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Current State of Autoimmune Thyroiditis Problem

Zhurakulova Zebuniso Akhtamovna

Bukhara State Medical Institute, zebi1919@mail.ru

Abstract: The review provides up-to-date data on pathogenetic mechanisms, diagnostic capabilities, and features of organizational and medical measures related to autoimmune thyroiditis (AIT). AIT is a polyethological disease, which is based on the influence of environmental factors, genetic predisposition and violation of immune regulation.

The review analyzes the association of AIT with an imbalance of a number of trace elements involved in the synthesis of thyroid hormones and affecting iodine metabolism. The results of studies that established the nature of immune disorders in AIT and hypothyroidism in the form of violations of subpopulations of lymphocytes, pro-inflammatory and anti-inflammatory cytokines, changes in the mechanisms of apoptosis, which were proposed for use as predictors of the severity of thyroid immune inflammation and hypothyroidism are presented. The criteria for selecting patients with an increased risk of developing complications in AIT remain unclear, which makes it necessary to develop and implement additional organizational and medical measures to monitor this population of patients and assess their quality of life.

Keywords: autoimmune thyroiditis, hypothyroidism, pathogenesis of autoimmune thyroiditis, organization of medical care.

Introduction

AIT is a chronic disease with a gradual onset, non-specific early signs, slow progression with an increase in destructive processes in the thyroid gland. AIT is one of the most common thyroid diseases and occupies from 20 to 50% in the structure of thyroid pathology [1]. In the scientific literature and clinical practice, the term AIT is used, referring to the "International Statistical Classification of Diseases and Related Health Problems, 10th revision" (class IV, block E 06.3-Hashimoto's thyroiditis, hashitoxicosis (transient), lymphadenomatous goiter, lymphocytic thyroiditis, lymphomatous struma (ICD-10, 1995).

Prevalence of AIT and hypothyroidism

An analysis of literature sources has shown that information on the actual incidence of AIT is rather sparse and contradictory. It is not possible to speak about the exact prevalence of AIT itself, since an independent clinical problem is practically not discussed in the modern foreign scientific literature, only the most important outcome is hypothyroidism [2, 3].However, domestic researchers consider this pathology separately [4]. At the same time, there is quite extensive information about the prevalence of antibodies to thyroid tissue in the population. Glands and the frequency of hypothyroidism. At the same time, according to available data, from 3 to 20% of the world's population currently suffers from AIT, which is the cause of the development of 70-80% of all cases of primary hypothyroidism [3, 5]. In various countries, AIT occurs with a frequency from 0.1 to 1.2 % in children and from 6 to 11 % in adults [3, 5, 6]. In the Russian Federation, AIT affects 3-4 % of

the population, which is estimated at the level of world data. Asymptomatic carriage of antibodies to thyroperoxidase (anti-TPO) in the general population reaches 30 % and varies depending on ethnic composition, gender and age [7].

Environmental factors in the development of AIT

In the structure of causal relationships between the development of autoimmune thyroid diseases, environmental factors occupy 31.8 %, being the trigger mechanism of the autoimmune process in individuals with a genetic predisposition to the development of AIT [9, 10].

The role of iodine supply in the development of AIT

Iodine deficiency in the environment of Belarus contributes to the formation of micro-foci of the maximum effect of hormonal and radiation-chemical factors on the genome of gland cells, which leads to the accumulation of long-lived radionuclides and trace elements in the thyroid gland and the development of autoimmune thyroid damage [15].

The concept of the relationship between dietary iodine intake and thyroid autoimmune diseases was initially formulated as a result of long-term epidemiological observations, which revealed the presence of more of them in iodine-deficient regions compared to iodine-deficient ones (89.5 and 34.2%, respectively). These conclusions were made on the basis of available evidence of a higher prevalence of antibody carriage to thyroid tissue in areas with adequate iodine supply. Data on the prevalence of autoimmune thyroid diseases themselves in the literature quite contradictory. To date, several mechanisms of development of autoimmune thyroid aggression associated with the trigger effect of excess iodine have been identified. They are conditioned by: 1) induction of autoreactive links of the immune system that cause a thyrotropic autoimmune effect; 2) activation of free radical oxidation and the appearance of oxidized forms of biomolecules in the thyroid gland; 3) excessive iodination of thyroglobulin (TG). The genotype of the organism is crucial for the implementation of these mechanisms, which can act together or independently of each other.

