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RELATIONSHIP OF ORGAN-SPECIFIC AUTOIMMUNE PATHOLOGY OF THE THYROID GLAND WITH INORGANIC AUTOIMMUNE RHEUMATIC DISEASES

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The problem of a pathology of a thyroid gland at rheumatic diseases, in particular at rheumatoid arthritis, remains actual and to this day. The work purpose was studying antitelogenesis to thyroid hormones at patients with mixt autoimmune pathology. In whey of blood of patients with RA and autothyroid pathology are found out antibodies (AB) to T3 and T4, their concentration correlates with activity of pathological process. It is shown, that level AB to T3 and T4 authentically differs from the maintenance of the given antibodies in whey of blood of healthy faces. Level of antibodies to thyroid hormones can be considered as the criterion predicting development of pathology of a thyroid gland at patients with RA.

Key words: thyroid gland, thyroid hormones, antibodies to thyroid gland hormones, rheumatoid arthritis.

Researchers drew attention to the relationship between rheumatic diseases and thyroid pathology back in the 19th century. In 1874, W. Gull described the phenomena of muscle stiffness and joint swelling in combination with cretinoid status in hypothyroidism (myxedema) in 5 women [9]. G. Means, in order to clarify the pathogenesis of damage to joints and soft tissues in hypothyroidism, conducted a number of studies on rats. During the experiment, the author revealed an increase in the production of hyaluronic acid and a decrease in chondroitin sulfate in the skin of the studied rats [3, 10].

Of particular interest to researchers is the organ-specific autoimmune pathology of the thyroid gland - Graves' disease (GD) and Hashimoto's autoimmune thyroiditis, as well as its possible relationship with non-organic autoimmune rheumatic diseases. A special place in this series is occupied by rheumatoid arthritis (RA), in which thyroid pathology occurs almost 3 times more often than in non-inflammatory joint diseases. In this case, the development of both hypo and hyperthyroidism is observed [1]. The most stable and well studied combination is RA and autoimmune thyroiditis (AIT) [1, 6, 7, 9, 11, 14]. Interest in this combination is due not only to its relatively high prevalence, but also to the fact that, according to a number of authors [1], patients with RA with concomitant AIT have a more favorable course of the underlying disease, primarily in terms of the severity of the destructive process in the joints and the rate of progression of the disease as a whole.

AIT is a large group of diseases that differ in clinical manifestations and are united by a common pathogenesis and a general morphological picture consisting of lymphocytic infiltration of thyroid tissue. Autoimmune disorders play a key role in the pathogenesis of AIT [12, 15]. Chronic AIT develops with violations of immunological tolerance, when the own proteins of thyroid cells are perceived as foreign. There are a number of variants of chronic AIT, united by similar immunological characteristics [4, 15].

According to the numerous available literature data, it seems obvious that autoimmune rheumatic diseases and autoimmune thyroid pathology (ATP) can simultaneously coexist in the same patients or members of their families. However, many aspects of this problem still remain

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controversial. Thus, according to some authors [9, 11], the connection between these two groups of diseases is undoubted and significant. According to J.V. Shiroky et al. [14], who studied the prevalence of thyroid pathology among patients with RA, among 91 patients, 29 (30%) were diagnosed with AIT or, less commonly, hypothyroidism compared to 10 (11%) of 93 healthy individuals. According to their data, the manifestations of AIT depended on age, duration of RA, the presence of rheumatoid factor and antinuclear antibodies. It was concluded that thyroid disease develops at least 3 times more often in women with RA than in comparable groups with non-inflammatory rheumatic diseases such as osteoarthritis and fibromyalgia.

According to a study conducted by V.V. Badokin et al., groups of RA patients with and without concomitant AIT did not differ significantly in the activity of the inflammatory process and the stage of RA, although among patients without thyroiditis there were slightly more patients with ankylosing of the joints. Systemic manifestations of RA, including secondary amyloidosis, were significantly more common in patients with AIT than in patients without autoimmune thyroid disease [1].

