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Environmental risk factors in autoimmune diseases: a review of literature

Środowiskowe czynniki ryzyka w chorobach autoimmunologicznych: przegląd piśmiennictwa

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ABSTRACT

Autoimmune diseases are a very common group of disorders, with prevalence rate over 5%–8% in the general population. The etiology of autoimmune diseases is very complex. It is considered that they are caused by a combination of several factors, such as pathological response of the immune system, hormones, genetic factors and environmental influence. It is assumed that an increase in the incidence of autoimmune diseases may be associated with growing exposure to environmental factors. Many environmental determinants may play an important role in triggering the autoimmune response. Identification and better knowledge of environmental risk factors could lead to better prevention and control of autoimmune diseases in the future. This paper is a literature overview concerning the role of environmental factors in the development of autoimmune diseases.

Key words: autoimmune diseases, environment, risk factors

STRESZCZENIE

Choroby autoimmunologiczne są rozległą grupą schorzeń, z częstością występowania od 5 do 8% w populacji ogólnej. Etiologia chorób autoimmunologicznych jest bardzo złożona. Uważa się, że są one spowodowane kombinacją kilku czynników, takich jak nieprawidłowa odpowiedź układu immunologicznego, hormonów, czynników genetycznych oraz wpływu środowiska. Zakłada się, że wzrost częstości występowania chorób autoimmunologicznych może wiązać się z rosnącym narażeniem na czynniki środowiskowe. Wiele czynników wpływających na środowisko może odgrywać ważną rolę w wywoływaniu odpowiedzi autoimmunologicznej. Identyfikacja i lepsza znajomość środowiskowych czynników ryzyka mogłaby prowadzić do lepszej profilaktyki i kontroli chorób autoimmunologicznych w przyszłości. W pracy przedstawiono przegląd literatury dotyczącej roli czynników środowiskowych w rozwoju chorób autoimmunologicznych.

Słowa kluczowe: choroby autoimmunologiczne, środowisko, czynniki ryzyka

INTRODUCTION

Autoimmune diseases are a large group of disorders involving pathological reaction of the immune system against the body's own cells and tissues [1].

The essence of autoimmunity is a disruption of immunological tolerance. Immunological tolerance is a group of controlling and suppressor mechanisms thanks to which the human body does not mount an immune response against its own cells. Disruption of this process leads to the situation in which the immune system attacks its own antigens and destroys healthy tissues [2].

There are over 80 different known types of autoimmune diseases. Among them there are more common diseases, such as rheumatoid arthritis, insulin dependent diabetes mellitus, systemic lupus erythematosus, thyroiditis and multiple sclerosis as

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well as some rare diseases, such as systemic sclerosis, Wegener's granulomatosis, or Sjögren's syndrome [3, 4]. These disorders can be classified into two general groups: organ specific autoimmune diseases (i.e., Graves' disease, type 1 diabetes, autoimmune thyroid disease, and multiple sclerosis) and systemic autoimmune diseases (i.e., systemic lupus erythematosus and scleroderma) [5, 6].

Autoimmune diseases are very common, with prevalence rate over 5%-8% in the general population and with a 3:1 female predominance [5, 7, 8]. It is assumed that an increase in the incidence of autoimmune diseases may be associated with growing exposure to environmental factors [9,10].

Despite the strong association with the genetic predisposition and familial history, the importance of the role of environmental factors and gene-environment interaction in the etiology of autoimmune disorders has been confirmed in numerous monozygotic twin studies. These studies show differences in the concordance for autoimmune diseases in monozygotic twins. They also indicate that the diseases which appear in childhood (i.e., diabetes mellitus type I) occur more frequently in both twins than autoimmune diseases that develop in the later years of life (i.e., rheumatoid arthritis), which more often develop in only one twin. The discrepancy in the occurrence rate of autoimmune diseases among identical twin pairs may suggest that environmental factors also play an important role in the development of autoimmunity [11-15].