In countries with iodine deficiency, the structure of thyroid diseases is dominated by iodine-deficient diseases and in regions with normal iodine availability, an increase in autoimmune thyroid pathology is observed. This explains the significant variation in data on the incidence rate, as well as the existence of different opinions of authors regarding the effect of iodine prophylaxis on the growth of thyroid AID [16].

In patients with subclinical or obvious AIT, there is a violation of iodine metabolism, including a decrease in the content of iodine in the thyroid gland and iodination of TG. Euthyroid women with a history of postpartum thyroiditis have a mild but not permanent deficiency in thyroid hormone synthesis; such patients are predisposed to iodine-induced hypothyroidism. A similar predisposition was noted in euthyroid individuals with AIT who underwent radioiodine therapy or surgery. Limiting iodine in the diet helps improve thyroid function in Hashimoto's thyroiditis. Studies have shown that the administration of high doses of iodine to genetically predisposed experimental animals can induce AIT due to the formation of free radicals. Powerful antioxidants, on the contrary, delay the development of AIT [8].

The revealed mechanisms of induction of auto-aggression of the immune system with an excess of iodine in the body give an unambiguous answer to the question of the risk of its uncontrolled consumption with food. When recommending daily doses of iodine, it is necessary to take into account national dietary traditions and the genotype of ethnic groups of the population. The decision on the iodine status of the population should be made on the basis of the results of monitoring studies of ioduria in homogeneous groups [16].

The ambiguity of data on the role of iodine deficiency in the formation of AIT morbidity requires additional research, taking into account the environmental situation in the Republic of Belarus after the Chernobyl accident and the implementation of the national program for the elimination of iodine deficiency.

Microelement imbalance in autoimmune thyroiditis

Analysis of current literature data shows that thyroid diseases are associated with an imbalance of a number of trace elements (selenium, zinc, copper, chromium, and others) involved in the synthesis of thyroid hormones and affecting iodine metabolism [9, 8, 17].

It is known that the daily requirement for selenium is 20-200 mcg (for a European person, an acceptable level is 50 mcg per day), depending on the region of residence, while the serum concentration is at the level of 0.9 — 1.8 mmol/l. Selenium is involved in the conversion of T4 to reverse or active T3 in the enzyme deiodinase, and also destroys excess hydrogen peroxide with the help of glutathione peroxidase and thiotedoxine reductase, and thus preserves the integrity of thyrocytes. In the experiment with selenium deficiency, the conversion of T4 to T3 decreased, which proved the role of selenium in the action of thyroid hormones. hormones. The action of selenium-dependent deiodinases in tissues is controlled by the selenium diet and has hormonal regulation (it is assumed that it is controlled by thyroid-stimulating hormone (TSH)). The effect of selenium deficiency on thyroid hormone metabolism depends on whether a single selenium deficiency has an effect or whether there is a combination of iodine and selenium deficiency. It is proved that the use of selenium in the treatment of AIT affects, depending on the dosage, interleukin-2, tumor necrosis factor, interferon gamma and other cytokines that play a role in the development of AIT. Thus, selenium directly and indirectly has an anti-inflammatory and antioxidant effect, which was periodically detected in the study of human and animal immune cells. Sufficient selenium intake affects the differentiation of T cells into T-regulatory cells (T-reg). A reduction in the number or dysfunction of CD25+CD4+T-reg cells leads to the development of AIT [17].

Derumeaux H. et al. (2003) investigated the relationship of selenium status with thyroid echostructure and volume. A group of patients consisting of 792 men and 1108 women was found to have a protective effect of selenium on the development of autoimmune thyroid diseases [16]. In the paper Mazopakis E. E. et al. (2007) analyzed the results of taking 200 micrograms of selenium in patients with AIT (80 women aged 24 to 52 years). After 6 months of treatment, the anti-TPO concentration decreased by 9.9 %, while continuing treatment in one of the groups, a further decrease in the anti-TPO concentration was found. Discontinuation of the drug resulted in an increase of 4.8 % [18].

