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The Value of Gene Polymorphism in the Choice of Tactics for the Treatment of Diffuse Toxic Goiter

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Abstract: In recent years, the reasons for the development of such postoperative complications as hypocalcemia have been studied. Current prevention of postoperative hypocalcemia insufficiently developed. In this regard, it is relevant to conduct additional studies to study methods for the prevention of postoperative hypocalcemia. Preoperative vitamin D treatment is likely to prevent postoperative hypocalcemia.

Keywords: diffuse toxic goiter, genes, postoperative hypocalcemia, pathogenesis.

In recent decades, the nature of the course of diffuse toxic goiter (DTG) has changed: there has been a decrease in the number of remissions of DTG and an increase in relapses of the disease [7]. It seems important to study the dynamics of the clinical course of DTG based on the results of conservative and surgical treatment over a long period of time.

Currently, there are no reliable criteria for remission of DTG. In the available clinical guidelines of the Russian Federation for the treatment of DTG, it is proposed to evaluate the remission of the disease after 12-18 months of conservative therapy. If, despite taking antithyroid drugs, the patient recurs thyrotoxicosis (TT), then the probability of remission is low. In this regard, it seems relevant to develop prognostic criteria for DTG remission at the time of diagnosis in order to resolve the issue of treatment tactics.

Despite a long course of antithyroid therapy (12-18 months of treatment), some patients do not achieve disease remission [1].

Further treatment tactics involve radical methods of treatment: extirpation of the thyroid gland (TG) or radioiodine therapy. However, long-term treatment with maintenance doses of antithyroid drugs in some cases can contribute to the formation of remission. Studies on achieving remission with long-term antithyroid therapy are controversial and require further study.

In recent years, the role of genetic factors in the pathogenesis and clinical course of DTG has been actively studied [5]. Polymorphism variants of the interleukin-6, 13 and microRNA-125A genes, as well as changes in their cytokine profile, affect not only the predisposition to DTG, but also the clinical course.

According to domestic recommendations, in patients with DTG, thyroid extirpation is performed, which excludes the recurrence of TT, but patients are forced to receive lifelong hormone replacement therapy with L-thyroxine preparations [3]. According to the results of a number of studies, after thyroidectomy, patients with DTG may develop undesirable phenomena: postoperative hypocalcemia, uncompensated hypothyroidism, weight gain [4].

However, the results of observations of operated patients are contradictory and require further study.

Patients with DTG who underwent thyroidectomy have a high risk of developing postoperative hypocalcemia [36]. Prevention of postoperative hypocalcemia in patients with DTG has not yet been developed. It seems important to conduct a study to study the effectiveness of preoperative preparation with vitamin D3 preparations in patients with DTG.

Promising are studies to compare the data of histological postoperative studies with long-term results of surgical treatment - 3-5 years or more after surgery.

The relevance of such studies is due to the need to find new approaches to predicting the results of surgical treatment in patients with DTG.

At present, the processes of proliferation and apoptosis of thyrocytes in patients with DTG have begun to be actively studied. The nuclear protein Ki-67 is a proliferation marker, including that of thyrocytes [1]. It is possible that the suppression of apoptosis and increased proliferation of thyrocytes in DTG is facilitated by an increase in the expression of antiapoptotic molecules, such as Bcl-2, and a decrease in the expression of the apoptotic Fas protein [3]. The study of the morphological and functional characteristics of the thyroid gland, factors of proliferation and apoptosis in patients with DTG is important for predicting postoperative outcomes.

Diffuse toxic goiter is an autoimmune disease [5], which is based on a congenital defect in the immune system [3]. Increased synthesis of autoantibodies to thyroid-stimulating hormone receptors leads to hypersecretion of thyroid hormones [7].

The clinical picture of DTG depends on various factors such as: genetic characteristics, the level of iodine and selenium supply, stress factors, the impact of adverse environmental factors [8].

DTG is based on a genetic defect in the immune system [5] associated with the HLA system (HLA DR3, B8, DQA1 × 0501, DR4, CTLA 4.

The level of iodine supply in the region where DTG patients live is the most important factor influencing the functional activity of the thyroid gland. It is known that iodine is a trace element that is necessary for the synthesis of thyroid hormones. As a result of a decrease in the intake of iodine in the body, iodine deficiency diseases develop - diffuse or nodular goiter, TT due to the functional autonomy of the thyroid gland. And with more severe iodine deficiency - hypothyroidism [10]. To prevent iodine deficiency diseases, since the 70s in many countries, and since 1999 in the Russian Federation, measures have been taken to eliminate iodine deficiency. A rapid change in the level of iodine supply in a population can lead to the manifestation of DTG in genetically predisposed individuals [11]. According to the results of a study conducted in Australia, studying the course of DTG against the background of a changing level of iodine supply (during mass iodine prophylaxis), it was shown that the detection of DTG significantly increased, while the development of TT due to the functional autonomy of the thyroid gland, on the contrary, decreased [2].

Stress factors play an important role in the manifestation of DTG. As a result of a stressful situation, cortisol secretion increases and, as a result, the activity of suppressor T-lymphocytes is suppressed and autoreactive lymphocytes are released. During the war in Yugoslavia, the prevalence of DTG increased from sixty to one hundred and sixty patients per one hundred thousand of the population, despite the absence of changes in the iodine supply of the region [358]. A study conducted in Japan showed that in 2004 the earthquake was associated with an increase in the recurrence of DTG [7]. Thus, the reduction of stressful situations is an important condition for improving the prognosis of patients with DTG [3].

