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SCIENTIFIC REVIEWS AND LECTURES

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GENETIC FACTORS OF PREDISPOSITION TO AUTOIMMUNE THYROID DISORDERS

ABSTRACT
The article presents a review of the literature about the genetic factors of predisposition to autoimmune to thyroid disorders, the main of which are diffuse toxic goiter and autoimmune thyroiditis. Studies of recent years have made it possible to establish that genetic factors make a significant contribution to the development of the autoimmune process in autoimmune to thyroid disorders.
Keywords: endocrine system diseases, autoimmune thyroiditis, diffuse toxic goiter, genetic factors, predisposition.

Significant changes in the function of the endocrine system in the human body occur in the North, first of all, under the influence of cold. Thus, the production of thyrotropin-stimulating hormones and glucocorticoids increases, the high level of which contributes to the increase of nonspecific resistance of the organism to the cold.

Thyroid hormones increase metabolism, separate oxidation and phosphorylation processes, and also activate the biogenesis of mitochondria. It is known that the level of thyroid hormones in the blood under physiological conditions is regulated mainly by internal (thermal) and external (cold) thermoreceptors [18].

Among the various effects of thyroid hormones, the greatest attention of researchers is drawn to the effect of these compounds on energy processes and basic metabolism, the so-called «caloric effect».

The introduction of thyroid hormones to animals significantly increases the thermogenesis and oxygen consumption of the body. The stimulating effect of thyroxin on the formation of brown fat in rats is shown, which is one of the manifestations of adaptation of small animals to cold.

Thus, the thyroid gland plays an important role in the regulation of heat exchange, and, consequently, the degree of adaptation of the organism to the effect of low temperatures on the human body. Because of how correctly the thyroid gland functions, the person's working capacity, his activity and vital activity depends.

The Republic of Sakha (Yakutia) refers to territories with extreme temperature and light conditions, a pronounced seasonality of the climate, which contributes to the high prevalence of thyroid pathology both among children and adults [15].

In the structure of diseases of the thyroid gland the leading place is occupied by autoimmune diseases [3, 9, 43], the main of which are such diseases, accompanied by pathological conditions as hyperthyroidism (diffuse toxic goiter) and hypothyroidism - autoimmune thyroiditis (Hashimoto's thyroiditis).

Autoimmune thyroiditis is an activation of the immune system in the thyroid gland with the phenomena of lymphocytic infiltration (the penetration of lymphocytes into the tissue), in which specific thyroid antibodies are detected in the blood, which is evaluated as a sign of inflammation. According to different authors, the prevalence of thyroiditis in the world is from 1% to 12%, more often this pathology occurs in older persons [14].

The autoimmune thyroiditis is characterized by the appearance of antibodies to thyroperoxidase(AT - TPO), thyroglobulin (TG). When antibodies (AT) are combined with T-killers, the latter acquire cytotoxicity and destroy the thyroid follicles. In their place, connective tissue proliferates.

Variants of the course of the hypothalamus thyroiditis:

1. Depending on the size:
- hypertrophic, can be combined with nodes;
-atrophic.
2. Depending on the function of the thyroid gland, distinguish:
- normal ;
- hyperthyroidism (phase of thyrotoxicosis or Hashimoto-toxicosis);
-lowed-hypothyroidism (it is a natural outcome of the disease).

Autoimmune thyroiditis develops slowly. There is no characteristic clinical picture, as well as with iodine deficiency goiter. There are clinical manifestations associated with an increase in the thyroid gland and a violation of its function:

1. Syndrome of a lesion of a thyroid gland. Complaints in patients are associated with an increase in the organ and are not specific for the disease. With palpation more often than with endemic goiter, it is possible to find a compaction of the thyroid gland; the consistency of the gland is uneven, it is mobile, there may be a sensation of the node (s). These signs target the doctor to exclude

autoimmune thyroiditis from the patient and must necessarily be supplemented by a set of changes in the ultrasound examination of the organ and the presence of AT to TPO according to the Consensus adopted in 2002.

2. Syndrome of functional disorders: distinguish between eutireosis, hyperthyroidism and hypothyroidism. In the early stages, hyperthyroidism can be diagnosed,euthyroid status is more likely to occur, later on, turning into hypothyroidism

In the recent past, when a clinically significant titer of thyroid antibodies was obtained, the diagnosis of autoimmune thyroiditis was considered to be verified. Currently, the Consensus (2002 II Russian Thyroid Congress) on the diagnosis and treatment of autoimmune thyroiditis, according to which the presence of antibodies to thyroid tissue (antibodies to thyroid peroxidase or microsomal fraction) and primary hypothyroidism (manifest or persistent subclinical) is one of the «Large» diagnostic signs, in the presence of only one of them, the diagnosis of autoimmune thyroiditis cannot be established [7].

The term autoimmune thyroiditis, classified by Davies and Amino, published in the journal Thyroid in 1993, implies both Hashimoto's thyroiditis and Graves' disease, subdivided into types 1 and 2, which in turn are subdivided into subtypes A, B and C [23].

