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Syndrome of Thyrotoxicosis, Approaches to Diagnosis and Treatment

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Resuem.

Thyrotoxicosis has multiple causes, in most cases it develops due to excessive synthesis of thyroid hormone (hyperthyroidism). The most common reasons of thyrotoxicosis are Graves' disease, multinodular toxic goiter and toxic adenoma. Clinical manifestations of thyrotoxicosis are independent of its causes, but have their own features in different diseases. The therapy depends on the etiology of the disease, thyroid size, presence of complications and comorbidities. Antithyroid drug, radioactive iodine therapy or surgery are shown in an excessive biosynthesis of thyroid hormones. Destroid forms of thyrotoxicosis with the release of stored hormones does not required antithyroid therapy. For any symptomatic thyrotoxicosis need βblockers. Key words: thyrotoxicosis, hyperthyroidism, Graves' disease, thionamides. Thyrotoxicosis is a syndrome in which there are clinical and biochemical manifestations of excessive levels of thyroid hormones in the blood, regardless of the reason for the increase in their level. Hyperthyroidism is a condition caused by excessive synthesis and secretion of thyroid hormones by the thyroid gland (TG) [1]. Thus, the terms thyrotoxicosis and hyperthyroidism are not synonymous, although in foreign literature they are often used as identical. The frequency of thyrotoxicosis is approximately 2% among women and 0.2% among men [2 In most cases, thyrotoxicosis is associated with Graves' disease (GD), multinodular toxic goiter and toxic adenoma [4].

The following classification of thyrotoxicosis syndrome is most often used: 1. Thyrotoxicosis due to increased production of thyroid hormones: Graves' disease; multinodular toxic goiter; toxic adenoma; iodine-induced thyrotoxicosis; TSH-producing pituitary adenoma; syndrome of inadequate secretion of TSH (resistance of thyrotrophs to thyroid hormones); gestational thyrotoxicosis; non-autoimmune autosomal dominant hyperthyroidism; trophoblastic thyrotoxicosis. 2. Thyrotoxicosis caused by production of thyroid hormones outside the thyroid gland: struma ovarii (ovarian tumor producing thyroid hormones); metastases of highly differentiated thyroid cancer. 3. Thyrotoxicosis not associated with hyperproduction of thyroid hormones: medication (amiodarone, iodine-containing contrast agents, α-interferons); iatrogenic thyrotoxicosis; stage of subacute de Quervain's thyroiditis; thyroid adenoma infarction; radiation thyroiditis; stage of AIT development; increased tissue sensitivity to thyroid hormones. In most cases, thyrotoxicosis is associated with Graves' disease (GD), multinodular toxic goiter and toxic adenoma [4]

With the exception of various thyroiditis and iatrogenic thyrotoxicosis, all other causes are extremely rare. HD is an autoimmune disease accompanied by the synthesis of antibodies to the thyroid stimulating hormone receptor (TSH), which stimulate the thyroid gland to produce an excess amount of thyroid hormones. Multinodular toxic goiter and toxic adenoma are a clinical manifestation of functional autonomy (FA) of the thyroid gland, a condition in which the

