β-THALASSEMIA AND DISEASE TOLERANCE

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Abstract: *Susceptibility to infections made it necessary to study the immune status of patients with β-thalassemia. This study examined the role of iron overload syndrome (hemosiderosis) and the interaction of pathophysiological determinants of thalassemia and components of the immune system. Chronic antigenic stimulation and oxidative stress from iron overload are two major pathophysiological factors in thalassemia that affect the immune system. Life-long blood transfusion therapy for thalassemia with its uncontrolled negative effect on the immune and coagulation systems of the blood leads to the accumulation of iron in the tissues and immunosuppression and, as a consequence, to the addition of intercurrent infection and immunization. The role of immunological interactions in the pathogenesis of β-thalassemia needs further investigation in future studies.*

Key words: *ferritin, splenectomy, hemosiderosis, immunoglobulins, interleukins.*

Introduction. Thalassemia patients require regular blood transfusions to maintain consistent hemoglobin levels for oxygenating organs. Thalassemia is a genetic disorder in the production of hemoglobin. Patients with thalassemia, who have been recipients of donated blood for many years, are at a high risk of infection with bioagents transmitted by transfusion [1,3]. These patients suffer from various complications such as infections, autoimmunity and alloimmunization due to transfusion. Such complications link the immune system to the pathogenesis of hemosiderosis. In this study, we reviewed the latest available data on the interaction of pathophysiological determinants of hemosiderosis and components of the immune system. Patients with thalassemia have an increased susceptibility to various infections [3]. As shown by the results

ISSN 3060-4567

of multicenter studies carried out in Italy, infections are the second most frequent cause of death in thalassemia after cardiac complications. Therefore, it is necessary to determine ferritin as an indicator of hemosiderosis of internal organs. Cardiac complications associated with hemosiderosis are the main cause of death in thalassemia patients. The listed complications explain the need to search for new safe methods of therapy for thalassemia.

The opinions of foreign authors also show the role of regular blood transfusions, which causes various complications such as iron overload and alloimmunization. In this case, regulatory T cells (Tregs) play an important role in the regulation of immune responses. With regard to innate immunity, the functional activity of neutrophils and natural killer cells (NKCs) decreases with thalassemia. On the other hand, higher levels of pro-inflammatory cytokines and C-reactive protein were observed in the serum of the patients. Thalassemia patients showed higher ratios of regulatory B lymphocytes, helper T cells, suppressor T cells, and T regulatory lymphocytes. Patients with thalassemia showed significantly higher levels of Ig G immunoglobin compared to normal counterparts [2]. The data on increased susceptibility to infections in thalassemia have generated interest in the study of the immune status of patients with β-thalassemia.

Objective: study of the influence of the immune status, in particular the cytokine profile, immunogobullins A, M, G and indicators of CD3 +,CD4 +,CD8 +,CD16 +, ferritin protein in patients with β-thalassemia.

Materials and methods. In the Republican Scientific and Practical Specialized Medical Center of Hematology, 200 patients registered with the dispensary with a diagnosis of thalassemia at the age from 1 to 27 years were examined. An immunological and biochemical study of the state of cellular and humoral immunity and the amount of iron-containing ferritin protein was carried out in 200 patients, girls and boys with various forms of thalassemia. All patients were registered and received treatment for the underlying disease by a hematologist.

ISSN 3060-4567

The material for the study was heparinized peripheral venous blood from the cubital vein, which was taken in the morning on an empty stomach.

We used a set of diagnostic methods for determining cellular and humoral immunity, which was determined by the enzyme immunoassay in which we used special test systems that have high sensitivity. Indicators of humoral immunity, Ig A, M, G, as well as some indicators of cellular immunity CD3 +, CD4 +, CD8 +, CD16 + were determined, the cytokine profile was studied by determining interleukin 6 and 18. Interleukins were determined in blood serum by enzyme-linked immunosorbent assay. The indicators of cellular immunity CD3 +, CD4 +, D8 +, CD16 + were determined by the enzyme immunoassay in which special tests are used - systems that are highly sensitive. The results obtained were mathematically processed using the known formulas for variation statistics. The reliability of the data was assessed using the criterion of reliability.

