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FEATURES OF IMMUNE REACTIONS IN AUTOIMMUNE THYROIDITIS IN RESIDENTS OF THE NORTHERN REGION

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Aim: to reveal the features of immune responses in autoimmune thyroiditis (AIT) in residents of the northern region.

Materials and methods: We examined 223 people living in the city of Arkhangelsk, aged 21 to 55, including 108 patients with AIT and 115 practically healthy people. A database was formed, including the data of the subject: date of birth, date of examination, age, sex and indicators of the immune background. Statistical analysis of the data was carried out using the Statistics 21.0 software package.

Results. In patients with AIT, compared with the level of the studied parameters in practically healthy individuals, an increase in the content of mature T-lymphocytes (CD3+), T-helpers (CD4+), cytotoxic T-lymphocytes (CD8+), activated cells with a transferrin receptor (CD71+) and cells labeled for programmed cell death (CD95+). The inflammatory process in AIT is manifested by systemic reactions - thrombocytopenia (27%), an increase in the content of IL-6 and TNF-α (26 and 18%, respectively). In patients with AIT, in addition to increased concentrations of antibodies to thyroid peroxidase, a high frequency of detection of elevated levels is recorded. antibodies to DNA (ds-DNA) (52.3%), RNA (RNP) (60.3%), antiphospholipids (aPhL) of the IgM and IgG classes (16.17%).

Conclusion. It was found that the inflammatory process in AIT in 15-27% of cases is manifested by systemic reactions-thrombocytopenia, increased levels of IL-6 and TNF-α, lymphocytosis and monocytosis. With AIT, the concentration of cytotoxic T-lymphocytes increases 3 times with a low activity of natural killer cells and the phagocytic ability of neutrophilic granulocytes. The development of cell-mediated cytotoxicity is formed at a low background level of activity of mature T-lymphocytes (CD3+), natural killer cells (CD3-CD16+CD56+), activated T-lymphocytes with a transferrin receptor (CD71+) and lymphocytes capable of proliferation (CD10+).

Keywords: autoimmune thyroiditis, antibodies, T-lymphocytes, pro-inflammatory cytokines, inhabitants of the north.

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Introduction. The autoimmune process is a physiological process that regulates secretion, tissue metabolism, use, and clearance of hormones and other biologically active substances in the body [9, 18]. Currently, the understanding of the spectrum of autoantibodies, their concentrations and physiological regulatory role is expanding [3]. It was revealed that autoimmune processes have a clear tendency to increase [12]. Increased concentrations of autoantibodies to thyroid peroxidase are detected in residents of areas affected by the Chernobyl accident [2], as well as in unfavorable climatic conditions [9, 10], during physical exertion [11], stressful situations [4], and also depends on the degree tissue metabolism of the amount of metabolic products entering the blood [10].

In addition, with pathology, new structures with antigenic properties may appear as a result of conformational changes in the formed complex or destruction of any biologically active substance with antigenic properties [7].

In connection with the above, the aim of the work is identification of the features of immune responses in autoimmune thyroiditis (AIT) in residents of the northern region.

Materials and methods. The objects of the study were residents of the city of Arkhangelsk. The work includes the results of an immunological examination of 223 people aged 21-55 years, including 108 people with AIT, who applied to the

center of professional diagnostics "Biolam" and 115 practically healthy people. Inclusion criteria for two groups: living in Arkhangelsk, the first group - practically healthy persons at the time of the study, the second group - patients with a diagnosis of autoimmune thyroiditis. The average age for the first group is 37.62 ± 1.53, for the second 44.93 ± 1.79. All studies were carried out with the consent of the surveyed and in accordance with the requirements of the World Medical Association Declaration of Helsinki on the Ethical Principles of Medical Research (2000).

All stages of clinical laboratory examination were carried out by medical workers of the laboratory of the "Biolam" center and research workers of the Institute of Physiology of Natural Adaptations of the Federal State Budgetary Institution FITSKIA UB RAS: instruction on the rules of preparation for laboratory research, taking of biomaterial and its preliminary processing, application of analytical technology using appropriate reagents and equipment, obtaining survey results. Clinical and diagnostic interpretation of the examination results, identification of risk factors and causes of the disease, the formation of recommendation protocols were carried out by the doctor of medical sciences, professor, immunologist Dobrodeyeva Lilia Konstantinovna. Before the clinical and laboratory examination, everyone was informed about the possibility of using the examination results for research purposes by the staff of the Institute of Physiology of Natural Adaptations of the FGBUN FITSKIA of the UB RAS while maintaining the confidentiality of the results.

