

Problems of diagnostics and treatment of diffuse — toxic goiter (Graves' disease)

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The article is devoted to prevalence, contemporary diagnostic methods and treatment of Grave's disease. Advantages and disadvantages of different treatment options are discussed. The cause of the disease can be environmental conditions, infectious diseases, severe operational intervention, drugs, trauma, especially brain traumas, iodine deficiency and radiation damage of thyroid in iodine deficiency conditions, familial predisposition. The ideal treatment of Graves' disease should ensure a fairly rapid elimination of clinical symptoms of thyrotoxicosis, return to an euthyroid state, with minimal risk of complications. The relapse rate of the disease can reach up to 80 %, using conservative treatment. The radioiodine ablation is relatively simple, non-invasive, effective and cheap. There are special indications for surgical treatment. Indications for surgical treatment: 1) large goiter (the volume of the thyroid gland is more than 45 ml); 2) frequent recurrences of thyrotoxicosis and failure of the drug and RIT; 3) malignancy of goiter; 4) allergic and toxic (leukopenic) reactions to thyreostatics. Patients with Graves' disease should be referred to a specialized center with multidisciplinary team.

Keywords: Graves' disease, diagnostics, treatment, radical therapy, thyroidectomy.

Historically, thyrotoxicosis in English-speaking countries is called “Grave's disease” (GD), in German-speaking countries it is called “Bazedov's disease”, and in Russia and Uzbekistan — diffuse toxic goiter.

Diffuse toxic goiter (DTG) is a multifactorial disease. This disease is referred to life-threatening diseases, since thyrotoxicosis causes irreversible changes in all tissues and organs of the body. In 80 % of patients with hyperthyroidism DTG is the main cause of thyrotoxicosis. Definition: Thyrotoxicosis syndrome (TS) is a collective concept that includes conditions with a clinic due to excessive levels of thyroid hormones (TH) in blood, regardless of the source of their origin (endogenous or exogenous TH). The ratio of sick women and men ranges from 7: 1 to 10: 1 [1]. Most sick people are of working age from 20 to 50 years, in connection with which the disease has a high social significance [2; 3]. Sociological and medical studies demonstrated that the prevalence of this disease continues to steadily increase [4].

Analysis of literature data in recent years suggests that there is a persistent tendency towards increase in the number of patients with diffuse toxic goiter. In Uzbekistan, the incidence rate is 48.2 per 100 thousand people.

According to statistics, about 2 % of residents of the Russian Federation suffer from thyrotoxicosis of various origins, the annual costs of various types of treatment and observation amount to approximately 7 billion rubles [5].

Disorders of thyroid syndrome are the following: thyrotoxicosis (Grave's-Basedow's disease), toxic adenoma, multinodular (nodular) toxic goiter, thyroid cancer (well differentiated), familial non-autoimmune thyrotoxicosis, autoimmune thyroiditis, subacute thyroiditis, ray thyroiditis, postpartum thyroiditis, iodine-induced thyrotoxicosis (Iodine-Basedow), Struma ovarii (atypically located hyperfunctioning thyroid tissue), pituitary adenoma (TSH-producing), hypophysial resistance to thyroid hormones, chorionepithelioma — a tumor that produces chorionic gonadotropin, artificial thyrotoxicosis.

In regions with sufficient iodine support, the incidence varies from 30 to 200 patients per 100 thousand of population per year, in the Russian Federation it competes with thyrotoxicosis against the background of functional autonomy — with nodal and multi-node toxic goiter [3].

For a long time, external factors were considered as the main cause of this disease. It was believed that the leading ones were the environmental conditions, infectious diseases, severe surgical interventions, drugs, injuries, especially craniocerebral [6]. Other authors noted the increased role of iodine deficiency endemicity [7], as well as radiation contaminations of thyroid gland under conditions of goitre endemia [6; 8]. Over last 10 years in some papers was indicated relation between the onset of DTG and enterovirus [9]. Some authors pointed to a family predisposition. About 70 % of patients with DTG had a burdened family history of autoimmune diseases of the thyroid gland [10; 11].

The diagnosis of DTG is made on the basis of clinical symptoms and laboratory data, first — detection in the blood St. T4 and TSH. It is also may use free thyroxine index and it is also increased. Some authors recommend detecting anti-thyroglobulin, microsomal fractions, especially in respect to differential diagnosis with non-thyroid pathology. Ultrasound imaging is recommended for dynamic monitoring of the size and morphology of thyroid gland, which, however, cannot always replace scanning. Scanning and ultrasound are not diagnostical methods of actual DTG and are used according to indications. In rare cases, a test with thyroliberin can be used [12]. DTG is characterized by increase in the basal level of thyroid hormones and by decrease in TSH. Usually the basal level of T3 is increased to greater extent than the level of T4. However, the definition of the T3 level is currently not recommended because T3 sets are impossible to certificate all over the world. The use of these kits is recommended in case of pregnancy. In doubtful cases, when T3 and T4 are slightly elevated and thyrotoxicosis is suspected, it is useful to conduct a test with rifatiroin (TRG). The absence of increase in TSH with introduction of TRH confirms the diagnosis of diffuse toxic goiter [13].