Main results. In connection with the recently established data on the significant role of inflammation in the pathogenesis of thalassemia, the importance of determining pro inflammatory cytokines as markers of destabilization of the immune system increases. One of the pro-inflammatory cytokines is interleukin (IL) 6, which has a wide range of humoral and cellular immune effects associated with inflammation and tissue damage. Also, interleukin (IL) 18, known as IFN-γ-inducing factor, rapidly activates cells monocyte / macrophage system, which leads to the activation of many antibacterial, antitumor, antiviral responses. When studying the indicators of IL 6 and IL 18, showed a significant increase in the content of interleukin 6 and interleukin 18 in all patients. Thus, the indices of interleukin 6 averaged 58.0 ± 2.4 p g / ml, and the indices of interleukin 18 were 595.7 ± 43.3 p g / ml. Normally, IL 6 values are 3.40-5.90 p g / ml, and IL 18 is 104-640 p g / ml, in our studies, interleukin 6 readings are tenfold higher than the norm. Perhaps this is due to liver hemosiderosis, which is confirmed with a significant increase in ferritin indicators. When studying interleukins in patients with thalassemia, we found an increase in the serum concentration of interleukin 6, their high content indicates a shift in the production of interleukins towards pro-inflammatory ones. The most informative indicator of iron stores in the body is serum ferritin, which rises much earlier than serum iron. According to the results of our study, the content of serum ferritin is 1513.1 ng / ml, this indicator exceeds normal values by 12.6 times, which indicates the risk of developing hemosiderosis of internal organs. In diagnostic studies, the greatest importance is attached to immunoglobulins A, M , G. IgA (1.01 g / L) is decreased, while IgM (1.78 g / L) and IgG are increased (16.1 g / L). With regard to innate immunity, the functional activity of neutrophils and natural killer cells (NKCs) decreases with TM. On the other hand, higher levels of the pro-inflammatory cytokines IL-6, IL-18 were observed in the serum of the patients. Thalassemia patients showed low ratios of helper T cells, suppressor T cells, and T regulatory (CD4 + / CD8 +) lymphocytes. Thalassemia patients showed significantly higher levels of Ig G immunoglobin compared to their normal counterparts, which may predispose them to diabetes and celiac disease. Immune cells are sometimes found to be lower than optimal activity in thalassemia patients, which may be due to malnutrition.

In patients with thalassemia due to iron overload, and its protein compounds have immunoregulatory disorders. At the same time, the high plasma ferritin content of thalassemia patients can cause the formation of antiferritin antibodies, which in turn leads to the formation of circulating immune complexes. This is confirmed by the fact that in patients with thalassemia, the indicator of cellular immunity CD3 + was 39.5%, which exceeds the norm. According to our data, CD4 + was 27.7%, CD8 + T-suppressor and cytotoxic lymphocytes were 28.6%. CD16 + EK, according to our analysis results amounted to 24.8%

Iron overload is considered a major factor in immune deficiency in thalassemia and is a complication of both the disease itself and therapy. It has been established that iron and its protein compounds are directly involved in immuno regulatory mechanisms, and therefore an excess of iron can adversely affect the immune balance [3, 4, 5]. The results of numerous studies indicate a negative effect of excess iron on immunological functions, which include suppression of phagocytosis of the monocytic-macrophage system, changes in T-lymphocyte subpopulations, increased secretion of immunoglobulins and suppression of the complement system. It has been shown both "in vitro" and "in vivo" that iron plays an important role in the regulation of expression of T-lymphocyte surface markers, affecting the expansion of various T-cell subpopulations and possibly affecting the function of immune cells [1,2,5]. The weak ability of lymphocytes to sequester extra iron in ferritin may also help explain the causes of abnormalities in the immune system in patients with iron overload [3,4]. Thalassemia have an increased risk of serious infections, and this again may be due to iron overload, chronic immune stimulation with repeated blood transfusions, splenectomy, and immune deficiency disorders. Changes in lymphocyte subgroups include higher numbers and activity of suppressor T cells (CD8 +), decreased proliferative capacity and the number and level of activity of helper T cells (CD 4+), leading to a decrease in the CD4 + / CD8 + ratio, and defective natural killer cell activity (NK +). Impaired secretion of immunoglobulins, accompanied by elevated levels of IgG, IgM and IgA, indicate liver dysfunction as a result of iron overload, associated with hemolysis of erythrocytes and regular blood transfusions, that is, a complication in the form of hemosiderosis of the internal organs of thalassemia patients.

Conclusions: Immune genetic determinants may be involved in modulating the clinical picture of thalassemia. Thalassemia patients usually have higher levels of immune cells, probably as a result of antigenic contamination from blood transfusion. However, these patients face impaired immune cell function. Thalassemia have an increased risk of serious infections, and this again may be associated with iron overload, chronic immune stimulation with repeated blood transfusions, splenectomy and immunodeficiency [2, 4]. Changes in lymphocyte subgroups include higher numbers and activity of suppressor T cells (CD8 +), decreased proliferative capacity and the number and level of activity of helper T cells (CD4 +), leading to a decrease in the CD4 + / CD8 + ratio, and defective natural killer cells (NK). High levels of interleukin 6 and 18 indicate

ISSN 3060-4567

a shift in the production of interleukins towards proinflammatory. Impaired secretion of immunoglobulins, accompanied by elevated levels of Ig G, Ig M and Ig A, indicate liver dysfunction as a result of iron overload, associated with hemolysis of erythrocytes and regular blood transfusions, i.e., a complication in the form of hemosiderosis of the internal organs of patients with thalassemia. The role of immunological interactions in the pathogenesis of hemosiderosis needs further disclosure in future studies. Potential research will continue between the state of the immune system in thalassemia and its other complications, including heart failure, hypertension, atherosclerosis, liver fibrosis, diabetes, thyroid dysfunction, and osteoporosis. The studies carried out expand our understanding of the dysfunction of immuno regulatory mechanisms in patients with thalassemia and allow us to outline new approaches to assessing the immunological status, therapy and prognosis. Timely diagnosis and treatment of disorders of the immune system will reduce overall morbidity, improve the quality of life, reduce hospital admissions, as well as the number of deaths and disabilities among patients with β-thalassemia

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