In the work of A. P. Weetman [15], 12% of 123 patients with RA were diagnosed with ATP, among them 65% were women, whose average age was 54 years, which emphasizes the autoimmune nature of the association and therefore justifies a screening study. It has been shown [2] that in most cases with RA there is a depression of the functional activity of the thyroid gland, which is more pronounced with systemic manifestations of the disease. The suppression of thyroid function was significant in patients with a disease duration of more than 7 years, with annual and frequent exacerbations. According to V.G. Stachinskaya [7], in patients with RA, thyrotoxicosis was detected in 21% of cases and hypothyroidism in 2% of cases. It was also noted that RA with concomitant AIT is characterized by a more benign course and takes on a malignant course in young and middle-aged patients in a euthyroid state [9].

In the diagnosis of ATP, a special place is occupied by the determination of antithyroid antibodies. Back in 1956, I. Roitt et al. [10], having published a report on the isolation of antibodies to thyroglobulin (ATTG) in patients with AIT, found that 3 out of 27 also had RA. Also worthy of attention is V. G. Serebryakov's message that D. Blake et al. in 1979, ATTG and antibodies to thyroid peroxidase (ATTPO) were detected in the synovial fluid of 34 out of 50 patients with various rheumatic diseases of the joints, such as RA, gout, ankylosing spondylitis, and osteoarthritis [9]. Only 4 of these patients had elevated titers of autothyroid autoantibodies in the blood serum, which suggests the possible local production of antibodies in the joints, the pathogenesis of which is similar to that in the thyroid gland itself.

Autoantibodies to thyroid hormones, directed specifically against T3 and T4, are less common. These antibodies have been known since 1956, when J. Robbins et al. first described the presence of T4-bound gamma globulin in papillary thyroid cancer. These autoantibodies are the IgG isotype [7].

S. Sakata, Li Calzi (cit. [6]), J.B. Peter [13] studied the presence of antibodies to thyroid hormones in healthy individuals. For this purpose, the sera of 880 healthy people (365 men and 315 women) were studied. Antibodies to T3 were not detected, antibodies to T4 were detected in 0.34% of the examined individuals. In contrast to these studies, the most recent studies using polyethylene glycol precipitation of radiolabeled complexes showed a predominance of 1–7% in autoimmune thyroid diseases of antibodies to T3 and T4 and 0–1.8% in a healthy population [6].

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Some researchers have studied the presence of antibodies to thyroxine and triiodothyronine in RA. D.J.B. Thomas et al. [9] detected antithyroid antibodies in 77 of 233 sera from RA patients.

Thus, the problem of thyroid pathology in rheumatic diseases, in particular RA, remains relevant today. Many issues require further detailed study both experimentally and in clinical practice, which will undoubtedly improve diagnosis and contribute to adequate treatment of rheumatic diseases.

Material and methods

We observed 93 people: 33 patients with thyroid pathology, 25 patients with combined pathology - RA and thyroid diseases, and 35 practically healthy individuals (24 women and 11 men) aged from 24 to 56 years - donors of the Volgograd blood transfusion station, who underwent examination. Patients were selected upon admission to the hospital after clinical, laboratory and instrumental examination. The study was conducted in accordance with the principles of the International Medical Association Declaration of Helsinki (1996). Compliance with bioethical requirements is confirmed by the results of the examination of the Regional Ethics Committee.

Criteria for inclusion in the study: age over 18 years, informed consent, reliably confirmed diagnosis according to WHO classifications. Exclusion criteria: age under 18 years, postoperative hypothyroidism, drug-induced thyrotoxicosis, malignant neoplasms of the thyroid gland, multiple endocrine neoplasia syndromes - MEN 1 and MEN 2, current pregnancy, history of viral hepatitis, HIV infection, severe concomitant diseases: terminal chronic renal failure , decompensated diabetes mellitus, chronic heart failure of functional class III–IV or stage III according to the classification of Strazhesko and Vasilenko, myocardial infarction, chronic respiratory failure of the III degree, severe liver dysfunction, dyscirculatory encephalopathy of the 2–3rd degree, acute cerebrovascular accidents .

Patients with autoimmune thyroid pathology. There were 33 patients under observation, of which 5 (15.15%) were men and 28 (84.85%) women. The average age of the patients was 52.48 ± ± 14.03 years, the average duration of thyroid pathology was 3.82 ± 3.21 years. The duration of the disease was less than 1 year in 9 (27.2%) people, from 1 to 5 years in 14 (42.4%), more than 5 years in 10 (30.3%) people. The onset of the disease occurred on average at the age of 48.6 ± 13.6 years. According to the presence of thyroid pathology, patients were distributed as follows: 10 (30.3%) patients had AIT in the euthyroid phase, 9 (27.2%) had primary hypothyroidism, 14 (42.4%) had hyperthyroidism, of which 4 (28.5%) had mixed toxic goiter and 10 (71.4%) patients had GD.

