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Dysfunctions of the immune system associated with age

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Abstract

Background: The human immune system consists of innate and adaptive responses. Innate immune response is the first line of the body's defense, while the adaptive response eliminates pathogens in later stages of infection. Cooperation between innate and adaptive immune response is important to effectively eliminate pathogens. An integral part of the aging of the human body is the aging of the immune system, which results in functional disorders directly affecting the deterioration of health. Abnormal functioning of the immune system is a predisposing factor to the occurrence of old-age diseases, as well as reduces the effectiveness of protective vaccination especially recommended to geriatric patients.

Material and Methods: The current state of knowledge on age-related immune dysfunctions has been reviewed. The analysis concerned publications in English and Polish language published in the years 2003-2018, which were collected in the PubMed and Google Scholar

database. Particular attention was paid to publications presenting the results of research conducted on a group of geriatric people in order to analyze the facts from the research. The publications were searched on the basis of key phrases, among others: the immune system of the elderly, chronic inflammation, innate immunity and adaptive immunity.

Results: A review of current knowledge showed the seriousness of the problem of the aging of the immune system. In addition to reducing the efficiency of the immune system, special attention should be paid to chronic inflammation that predisposes to old-age diseases, as well as to reduce the effectiveness of immunization, which is a serious threat.

Conclusion: Analyzing the sources of chronic inflammation in the elderly, particular attention was paid to the phenotype of aging cells, changes in the intestinal microflora of the elderly, the role of adipose tissue in the process of inflammation and changes in the levels of steroid hormones. Public awareness of the etiology of the problem is an excellent method of counteracting the negative effects of immunodeficiency. One of the recommendations is physical activity as part of the elimination of adipose tissue capable of securing an infinite number of pro-inflammatory cytokines.

Key words: immune system, older people, chronic inflammation, innate immunity, adaptive immunity, protective vaccination

Introduction

The human immune system consists of innate and adaptive responses. Immunological innate response is the first line of the body's defense against foreign pathogens, while the adaptive response participates in the elimination of pathogens during the subsequent infection phase in which T and B lymphocytes are involved [1].

It has been observed that the aging of the immune system (immunodeficiency) is an integral process of the aging of the human body. In older people, disorders of the immune system are more often observed, which have negative effects on health and deterioration of the quality of life. This process starts at the molecular level when it comes to accumulate many irreversible damage within the cells, tissues and organs. Abnormal synthesis of proteins with altered structure is the effect of dysfunction of the immune system related to age, the body classifies altered proteins as foreign antigens. In addition, mutations within the T and B

lymphocyte genes result in disturbances in the proper functioning of the elements of the immune system. The effect of the described abnormalities is the intensification of autoimmune reactions. [2]

The consequences of immunodeficiency include chronic inflammation associated with the constant stimulation of the immune system, which is caused by chronically elevated levels of proinflammatory cytokines. The conducted research indicates the coexistence of chronic inflammation with cardiovascular events, cancer, diabetes and dementia diseases. [2,3]

In older people, besides chronic inflammation, the effectiveness of the immune system is also reduced. The decrease in efficiency results mainly from the decrease in the diversity of T lymphocytes and the number of B lymphocytes, resulting in a reduced ability to respond to immunization, as well as increased susceptibility to infections, among others urinary and respiratory infections. [2,3,4]

Cooperation of innate and adaptive responses

The innate immune response is an immediate reaction in response to foreign microorganisms in order to eliminate them. The cellular elements involved in the action of this immune response are neutrophils, macrophages, NK cells and dendritic cells. Sometimes complete elimination of pathogenic microorganisms requires the involvement of advanced mechanisms based on the activity of T and B lymphocytes, which fall within the scope of the immune response of an adaptive response that occurs with a certain delay. [5]

A very important element of an effective immune response is the cooperation between the mechanisms of innate and adaptive response. The interaction of the two mechanisms allows to inhibit the infection through the activity of innate response as well as complete elimination of the microorganism (with the creation of permanent immunological memory) through the activity of the adaptive response. [5]