On the other hand, data from a number of meta-analyses show contradictory results on the role of selenium in improving the structural and functional state of the thyroid gland in AIT. So, in the systematic review of Fan Y. et al. (2014) confirmed the role of selenium in reducing the level of anti-TPO, improving the condition of patients, thyroid morphology, and the course of AIT. This allowed the authors to recommend the use of selenium in the complex treatment of AIT [19]. In a systematic review by van Zuuren E. J. et al. (2014), indicates that there is a lack of current knowledge to support or deny the effectiveness of selenium in the treatment of AIT [20].

Zinc also belongs to essential trace elements and has a regulatory effect on the synthesis of T4 through the thyroid-binding protein of the nuclear receptor, T3 has an effect on TSH secretion, which explains the need for this trace element to realize the biological effect of thyroid hormones. Changes in the level of zinc in the daily urine are an indicator for assessing thyroid dysfunction; for example, with its hypofunction, reduced excretion of zinc in the urine was detected. Copper, as metalloenzymes, takes part in the process of converting inorganic iodine into organic compounds, and it has a significant role in the formation of organic compounds. role in ensuring thyroid synthesis. It was found that copper deficiency contributes to the development of hypothyroidism through a decrease in the activity of iodinase involved in the addition of iodine to tyrosine, as well as through a decrease in the activity of cytochrome oxidase, ceruloplasmin. The dependence of the prevalence of non-toxic goiter on the level of copper content in the environment was studied; a decrease in the level of copper in the blood in children with diffuse goiter by 1.3-1.8 times compared to the control was found [21].

A number of trace elements are able to alter the immune response, while many elements are selective in the implementation of their regulatory functions. The possibility of the effect of trace elements on the immune system, specific points of application of their effects, and the effect on various stages of the metabolism of immunocompetent cells are established. All of the above gives grounds to

consider thyroid diseases as a result of the development and progression of polymicroelementosis, which requires additional research taking into account the specifics of regions with different ecological conditions and iodine availability.

The role of genetic factors in the development of AIT

As noted above, AIT is a polyethological disease based on a genetic predisposition, the contribution of which to the causal relationship of the development of autoimmune thyroid diseases is 75 % [2, 10].

Over the past two decades, significant progress has been made in uncovering genetic risk factors for the development of autoimmune thyroid diseases, including AIT. According to the results of V. I. Kandor's study in 2001, genes that are involved in the development of autoimmune thyopathy and are localized in chromosomes 2 (33), 6 (6p21), 8 (24), 12 (12q22) and 13 (13q32) [23]. Candidate genes predisposing to the development of autoimmune thyroid diseases were identified, which were divided into three main types: thyroid-specific genes, HLA system genes, and non-HLA immunoregulatory genes. The last group included genes C^A4 (CD152-cytotoxic T-lymphocyte-associated anti-gene-4), RTR no.2. The C^A-4 gene is considered as one of the most likely candidate genes associated with AIT. Carrier of the T allele of the C1858T polymorphism of the RTR gene No2 in women is associated with an increased risk of developing AIT [2, 24].

The genetic predisposition to the development of AIT is confirmed by the fact that it is associated with certain antigens of the main histocompatibility complex system-mainly with HLA class II antigens. According to available data, the hypertrophic form of AIT is combined with HLA DR5, while the atrophic form is combined with HLA DR3. It is believed that the HLA-DRW5 antigen is involved in the mechanism of goiter formation and induces the helper function of T-lymphocytes.

It is known that HLA antigens are markers of many autoimmune diseases, and therefore their detection can only indicate the presence of an innate predisposition to autoimmune reactions. Domestic and foreign researchers suggest that the immunogenesis of AIT is not a "morbidity gene", but a predisposition to this pathology. The latter fact is evidence of the presence of a genetic background, that is, the disease develops against the background of a genetically determined defect in the immune response, leading to T-lymphocytic aggression against its own thyrocytes, ending in their destruction. Under the influence of unfavorable factors, genetically determined defects of immune cells (defects of T-suppressors) lead to a breakdown of natural tolerance and T-helpers are able to stimulate B-lymphocytes and simultaneously produce cytokines [2, 8, 10, 24].

It should be noted that studies of genomic association with autoimmune thyroid diseases have established very low odds / risks ratios for most loci, and therefore it is of interest to conduct research taking into account national characteristics.

