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Diffusetoxic Goiter, Diagnosis and Treatment

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Abstract: Graves' disease (Bazedov's disease, diffuse toxic goiter) is a systemic autoimmune disease that develops due to the production of stimulating antibodies to the thyroid-stimulating hormone (TSH) receptor, clinically manifested by thyroid gland damage with the development of thyrotoxicosis syndrome in combination with extrathyroid pathology (endocrine ophthalmopathy, pretibial myxedema, acropathy).

Keywords: Graves ' disease, goiter, tachycardia, exophthalmos, thyrotoxicosis, thiamazole.

Introduction

The frequency of new cases of HD varies from 30 to 200 cases per 100 thousand population per year. Women develop HD 10-20 times more often. In regions with normal iodine supply, Graves ' disease (HD) is the most common cause of persistent thyrotoxicosis, and in iodine-deficient regions, HD competes with the functional autonomy of the thyroid gland (nodular and multi-nodular toxic goiter) in the etiological structure of toxic goiter. In Russia, the term diffuse toxic goiter is traditionally used as a synonym for Graves ' disease (Bazedov's disease), which is not without a number of significant drawbacks. First, it characterizes only macroscopic (diffuse goiter) and functional (toxic) changes in the thyroid gland, which are not obligate for Graves ' disease: on the one hand, there may not be an increase in the gland, on the other, it may not be diffuse. On the other hand, diffuse thyroid enlargement in combination with thyrotoxicosis can occur in other diseases, in particular in the so-called diffuse functional autonomy.

The use of the broader term "disease" (and not just toxic goiter) in relation to the disease under discussion is most likely more justified, since it more strongly emphasizes the systemic nature of the autoimmune process. In addition, the term Graves ' disease is traditionally most commonly used and thus recognized all over the world, and in German-speaking countries –Bazedov's disease.

Pathogenesis

HD is a multifactorial disease in which the genetic features of the immune response are realized against the background of environmental factors. Along with ethnically associated genetic predisposition (carriage of haplotypes HLA-B8,-DR3 and-DQA1*0501 in Europeans), psychosocial and environmental factors are of particular importance in the pathogenesis of HD. For example, the importance of infectious and stressful factors has been discussed for quite a long time, in particular, a number of works put forward the theory of "molecular mimicry" between thyroid antigens, retrobulbar fiber and a number of stress proteins and bacterial antigens (Yersinia enterocolitica). Emotional stressors and exogenous factors, such as smoking, can contribute to the realization of-genetic predisposition to HD. Thus, a temporal relationship was found between the manifestation of HD and the loss of a spouse (partner) and other major stressful events. It has been shown that the incidence of HD in Serbia grew significantly during the 1991-2001 Yugoslav Wars. Smoking increases the risk of developing HD by 1.9 times, and the development of EOP with existing HD-by 7.7 times.

As a result of impaired immunological tolerance, autoreactive lymphocytes (CD4+- and CD8+-T-lymphocytes, B-lymphocytes) indirectly infiltrate the THYROID parenchyma by adhesive molecules (ICAM-1, ICAM-2, E-selectin, VCAM-1, LFA-1, LFA-3, CD44), where they recognize a number of different types of cells. antigens that are presented by dendritic cells, macrophages, B-lymphocytes, and HLA-DR-expressing follicular cells. Subsequently, cytokines and signaling molecules initiate antigen-specific stimulation of B-lymphocytes, resulting in the production of specific immunoglobulins against various components thyrocytes. In the pathogenesis of HD, the main importance is attached to the formation of stimulating antibodies to the TSH receptor (AT-RTG). These antibodies bind to TSH receptors and bring it into an active state, triggering intracellular systems (cascades of cAMP and phospho-inositols), which stimulate thyroid uptake of iodine, synthesis and release of thyroid hormones, and proliferation of thyrocytes. As a result, thyrotoxicosis syndrome develops, which dominates the clinical picture of HD.

Clinical Picture

The classic Merseburg triad (goiter, tachycardia, exophthalmos), described by Karl Bazedov in 1740, is clearly found in about 50% of patients. Approximately 2/3 of cases of HD develop after the age of 30, at least 5 times more often in women. As mentioned above, the clinical picture of HD is determined by thyrotoxicosis syndrome, which is characterized by: weight loss, often against the background of increased appetite, sweating, tachycardia and palpitation, internal anxiety, nervousness, trembling of the hands, and sometimes the whole body, general and muscle weakness, rapid fatigue and a number of other symptoms, described in detail in the literature. Unlike multi-node toxic goiter, which is associated with thyroid functional autonomy, HD usually has a short history: symptoms develop and progress quickly and in most cases lead the patient to the doctor within 6-12 months.

