nervous and endocrine systems [2, 5]. Presumably these interactions contribute to im-

mune dysregulation and altered or amplified cytokine production, resulting in development of autoimmune diseases [3, 5].

The most important transmitter substances identified as components of neuroendocrine-immune network include adrenaline, noradrenaline, acetylcholine, substance P, vasoactive intestinal peptide, insulin, glucagon, cytokines, and growth factors [3]. The immune response to stressors, via the major stress hormones catecholamines and glucocorticoids, results in changes in the regulation of cytokines production. It suppresses the production of proinflammatory cytokines, such as interleukin (IL)-12, tumor necrosis factor (TNF)- α , and interferon (IFN)- γ , and stimulates the production of antiinflammatory cytokines, such as interleukin (IL)-10, IL-4, and transforming growth factor (TGF)- β . Glucocorticoids also affect the balance between T *helper* (Th) lymphocyte subclasses – Th1 and Th2 – which are components of acquired (adaptive) immunity [6]. Another suggested mechanism by which stress may act is through regulation of telomerase and telomere length in T-cells. In patients with rheumatoid arthritis, accelerated telomere attrition in CD41 T-cells has been reported [7].

Repeated episodes of acute or chronic psychological stress can induce immune inflammatory response and contribute to the onset of specific diseases and premature death [3]. Epidemiological studies reveal the connection between traumatic stress exposure and diabetes, cardiovascular and gastrointestinal diseases, fibromyalgia, chronic fatigue syndrome, and musculoskeletal disorders [1, 3].

ASSOCIATION BETWEEN STRESS AND AUTOIMMUNE DISORDERS

Several studies focusing on the relationship between stress and the development of autoimmune diseases have so far been performed. The assessment of stressful events in the premorbid period was primarily conducted with the use of self-rating questionnaires or semi-structured interviews. However, not all the studies confirmed a clear relation between stressors and autoimmune diseases [5, 8]. Although stress may have an impact on the majority of autoimmune diseases, in this article the focus is on rheumatic diseases, autoimmune endocrine disorders, multiple sclerosis, and psoriasis. In addition, the role of post-traumatic stress disorder is underlined, as well as the possible association between occupational stress and the development of autoimmune diseases among employees.

Rheumatic diseases

The results of research investigating the links between stress and rheumatic diseases remain conflicting [8]. In a study conducted by Stojanovich, patients with rheumatoid arthritis, systemic lupus erythematosus, and primary antiphospholipid syndrome completed a questionnaire about different stressors which occurred prior to the onset or exacerbation of their disease [2]. The most frequently indicated types of stress which contributed to prolonged anxiety were sickness or death in the family, financial problems, loss of job, or unstable political situation. Patients with systemic lupus erythematosus selected stress in 75.8% of the cases, more often than other known triggers, such as smoking (46.8%) and family history (21.3%) [2]. Over 40% of patients with rheumatoid arthritis and primary antiphospholipid syndrome considered prolonged stress to be the lead cause of their disease [2]. The research carried out by Stewart et al. in New Zealand with the use of the Schedule of Recent Experiences Questionnaire demonstrated that the group of patients with rheumatoid arthritis seropositive for rheumatoid factor had significantly higher scores than the group of seronegative patients or healthy controls [5]. By contrast, the results of a study conducted by Currence et al. in the UK did not reveal more stressful events prior to the onset of symptoms in patients with rheumatoid arthritis than in a group of healthy controls [5]. On the other hand, several studies investigated the role of stress in the exacerbation of a disease and demonstrated that stress can modulate the disease activity and, in particular, that minor stressors may increase rheumatoid arthritis symptoms [8].

Diabetes mellitus (DM)

The role of stressful events in patients diagnosed with type I (autoimmune) and type II (non-autoimmune) diabetes was the focus of a study carried out by Linn et al. in the US. The data obtained with the use of Holmes and Rahe Social Readjustment Scale showed that the group of patients with DM type I reported a significantly higher number of stressful events in the 6 months before the diagnosis than the group with DM type II and a healthy control [9]. However, research conducted by Häggglöf et al. in Sweden did not confirm this observation, as a group of children with DM type I did not report significantly more stressful events in the 12 months before the diagnosis than a control group of children of the same age [10]. Similarly, Nygren et al. failed to show the association between psychological stress in the family during the child's early life and the risk of childhood DM type 1 [11].

Autoimmune thyroid disease (AITD)

The risk factors for the autoimmune diseases of the thyroid gland are both genetic and environmental. It is estimated that the genetic factors account for about 70% of the risk to contract AITD, while the remaining 30% is supposed to be connected with the environmental factors, which include stress [12]. The increased levels of glucocorticoids and catecholamines and a shift toward Th2 mediated humoral immunity caused by stress may promote the development of Grave's disease. Alternatively, a hypoactive hypothalamus-pituitary-adrenal axis may lead to a predominantly Th1-mediated immunity, which may promote thyroid cell destruction and Hashimoto's thyroiditis [12].