Although there is no one specific cause of autoimmune diseases, it is considered that the development of autoimmune disorders is a result of complex interactions of genes and environmental factors. The role of environmental factors in the pathogenesis of autoimmune disorders is very important as they may: trigger the autoimmune reaction in the genetically predisposed human body, trigger both pro- and anti-inflammatory activities, and modulate immune response [16, 17].

Among triggers caused by environmental factors, the following mechanisms are mentioned: DNA methylation, citrullination of proteins which are transformed into autoantigens, HSP90 activation, production of pro-inflammatory interleukins, and increased production of ROS [18].

Studies of the effects of environmental exposure in humans are difficult to perform because of many limitations, such as individual genetic predisposition, long latency period - often with many years or decades between exposure and first symptoms of disease - and exposure to various environmental factors that may interact with each other [16, 17].

DIET

Diet has a major impact on human health. Increasing urbanization and industrialization over the years have caused significant changes in lifestyle and diet. The potential link between diet and autoimmune diseases is suggested by the coincidence of a recent increase in both: the number of autoimmune disorders and the consumption of high processed food. There are several nutritional factors that may play an important role in the autoimmune response development, such as fatty acids, cow's milk, gluten, iodine excess, vitamin D deficiency, or obesity [9].

Fatty acids

Worth noting is the role of fatty acids - mainly omega-6 and omega-3 - in systemic inflammation. Omega-3 and omega-6 fatty acids are considered to be essential because the body does not produce them, they are provided only with food, and they have divergent impact on the human immune system. Linoleic acid, an omega-6 fatty acid contained in the seeds of most plants, is a precursor of pro-inflammatory prostaglandins which may cause an immune response. By contrast, three main types of omega-3 fatty acids - -linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) contained, inter alia, in fish oil - have anti-inflammatory effect. Both the omega-3 and omega-6 fatty acids compete for the same enzymes in the production of prostaglandins, so a proper balance between omega-6 and omega-3 in daily diet seems to be very important in protection against chronic inflammation, one of the underlying mechanism for autoimmunity [19].

There are several studies that indicate a link between the increasing prevalence of autoimmune diseases and the Western diet. For example, Tjonneland et al. conducted a case-control study within a European prospective cohort study, which revealed that a high intake of dietary linoleic acid, an n-6 polyunsaturated fatty acid, increased the risk of ulcerative colitis ((OR) = 2.49, 95% confidence interval (CI) = 1.23 to 5.07, p = 0.01) [20].

Similarly, a recent study conducted by Niinistö et al., which consisted in the evaluation of data gathered between 1997-2004 on 7782 infants genetically predisposed to the type 1 diabetes, revealed that high serum levels of n-3 fatty acids - docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) - were associated with a lower risk of insulin autoimmunity [21]. A study performed by Xinyun et al. using a mouse model also confirms these findings [22].

Cow's milk

Cow's milk, especially as a component of children's daily diet, is one of the major dietary controversies nowadays. According to current studies, early cow's milk intake and shorter breastfeeding duration may be associated with an increased risk of autoimmune disorders - primarily with type 1 diabetes [23-26].

A prospective study of 1835 American children at increased genetic risk for type 1 diabetes mellitus found that greater consumption of cow's milk was associated with the β-cell autoimmunity and later type 1 diabetes development [26]. The association between cow's milk intake during childhood and autoimmune diseases was the subject of a population-based control study which revealed an increased prevalence of insulin-dependent diabetes mellitus in children exposed to cow's milk during first months of life. According to this study, breastfeeding for 7 months and exclusive breastfeeding for 3 months were associated with a smaller prevalence of type 1 diabetes among children [27].

In case-control study conducted in Brazil, Alves et al. compared breastfeeding duration in 123 children with type 1 diabetes mellitus and their unaffected siblings. The results of this study showed that children with diabetes mellitus type 1 had an earlier introduction of cow's milk and were breastfed shorter than controls [28].

The results of the study performed by Hyppönen et al. also suggest that early introduction (before or at 3 months of age) of cow's milk formula-feeding and faster growth in infancy are associated with an increased risk of type 1 diabetes in childhood [29].