Patients with RA in combination with thyroid disease. We examined 25 RA patients with concomitant autoimmune thyroid pathology (AIT in the euthyroid phase, primary hypothyroidism as a result of AIT, HD). All patients were women aged from 21 to 77 years (average age was 55.16 ± ± 15.3 years), duration of RA was 5.08 ± 3.29 years. The average duration of thyroid disease was 3.01 ± 1.74 years, which in most cases indicates the development (progression) of thyroid pathology against the background of existing RA. Most of the examined patients had radiological stages 2–3 and degree II of RA activity.

Commercial preparations “L-thyroxine” and “Triiodothyronine” (Berlin-Chemie, Menarini, Germany) were used as antigens; the protein concentration for the T4 solution was 245 μg/ml, triiodothyronine – 160 μg/ml. Antibodies to T3 and T4 were determined by the enzyme immunoassay method when fixing the antigen in magnetically controlled sorbents. To obtain the immobilized form of T4 and T3, its solution with a concentration of 100 μg/ml and a working

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dilution of serum (1 : 100) were used. Considering the low molecular weight of hormones, amounting to 776.8 D for T4 and 650.98 D for T3, immobilization was carried out by emulsion polymerization in a flow of nitrogen gas with the inclusion of magnetic material modified by I.P. Gontarya et al. [5, 7]. The results were taken into account on an AS-8K multichannel spectrophotometer at a wavelength of 450 nm; the obtained values were expressed in conventional units of optical density (opt. pl. units). The presence of antibodies was considered positive when the optical density values exceeded 2 standard deviations from the values of the control group. When comparing optical density values reflecting the concentration of antibodies to T3 and T4, the control group and patients with RA using ROC analysis [16], the indicators exceed the separation points (0.106 units of optical density for antibodies to T3 and 0.108 units of optical density . for antibodies to T4) were considered positive, otherwise the result was considered negative.

The concentration of free T4 in blood plasma was determined by enzyme immunoassay using kits from ZAO Alkor-Bio (St. Petersburg, Russia) according to the manufacturer's instructions. The concentration of free T3 in blood plasma was determined by enzyme immunoassay using kits from Hema-Medica LLC according to the manufacturer's instructions. The effectiveness of treatment of patients was assessed using the same clinical, laboratory and immunobiochemical parameters.

Statistical processing of the obtained results was carried out using the software packages Statistica 6.0, SPSS 12.0, Statgraphics 3.0, Graph Pad Prism 4, Biostatistics and according to original programs using the formulas given in the relevant manuals (Glantz S., 1998; Zaitsev V.M. et al. ., 2003; Greenhalgh T., 2006). With a normal distribution of a trait, its central tendency and variability were characterized as the arithmetic mean standard deviation ($M \pm \sigma$), otherwise - as the median (Me) (25%, 75% percentile). Differences were considered significant if the probability of type I error (p) was less than 0.05. The search for optimal cutoff points, assessment of the overall accuracy of a single diagnostic test, and comparison of two diagnostic studies were carried out using a nonparametric version of ROC analysis.

Results and its discussion

Control group. The mean free T4 concentration in the control group was 15.2 ± 2.25 pmol/L (with normal values ranging from 10.3–25.7 pmol/L). The average free T3 concentration in the control group was 3.51 ± 0.44 pmol/L (with normal values ranging from 2.5–5.8 pmol/L). The average concentration of antibodies to T4 in the blood sera of healthy individuals was 0.052 ± 0.008 units. wholesale pl., and to T3 – 0.041 ± 0.008 units. wholesale pl. The studies conducted did not reveal significant differences between the activity of these hormones and antibodies to them in healthy individuals depending on gender and age.