The well-known immunologist R. Volp (1999), only indicates that the treatment of autoimmune thyroiditis reduces to the treatment of hypothyroidism, if it has already developed, and specific methods of treatment are not yet available. In the works of Arbelle J.E. and Porath A., [20] analyzed and compared the recommendations of the American Association for Clinical Endocrinology (AASE), the American College of Physicians (ACP), the Royal College of Doctors UK (RCP) and the American Thyroid Association (ATA), diagnosed and treated autoimmune thyroiditis in phase of euthyroidismis not discussed. In foreign scientific literature, autoimmune thyroiditis as an independent clinical problem is practically not considered. Only the most important outcome of the autoimmune thyroiditis - hypothyroidism - is discussed in detail. At the same time, in the domestic literature, autoimmune thyroidism is regarded as an independent clinical problem. [11].

According to researchers, in the role of a trigger in autoimmune thyroiditis, the main role is played by environmental factors and infections, while data on infections as triggers of the autoimmune process is not enough [19]. In 2012, Zemskova E.A. with et al. using the method of mass spectrometry of microbial markers for assessing the parietal intestinal microbiota [12] suggested that the growth factor of autoimmune thyroiditis in children may be excessive growth in the parietal intestinal microflora of eubacterium (Eubacteriumlentum) [5].

For the first time in the 1960s, the term «thyroid-gastric syndrome» arose which refers to the simultaneous presence of autoantibodies to the thyroid gland in patients with pernicious anemia and atrophic gastritis [4]. It is proved that among patients with atrophic gastritis, autoimmune thyroiditis is diagnosed in 40% of cases [33].

Especially relevant diagnosis for the first time in the 60s of the twentieth century the term thyroid-gastric syndrome appeared which denotes simultaneous presence of autoantibodies to the thyroid gland in patients with pernicious anemia and atrophic gastritis [4]. It is proved that among patients with atrophic gastritis, autoimmune thyroiditis is diagnosed in 40% of cases [33].

Especially relevant is the diagnosis of autoimmune thyroiditis for people living in ecologically unfavorable zones. It is known that women (3-20 times) are sick more often than men.

As the etiological factors, we can now consider:

1. Environmental factors (radiation, chemical factors);
2. For children, an important role is chronic tonsillitis, considering the general lymphoid ring with thyroid gland;
3. Severe infectious and somatic diseases;
4. Excess iodine during therapy with drugs containing it;
5. Combination with autoimmune diseases of endocrine and non-endocrine origin;
6. The second disease on the background of iodine deficiency;
7. Medicinal preparations;
8. Stress.

A large share in the development of the autoimmune process in autoimmune thyreopathy is heredity. According to the results of the study Kandror VI In 2001, genes were detected that are involved in the development of these diseases, localized in chromosomes 2 (2q33), 6 (6p21), 8 (8q24), 12 (12q22) and 13 (13q32) [8].

It is established that autoimmune thyroiditis develops in hereditarily predisposed individuals and a connection with the HLA system is revealed. It is believed that the antigen HLA-DRW5 is involved in the mechanism of goiter, and HLA-DR3 induces the helper function of T-lymphocytes. A number of studies have shown that atrophic thyroiditis is associated with HLA-DR3, and hypertrophic - with HLA-DR5 antigens [13].

Genetic factors make their significant contribution. Under the influence of unfavorable factors, genetically caused immune cell defects (defects of T-suppressors) lead to a breakdown in natural tolerance and T-helpers are able to stimulate B-lymphocytes and simultaneously produce cytokines. All this leads to a change in the function of target cells, which express class II antigens, heat shock proteins, and intercellular adhesion molecules, and thereby enhance the immune response.

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In the works of O.Kochetova. (co-authored, 2014) showed the association of polymorphic variants of the gene DI02 (274A> G) with an increased level of antibodies to TPO and the TPO gene (2173A> C) with an increased level of free T4. The genotype GG and the allele G of the D102 gene (274A> G), the genotypes of the CT and CC of the CYP1A1 gene (-3798T> C), and the genotypes of the TD and DD of the CYPIA2 gene (-2467delT) were proposed as markers of predisposition to the development of nodular goiter associated with the development of autoimmune thyroiditis [10] .If association study of polymorphic variants of genes CYP1A1 and CYP1A2 with the development of thyroid disease in women employed in the petrochemical industry, also identified markers of predisposition to the node goiter (SSCYP1A1 allele gene) and homozygous TTCYP1A2kotory gene is associated with Hashimoto's thyroiditis in women [1].

Diffusive-toxic goiter (first described in 1825 by C. Parry, in 1835 by R. Greaves, and in 1840 by K. Bazedov), or the so-called Graves' disease, a frequently diagnosed autoimmune disease of the thyroid gland . The prevalence of diffuse toxic goiter reaches 0.5%, the frequency of detection during pregnancy is 0.05-3%. It occurs mainly at the age of 20-50 years, in women 7 times more often than in men. Toxic goiter in 90% of patients is diffuse and in 10%

The prevalence of nodular goiter in regions with iodine deficiency regions 30% and is the most common change on the part of the endocrine glands [40, 35].