The role of interleukins, including IL-6 and IL-13, has been actively studied in recent years in many diseases, including DTG. IL-6, participating in cell proliferation and differentiation, control of their vital activity and apoptosis [13], plays an important role in the regulation of the cardiovascular, nervous, endocrine, immune and hematopoietic systems. Most cells (T-cells, B-lymphocytes, eosinophils, dendritic cells, macrophages/monocytes, etc.) in the human body produce IL-6. It is known that IL-6 is involved in the regulation of both types of T-helper cells and can stimulate the differentiation of B-lymphocytes, the production of immunoglobulins, influence the differentiation of T-cells [1], as well as the differentiation of antigen-presenting cells [8]. Due to the variety of

properties of IL-6, there are works on the study of this indicator in healthy individuals and in patients with DTG.

In the work of T.P. Maklakova et al. (2019) evaluated the concentration of IL-6 in patients with DTG before the start of antithyroid therapy and after the end of treatment. In patients with DTG, the concentration of IL-6 was higher both at the time of diagnosis and after 4-6 months of therapy, compared with the results in the control group [10]. In the work carried out by LF Lv et al . similar results were obtained in 2017 [13]. When comparing the level of IL-6 in patients with DTG and healthy individuals, it was shown that this indicator is significantly higher in patients with DTG. The level of IL-6 correlates with the severity of the TT syndrome.

It is known that the synthesis of IL-13 is carried out by activated type 2 T-helpers and IL-13 is involved in the maturation of B-lymphocytes. By suppressing the synthesis of other pro-inflammatory ILs (interleukin-1, interleukin-6, interleukin-10) and chemokines, IL-13 exhibits immunosuppressive and anti-inflammatory activity, and is also involved in the synthesis of immunoglobulin E (IgE).

According to a study conducted in Japan, it was shown that the level of IgE increased by more than 30-40% in patients with no remission of DTG. A positive correlation was also found between IgE and St. T4 and St. T-34]. Possibly, through its influence on IgE, IL-13 can play a significant role in the initiation of TT in patients with DTG. In this regard, it is relevant to study the role of cytokines in the pathogenesis of DTG, as well as to identify the relationship between the clinical course of DTG and single nucleotide substitutions of the IL6 and IL13 genes. A variant in the genes of various pro-inflammatory cytokines may affect the risk of developing DTG and EO [10]. A search for genome-wide associations in patients with DTG found loci on chromosomes 7 and 5q31-q33, with gene clusters that encode T-helper type 2 interleukins [15]. On the basis of these studies, studies have been carried out on the study of variants of the IL6, IL13 and other pro- inflammatory cytokines genes in patients with DTG [15]. The IL6 gene is located on chromosome 7p21; it has 4 introns and 5 exons [128]. This variant in the promoter zone affects the change in the transcriptional activity of the gene [12].

In this regard, single- nucleotide variants of the IL6 gene are of the greatest interest: −174G/C (rs1800795) and −572G/C (rs1800796) in the gene promoter. Treatment of DTG, as a rule, begins with the appointment of antithyroid drugs for a period of 12-18 months.

Thionamides are the main group of drugs used in the relief of TT and the treatment of DTG. Thionamides, inhibiting the activity of the thyroid peroxidase enzyme, reduce the synthesis of thyroid hormones.

According to the results of the studies, by reducing the activity of lymphocytes, thionamides can also contribute to correction in the immune system. In addition, by reducing the iodination of thyroglobulin, its immunogenicity decreases. Probably, thionamides also reduce the synthesis of prostaglandins and pro - inflammatory cytokines.

After treatment with antithyroid drugs for a period of 12-18 months, the likelihood of developing remission of DTG is assessed. Currently, reliable prognostic criteria for the onset of remission of DTG have not been developed. In this regard, as a rule, a combination of clinical and laboratory indicators is used. Unfavorable remission prognosis factors include young age, female gender, smoking, heredity [4]. A number of studies have shown that young patients with DTG have more pronounced immune disorders [7] and, accordingly, insufficient efficacy of antithyroid therapy and a higher risk of TT recurrence. In the study of B. Winsa et al. It has been shown that DTG patients under 40 years of age have a higher percentage of TT relapses than older patients [14]. In A. Bano (2019) et al. it has been shown that antibodies to rTSH at diagnosis have a better prognostic value in younger patients with DTG [8]. Women have a higher incidence of DTG than men [14], but men have a higher risk of recurrent TT after discontinuation of antithyroid therapy. This may be due to both the large volume of the thyroid gland and genetic features [13]. T. Diker-Cohen et al. did not reveal differences in the course of DTG between men and women [15]. Men treated with antithyroid therapy have high remission rates and a similar relapse rate compared to women, with fewer side

effects and treatment discontinuations. Thus, according to the authors, antithyroid drugs are the first line of treatment for both men and women [15].

In a number of studies, the combination therapy of high doses of methimazole with L-thyroxine (such a scheme is called “block and replace”) has been studied for the likelihood of achieving a longer remission of the disease. So in the work of K. Hashizume et al. (1992), DTG patients were divided into two groups of observation and treatment: group 1 - took methimazole for 6 months, and then L-thyroxine was added to the treatment at a dose of 100 μg per day. Patients continued to take this treatment regimen for one year. Then methimazole was canceled, and therapy with L-thyroxine continued for three years. Group 2 patients with DTG took placebo instead of L-thyroxine. The authors showed that the combination of methimazole with L-thyroxine significantly reduced the frequency of TT relapses. Researchers suggest that it is due to both suppression of blood TSH and immunocorrection of L- thyroxine. However, with further monitoring of these patients, DTG did not reveal a significant difference in the number of TT recurrences between these two groups of patients. Similar results were obtained by other researchers [6].

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