On the other hand, not all studies indicate an association between early exposure to cow's milk proteins and risk for type 1 diabetes mellitus. The results obtained by Couper et al. did not confirm an increased risk of type 1 diabetes in children who were exposed to cow's milk very early in infancy. In addition, according to this study, the duration of breastfeeding did not appear to be associated with the development of type 1 diabetes [30, 31].

The divergence of the results of these and other studies may be due to differences in study group selection or in the genetic predisposition of the study population. A better understanding of the association between cow' s milk intake and autoimmune disorders requires further study.

Obesity

Obesity is defined as an abnormal accumulation of fat tissue in the human body. According to the World Health Organization (WHO), in 2014 more than 1.9 billion adults were overweight, and over 600 million of these were obese [32].

There are many literature data concerning the association between obesity and the risk of developing autoimmune conditions. Obesity and overweight can be involved in autoimmune pathogenesis through several mechanisms. First of all, adipose tissue is an active endocrinal organ, able to produce many bioactive peptides - called adipokines. Adipokines are a large, heterogeneous group of proteins, such as leptin, adiponectin, resistin, and many more, which take part in stimulation of the production of major pro-inflammatory cytokines, such as IL-6, TNF-alfa, and IL-1, that are involved in the pathogenesis of rheumatic diseases [33, 34].

The association between adipokines and autoimmune diseases was also a subject of a study conducted by Chung et al., who noticed higher concentrations of three main adipokines: leptin, adiponectin and resistin in patients with systemic lupus erythematosus (SLE) [35].

Versini et al. performed a review analysis of data provided by 329 international studies investigating the relationship between obesity and autoimmune disorders, like rheumatoid arthritis, multiple sclerosis, type-1 diabetes, psoriasis, inflammatory bowel disease, psoriatic arthritis, and Hashimoto thyroiditis. The authors focused on the role of obesity and adipokines in promotion of systemic autoimmunity. Their research indicates that obesity is associated with an increased risk of rheumatoid arthritis (OR = 1.2–3.4), psoriasis and psoriatic arthritis (OR = 1.48–6.46), and multiple sclerosis (OR = 2). The possible link between obesity and autoimmune disorders may lie in a higher accumulation of white adipose tissue – an active endocrinal organ – and as a consequence, increased secretion of adipokines [36].

Vitamine D

There are numerous studies investigating the association between vitamin D3 deficiency and autoimmunity [37–39]. It is considered that Vitamin D deficiency plays a role in the pathogenesis of several autoimmune diseases, such as: rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, multiple sclerosis, type 1 diabetes, and autoimmune thyroid diseases [40].

Apart from the well-known role in calcium, phosphate, and bone homeostasis, Vitamin D plays a significant role in other body functions, especially in the immune system. The potential role of Vitamin D in the regulation of immune responses and its protective effect result from the inhibition of se-

cretion of Th1 and Th17 cells - thought to be pathogenic in autoimmune diseases - and stimulation of secretion of Th2 and Treg cells, suppressive for immune response and reducing the generation of proinflammatory cytokines IL-1, -2, -6, -12, -17, or TNF α [41].

In a meta-analysis comprising 15 studies on 1143 patients with rheumatoid arthritis and 963 controls in total, Lee et al. conclude that vitamin D level was significantly lower in the rheumatoid arthritis group than in controls [42]. Kamen et al. analyzed data from a population-based study of 123 patients with recently diagnosed systemic lupus erythematosus and 240 controls. As in the case of rheumatoid arthritis, the results of this study revealed lower blood level of Vitamin D in SLE patients compared to controls [43].

Expanding our knowledge of the role of Vitamin D in autoimmunity and its potential therapeutic effect can be useful in both: prevention and treatment of autoimmune diseases.

