as coronary heart disease and a cerebral stroke. The high risk of development of cardiovascular complications dictates need of further profound studying of all factors influencing formation of health of the population in the remote districts of Yakutia.

The research was carried out within the framework of the research work of the YSC CMP "The contribution of the metabolic syndrome to the development of atherosclerosis of coronary arteries in Yakutia residents" and the research and development of new technologies for the treatment and prognosis of the risk of arterial hypertension and stroke in the Republic of Sakha (Yakutia) "(State Contract No. 1133).

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GRAVE'S DISEASE. MODERN REPRESENTATIONS AND DISTRIBUTION IN THE TERRITORY OF THE REPUBLIC OF SAKHA (YAKUTIA)

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ABSTRACT

The article presents historical and modern ideas about Graves' disease (GD), new approaches in treatment and diagnostics and the results of studies of foreign and domestic scientists on the role of genetic factors in the development of GD. In the Republic of Sakha (Yakutia), the share of GD in the structure of endocrine pathology ranks 2.3%. The Arctic regions are in the first places by the frequency of occurrence of GD.

Keywords: thyroid gland, Graves' disease, thyrotoxicosis, genetic markers, genetic predisposition.

Diffusive-toxic goiter (DTG) 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.

The first mention of this disease was made in 1722 - the Irish doctor Ives S. and then in 1786, described in more detail the English physician Parry (1786). The most famous description of this disease was made in 1835 by Robert Graves, and in 1840 by the German doctor Karl Bazedov, who described in more detail about 4 cases of the disease and classically classified the so-called «Merzebur tribes», characteristic symptoms of bladder, goiter and tachycardia.

The opinion of researchers about the genetic conditionality of this disease diverge, the authors believe that the days are inherited by the AR type, others by the AD type, and some - by the fact that there is a multi-factor (polygenic) type of inheritance.

Genetic studies show that if one of the monozygotic twins is ill with diffuse toxic goiter, then for another, the risk of getting sick is 60%; In the case of dizygotic pairs, this risk is only 9%.

Outstanding domestic clinician S.P. Botkin (1884) wrote about the role of mental trauma, both on development and the course of DTG. Also, according to the data of the Soviet endocrinologist N.A. Shereshevsky, 80% of patients with this disease had a history of mental trauma. V.G. Baranov and co-authors (1961) established a connection with a trauma in 7.5% of the 480 respondents with this disease. And according to Trotter (1962), etc., the mental trauma has no clear connection with the development of the disease.

Scientists also suggest the relationship between the development of DTG and the provision of the body with zinc. In the studies of D.S. Vinchenko (with co-authors, 2016) showed that in patients with diffuse-toxic goiter in 70% of cases, the level of zinc in the hair is reduced [12].

Autoimmune diseases of the thyroid gland, including DTG and AIT, are common and affect up to 5% of the population as a whole. Over the past decades, there has been significant progress in understanding the genetic contribution to the etiology of autoimmune thyroid diseases. Several genes of susceptibility to these diseases have been identified and characterized. So the genes of predisposition to DTG, AIT, and genes to both of the above diseases were found.

It is believed that DTG is a disease in which genetic features of immunity are realized against the background of environmental factors such as stress, viral infections, the use of antiviral drugs, excess in the body of iodine.

The first locus of the susceptibility gene to autoimmune thyroid diseases was the locus of the human DR leukocyte antigen (HLA-DR) genome [26].

At present, close cohesion of a number of large histocompatibility complex antigens (DW3, CW4, B8, WHO, B27, A3, AT A28) and DTG has been established. In most cases, the presence

of the alleles HLA-B8 BW-35 in patients with diffuse toxic goiter is described. The link between the disease and antigens of HLA DR3 was also proved. At the same time, the frequency of occurrence of HLA DW3 antigen in people with relapses of thyrotoxicosis is reported [2, 13, 15, 18, 23, 24, 27].

A study of Caucasian patients with DTG showed that the high prevalence of haplotype DRB1 * 03 DQA1 * 05 DQB1 * 02 indicates association with the disease [30].

At studying the distribution of the alleles of the loci HLA-B, C, DRB1, DQA1, and DQB1 among 500 patients and control groups from the UK, it was noted that the strongest link was with HLA * C, and the next most strongly associated locus was DRB1 [20].

In 2011, Chen et al. published the results of studies of the association of HLA with DTG in the Asian population, in which the authors found that HLA-DPB1 * 05: 01 was the main gene predisposing to DTG among Han Chinese.

Relatively few studies on HLA-associations with GD were conducted among blacks. And basically the research was done on a limited number of patients, and only in the studies of M.A. Omar (et al., 1990) found an association with variant DRB1 * 03 [25].