synthesis of thyroid hormones does not depend on TSH and the presence of thyroid-stimulating antibodies [3]. The natural course of nodular goiter can eventually lead to the formation of autonomy of the node in conditions of iodine deficiency. There are somatic activating mutations in the genes responsible for the synthesis of thyroid hormones, which leads to autonomous production of hormones. Noted that the incidence of these diseases depends on the initial level of iodine intake. Thus, in regions with adequate and high levels of iodine intake, HD is more common (80–85% of cases) and FA is rare (3–10% of cases). In regions of iodine deficiency, especially among the elderly, FA prevails, it accounts for up to 60% of cases of thyrotoxicosis (10% for toxic adenoma and 50% for multinodular toxic goiter) [5]. There are manifest and subclinical thyrotoxicosis. Subclinical thyrotoxicosis is determined by a decrease in the level of TSH and a normal level of thyroxine (T4) and triiodothyronine (T3), in these patients, the symptoms of thyrotoxicosis may be absent or be mild. The persistent nature of the changes should be confirmed by repeated measurement after 3–6 months. The most common cause of subclinical thyrotoxicosis is multinodular toxic goiter [2]. Subclinical thyrotoxicosis is associated with a risk of atrial fibrillation in the elderly and fractures in postmenopausal women. The question of the expediency of treating subclinical thyrotoxicosis remains debatable. In 2010, the Clinical Guidelines of the Association of Clinical Endocrinologists and the American Thyroid Association were published, according to which it is necessary to treat subclinical thyrotoxicosis with a persistent decrease in TSH less than 0.1 mU / l in patients older than 65 years, postmenopausal women not receiving HRT or bisphosphonates, in patients with high cardiovascular risk, heart disease or osteoporosis and patients with symptoms of thyrotoxicosis [6]. When TSH is consistently below the lower limit of normal, but ≥0, 1 mU/l discusses treatment for persons over 65 years of age and patients with cardiovascular disease or symptoms of thyrotoxicosis [66]. Treatment is the same as for overt thyrotoxicosis. The diagnosis of thyrotoxicosis is established on the basis of data from clinical, laboratory and instrumental studies. The clinical manifestations of thyrotoxicosis, for the most part, do not depend on the cause, however, some features of thyrotoxicosis, such as the duration of the course, the size and presence of nodes in the thyroid tissue, the presence of endocrine ophthalmopathy (EOP), suggest the nature of the disease. The main clinical symptoms of thyrotoxicosis are nervousness, fatigue, weakness, sweating, poor heat tolerance, tremors, palpitations, weight loss, and increased appetite. Patients have arrhythmia, systolic hypertension, warm and moist skin, tremors, muscle weakness, various eye symptoms of thyrotoxicosis. Laboratory tests are needed to confirm the diagnosis of thyrotoxicosis. With an increase in the level of free T4 and a decrease in TSH, a manifest form of thyrotoxicosis is diagnosed. In conducting a differential diagnostic search, ultrasound examination (ultrasound) and thyroid scintigraphy are of great importance. So, with GD, a diffuse decrease in the echogenicity of the gland tissue and its increased vascularization are determined, with nodular toxic goiter against the background of a normal echostructure, nodular formations are detected. Increased capture of the radiopharmaceutical during scintigraphy indicates hyperproduction of thyroid hormones in the thyroid gland. FA reveals a “hot” nodule and reduced uptake of the radiopharmaceutical by the rest of the thyroid tissue. To date, three methods of treatment for thyrotoxicosis are available: conservative, radioiodine therapy and surgical. Conservative therapy can be used as an independent method of treatment, and in order to prepare for radioiodine therapy or surgery. The appointment of drugs that block thyroid function is necessary in cases of hyperthyroidism due to Graves' disease, multinodular toxic goiter, toxic adenoma, or iodine-induced thyrotoxicosis type 1 [1]. All other diseases leading to thyrotoxicosis, as a rule, do not require treatment with thyreostatics. Against the background of treatment with thyrestatic drugs, immunological remission of HD occurs in 30% of patients; therefore, conservative therapy for 12–18 months is accepted as an independent method of treating HD. With FA, it is impossible to achieve remission and the main method of treatment is radical, after preliminary preparation with a short course of thyreostatics. However, long-term (lifelong) low-dose therapy is possible in elderly patients with a high operational risk or in case of refusal of radical therapy [6]. Iodine compounds, potassium perchlorate, lithium carbonate and thionamides have a thyreostatic effect. The main means of conservative therapy