Iodine excess

The increasing incidence of one of the most common autoimmune disease, Hashimoto's thyroidtitis, raises the question of the potential role of iodine excess as an environmental risk factor. Iodine is the main component of the thyroid hormones and is necessary for proper thyroid function. Its dietary supplementation (mainly by salt iodization) is commonly used to prevent iodine deficiency and hypothyroidism. However, some studies indicate that iodine excess (MUIE>300 μg/l) may be a risk factor for autoimmune thyroid disease development - mainly Hashimoto's thyroidtitis [44-46]. Although the exact mechanism of iodine-induced Hashimoto's thyroiditis is unknown, it is postulated that iodine excess can induce oxidative stress of thyrocytes, causing their damage and subsequently leading to the autoimmune response [45].

In their cross-sectional study in China, Teng et al. compared the prevalence of hypothyroidism and autoimmune thyroiditis in two groups from two different regions of China. This study showed that the areas with excessive iodine intake had a higher incidence of autoimmune thyroiditis compared to regions with normal iodine exposure [47].

These findings are similar to the results of a recent study on children in South India, which also revealed an association between iodine excess and autoimmune thyroiditis. The study compared levels of urinary iodine between 43 children with autoimmune thyroiditis and 43 controls. The results showed an increased levels of urinary iodine among children with autoimmune thyroiditis in comparison to the control group [48].

CHEMICALS

The increased incidence of autoimmune disease in developed societies over the last 30 years is believed to be due to the growing number of chemicals that have been widely used in industrial agriculture throughout the world during the last 50 years [9, 49].

One of the theories of potential association between chemicals and autoimmune disorders suggests that through binding to the tissues of the human body, chemical substances may cause formation of neoantigens. This modification of healthy tissues may result in the immune response against neoantigens and healthy tissue damage [18].

Pesticides

In the discussion of chemicals, it is worth to point out the role of pesticides, one of the main source of toxins in our environment. Because of a large variety of pesticides used in agriculture, exposure to these chemicals is considered as an important environmental threat to human health, including the risk of autoimmune diseases.

According to the study of 76,861 post-menopausal women performed by Parks et al., there is an association between insecticide exposure and the risk of autoimmune rheumatic disease. The study shows that the use of insecticides increases the risk of two autoimmune diseases: rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) compared to women who have never used pesticides. It also suggests that the greater risk of autoimmune rheumatic disease is associated with a long-term exposure to pesticides [50].

BPA

Bisphenol A, widely known as BPA, is a chemical mainly used in the production of polycarbonate plastics or as an additive in other plastics from which food containers or water bottles are made. It has been demonstrated that high temperature or acidic pH of liquids may result in BPA leaching into food or beverage [51, 52]. Fax or copy paper and sale receipts can also contain BPA compounds, so dermal contact with them can lead to BPA exposure [51]. BPA is a nonsteroidal xenoestrogen which can bind to estrogen receptors and lead to agonistic or antagonistic response; it is considered to be an endocrine disruptor which influences autoimmunity development [51-53].

Studies showed that over 90% of the US population have BPA in urine samples [54]. There is no clear evidence that BPA is a risk factor for autoimmune diseases. The study conducted in the US by Lang et al. revealed the association between a higher urinary concentration of BPA and a higher prevalence of cardiovascular diseases or diabetes and no significant connection between urinary BPA level and other diseases, such as arthritis or thyroid diseases [52]. However, in vitro studies suggest that BPA can have some effect on the immune system by inhibiting the synthesis of monocyte-chemoattractant protein (MCP-1) in a tumor cell line - an effect three times greater than that of estradiol [55]. Also studies in animal models demonstrate that BPA can convert normal antigen-specific CD4+T lymphocytes into autoreactive, cytotoxic, pro-inflammatory cells that are sufficient to cause lupus-like autoimmunity [53].