A database was formed, including the data of the subject: date of birth, date of examination, age, sex and indicators of the immune background.

The complex of immunological research included the study of hemogram (number of platelets, erythrocytes, leukocytes, total hemoglobin in the blood, leukogram with 5-component differentiation of leukocytes) on an automatic hematological analyzer XS-500i (Japan), phagocytic activity of neutrophilic leukocytes in peripheral blood in blood smears stained by the Romanovsky-Giemsa method. Phagocytic activity of blood neutrophils was determined by the absorption of latex particles with a diameter of 0.9 μm. Under a microscope (magnification x 1000), the percentage of neutrophils that included latex particles (phagocytic index - PI, %) and the average number of granules per phagocytic neutrophil (phagocytic number - FP) were determined.

The content of lymphocyte phenotypes (CD3+,CD4+, CD8+, CD3+CD16+CD56+, CD3-CD16 +CD56+, CD10+, CD95+, CD71+) was studied by flow cytometry using an Epics XL apparatus from Beckman Coulter (USA) with Immunotech and Beckman Coulter Company reagents "(France) and by the method of indirect immunoperoxidase reaction using monoclonal antibodies (" MedBioSpektr "," Sorbent ", Moscow).

The concentration of cytokines (TNF-α, IL-6) in the blood serum was determined by enzyme-linked immunosorbent assay. Reactions were assessed using a Multiskan MS photometer (Labsystems, Finland) and an Evolis automatic immunoassay analyzer (Bio-RAD, Germany).

Quantification of circulating IgG antibodies to thyroid peroxidase (antibodies to TPO) was carried out using the test systems of the company "Orgentec" (Germany), autoantibodies to double-stranded DNA (ds-DNA) and to nucleoproteins (RNP) - a kit "Bio Rad", USA; autoantibodies of IgM / IgG classes to phospholipids (aPL) - "Orgentec", Germany.

The results of the study were statistically processed with the determination of mean values and are presented as the arithmetic mean ± error of the mean (M ± m), reliability differences were assessed using Student's t-test. The package of the computer program "Microsoft Excel MX" was used. Statistical analysis of the data was carried out using the Statistics 21.0 software package.

Results and discussion. Pathological processes in AIT are distinguished by insignificant reactions of an increase in the content of leukocytes (from 4.34±0.16 to 6.48±0.19x10^9 cells/l; p<0.001), lymphocytes (from 1.73±0.08 to 2.78±0.11x10^9 cells/l; p<0.001), neutrophilic granulocytes (from 2.6±0.09 to 3.70±0.17x10^9 cells/l; p <0.001) and platelets (from 156.52±10, 37 to 204.63±5.45x10^9 cells/l; p<0.001). In some cases, thrombocytopenia (27.78 ± 0.76%), monocytosis (20.37±0.66%) and lymphocytosis (15.74±0.58%) were recorded. The frequency of registration of hemoglobin deficiency in patients with AIT, compared to that in practically healthy individuals, is 4.7 times higher (21.30±0.67 and 4.35±0.48%, respectively); erythrocytosis was recorded 2.5 times more often (16.67±0.60 and 6.96±0.59%), respectively, which indicates a compensatory response to tissue oxygen supply. The inhabitants of the North have a lower life span of an erythrocyte, the average content of hemoglobin in them, a change in the shape of an erythrocyte and a thickening of its cell wall have been established, which reduces the activity of providing oxygen to tissues [7]. An increase in the microviscosity of lipids with an increase in the content of cholesterol and monounsaturated fatty acids in membranes slows down the release of O2 from the erythrocyte, impairs the rheological properties of blood, and reduces the rate of deoxygenation of intracellular Hb [13]. In venous blood, regardless of age and length of residence in the North, oxygen tension and blood saturation are markedly reduced compared to those in the control group [5]. As a result, the capillary-venous difference in residents of the northern regions is reduced. Thus, in northerners, the difference in the venous-capillary partial pressure of CO2 and O2 is higher, but the partial pressure in the venous blood is lower. One of the reasons for this phenomenon may be the increased activity of erythrocyte aggregation in northerners; there is evidence that the aggregation of erythrocytes is accompanied by a decrease in tissue oxygenation [12].