The assessment of the relation between stressful events in the last 12 months and positivity for thyroid peroxidase antibodies (anti-TPO) in a large sample of women demonstrated no significant differences in the number of stressful events between women positive and negative for anti-TPO [13]. Similarly, studies conducted by Effraimidis et al. showed no differences in exposure to stress between subjects who developed or did not develop anti-TPO. In the same research, no differences were observed in stress questionnaires between hyper-/hypothyroid cases and controls at any time point [12].

Multiple sclerosis (MS)

The assessment of the association between non-traumatic stressful life events and an increased risk of multiple sclerosis exacerbation was the aim of Mohr et al.'s meta-analysis of 14 empirical studies [14]. Their results support the hypothesis that stress is related to the exacerbation of MS [14]. Similarly, Mitsionis et al.'s findings indicate that stress may contribute to the progression of MS [15]. The impact may vary according to duration, frequency, severity, and the type of stress, the patient's optimism, perceived social support, and coping strategies [2].

Psoriasis

Psoriasis is a chronic disease of the skin in which stress is a well-known triggering factor. Psychological stress contributed to the onset or exacerbation of psoriasis in approximately 40-80% of cases [16]. Devrimci-Ozguven et al. conducted a study in which 68% of psoriatic patients recalled a psychologically stressful event in the last three months prior to the onset of the disease, and 88% declared that new lesion formation was related to psychological stress [16]. Similarly, Simonić et al. found that patients diagnosed with psoriatic arthritis re-

ported stressful events during childhood and adolescence more frequently than a control group without arthritis [5].

POST-TRAUMATIC STRESS DISORDER (PTSD)

A large study of Iraq and Afghanistan veterans indicates that PTSD is associated with an increased risk for autoimmune disorders, such as thyroiditis, rheumatoid arthritis, inflammatory bowel disorders, multiple sclerosis, and lupus erythematosus. The results presented by O'Donovan et al. showed that veterans with PTSD had twice the risk of being diagnosed with an autoimmune disorder compared to those without any psychiatric disorders [17].

OCCUPATIONAL STRESS AND AUTOIMMUNITY

Noteworthy is the potential role of occupational stress in increasing the risk of autoimmunity. Stressors may originate in the work environment as a result of the type of job, work overload, shift work, repetitive work without gratification or promotion perspectives, or insufficient social support [18]. These elements may contribute to chronic stress among employees and its health consequences. For instance, shift work has a significant impact on workers' health, primarily due to sleep restriction and circadian disruption [19]. A study conducted by Magrini et al. in a large hospital in Italy revealed that the prevalence of subclinical autoimmune hypothyroidism among shift workers was nearly double in comparison to day-time workers [20]. Similarly, the isolated increase of anti-TPO antibodies level, a risk factor for the development of AITD, was significantly higher in shift workers than in day-time workers [20]. Night-shift workers are also at an increased risk of developing multiple sclerosis [19] or systemic lupus erythematosus [21]. In addition, occupational factors, such as anxiety, job strain, and insecurity, may increase the risk of autoimmunity among workers due to the reduction of the NK cells activity [22].

CONCLUSIONS

The pathogenesis of autoimmune diseases is multifactorial, resulting from the interaction between genetic predisposition and environmental factors, such as nutrition, infection, chemicals, and stress. Therefore, the approach to autoimmune diseases

should be multidimensional as well. The data presented above demonstrate that stress is a risk factor for the onset or exacerbation of many autoimmune diseases. Despite the fact that many studies have focused on the mechanisms by which stress affects autoimmune disorders, they are still not fully understood. Behavioral intervention and the development of stress management techniques require further investigation as a part of therapy of stress-induced or stress-aggravated illnesses and other autoimmune diseases [2, 3]. Although stress management alone would not induce remission of the disease, combining the implementation of stress management techniques with pharmacotherapy may result in decreasing the need for medications and thus reduce side effects of treatment.

It is worth pointing out that the role of psychological factors in the autoimmunity development is difficult to investigate because of several, mainly methodological, issues. First of all, there are no objective measures for psychological stress, and all studies are based on self-reported questionnaires. The subjective feeling of stress can vary depending on many factors, such as age, sex, or socio-epidemiological factors. For instance, stressful life events can have a more limited impact on the development of autoimmune diseases in females than in males, due to sex-related hormonal factors [5]. Moreover, there is no evidence from large prospective studies that would support the association between stressful life events and autoimmune diseases. Further study is required to better understand the role of stress in autoimmunity.

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