There are several potential mechanisms by which BPA can affect the organism response toward autoimmunity [51]. As an environmental estrogen and a compound inhibiting DNA methylation, it has an impact on cell proliferation, cytokine production, immune signal transduction pathway alteration, and the balance between T helper lymphocyte subclasses - Th1 and Th2 [52]. Female predominance in autoimmune diseases supports the theory that sex hormones play a role in immune system modulation. Androgens are described as anti-inflammatory. Estrogens can induce both anti- and pro-inflammatory response via specific receptors for estrogens on several effector cells of the immune system [52, 55]. The connection between estrogens and autoimmunity can be illustrated by the example of systemic lupus erythematosus (SLE) and the fact that the incidence of SLE increases after puberty and decreases after menopause. The physiological fluctuations of estrogen levels depending on the menstrual cycle or pregnancy correspond to changes in the severity of the disease [52]. The quantities of estrogens were found to be higher and those of androgens lower in both female and male patients with SLE in comparison to the population without autoimmune disorders [55]. Also the SELENA trial study demonstrated that hormonal replacement therapy contributed to a mild to moderate increase in lupus flares [56].

In conclusion, further investigations are needed to establish the exact role of BPA in the development of autoimmune diseases.

Heavy metals

Exposure to various heavy metals in occupational and non-occupational environments can trigger or accelerate the development of autoimmune disorders. Several studies in animal models demonstrated that mercury (Hg), silver (Ag), or gold (Au) can induce an alteration of the immune system cells [57].

Heavy metals are known for their immunomodulatory potency, especially with respect to lymphoproliferation and alteration of the balance between Th1 and Th2, which may lead to the onset or exacerbation of autoimmune disorders. In animal models, administration of Hg or Au compounds caused Th2-associated autoimmune disorders characterized by the induction of IL-4 at the gene and protein levels, production of autoantibodies, elevation of serum IgE, and tissue injury in the form of vasculitis and arthritis. Mercury is not only a neurotoxicant but also an immunotoxicant. In animal models, Hg can contribute to both autoimmune dysfunction and immunosuppression [58]. A case control study conducted by Marie et al. revealed the impact of occupational risk factors in the development of systemic sclerosis (SSc) for antimony, cadmium, lead, mercury, molybdenum, palladium, and zinc. This study also showed that the association between SSc and occupational exposure may vary according to patients' gender. Median levels of antimony and platinum were increased in male patients with SSc; men also tended to exhibit higher median levels of cadmium and palladium [59]. Several studies analyzed the relationship between mercury exposure and the level of the thyroid antibodies: thyroglobulin antibody (TgAb) and thyroid peroxidase antibody (TPOAb). Elevated levels of thyroid autoantibodies were observed in patients with various autoimmune disorders, such as systemic lupus erythematosus, autoimmune thyroiditis, rheumatoid arthritis, fibromyalgia, and diabetes [60]. Research conducted in a non-occupationally-exposed, fish eating riverine population by Silva et al. showed that higher levels of hair mercury, which is an indicator of organic mercury exposure, were associated with detectable antinucleolar autoantibodies, biomarkers of cellular autoimmunity [61]. Results of Gallagher et al.'s study suggest that there is an association between blood mercury and thyroglobulin antibody positivity in US women [60].

The potential role of metals as trigger factors for multiple sclerosis (MS) has also been discussed. Madeddu el al. assessed the concentration of Al, Cd, Cu, Fe, Mn, Pb, and Zn in the cerebrospinal fluid (CSF) of 29 MS patients and 22 controls. However, the mean values of metals were found to be similar in the group of patients with MS and the control group [62].

Cigarette smoking

Cigarette smoking is one of the main civilization problems. A large number of studies have shown that cigarette smoking may be one of the important environmental risk factors for autoimmune diseases, especially for rheumatoid arthritis.

The role of cigarette smoking in aetiopathology of rheumatoid arthritis (RA) and its influence on the immunological system are unknown. Studies aiming to explain this correlation have proposed several mechanisms. The effect of tobacco smoking on the autoimmune response may be related to the higher level of pro-inflammatory cytokines, DNA methylation, or an increased oxidative stress in the body. It is also presumed that smoking is related to an increased protein citrullination. Citrullination of proteins is a process in which the amino acid arginine in a peptide is converted into the amino acid citrulline. This mechanism may trigger an autoimmune response by inducing production of antibodies against citrullinated proteins, which are considered to be major diagnostic factors for RA [63, 64].