are derivatives of imidazole and thiouracil. In RF, thiamazole (1-methyl-2-mercaptoimidazole) and propylthiouracil (6-propyl-2-thiouracil) are used. Thionamides have intrathyroid and extrathyroid effects. The mechanism of their action is to inhibit the synthesis of thyroid hormones by inhibiting the phase of organization and condensation of hormone biosynthesis, i.e. in inhibition of reactions catalyzed by thyroperoxidase (TPO) [1]. In addition, it was shown that thyreostatics can have an immunosuppressive effect, causing intrathyroid apoptosis of lymphocytes [7], reducing the expression of HLA-class II molecules [8], the number of active T-lymphocytes and NK-cells (killers) [9]. Propylthiouracil also has an extrathyroidal effect, reducing the activity of type I 5'-deiodinase and thereby the conversion of thyroxine (T4) to triiodothyronine (T3) [1, 10]. Thiamazole is used at a starting dose of 30–60 mg/day, depending on the severity of thyrotoxicosis, the full daily dose can be administered in one dose. The drug is almost completely absorbed from the gastrointestinal tract, the peak serum concentration occurs 1–2 hours after administration, the drug practically does not bind to plasma proteins, and the serum half-life is 6–8 hours. The clearance of thiamazole does not change in patients with decreased renal function, but slows down in patients with hepatic insufficiency. The duration of action of the drug is up to 40 hours. Propylthiouracil is also almost completely absorbed from the gastrointestinal tract, the peak concentration occurs at 1 hour after absorption and depends on the dose of the drug, the half-life is in the range from 1 to 2 hours and does not depend on renal or hepatic function , the severity of thyrotoxicosis or the age of the patient. Propylthiouracil is 80–90% bound to plasma proteins and ionized at physiological pH. This property is important in the treatment of pregnant and lactating women, since the concentration of free propylthiouracil in plasma is low, and the ionized drug cannot pass through biological membranes, including the placenta. The duration of action of the drug is about 12–24 hours; it is used at a dose of 400–600 mg/day every 6–8 hours [3, 11]. The most common side effects of thionamides are allergic reactions in the form of an itchy rash, fever, arthralgia, transient granulocytopenia, occur in 1-5% of patients during the first weeks of treatment and more often in patients receiving high doses of thyreostatics. More serious, potentially dangerous and rare side effects are agranulocytosis, aplastic anemia, thrombocytopenia, toxic hepatitis (for propylthiouracil), cholestatic hepatitis (for thiamazole), polyarthritis, lupus-like syndrome and vasculitis [3, 12, 13]. Most of them, with the exception of agranulocytosis, are more common with propylthiouracil therapy [3]. Patients should be informed about the possible side effects of thyrostatic therapy and the need to contact a doctor if itchy rash, jaundice, colorless stools, dark urine, arthralgia, abdominal pain, nausea, fever or pharyngitis [6]. Granulocytopenia less than 1000 ml is an indication for discontinuation of the drug [11, 12]. Minor skin reactions do not require discontinuation of the drug and can be treated with antihistamines. Serious side effects require immediate discontinuation of the drug and the appointment of radical methods of treatment. Monitoring of patients receiving thyreostatics treatment includes laboratory monitoring with assessment of TSH, F.T4, clinical blood count and liver function tests at the beginning of treatment every 4–6 weeks until euthyroidism is achieved, then every 2–3 months. Thiamazole is the drug of choice for thyrostatic therapy, except in cases of the first trimester of pregnancy, when propylthiouracil is preferable, and refusal of radical treatment in case of intolerance to thiamazole [6]. The advantage of thiamazole is the ability to use it once a day and the low risk of side effects compared to propylthiouracil [6]. The activity of thiamazole is approximately 10 times higher than that of propylthiouracil [3, 11]. On the domestic market, thiamazole is represented by the drug "Tyrozol". The presence of two dosages - 5 and 10 mg each - ensures the convenience of therapy and allows you to reduce the number of tablets taken by 2 times, which increases patient compliance. Recently, rituximab, a recombinant chimeric monoclonal antibody against CD20 expressed by B cells, has been proposed for the treatment of HD resistant to conventional thyrostatic therapy. It affects the pathogenetic mechanisms of HD development by suppressing B-cell activity. The combination of rituximab with thiamazole has been shown to be more effective, than thiamazole monotherapy to achieve long-term remission of HD [14]. However, the data are preliminary and require further study in clinical trials. Since the effect of thyrostatic therapy manifests itself 7-10 days after the appointment, b-blockers are used as symptomatic