Innate immune response- components subject to aging

Neutrophils are produced by the bone marrow in the amount of 2 × 109 granulocytes / kilogram of body weight, while the infection may increase their number up to 10 times. In response to chemotactic factors (including IL-1, IL-8, TNF-α) released by monocytes and macrophages, neutrophils first leave the blood vessels migrating to the places affected by the infection. They exhibit strong phagocytic and cytotoxic properties. In the progressing aging process, there is no decrease in the number of neutrophils, however, when compared to the

young body, the level of neutrophil activity decreases. Is characterized as a loss of chemotactic, resulting in damage to tissue by inflammatory processes. [5,6]

NK (natural killers) is the most important component of innate immune response with cytotoxic and immunoregulatory properties, responsible for the elimination of infected cells or cancer cells. It has been observed that NK cells in the elderly are characterized by a reduced level of cytotoxicity. It is assumed that the above-described changes result from the disturbance of zinc homeostasis, therefore it is recommended to administer this microelement to the elderly in order to improve the functioning of cells. [7,8]

Dendritic cells (DCs) migrate to the lymph nodes and present the phagocytized material (antigen) of the so-called virgin T lymphocytes. DCs are defined as a "bridge" between innate and adaptive response. As a result of the aging of the body, dendritic cell function impairment is observed. [6,9]

Adaptive immune response - components subject to aging

The main role in the adaptive immune response is played by virgin T lymphocytes. T lymphocyte maturation occurs in the central lymphatic organ of the thymus. This is where the lymphopoiesis process occurs, which provides the appropriate level of T lymphocytes. T-lymphocytes that leave the thymus are called virgin cells that are present in peripheral organs acting as effector cells. Along with age (especially after the age of 65), the functioning of T lymphocytes is impaired, mainly due to the disappearance of thymus progressing with age. The effect of disappearance of the thymus is the weakening of lymphopoiesis, the decreasing number of T-cell precursors in older people results in lowering the regenerative capacity, the consequence is less strength to fight infective agents. [2,10]

T cells in the elderly are formed from the division of existing lymphocytes, the reduced lymphocyte pool thus affects the low level of diversity, which ultimately results in a difficult reaction to the previously unknown antigen. Therefore, any condition in the body of an elderly person (after the age of 65) that leads to damage to a certain pool of T lymphocytes (cancer treatment - radiotherapy, chemotherapy or HIV infection) is associated with serious complications. [2,11]

B lymphocytes play an important role in the adaptive immune response by producing antibodies. Studies have shown that with age, there is a decrease in the number of B lymphocytes on the periphery, as well as B cell lymphocytes. This situation is caused by the decrease in the number of early precursors of B, probably related to the "quality" of

hematopoietic stem cells, where the dysfunctions of gene expression at the molecular level have been noticed. [2,12,13]

Chronic inflammation in the elderly

The inflammation belongs to the immune system's response to the infection in the body. This type of body's defensive strategy eliminates harmful stimuli while maintaining tissue homeostasis. The inflammatory response begins when IL-6 and TNF-α are released from damaged tissue, while IL-6 influences the induction of acute phase protein production - CRP, which clearly indicates the ongoing inflammatory process. [14,15]

In the physiological state, the inflammation disappears after the elimination of the pathogen, allowing the tissue to be rebuilt. It was observed that, unlike young people, older people have elevated levels of inflammatory cytokines (IL-6, TNF-α), a consequence of which are chronic inflammations with a low degree of severity. According to the current state of knowledge, the elderly most often suffer from hypertension, diabetes, atherosclerosis and cancer, where one of the predisposing factors is chronic inflammation. [3]

Sources of chronic inflammation

One of the primary causes of chronic inflammation is cellular aging. With increasing age, the number of aging cells that secrete inflammatory cytokines increases, resulting in inflammatory processes with a low degree of severity. Aging cells with a secretory phenotype are referred to as SASP (Senescence Associated Secretory Phenotype), tt is assumed that cells with the SASP phenotype are directly related to diseases associated with age, including atherosclerosis and diabetes.

The number of anti-inflammatory bacteria belonging to Clostridium, Bifidobacterium spp., and F. prausnitzii decreases with age, which is why it is thought to be one of the causes of chronic inflammation in the elderly. Studies have been carried out which have shown that with increasing age the number of pathogenic microbiota increases and the number of anti-inflammatory microbiota decreases, the consequence of which is an increase in the concentration of inflammatory cytokines in the serum. It is believed that changes in the intestinal microflora contribute to increased susceptibility to infectious agents, resulting in chronic inflammation. [3]

Adipose tissue capable of secretion of inflammatory cytokines is another source of chronic inflammation. The increase in total and visceral fat is associated with an increased amount of inflammatory cytokines. There are studies that unequivocally indicate a high-fat diet

as the cause of the increase in pro-inflammatory markers, while the Mediterranean diet is associated with lower levels of IL-6 and CRP [16].