In elderly patients, thyrotoxicosis of any genesis often occurs oligo - or monosymptomatically (evening subfebrility, arrhythmias) or even atypically (anorexia, neurological symptoms). Palpation examination of approximately 80% of patients reveals an increase in the thyroid gland, sometimes very significant: palpation of the gland is dense, painless.

In some cases, in HD, manifestations of endocrine orbitopathy may come out in the first place (pronounced exophthalmos, often having an asymmetric character, diplopia when looking in one direction or up, lacrimation, a feeling of "sand in the eyes", puffiness of the eyelids). Here it should be noted that the presence of a pronounced endocrine ophthalmopathy (EOP) in a patient allows you to almost accurately establish an etiological diagnosis for the patient already based on the clinical picture, since among the diseases that occur with thyrotoxicosis, EOP is combined only with HD (EOP is the "business card" of HD). It is important to understand, that EOP is not a manifestation of thyrotoxicosis proper, but develops as a result of autoimmune inflammation of the retrobulbar tissue and oculomotor muscles. That is, EOP, along with thyroid damage with the development of thyrotoxicosis, is another manifestation of the systemic autoimmune process in HD. Elimination of thyrotoxicosis proper by thyrostatic therapy or other methods often does not affect the course of EOP in any way.

Diagnostics

In typical cases, it does not cause significant difficulties. If the patient is suspected of having thyrotoxicosis, he is shown to determine the TSH level. If a low TSH level is detected, the patient is assessed for the level of free T4 and T3: if at least one of them is elevated – we are talking about manifest thyrotoxicosis, if they are both normal – about subclinical. After confirming the presence of thyrotoxicosis in the patient, an etiological diagnosis is performed to identify the specific disease that caused it. Here it should be noted that thyrotoxicosis is a syndrome, which occurs in many thyroid diseases that are completely different in etiology and pathogenesis and treatment approaches. Unfortunately, in the minds of many doctors, all these diseases are sometimes perceived as a whole, and the detection of thyrotoxicosis without any proceedings is followed by the appointment of thyroostatic therapy. Here, when discussing the differential diagnosis of thyrotoxicosis syndrome, it should be recalled that there are at least three pathogenetic variants of it.

Hyperproduction of thyroid hormones (hyperthyroidism) - the thyroid gland produces thyroid hormones in excess. This variant of thyrotoxicosis is precisely what occurs in HD and a number of other diseases (nodular and multi-nodular toxic goiter). In this situation, thyrotoxicosis is the most severe, it is effectively stopped by thyrostatic therapy, but diseases that occur with hyperfunction of the thyroid gland have the worst prognosis and often require ablative therapy (thyroidectomy, radioactive iodine therapy).

Destructive (thyolytic) thyrotoxicosis develops as a result of the destruction of thyroid follicles and the entry into the bloodstream of excess thyroid hormones contained in the colloid and thyrocytes. This type of thyrotoxicosis develops in subacute (de Quervain's thyroiditis), postpartum, pain-free ("silent") and cytokinin-induced thyroiditis, as well as in amiodarone-induced thyrotoxicosis of the 2nd type. With the exception of the latter disease, destructive thyrotoxicosis, as a rule, does not differ in significant severity, thyrostatics are ineffective in it, and diseases that occur with it, As a rule, they have a fairly good forecast.

Drug-induced thyrotoxicosis develops with an overdose of thyroid hormone preparations. In the complex treatment of highly differentiated thyroid cancer, this overdose is done deliberately (suppressive therapy).

The method that should always be used if thyroid pathology is suspected is ultrasound. In HD, about half of the patients present with diffuse thyroid enlargement. In addition, ultrasound can reveal thyroid hypoechoicity, which is characteristic of most autoimmune diseases. According to scintigraphy data, a diffuse increase in iron isotope capture is detected in HD (Fig. 2). As with all other autoimmune thyroid diseases, HD can show high levels of classic thyroid antibodies (antibodies to thyroid peroxidase-AT-TPO and antibody to thyroglobulin-AT-TG). This is observed no less than in 70-80% of cases of HD. Thus, the detection of classical antibodies does not allow us to distinguish HD from chronic autoimmune, postpartum, and "pain-free" ("silent") thyroiditis, but it can, together with other signs, significantly help in the differential diagnosis of HD and thyroid functional autonomy. It should be remembered that classical antibodies can be detected in healthy people (in 10% of women) without any thyroid diseases. Determination of the level of antibodies to the TSH receptor (AT-RTG) is of greater diagnostic importance.