Violation of the mechanisms of immune regulation in AIT and hypothyroidism

The issue of primary immune system damage in AIT continues to be discussed in Russian and foreign literature. Despite this, the hypothesis of the development of autoimmune thyroid diseases proposed by R. Volpe (1991) remains relevant today. Thus, autoimmune thyroid pathology occurs as a result of a violation of regulatory processes in the immune system itself, and this violation is associated with a hereditary defect in antigen-specific T-suppressors (CD3+CD8+) and the influence of environmental factors on immunoregulation. As a result of this defect, a "forbidden" clone of organ-specific cells survives. T-lymphocytes that appear as a result of a random mutation. Due to the interaction of the "forbidden" clone of T-lymphocytes with complementary organ-specific antigens, damage to target cells occurs, which leads to the launch of a localized immune response of the delayed hypersensitivity type. Activation of T-lymphocytes is accompanied by the release of mediators that also have a cytotoxic effect. The action of T-helper lymphocytes (T-CD3+CD4+) on B-lymphocytes, followed by the transformation of the latter into plasma cells, leads to the formation of antibodies to TG and microsomal cells. protein structures of the follicular epithelium (anti-TPO). Circulating antibodies cooperate with killer T-lymphocytes on the surface of follicular

epithelial cells and have a cytotoxic effect on thyrocytes. This leads to cell destruction, gradual weight loss, and decreased thyroid function. The observed thyroid hyperplasia is a compensatory reaction that occurs in response to autoaggression and allows you to maintain the state of euthyroidism. In some cases, there are signs of hyperfunction of the thyroid gland, which is based on the destruction of tissue and the entry of previously synthesized hormones into the blood. An increase in the level of thyroid hormones is observed in 16 % of cases. At the same time, the production of TSH by the pituitary gland increases according to the principle of negative feedback. A long-term autoimmune process leads to progressive destruction of the thyroid parenchyma, an increase in dysregulatory disorders and the formation of fibrosis. Against this background, functional insufficiency of the organ develops — hypothyroidism [3, 8].

Numerous studies in AIT have revealed an imbalance in the subpopulations of T lymphocytes, pro-inflammatory and anti-inflammatory cytokines, and an increase in the number of activated polyclonal B lymphocytes and plasma cells that synthesize a wide range of autoantibodies [3, 6, 8].

In addition to a defect in the cellular immune system, the production of pro-inflammatory cytokines and disorders of apoptosis play an important role in the pathogenesis of AIT. During autoimmune processes in the thyroid gland, the expression of apoptosis molecules — the Fas receptor Fas ligand-increases on the surface of the thyrocyte membrane, and autocrine interaction between them induces a signal for switching on genes for programmed thyrocyte death. It is important to note that this process is significantly inhibited by TSH. In subclinical hypothyroidism, the expression of the Fas receptor is quite high; in clinically expressed hypothyroidism, its concentration decreases, but remains significantly higher than in healthy individuals. This fact indicates the reason for the transition of subclinical hypothyroidism to manifest hypothyroidism, which causes a heavier course of the disease, along with the inclusion of serious protective mechanisms in the late stages of the disease development, in particular, the inhibitory effect of TSH increasing in hypothyroidism [26].

In recent studies concerning the pathogenesis of AIT, an important place is given to studying the level of various cytokines. Interferon is considered the main candidate among known cytokines for a key role in the initiation of AIZ and regulation of autoantibody production. Interferon-y has been found to modulate the functioning and proliferation of thyroid follicular cells, as well as promote the induction of HLA class II expression. In the study Zdorov V. V. (2017), predictors of the severity of the clinical course of hypothyroidism and immune inflammation in the thyroid gland in AIT were established. Excess production was noted.-, TY2 -, TY7 -, and T-reg marker cytokines are closely associated with the severity of hypothyroidism. Interleukin-1a, interleukin-6, and interferon were repeatedly elevated in patients with AIT and, according to the results of ROC analysis, were predictors of the severity of the clinical course of hypothyroidism and autoimmune inflammation in the thyroid gland in AIT. The parallel increase in interleukin-6, inteleukin-10, tumor necrosis factor-a, and interleukin-17 parameters in AIT was considered by the author as a criterion for the progression of autoimmune thyroid inflammation and activation of thyrocyte apoptosis. Increasing dynamic levels of the factor tumor necrosis factor-a against the background of a dynamic decrease in the initially high level of interleukin-8 and the preservation of a low transforming growth factor-P 1 were prognostically unfavorable signs of the course of AIT. Interleukin-8 and interleukin-22 were indicators of functional thyroid epithelium preservation in AIT. For the mechanisms of persistence and progression of chronic autoimmune thyroid inflammation and thyroid epithelial proliferation in AIT, the absolute and relative deficiency of transforming growth factor-P1 against the background of an excess of interleukin-6 was pathogenetically significant, which was associated with a worsening of the imbalance between T2 cells and TY7 [27].