The conducted research also indicates steroid hormones as a factor affecting the increase in the number of pro-inflammatory markers. Studies show that testosterone and estrogen inhibit the secretion of IL-6, so an increase in the number of cytokines after the onset of menopause, indicates the disappearance of estrogen with regulatory capacity. [16]

Consequences of elevated levels of inflammatory markers

The incidence of cardiovascular events increases with age, most often these incidents occur in people over 65 years of age. In the diagnosis of cardiovascular risk assessment, inflammatory markers are used, which are an excellent prognostic indicator, with IL-6 and TNF-α being the most useful markers. Studies conducted by Bruunsgaard's indicate that high TNF-α levels increase the incidence of atherosclerosis, and studies conducted by Health ABC show that high levels of IL-6 and TNF-α are associated with an increased risk of ischemic heart disease. [15,16]

There are more and more studies suggesting that pro-inflammatory cytokines are the main cause of insulin resistance. High levels of IL-6 and TNF-α have been demonstrated in people with diabetes.

Recently, there has also been an increased interest in research that has provided evidence of a link between chronic inflammation and the onset of cancers such as multiple myeloma and lymphoid cancer. [15]

The effect of an increased level of inflammatory markers in the elderly is also cognitive impairment. The study involved a group of people in good intellectual condition, where the average age was 74 years. It has been proven that inflammatory markers in serum, in particular IL-6 and CRP, have a strong relationship with the decline in cognitive functions. [17]

Physical activity is a potential benefit

Analyzing the sources that cause the chronic inflammation, particular attention was paid to adipose tissue capable of secretion of cytokines. Research was conducted on the population aged 70-79 years. It was observed that people leading an active lifestyle are characterized by low levels of IL-6 and CRP, therefore the effect of physical activity on the decrease in the number of inflammatory markers was analyzed. Research provides a promising perspective, providing a basis for controlling high-level markers. The authors of the study point to the large

benefits associated with increased physical activity, which is why it is suggested to perform clinical trials to confirm potential benefits. [18]

Vaccinations and the immune system of the elderly

The essence of protective vaccination is based on the formation of memory cells and antibodies by the immune system, which allows for a rapid response of the immune system to the next contact with the pathogen. In the elderly, a weakening of the immune response is observed, thus these people are particularly susceptible to the development of bacterial and viral infections. In accordance with current recommendations, prophylactic protective vaccination is used, it is recommended to vaccinate against influenza especially for people over 65 years of age. Studies have been carried out where after vaccination it was noticed that older people are characterized by prolonged production time of antibodies, moreover, studies have shown that only 29% -46% of subjects received seroprotection against influenza virus strains from the group of people over 75 years of age. In addition, the efficiency of the cellular response in terms of proliferative activity of lymphocytes was evaluated, the results showed a low degree of cellular response activity. [19,20]

Conclusions

An integral aging process is the aging of the immune system, in which the functioning of the innate and adaptive responses has been observed.

The most characteristic effects are chronic inflammation associated with an increased level of inflammatory cytokines. It has been proven that the source of the increased level of cytokines are primarily aging cells with the SASP phenotype, reduction of the number of anti-inflammatory bacteria with simultaneous increase in the number of pathogenic bacteria, excessive amount of fatty tissue capable of secretion of cytokines and loss of steroid hormones after menopause. In addition, it has been shown that chronic inflammation predisposes to old-age diseases (cardiovascular events, diabetes, atherosclerosis, dementia).

In addition to chronic inflammation, a reduction in the immune system's efficiency in the range of T and B lymphocyte activity was also observed. An analysis of current scientific reports indicates that the decrease in T-cell diversity and the decrease in B-cell counts is strongly associated with a decrease in the immune system's efficiency. The above facts justify the reduced ability to respond to immunization in older people and the increased frequency of respiratory or urinary infections.

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