In patients with AIT (table), compared with the level of the studied parameters in practically healthy individuals, an increase in the content of mature T-lymphocytes (CD3+), T-helpers (CD4+), cytotoxic T-lymphocytes (CD8+), activated cells with a transferrin receptor (CD71+) and cells labeled for programmed cell death (CD95+). Attention is drawn to the lack of response from lymphocytes ready for proliferation (CD10+), T NK cells (CD3+CD16+CD56 +) and a decrease in the content of NK cells (CD3-CD16+CD56+) in persons with AIT.

The activation of cell-mediated and antibody-dependent immune responses in AIT is rather low. A statistically significant increase in the content of T-helpers was confirmed on average only in 5 patients (4.63±0.31%), an increase in the concentration of cytotoxic T-lymphocytes was found in 8 cases (7.41±0.40%). This situation is possible with the formation of a low initial background of the content of immunocompetent cells in the circulation. Thus, the deficit in the content of mature T-cells in patients was established in 57.14±1.09% (60 patients), the deficiency of T-helpers was detected in 20 cases (18.52±0.64%); a low content of activated T-lymphocytes with a transferrin receptor was in 76 patients (70.37±1.23%). It is unlikely that apoptosis of lymphocytes is the main mechanism for the formation of a low immune background; an increased level of cells labeled for apoptosis was not recorded, their low content was found in 72 patients (66.67±1.20%).

The content of cells capable of proliferation (CD10+) [6] in all patients did not exceed the levels of their concentration in practically healthy individuals. Thus, a low initial background of the level of immune reactivity could be provided by a decrease in the activity of proliferative processes.

The activation of natural killer cells with an increase in their concentration >0.4x109 cells/l is recorded very rarely (in 5 patients, 4.63±0.16%). There is evidence that a decrease in the number of NK cells correlates with the loss of immunological control over autoreactive clones of lymphocytes and affects the activity of autoimmune inflammation in AIT [15].

Damage to thyroid cells in autoimmune processes can be provided by antibody-dependent cytotoxicity, which can be manifested by free membrane antibodies, activating the complement system, as well as immunoglobulin complexes on the phagocyte membrane [1]. Neutrophilic leukocytosis was rare (in 9 people, 8.33±0.43%), monocytosis was established in 22 cases (20.37±0.66%). It seems that the main role in antibody-dependent cytolysis is provided by cytotoxic lymphocytes, the content of which is, on average, 3 times higher than that of practically healthy individuals. Removal of cell decay products is provided by phagocytes and in this case mainly by monocytes; the deficit of actively phagocytic neutrophils in patients with AIT was established in 95.45±1.43% of cases, which is 10 times higher than in practically healthy individuals (9.30±0.69%). This defect can play a significant role in the further activation and prolongation of autosensisbilization.

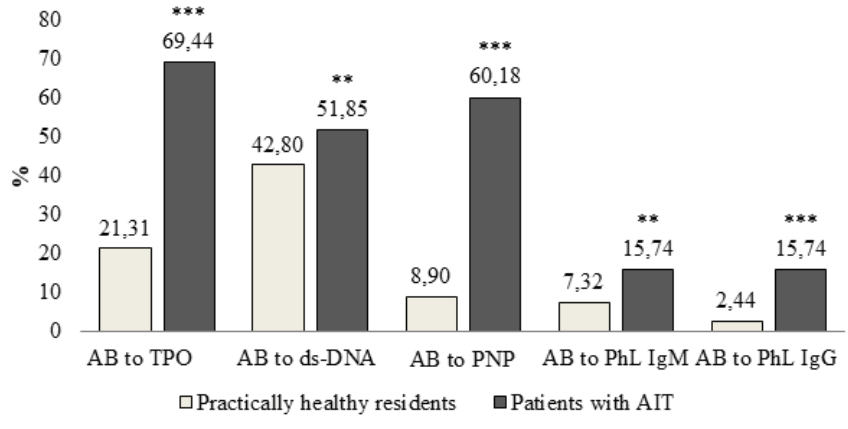
Autoimmune inflammation is accompanied by an increase in the blood levels of IL-6, TNF-α (26.67±1.71 and 18.36±0.63%, respectively). Thus, in some cases, the reaction of cytokines is systemic. IL-6 regulates the synthesis of acute phase proteins [17]. C-reactive protein induces TNF-α secretion through a signaling mechanism involving p38 MAP kinase, a Toll-like receptor [16]. The main manifestations of the biological activity of TNF-α are selective cytotoxicity with inhibition of the synthesis of the key enzyme of lipogenesis, lipoprotein kinase.