Investigation of the role of each specific cytokine in the context of a specific immune response in different thyroid functional states is of fundamental importance for integrating these mechanisms into the pathogenesis of autoimmune thyroid diseases and developing appropriate strategies for their modulation.

Organizational medical approaches for identifying and dynamically monitoring AIT patientsFor patients of dispensary group D 3 who have chronic diseases with impaired functions of organs and systems of the body and/or with periodic exacerbations, the scheme of dispensary observation is

determined. So, at the age of 0-18 years, the diagnosis of AIT can be made with normal thyroid function or with impaired thyroid function. The list of diagnostic tests for this category of patients includes:

- palpatory examination of the thyroid gland-1 time when AIT is detected, then-for medical reasons;
- measurement of body weight and length, blood pressure — at each visit;
- performing a general blood test, determining blood glucose — once when a disease is detected;
- determination of TSH, free T4, anti-TPO levels in the blood, thyroid ultrasound, electrocardiography-1 time for disease verification and then-for medical reasons;

The criterion for evaluating the effectiveness of follow-up is normalization of thyroid hormone levels. Children are removed from the dispensary register when they reach the age of 18. In the scheme of dispensary observation of the adult population, there is no diagnosis of AIT.

In the foreign literature, the organizational issues of dynamic observation are presented to a limited extent; there is information about the diagnostic value of determining antithyroid antibodies. According to a number of authors, TPO is the main component of the thyroid microsomal antigen, is expressed on the apical surface of thyrocytes, and is a glycosylated heme-containing protein that plays an important role in the process of iodination and synthesis of TG. Thyroperoxidase can be a surface-cell antigen that is involved in the process of complement-dependent cytotoxicity and is capable of cause cytotoxic damage to the thyroid gland and death of thyrocytes. However, it is rather difficult to state that antibodies to the membrane antigen — anti-TPO-play a pathogenetic role in autoimmunity of thyroid diseases. Antibodies can simply respond to the release of antigen from the damaged thyroid gland [29]. There was a correlation between the anti-TPO titer and histological changes in AIT. The an-ti-TPO titer also correlates well with the severity of thyroid tissue infiltration by autoreactive lymphocytes and the degree of hypoechogenicity during ultrasound examination [8].

Antithyroglobulin antibodies are produced against TG, one of the most studied thyroid antigens, which is a precursor of thyroid hormones. Anti-TG binds to TG, disrupting hormone synthesis and causing hypothyroidism. Determination of anti-TG is performed to assess the severity of autoimmune reactions in thyroid diseases. It was found that increased amounts of anti-TG in a high titer circulate in the blood serum of 60-80 % of patients with AIT. In order to diagnose AIT, simultaneous detection of anti-TPO and anti-TG is recommended. Although there is an opinion that from the point of view of diagnosis and economic benefits, the definition of anti-TG is hardly justified, there is no strong correlation between the levels of 2 of these antithyroid antibodies. It was shown that among all patients positive for thyroid antibodies, only anti-TPO is detected in 64% of cases, and only anti-TG-in 1 % [29].

Conclusions

1. Conflicting literature data do not indicate the true level of morbidity AIT and do not make it possible to draw a parallel between the incidence of hypothyroidism and AIT, which is the cause of primary hypothyroidism in more than 70-80% of cases. This may be based on the lack of unified organizational medical approaches and diagnostic capabilities of medical institutions.
2. The current direction of research is to search for objective criteria for selecting patients with an increased risk of developing complications of AIT in order to develop and personalize dynamic follow-up. This will optimize organizational and medical measures for this category of patients.

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