First of all, when planning treatment, you need to clearly understand that HD is an autoimmune disease caused by the production of antibodies to thyroid gland by the immune system. As you know, there is currently no specific immunotropic therapy for any autoimmune diseases, and HD is no exception in this regard.

Contrary to this, unfortunately, one often comes across the idea that surgical removal of a part of the thyroid gland itself can cause remission of the disease, although both HD surgery and radioactive iodine-131 therapy should be ideologically perceived only as removing the "target organ" for antibodies from the body, eliminating thyrotoxicosis. The same applies to thyroostatic therapy: it effectively eliminates thyrotoxicosis, preventing its severe complications in the patient, but it hardly affects the immunopathogenesis of the disease, as evidenced by the fact that thyrotoxicosis recurs after the withdrawal of thyrostatics in the vast majority of patients (75%). Currently, there are 3 methods of treating HD, each of which is not without significant drawbacks.

1. Conservative treatment of HD

It is prescribed to achieve euthyroidism before surgical treatment, as well as in certain groups of patients as a basic long-term course of treatment, which in some cases leads to persistent remission. It makes sense to plan long-term conservative therapy not for all patients. First of all, we are talking about patients with a moderate increase in thyroid volume (up to 40 ml); with a large goiter, thyrotoxicosis will inevitably develop after the withdrawal of thyrostatics. In addition, conservative therapy should not be planned in patients with severe complications of thyrotoxicosis (atrial fibrillation). arrhythmia, severe osteoporosis, etc.). The probability of remission of the disease is extremely low in a situation of a pronounced increase in the level of thyroid hormones (the level of sv. T4 is more than 70-80 pmol/l, the level of sv. T3 is more than 30 pmol/l). This probability is significantly lower in men, in smokers, as well as in young patients (under 30 years of age) and

children. As a rule, it is unpromising and, most importantly, unsafe for the patient to prescribe repeated courses of treatment with the development of a relapse of thyrotoxicosis after 12-18 months. thyrostatic therapy. An important condition for planning long-term thyrostatictherapy is readiness follow the doctor's recommendations (compliance) and the availability of qualified endocrinological care.

For more than 60 years, thionamide preparations have been used as thyrostatics all over the world: thiamazole (tyrosol, mercazolil, metisol, methimazole) and propylthiouracil (PTU, propicil). According to the latest international guidelines, the drug of choice for thyrostatic therapy is thiamazole (tyrosol). Vocational training is recommended for the treatment of thyrotoxic crisis and thyrotoxicosis in the first trimester of pregnancy.

The key mechanism of action of thionamides is that when they enter the thyroid gland, they inhibit the action of thyroid peroxidase, inhibit the oxidation of iodine, the iodination of thyroglobulin, and the condensation of iodothyrosines. What is the reason for the fact that a small part of patients develop remission after a one-year course of thyrostatic therapy is not entirely clear. According to one version, these drugs still have some effect on the autoimmune process itself, in particular, it was shown that thionamides affect the activity and number of certain subpopulations of lymphocytes, reduce the immunogenicity of thyroglobulin by reducing its iodination, they reduce the production of prostaglandins E2, IL-1, IL-6 and the production of heat shock proteins by thyrocytes. On the other hand, these effects may be mediated by the elimination of thyrotoxicosis provided by thyrostatics. One way or another, approximately 25% of patients with initially small goiter and mild thyrotoxicosis can expect spontaneous immunological remission of the disease and preservation of the euthyroid state after drug withdrawal after a year of thyrostatic therapy.

If the patient is planning a course of thyrostatic therapy, thionamides are initially prescribed in relatively large doses: 30-40 mg of thiamazole (1-2 doses). At the beginning of treatment, it is more convenient to use drugs containing a large dose of thiamazole in one tablet (Tyrosol-10).

On the background of such therapy after 4-6 weeks. in 85% of patients with moderate thyrotoxicosis, it is possible to achieve a euthyroid state, the first sign of which is a normalization of the level of free T4 and T3. TSH levels may remain low for a long time. For the period before reaching euthyroidism, and often for a longer period, most patients should be prescribed beta-blockers (anaprilin-120 mg / day, atenolol-100 mg/day). After normalization of the level of free T4, the patient begins to reduce the dose of thyrostatics and after about 2-3 weeks. they switch to receiving a support service dosage (5-15 mg per day). Further, the patient can be treated on thyrostatics alone under monthly monitoring of thyroid function and the necessary dose adjustment (titration regimen or "block" scheme). If it is difficult to maintain persistent euthyroidism, as well as if it is impossible to monitor the patient so often, the so-called "block and replace" scheme can be prescribed, when a relatively large dose of thyrostatics (10-15 mg of thiamazole), which reliably blocks the thyroid gland, is supplemented with replacement therapy with levothyroxine (L–T4) (50-75 mcg). The block-and-replace scheme is easy to use because allows you to completely block the production of thyroid hormones, which eliminates the possibility of returning thyrotoxicosis. The criterion for the adequacy of therapy is the persistent maintenance of normal T4 and TSH levels.