The range of autoantibodies in AIT is not limited to antibodies to TPO. Anti dsDNA concentrations exceeding the physiological limit (> 50 IU/ml) were found in 56 patients (51.85 ± 0.67%), anti RNP (>1.00 IU/ml) - in 65 patients (60.18±0.71%), antiphospholipids (aPL) of the IgM and IgG classes (> 10.00 IU/ml) were increased in 17 patients (15.74±0.37%). Antibodies to TPO exceeding the physiological level of the limit (>30 IU/ml) are set at 69.44±0.76% (75 people), Figure 1.

Comparative data on the content of phenotypes of lymphocytes in practically healthy people and patients with AIT (M ± m)

Cells, ×10⁹ Cells/l	Practically healthy residents	Patients with AIT	Reference limits of content
CD3+	0.74±0.02	0.98±0.03**	1.0–2.5
CD4+	0.37±0.02	0.53±0.02**	0.4–0.8
CD8+	0.33±0.02	1.01±0.56***	0.2–0.6
CD10+	0.32±0.02	0.27±0.02	0.05–0.6
CD3+CD16+CD56+	0.30±0.02	0.39±0.02	0.1–0.5
CD3– CD16+CD56+	0.42±0.03	0.28±0.02**	0.4–1.0
CD95+	0.26±0.02	0.46±0.01***	0.2–1.5
CD71+	0.34±0.02	0.41±0.02*	0.4–1.5

* p <0.5, ** p <0.01, *** p <0.001.



Frequency of registration of increased concentrations of antibodies in apparently healthy people and patients with AIT. *** – p <0,01, **** – p <0,001*

Conclusion. So, in patients with AIT, in addition to increased concentrations of antibodies to thyroid peroxidase, a high frequency of detecting increased levels of antibodies to DNA (ds-DNA) (52.3%), RNA (RNP) (60.3%), antiphospholipids (aPL) is recorded. classes IgM and IgG (16.17%). It seems that with autoimmune pathology, not only the concentration of autoantibodies increases, but also the spectrum of their specificity expands.

The inflammatory process in AIT is manifested by systemic reactions - thrombocytopenia (27%), increased levels of IL-6 and TNF-α (26 and 18%, respectively), lymphocytosis and monocytosis (15 and 20%, respectively). It is possible that platelet lysis initiates the development of the cytokine reaction and mononuclear cells.

Concentrations of T-lymphocytes (CD8 +) increase with AIT in fact 3 times with low activity of natural killer cells and phagocytic capacity of neutrophilic granulocytes. The clearance of cytolysis products is provided mainly by monocytes; deficiency of phagocytic ability of neutrophilic granulocytes can significantly prolong autosensitization. The development of cell-mediated cytotoxicity is formed at a low background level of activity (in 72%) of mature T-lymphocytes (CD3 +), natural killer cells (in 79%), as well as activated T-lymphocytes with a transferrin receptor (CD71 +) (in 70.37 %) and lymphocytes ready for proliferation (CD10 +) (in 96%), which is generally typical for residents of high latitudes.

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EFFICIENCY OF HOMEOBOX GENE EXPRESSION ASSESSMENT FOR PREDICTING OUTCOMES OF ASSSISTED REPRODUCTIVE TECHNOLOGY PROGRAMS

An analysis of the effect of *HOXA10* and *HOXA11* expression in the endometrial stroma of late reproductive women with tubal infertility factor on the outcomes of assisted reproductive technology (ART) programs was performed.

There was a tendency to a statistically significant decrease in the expression of *HOXA11* in the endometrial stroma during effective attempts to treat infertility.

Using the ROC (Receiver operator characteristic) method of analysis and calculations of the area under the ROC curve (AUC), it was found out that favorable levels of *HOXA11* expression for successful blastocyst implantation and live births in infertile women with their own and donor oocytes.

Keywords: *HOXA10*, *HOXA11*, expression, assisted reproductive technologies, implantation.

The potential role of *HOXA10* and *HOXA11* in the processes of implantation and functional regulation of tissues of the reproductive tract is recognized, however, the causes and consequences of expression features are actively discussed.

The ability to regulate the anatomical and functional identity of body segment structures by homeobox genes has been determined since the period of embryogenesis [10]. The relationship between the development of anomalies in *Hox/HOX* genetic mutations with a violation of not only organogenesis, but also the regulation of the encoding of transcription factors affecting the activity of "downstream" genes has been established.

Data on the *HOXA* genes and their probable role for implantation in women are insufficient and contradictory. The expression of *HOXA10* in the endometrium