therapy to stop the clinic of thyrotoxicosis caused by the action of catecholamines (tremor, sweating, anxiety, palpitations). In addition, non-selective b-blockers, such as propranolol at a dose of 40-120 mg / day, reduce the peripheral conversion of T4 to T3. This therapy should be given to elderly patients with symptoms of thyrotoxicosis and to all patients with a resting heart rate of more than 90 beats/min or in the presence of concomitant cardiovascular pathology [6]. In the presence of contraindications to β-blockers or intolerance, calcium channel blockers such as verapamil and diltiazem can be used [6]. Surgical treatment as a radical treatment option is indicated when conservative treatment of patients with severe course of Graves' disease is ineffective or impossible, when combined with thyroid nodes, with a large goiter or retrosternal position, toxic adenoma and multinodular toxic goiter, with recurrence of thyrotoxicosis against the background (or after discontinuation) of drug therapy [1]. The advantage of this method of treatment is the rapid achievement of a euthyroid state. The main complications of surgical treatment include paresis of the recurrent laryngeal nerve and hypoparathyroidism. The frequency of complications depends on the skill of the surgeon and occurs in less than 1% of patients in specialized hospitals [3]. Other complications: transient hypocalcemia, postoperative bleeding, wound infection, keloid scarring. Postoperative hypothyroidism should not be considered a complication, but rather a natural outcome of surgical treatment. Another radical treatment option is radioiodine therapy. Indications for radioactive iodine therapy are: the ineffectiveness of conservative therapy for Graves' disease, the recurrence of thyrotoxicosis after surgical treatment, the impossibility of long-term conservative therapy due to allergies, leukopenia, the presence of severe cardiovascular disorders in patients with small thyroid gland, the impossibility of surgical treatment, toxic adenoma or multinodular toxic goiter [1]. Practical experience shows the need to achieve euthyroidism with thyreostatic drugs before treatment with 131I with their withdrawal a week before the procedure [12]. Numerous studies have shown that radioactive iodine treatment does not increase the risk of leukemia, cancer of the thyroid gland and other organs [15, 16]. After treatment with radioactive iodine, an aggravation of the course of EOP is possible, therefore, a severe course of ophthalmopathy may be a contraindication to this method of treatment. Another common side effect is transient thyrotoxicosis in the first few weeks after radioactive iodine therapy due to the release of thyroid hormones from destroyed thyroid follicles [17]. Pregnancy and lactation should be considered absolute contraindications to radioactive iodine treatment. Destructive forms of thyrotoxicosis do not require treatment with thionamides, since there is no increase in hormone biosynthesis, symptomatic therapy with b-blockers is sufficient. In subacute and amiodarone-induced thyroiditis, glucocorticosteroids may be prescribed. For TSH-producing pituitary adenomas, the treatment of choice is transsphenoidal surgery, with or without subsequent radiation therapy. Perhaps the use of octreotide and bromocriptine, but their effect is weak and short-lived.

Treatment of iatrogenic thyrotoxicosis caused by an acute overdose of levothyroxine is aimed at rapid elimination of the drug from the body, gastric lavage with charcoal and fatty acid sequesters (cholestyramines) is performed, in severe cases, plasmapheresis or dialysis is performed. thyrotoxicosis, associated with struma ovarii requires surgical treatment of an ovarian tumor; in case of a malignant tumor, subsequent thyroidectomy is performed [3]. Radioactive iodine is used to treat metastatic differentiated thyroid cancer after euthyroidism has been achieved with thyrostatic therapy. Trophoblastic thyrotoxicosis (with hydatidiform mole or choriocarcinoma) requires treatment of the underlying disease. Thus, the choice of treatment method depends on the etiology of the disease, the size and location of the thyroid gland, the presence of complications of thyrotoxicosis and concomitant pathology. For diseases associated with hyperproduction of thyroid hormones in the thyroid gland, conservative therapy with thyreostatics, radioiodine therapy with 131I, or surgical treatment is indicated. Surgical treatment occupies an important place in the treatment of DTG. The use of this method provides the fastest elimination of thyrotoxicosis syndrome compared to other methods. Currently, the optimal indications for surgical treatment of DTG have not been determined, they continue to be discussed. For example, most endocrinologists recommend surgical treatment for large goiters