In recent years, radioisotope study of thyroid function (thyroid gland) is used much less frequently due to possibility determining the level of thyroid hormones and TSH. The method is based on the ability of thyroid gland to selectively accumulate iodine. Evaluation of its function is carried out by rate of iodine absorption, its maximum accumulation and by the rate of decline its activity [14].

The goal of DTG treatment is persistent euthyroidism, or hypothyroidism, which is currently not considered as a complication, since it is successfully compensated by substitution therapy, while relapses of thyrotoxicosis pose a serious threat to health. Treatment of patients with DTG remains an unsolved task of modern medicine. And, above all, this

is due to the fact that there is no single generally accepted approach to the treatment of this category of patients.

Opinions of various authors regarding the choice of the optimal treatment method for DTG differ significantly. It is generally accepted that treatment with thyrostatics should be carried out for 2 years, while only 30 % of patients experience immunological and clinical remission of the disease.

Today in case DTG there is no treatment method that may provide correction of autoimmune disorders, restoring normal function of thyroid gland. Ideal DTG treatment may ensure a fairly rapid elimination of clinical symptoms of thyrotoxicosis as well as restoration of euthyroid state and must provide minimal risk of complications. There are three main methods of DTG treatment: conservative therapy with thyreostatics, treatment with radioactive iodine and surgical intervention. The choice of the method depends on external factors (country of residence, level of iodine maintenance, preferences of endocrinologists and surgeons) and on the characteristics of each patient (age, course of the disease, thyroid gland volume, comorbidities and severity of thyrotoxicosis).

It is known that using conservative therapy it is not always possible to achieve persistent clinical effect, and relapse of the disease, according to various sources, can reach 80 % [15]. Regardless of the treatment method used, it is necessary first to eliminate thyrotoxicosis medically. The leading thyrostatics are thionamides, which include methimazole (MMI), carbimazole and propylthiouracil. Carbimazole is precursor of methimazole (10 mg of carbimazole is metabolized to 6 mg MMI). Both are effective as a single daily dose (10–20 mg daily). Propylthiouracil can cause fulminant hepatic necrosis, which can be fatal. Hepatotoxicity of MMI is manifested by cholestasis, but hepatocellular disease is rarely observed. Babies born to mothers who have taken MMI may have scalp aplasia, embryopathy, including atresia of anus and stomach (when taken in the first trimester of pregnancy). Before initiating therapy with antithyroid drugs (ATP) in DG, a complete general blood test is recommended, including leukocytes with differentiation, a hepatic profile, including bilirubin and transaminases.

Patients should be informed about the side effects of ATP drugs and the need for immediate medical attention if itchy rashes, jaundice, acholic stools or dark urine, fever, or pharyngitis develop. Before starting therapy and at each visit, the patient should be warned immediately to stop treatment and inform the physician if symptoms indicate the development of agranulocytosis or hepatic lesion. The initial dose of tyrosol is 20–30 mg, with large goiter and severe thyrotoxicosis, the dose can be increased to 40–60 mg per day.

After reaching euthyroidism, the dose of tyrosol is reduced to maintenance: 5–10 mg per day. The use of the “block and replace” scheme is not recommended, since it lead to a higher frequency of side effects of ATP.

Clinical Blood count: 1 time per 14 days at the beginning of St. T4 treatment, determined in 4–6 weeks. Subsequently monitoring of thyroid gland function is carried out every 6–8 weeks, and if at second visit euthyroidism was detected, control is carried out every 3 months; TSH after 4–6 months.

Anti-TSH receptor before the abolition of thyreostatics.

Agranulocytosis is an extremely rare complication of therapy (0.1–0.2 %).

The duration of conservative treatment is at least 12–18 months, then reduce the dose or stop, if the level of TSH and TRab at this point is normal.

In many DTG treatment guidelines in absence of remission of this disease against the background of ongoing conservative therapy for 18 months, admission of repeated course of thyreostatics is not recommended. In these cases, the question of radioiodine therapy (RIT) or surgical treatment should be considered.

Radioactive iodine therapy is relatively simple, non-invasive, alternative, effective, and probably the most economical method for treating DTG and due to absence of incomplete compensation for thyrotoxicosis (which is dangerous during surgical treatment), relatively cheap. The need for re-treatment after RIT varies from 10 to 48 % [2; 16; 17].