Patients with autoimmune thyroid pathology. Of the 33 patients with ATP, 91% had elevated levels of antibodies to T4 and 87% had elevated levels of antibodies to T3. Only in the group with hypothyroidism, 3 patients had levels of antibodies to T4 that did not exceed normal values, and 4 patients had normal values of antibodies to T3. The average level of antibodies to T4 was 0.156 ± 0.0.065 units. wholesale square, antibodies to T3 – 0.132 ± 0.027 units. wholesale pl. ($p < 0.01$ and $p = 0.03$ compared with similar indicators for donors), the number of St. T4 – 31.02 ± 5.16 pmol/ml (significantly compared with that in donors, $p = 0.39$), st. T3 – 8.09 ± 3.97 pmol/ml. A statistically significant increase in the level of antibodies to T3 and T4 in patients with hyperthyroidism was also revealed compared to the level of these antibodies in patients with

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hypothyroidism (p = 0.3 and p = 0.045, respectively). The quantitative content of antibodies to T3 was lower than the content of antibodies to T4 in the blood (p = 0.05), which is explained by the lower content of free forms of triiodothyronine in the blood. Correlation analysis revealed the presence of weak negative relationships between TSH and T3 and T4 (r = −0.3, p = 0.17 and r = −0.26, p = 0.23). A high degree of correlation was found between T3 and T4 (r = 0.97, p = 0.0001) and between antibodies to T3 and T4 (r = 0.55, p = 0.001), while in donors there were significant connections between T3 and T4 was not noted.

Patients with RA in combination with autoimmune thyroid pathology. Under our observation in a hospital setting there were 25 patients with RA with concomitant thyroid pathology. During the research, a significant increase in the content of antibodies to T3 and T4 was revealed in RA patients with ATP compared to donors - 0.198 ± 0.003 units. wholesale pl. for antibodies to T4 and 0.155 ± 0.05 units. wholesale pl. for antibodies to T3 (p < 0.001 and p < 0.01, respectively). In the group of patients examined, elevated values of antibodies to T4 and T3 were detected in 100% of cases.

Correlations were identified between the content of T3 and T4 and the level of antibodies to them and the DAS 28 parameter. With DAS 28 > 5.1 (III degree of activity), a significant correlation was observed with the level of antibodies to T4 (r = 0.51, p = 0.039) and the opposite – with level T3 (r = −0.44, p = 0.048). Correlations were also observed with the level of antibodies to T3 and T4 content (r = 0.28, p = 0.035 and r = 0.26, p = 0.029). At degrees I and II of activity, no significant correlation was found.

In RA patients with ATP, significantly higher levels of antibodies to T3 and T4 were found than in RA patients without ATP.

The changes we found in the level of thyroid hormones in patients with RA correspond to the existing ideas about their content in the blood plasma in this pathology, described in recent studies from 1998–2010. [6, 8]. The study revealed a relationship between the severity of thyroid dysfunction, on the one hand, and the activity of the process, the stage of arthritis, the duration of the disease, and the frequency of its exacerbation, on the other. We were able to identify clearly pronounced changes in patients with RA when analyzing one of the indicators of thyroid function - the level of T3 in the blood serum, a decrease in which was found in 68.4% of patients with the articular form and in 80% of those examined with systemic manifestations of the disease. The T3 level was statistically significantly lower in RA patients with high process activity. The decrease in T3 content turned out to be significant in stages III and IV of the disease. The greatest decrease in the level of T3 in the blood serum was also observed with a long course of the disease and its frequent exacerbations.

In advanced stages of AIT, a decrease in thyroid function indicators is due to its morphological changes - stromal fibrosis, follicular atrophy, proliferation of connective tissue with lymphoid-plasmacytic infiltration, sclerosis of the vascular walls [2, 11]. On the other hand, this can be partly explained by the fact that, in addition to autoimmune mechanisms, the direct influence of pro-inflammatory cytokines, high levels of which are determined in RA, plays an important role in thyroid damage - interleukin-1 and interleukin-6, tumor necrosis factor, which can enhance immune responses. reactions [1, 4, 8].

conclusions

1. With autoimmune pathology of the thyroid gland in patients with RA, active antibody formation to thyroid hormones is observed.

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2. The level of antibodies to thyroid hormones can be considered as a criterion predicting the development of thyroid pathology in patients with RA.

3. Determination of antibodies to thyroid hormones (in combination with the concentration of T3 and T4) can serve not only as an indicator of the activity of the clinical and anatomical form, the nature of the course, and the clinical variant of RA, but also as an additional criterion for the effectiveness of the therapy.

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