Italian researchers discovered three SNP markers rs13097181, rs763313 and rs6792646 at the 3q locus, which showed little association ($p < 0.05$). There were also significant associations with the thyroid-stimulating hormone receptor gene (TSHR), the cytotoxic T-lymphocyte antigen-4 (CTLA-4) gene and the thyroglobulin (TG) gene [21].

At present, the role of immunological and genetic factors in the development of DTG has been sufficiently studied [7, 5, 1], in recent years, studies in the field of using immunological, genetic and morphological markers in predicting the results of conservative and operative treatment of DTG have become topical [5, 9].

In the course of the research L.V. Trukhina (2006) revealed the most informative risk factors for postoperative relapse of DTG, which include the immunological parameters of AT and RTTG and AT to TPO. She also showed that the polymorphism of genetic markers D6S1271 and D6S2414 (HLA DQ) cannot be used to predict the outcomes of surgical treatment [16].

Diagnosis DTG consists of the study of thyroid hormones, visual-palpatory evaluation and ultrasound. The main complaints of patients are associated with cardiovascular (tachycardia), neurological disorders and endocrine ophthalmopathy (Graves' ophthalmopathy, autoimmune ophthalmopathy). Upon examination, the thyroid gland is diffusely enlarged, painless, mobile, of moderate density, due to significant blood supply, systolic noise can be heard. In the study of hormones, the concentration of free thyroxin and triiodothyronine is increased, and the production of thyroid-stimulating hormone is reduced. When ultrasound is detected diffuse increase in the thyroid gland, the structure is hypoechoic, a significant increase in blood flow to the tissue. When carrying out scintigraphy with 99mTc - diffuse enhancement of the isotope capture by the gland (131I and 99mTc). «On the ECG - note the increase in heart rate, observe high pointed teeth P and T, in complicated cases - atrial fibrillation, extrasystole, ST segment depression, negative T wave. In 1/3 of patients, signs of left ventricular functional hypertrophy disappear after elimination thyrotoxicosis «[4].

In 1871 Lister conducted the world's first DTG operation. In Russia, the first surgical intervention on the thyroid gland in DTG was performed by I.D. Sarychev in 1893, Moscow [10]. The resection technique of the thyroid gland, developed by O. Nikolaev (1952) was widespread in the USSR. An effective method of conservative treatment using thyreostatic drugs was proposed by E.V. Astwood (1943).

Currently, there are three main methods of DTG treatment - drug, surgical and radiological. The attitude towards the latter method in different countries is not unambiguous [11]. The main and widespread approach due to the relatively high therapeutic effect is conservative therapy. But therapy with thyreostatics has its drawbacks due to the high risk of recurrence of the disease and the occurrence of complications. In many European countries, in the United States and Canada, the use of artificial radioactive isotope iodine (iodine-131) is becoming increasingly important because it is relatively simple and economical. At the same time, many researchers believe that radioiodine therapy negatively affects the course of endocrine ophthalmopathy (2, 22, 29, 31). In the studies conducted by A.V. Dreval, A.F. Tsyb [et al.] (2007) worsening of the course after was observed in 47.7% of patients. In doing so, they argue that the treatment of ophthalmopathy before the application of radioiodine therapy improves the course of endocrine ophthalmopathy after radioiodine therapy [11].

The use of radioiodine therapy for effective elimination of thyrotoxicosis is confirmed by Russian and Ukrainian doctors [6, 8]. Studies conducted in 2014-2015 by E.V. Krizhanovskaya and S.A. Nabokov, showed that in the period up to 4 months after therapy only in 6.7% of patients there was thyrotoxicosis, but in the subsequent recurrence of the disease was not revealed, a complication of endocrine ophthalmopathy was noted in one patient [8].

Recently, a number of European countries, as well as in the US, widely used thyroidectomy (complete removal of the thyroid gland) followed by the use of hormone replacement therapy throughout life.

In Russia, unlike in other countries, the treatment of patients with DTC is carried out in a conservative manner, and they are subjected to surgical intervention mainly with relapses of the disease. With relapse of thyrotoxicosis after surgical treatment and conservative therapy, radioiodine therapy is used [28]. In Russia, with surgical treatment of DTG, subtotal resection is used according to O. Nikolaev's technique, leaving 4-6 grams of tissue.