(more than 40-45 ml) [2]. However, some clinicians consider radioiodine therapy appropriate even for large goiters [3]. Other authors believe that after surgical treatment of DTG, EOP may progress [4]. Influence of radioiodine therapy with DTG on the course of endocrine ophthalmopathy: RIT is based on the selective uptake of 11I by the thyroid gland. The destructive effect of 11I on thyroid tissue is exerted by beta particles, which have a short path length in tissues. 90% of the decay energy of beta particles in the thyroid tissue is absorbed within 1–2 mm. Gamma quanta emitted by 13I do not have a noticeable biological effect (due to their high penetrating power), but they allow monitoring the location and amount of 13I in the body. Through the Na-I-symporter, 13I specifically penetrates into the cells of the follicular epithelium of the thyroid gland. This minimizes the risk of damage to normal tissues and reduces radiation exposure to the body. The half-life of 13I is 8.04 days, which also helps to reduce radiation exposure to the body. The excretion of 16I from the body is carried out mainly by the kidneys in the first hours after its administration (up to 70–80% of the administered amount) and partially by other secretory glands (salivary glands, gastric mucosa). The simplicity of RIT technologies, which practically do not differ from the technologies for introducing diagnostic radiopharmaceuticals into the body, and the possibility of performing it on an outpatient basis determine the main advantages of RIT for use in wide clinical practice [7]. There are two treatments for I131, both of which are dosing related. One technique involves precise dosing of radioiodine to prevent its overdose and reduce radiation exposure to the patient's body. The reason for the development of this technique is due to the fact that the studies show the relationship of the therapeutic effect of radioiodine therapy with various factors. The effectiveness of therapy is influenced by the age, gender of the patient, the cause of thyrotoxicosis (nodular or diffuse toxic goiter), the mass of thyroid tissue, previous drug therapy, etc. [2]. The exact therapeutic dose of a drug can be, for example, calculated in microcurie using the following formula: 80–20 µCiI131/g shield. glands x gland mass (g) % absorption of I131 in 24 hours Therefore, more often empirically select a dose of radioiodine that provides persistent hypothyroidism in 2/3 of patients. In the UK, this is achieved by prescribing standard dosages of the drug at 200, 400, 600, or 800 MBq, depending on the size of the goiter, complications of thyrotoxicosis, and other concomitant factors [5]. The above information shows that the dosages of radioactive iodine used for the effective treatment of diffuse toxic goiter vary greatly [2]. 80–20 µCiI131/g shield. glands x gland mass (g) % absorption of I131 in 24 hours Therefore, more often empirically select a dose of radioiodine that provides persistent hypothyroidism in 2/3 of patients. In the UK, this is achieved by prescribing standard dosages of the drug at 200, 400, 600, or 800 MBq, depending on the size of the goiter, complications of thyrotoxicosis, and other concomitant factors [5]. The above information shows that the dosages of radioactive iodine used for the effective treatment of diffuse toxic goiter vary greatly [2]. 80–20 µCiI131/g shield. glands x gland mass (g) % absorption of I131 in 24 hours Therefore, more often empirically select a dose of radioiodine that provides persistent hypothyroidism in 2/3 of patients. In the UK, this is achieved by prescribing standard dosages of the drug at 200, 400, 600, or 800 MBq, depending on the size of the goiter, complications of thyrotoxicosis, and other concomitant factors [5]. The above information shows that the dosages of radioactive iodine used for the effective treatment of diffuse toxic goiter vary greatly [2]. 600 or 800 MBq, depending on the size of the goiter, complications of thyrotoxicosis, and other concomitant factors [5]. The above information shows that the dosages of radioactive iodine used for the effective treatment of diffuse toxic goiter vary greatly [2]. 600 or 800 MBq, depending on the size of the goiter, complications of thyrotoxicosis, and other concomitant factors [5]. The above information shows that the dosages of radioactive iodine used for the effective treatment of diffuse toxic goiter vary greatly.

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