Di Giuseppe et al.'s meta-analysis focused on the association between the lifelong exposure to smoking and the risk of rheumatoid arthritis (RA). This study based on data from 3 prospective cohorts and 7 case-control studies (in total 4,552 cases of rheumatoid arthritis). The authors conclude that lifelong smoking is positively associated with the risk of rheumatoid arthritis. According to this study, the risk of developing RA was increased by 26% for smokers with low lifelong exposure (less than 10 pack-years) and twice as high for higher lifelong exposure to smoking (more than 20 pack-years). The results of this study also revealed that still higher exposure to smoking (>20 pack-years) did not further increase the risk of developing RA [65].

The association between tobacco smoking and systemic lupus erythematosus (SLE) is less established. There are numerous studies suggesting an association of cigarette smoking with SLE, but the exact role of smoking in the etiology of SLE is not sufficiently known [66-70].

A meta-analysis of the association between smoking and SLE, including data from 9 studies, revealed a higher risk for the development of SLE among active smokers compared to non-smokers (OR 1.50, 95% CI 1.09-2.08). It is important to point out that there was no such association for ex-smokers in comparison to those who had never smoked, a finding that may indicate that current smoking is a more important risk factor for SLE development in comparison to former smoking [66].

Another case-control study of 150 SLE patients and 300 controls from Nottingham in the United Kingdom performed by Hardy et al. also confirms these findings [67].

Another group of disorders which may be related to cigarette smoking are autoimmune thyroid diseases. It is considered that some substances contained in the cigarette smoke, such as thiocyanate and benzpyrene, may have a negative influence on thyroid gland function [71]. The association between current smoking and the increased risk for Graves' hyperthyroidism was confirmed in several studies [72–74].

Vestergaard's meta-analysis based on 25 studies on the association between smoking and thyroid disorders revealed that odd ratio for Graves' disease in current smokers was significant (3.30 [95% CI: 2.09-5.22]). Quitting smoking and staying smoke-free greatly reduces the risk of developing Graves' disease (OR = 1.41, 95% CI: 0.77-2.58) [75].

On the other hand, a cross-sectional, population-based study conducted by Asvold et al. showed a lower risk for overt hypothyroidism in current smokers [76].

CONCLUSIONS

Autoimmune diseases are still a riddle for doctors and scientists, their causes are little-known, and their treatment often remains problematic. These multifactorial diseases may have various clinical manifestations and can affect almost every tissue or organ in the human body. Many environmental determinants may play an important role in triggering the autoimmune response. Identification of the exact environmental triggers and estimating the dose of exposure and genetic susceptibility mechanisms could significantly contribute to the prevention and control of autoimmune diseases.

On review of the literature, we conclude that there is a potential link between increased exposure to environmental toxins and the increase in autoimmunity. Several studies have attempted to explain this correlation. It is hypothesized that it may be due to many mechanisms triggered by environmental factors, such as: DNA methylation, proteins citrullination, HSP90 activation, or increased production of ROS (reactive oxygen species). Subsequently, these mechanisms may cause damage and changes in immune system functioning.

Among the various environmental factors affecting human health, we highlighted those which are considered to be most influential in the autoimmu-

nity development. It is important to point out that the environmental factors can affect the human immune system through many physical exposures, such as diet, tobacco smoking, or heavy metals.

Expanding our knowledge about the modifiable causes of autoimmunity is necessary to improve prevention and minimize the risk of autoimmune diseases. Awareness of non-genetic factors can help us identify them in our life and change them. One of the challenges of modern interdisciplinary medical research is attempting to identify the particular interactions of gene and environmental factors that could explain why some individuals are more susceptible to develop autoimmune response than others. Other challenges connected with studies focusing on the role of environmental triggers on the risk of developing autoimmunity are associated with either methodological or practical issues.

Although the incidence of autoimmune disorders appears to be increasing and seems to be associated with the problem of environmental pollutants, more studies to clarify the exact relationship between environmental factors and autoimmune diseases are needed.

Conflict of Interest:
The authors declare no conflict of interest.

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