The clinic of the Samarkand State Medical Institute analyzed two methods of surgical intervention for DTG. In the first group of patients after surgery about 8 grams were preserved, and about 2 grams of the thyroid parenchyma was left after the total thyroidectomy in the 2nd group. So relapse of the disease in the first group of operated patients was 11.1%, and in the second group there were no relapses. Thus, the preservation of 2-3 grams of the thyroid parenchyma with total thyroidectomy makes it possible to maintain the hormonal status without the risk of relapse of DTG [17].

In 2012, the results of a study of the use of intravenous ozonotherapy in patients with DTG along with traditional treatment were published, and a comparative analysis showed that the use of infusion ozonotherapy beneficially affects the regression of symptoms and accelerates the rate of occurrence of euthyroidism [14].

In the structure of the endocrine pathology, thyroid diseases are in the second place [19]. In the Russian Federation, the incidence of DTG is about 1%.

It is believed that Yakutia belongs to iodine-deficient regions, on the territory of the republic there are areas with anthropogenic pollution of the biosphere (industrial areas), areas in which underground nuclear explosions were produced with the release of plutonium isotopes into the atmosphere. Also, a huge role in the pollution of the biosphere

was played by the construction of one of the largest reservoirs of Siberia. During the construction of the Viluiskaya HPP, huge areas of the taiga were flooded, the main component of the forest was occupied by coniferous trees, with the decomposition of which a lot of zobogenic microelements are allocated [3].

As of 2017, the number of registered with the diagnosis of DTG was 1274 patients, this is 2.3% of all patients with endocrine pathology (54765 patients).

As can be seen from the table, the greatest number of DTG patients is found in Yakutsk, as well as in industrial areas (Myrninsky, Nyurbinsky, Neryungrinsky), as well as agricultural areas (Table 1). According to V.I. Gagarin (since 2002) this is due to the fact that in this group of regions the only source of drinking water is inaccessible water bodies.

An analysis of the frequency of occurrence of DTG in relation to the average population shows that the highest incidence of DTG is observed in the Arctic (northern) regions of Yakutia: Momsky (0.73), Bulunsky (0.65), Abyisky (0.56) and in the Churapchinskiy district (0.50).

Conclusion

It can be concluded that the development of DTG is the result not only of ecological (environmental) factors, but also genetic ones. According to the State Bank of the Republic Sakha (Yakutia) «Yakut Republican Endocrinology Dispensary» in 2017, the number of patients with diffuse-toxic goiter was 1274 patients, and in 2015 this number was 1298 people, i.e. over the past two years, a significant shift in the number of patients with this disease is not observed. And based on the above data, domestic and foreign researchers, we can say with confidence that the study of genetic factors in the development of diffuse-toxic goiter among residents of the Republic of Sakha (Yakutia) remains relevant.

List of areas of the Republic Sakha (Yakutia) with the highest prevalence of DTG *

Area	Number of patients	Average annual population	% in relation to the average population
Yakutsk	273	324651	0,08
Mirninsky	133	72914	0,18
Churapchinsky	97	19200	0,50
Nyurbinsky	71	24135	0,29
Bulunsky	55	8404	0,65
Aldan	47	39858	0,12
Neryungri	45	74986	0,06
Tattinsky	44	16358	0,27
Viluysky	39	24719	0,16
Momsky	30	4099	0,73
Abyisky	23	4044	0,56
Ust-May	23	7368	0,31
Total for the RS (Ya)	1274	962 835	0,13

* for 2017 (according to the State Bank of the Republic of Sakha (Yakutia) «Yakut Republican Endocrinology Dispensary»).

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SINGLE NUCLEOTIDE POLYMORPHISMS OF ADD1α, AGT, AGTR1 AND AGTR2 GENES IN DIFFERENT ETHNIC GROUPS OF YAKUTIA ARCTIC ZONE RESIDENTS, SUFFERING FROM ARTERIAL HYPERTENSION

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ABSTRACT

The article presents the results of the study of the frequencies of occurrence of single nucleotide polymorphisms of the genes *ADD1α (1378 G> T), AGT (704 T> C and 521 C> T), AGTR1 (1166 A> C)* and *AGTR2 (1675 G> A)* groups of residents of the Arctic zone of the RS (Ya), suffering from essential arterial hypertension. Subjects of the research were represented by the most widespread ethnic groups in the territory, including the Slavs, Yakuts, Evens and Evenks. To reveal the above mentioned polymorphisms, a real-time PCR method was used with detection of the melting temperature of duplexes. In the course of the study statistically significant differences between the study groups were identified by the points ADD1α 1378 G> T; AGT 521 C> T and AGTR1 1166 A> C.

Keywords: arterial hypertension, single nucleotide polymorphisms, *ADD1α, AGT, AGTR1, AGTR2*, real-time PCR, ethnic groups of the Arctic zone.