The disease affects the functional work of various human organs. Especially it violates the work of the central nervous system and cardiovascular system. It is characterized by a diffuse increase in the thyroid gland and a persistent pathological increase in the production of thyroid hormones - thyrotoxicosis [16].

The reasons for the development of thyroid nodules are not fully known. Factors contributing to development include both endogenous and exogenous factors [29, 28].

Diffusive-toxic goiter is an autoimmune disease with a genetic predisposition. Violations are inherited from parents to children. A persistent pathological increase in the production of thyroid hormones is due to thyroid-stimulating antibodies, which are more active than thyroid hormones, and last longer. In fact, antibodies simulate the action of the natural thyroid hormone, they are able to enhance the synthesis and secretion of thyroid hormones. Antibodies are formed as a result of the development of the body by «incorrect» T-lymphocytes (suppressors), which instead of controlling the adequacy of the immune response, begin to destroy the thyroid gland.

These antibodies contribute to an increase in the thyroid gland, increase proliferation of thyroid cells and inhibit apoptosis. Increased thyroid volume, increased blood flow in the gland and its lymphatic infiltration leads to hypertrophy of thyroid cells and hyperplasia.

In the opinion of some authors, the diffuse-toxic goiter is autosomal recessive, in the opinion of others it is autosomal dominant. Most likely, there is a multifactorial (polygenic) type of inheritance. In the relatives of persons suffering from thyroid gland diseases (diffuse toxic goiter, idiopathic myxedema, autoimmune thyroiditis), an increase in the antibody titer to various components of the thyroid gland, as well as antibodies to other organ-specific antigens (gastric, adrenal, ovarian, etc.) compared with persons who are not suffering from thyroid disease. Genetic studies show that if one of the monozygotic twins is ill with diffuse toxic goiter, then for another, the risk of the disease is 60%; In the case of dizygotic pairs, this risk is only 9%

However, the genetic apparatus is not the determining and sole cause of the development of diffuse toxic goiter. It is believed that Graves' disease is a disease in which the genetic features of immunity are realized against the background of environmental factors such as:

- stress;
- viral infections;
- use of antiviral drugs;
- excess in the body of iodine;

Syndrome of thyrotoxicosis is the main clinical manifestation of diffuse-toxic goiter. Thyrotoxicosis is a syndrome that occurs in various pathological conditions of the human body. The frequency of thyrotoxicosis in Europe and Russia is 1.2% [17].

Syndrome of thyrotoxicosis is confirmed by the content of blood TSH (thyroid stimulating hormone) and free hormones T3 and T4 (thyroid). TSH decreases, and T3 and T4 increases with diffuse-toxic goiter. When diagnosing diffuse-toxic goiter, it is established that the level of the hormone T4 in the blood is less than T3, and the hormone T4 normalizes much faster than T3.

It was suggested that mutations of the pTTG gene [34] and Gs proteins precede the appearance of toxic adenomas of the thyroid gland [27].

Other studies have also revealed activating mutations of the TSH receptor gene in autonomous functioning thyroid nodules [36, 32, 38, 42, 22, 39, 30, 24, 2]. In iodine-deficient regions, mutations in the TSH receptor gene are more common and occur in about 57-82% of cases, making them the most frequent genetic abnormalities found in autonomic thyroid nodules [26, 37, 31, 25, 21].

A study of genetic disorders at the GNAS-1 locus that encodes the Gs protein (the replacement of Asp 619 Gly) revealed a point mutation, a subunit of the Gs protein (Asp 619 Gly), which results in a persistent receptor activation, but the mutations of this gene were detected only in a small number (2-10%) of autonomously functioning nodes [34, 37, 37]. Activating mutations of the TSH receptor are found in both safe and iodine-deficient regions [41].

A close cohesion of a number of antigens of a large histocompatibility complex (DW3, CW4, B8, WHO, B27, A3, At A28) and Graves disease (in mainland Europe it is called Basedow disease) disease was also established. In most cases, the presence of the alleles HLA-B8 BW-35 in patients with diffuse toxic goiter is described. The presence of this antigen increases the genetic risk by 2.02 times, and the haplotype A1-B8 - by 4.23 times. In persons with thyrotoxicophthalmopathy, adhesion to the haplotype HLA B8-CW3 was found. The association of the disease with HLA DR antigens is also proved. At the same time, the frequency of occurrence of HLA DW3 antigen in people with relapses of thyrotoxicosis is reported. HLA B40 antigen can serve as a prognostic sign of a severe course of the disease.

Based on the above data, domestic and foreign researchers, we can conclude that the development of autoimmune thyroiditis and diffusive-toxic goiter is

the result of a joint action of genetic and environmental factors. Yakutia belongs to territories with extreme temperature and light conditions, sharply pronounced seasonality of the climate, to the most unfavorable regions of the Russian Federation for iodine deficiency, with high prevalence of thyroid pathology both among children and adults. In Yakutia, endocrine diseases such as type 2 diabetes [6] and autoimmune thyroiditis are the most common. In this regard, the study of genetic risk factors for the development of autoimmune thyrepatitics among residents of the Republic of Sakha (Yakutia) is relevant.

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