Contrary to popular beliefs, thiamazole and PTU by themselves do not have the so-called "goiter" effect. An increase in the size of the thyroid gland against the background of their intake naturally develops only with the development of drug-induced hypothyroidism, which can be easily avoided by prescribing levothyroxine as part of the "block and replace"scheme.

Maintenance therapy " block and replace "(10-15 mg of thiamazole and 50-75 mcg of L-T4) lasts 12-18 months. A further increase in thyroid volume during therapy, even if euthyroidism is sustained (this will naturally occur with drug-induced hypothyroidism or, conversely, with insufficient thyroid blockade), significantly reduces the chances of treatment success. Agranulocytosis is very rare (0.06%), but a serious complication of thionamides, and isolated thrombocytopenia is casuistically rare. Relapse of thyrotoxicosis after the end of the course of treatment with thyrostatics most often develops during the first year after their cancellation.

2. Surgical treatment

According to modern concepts, the goal of surgical treatment, as well as the iodine-131 therapy discussed below, is to remove most of the thyroid gland, on the one hand, ensuring the development of postoperative hypothyroidism, and on the other, which is most important, eliminating any possibility of a relapse of thyrotoxicosis.

For this purpose, it is recommended to perform an extremely subtotal resection of the thyroid gland with the thyroid residue remaining no more than 2 ml. From a functional point of view, such an operation is essentially identical to thyroidectomy. Subtotal resections, on the one hand, carry a high risk of persistence or long-term recurrence of thyrotoxicosis (at least 15%), and on the other hand, do not exclude the development of hypothyroidism (at least 80%). When performing partial thyroid resections, the body, in fact, remains a "target" for antithyroid antibodies produced by cells the immune system. Thus, postoperative hypothyroidism is now no longer considered a complication of surgical treatment of HD, but is its goal (with the availability of available synthetic L-T4 preparations and effective methods for controlling hypothyroidism compensation). Against the background of taking an adequate replacement dose of L-T4, which ensures stable maintenance of normal TSH levels, the vast majority of patients do not complain and do not have any restrictions in their lifestyle.

3. Radioactive iodine therapy

It is no exaggeration to say that most patients worldwide with HD, as well as with other forms of hyperthyroidism, are treated with radioactive iodine-131. This is due to the fact that the method is effective, non-invasive, relatively cheap, and free of the complications that can develop during thyroid surgery. The only contraindications to treatment with iodine-131 are pregnancy and breastfeeding.

If in our country to this day there continues to be an opinion that iodine-131 therapy is indicated only for elderly patients who, for one reason or another, cannot perform surgery, in fact, there is practically no lower age limit for prescribing iodine-131 and in many countries iodine-131 is successfully used for treatment HD in children. It has been proven that regardless of age, the risk of I-131 therapy is significantly lower than that of surgical treatment.

In significant amounts, iodine-131 accumulates only in the thyroid gland; after entering it, it begins to disintegrate with the release of beta particles, which have a path length of about 1-1.5 mm, which ensures local radiation destruction of thyrocytes. The safety of this method of treatment is demonstrated by the fact that in a number of countries, such as the United States, where most patients with HD receive iodine-131 as the first-choice treatment, treatment with iodine-131 for HD is carried out on an outpatient basis. A significant advantage is that treatment with iodine-131 if necessary (for example, in case of intolerance thyrostatics) can be performed without prior preparation with thionamides.

In HD, when the goal of treatment is to destroy the thyroid gland, the therapeutic activity, taking into account the volume of the thyroid gland, maximum capture and half-life of iodine-131 from the thyroid gland, is calculated based on the estimated absorbed dose of 200-300 Gray. Hypothyroidism usually develops within 3-6 months. after the introduction of iodine-131. A serious problem of Russian endocrinology is the actual lack of such an excellent method of treating HD as iodine-131 at the disposal of endocrinologists.

This approach to the treatment of this disease is most common in Europe and in our country. In the United States, Canada, and several other countries, most patients receive only iodine-131 therapy. Along with this, the choice of treatment option is determined not only by the traditional approach for a particular country, but also by many other factors, which include both individual characteristics of the patient (very large goiter, concomitant pathology, pregnancy planning) and social factors (lack of iodine-131).

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