The use of radioiodine in patients without prior removal of thyrotoxicosis can lead to thyrotoxic crisis (5–10 % of cases). The mechanism of its influence is in massive destruction of the follicular epithelium by β -particles with significant amount of thyroid hormones simultaneously entering bloodstream, which causes thyrotoxic crisis. Therefore, a common treatment regimen consist in receiving by patients pre-treatment with thyreostatics. The previous use of thyreostatics does not suppress the penetration of ^{131}I into the thyroid gland and does not reduce the effectiveness of RIT, if they are canceled in 8–10 days before the introduction of radioactive iodine [18]. Results of foreign studies show that, despite the high efficacy of RIT, in 17–20 % of cases after treatment, a relapse of thyrotoxicosis develops. The article presents analysis of unsatisfactory RIT results in patients with DTG described in the literature, as well as their own experience of unsuccessful treatment of this disease [19].

Currently, in most cases of ineffective conservative therapy and RIT, surgical treatment is performed.

Indications for surgical treatment are: 1) large goiter (volume of thyroid gland exceeds 45 ml); 2) frequent recurrences of thyrotoxicosis and failure of the drug and RIT treatment; 3) malignancy of goiter; 4) allergic and toxic (leukopenic) reactions to thyreostatics.

Surgical intervention enables to quickly eliminate thyrotoxicosis. If surgery is preferred as a method of first choice for DG, peritotal or total thyroidectomy are preferable methods [20; 21; 22–26]. It is necessary to achieve clinical euthyroidism (hypothyroidism) (dry skin, slow motion, weight gain by 4–5 kg, no tremor, irritability, tachycardia) with TSH level 7–10 mU/L, taking Lugol solution 7 drops twice a day for 10–30 days.

Total thyroidectomy completely excludes the possibility of disease recurrence, and hypothyroidism is the expected outcome. But this approach has a certain drawback. It lies in the fact that in the postoperative period various specific complications often develop [27]. Thus, transient hypocalcemia after surgery can reach 68 % [28–30], and in 1–10 % of patients entails persistent hypoparathyroidism [25; 31; 32]. In the overwhelming majority of cases, it remains asymptomatic and undetected if you do not re-determine the level of free calcium. The probability of developing persistent hypoparathyroidism in institutions specializing in the surgical treatment of thyroid pathology after thyroidectomy (in the case of the first thyroid surgery) is at least 2 %. The more frequent complications include the formation of keloid scar (2.8 %), paralysis of the recurrent nerve (2 %) [27]. Damage to the laryngeal nerves when performing TE is observed in 0.5–20 % of patients [33–35]. Another 13 % of patients possess paresis of larynx [36; 37]. This is most often manifested by varying severity degrees of dysphonia and difficulty in breathing.

In the work of S. I. Ismailov and co-authors patients were long-term monitored after completion of the total TE against DTG. When comparing such indicators as physical

activity, body pain, general health perception, vitality, social activity and many other indicators characterizing the quality of life, the assessment of the quality of life in the group of patients after TE was significantly less than in the group of healthy individuals. The authors concluded that the decline in life quality is specifically attributed to majority of patients undergoing thyroidectomy, which may be caused by hypothyroidism [38]. It is considered that postoperative hypothyroidism is an easily avoidable complication. However, the study of long-term results in patients with uncompensated postoperative hypothyroidism showed that in this category the mortality from diseases of the cardiovascular system is at 15 % higher than in the general population [39].

In children with DG, methimazole, radioiodine therapy or thyroidectomy should be used for treatment. If methimazole is selected as a treatment method for children, it should be prescribed for 1–2 years, then canceled or continued with reduced dose to assess the presence of remission (1 / ++ 0).

When using ATP in children within 1–2 years, the frequency of remission is 20–30 %, where the euthyroid state is considered to be in remission for 1 year after discontinuation of therapy. The possibility of remission is low if the child is younger than 12 years, the thyroid gland is more than 2.5 times greater than normal size for age, serological levels of TRAb are higher than normal during therapy, or levels of free T4 are significantly increased with a diagnosis (> 50 pmol/L).

¹³¹I therapy should not be used in very young children (under 5 years). In most children of 5–10 years old, radioactive iodine therapy is acceptable if the calculated activity of applied ¹³¹I is less than 10mCi. ¹³¹I therapy in patients older than 10 years is acceptable if the activity exceeds 150mCi/g of thyroid tissue [40].

Thyroidectomy should be recommended when radical therapy is required, the child is too young for ¹³¹I, and the operation can be performed by surgeon operating on a large volume gland.

Thus, all of the above confirms the urgency of the problem: identifying and studying the predictors of postoperative complications will help to differentiate the choice of surgery volume in patients with DTG, which will contribute to prevention of postoperative complications. It can be stated that a unified approach to the choice of the volume of surgery in patients with DTG the present day remains the subject of discussion.

We believe that patients with DTG should be referred for surgical treatment to a specialized centre with a multidisciplinary team that includes an endocrinologist, a surgeon with extensive experience in thyroid surgery, and an anesthesiologist.

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