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Diagnosis and treatment of Graves' disease with particular emphasis on appropriate techniques in nuclear medicine. General state of knowledge

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Abstract

Graves' disease is an autoimmune disease. It accounts for 50–80% of cases of hyperthyroidism. Antibodies against the TSH receptor (TRAb) are responsible for hyperthyroidism (TRAB). The key role in monitoring and diagnosis of Graves' disease plays the level of hormones of free thyroxine and triiodothyronine. Helpful is an ultrasound of the thyroid scintigraphy which due to its functional character is both a valuable addition to morphological studies as well as plays an important role in the diagnosis and therapy in patients with Graves' disease. There is no perfect treatment for Graves' disease. The reason for this is the lack of therapy directed against primary pathogenic mechanisms. Currently available treatments need to be thoroughly discussed during the first visit as the patient's understanding of the choice of a treatment constitutes a vital role in the success of therapy. Graves' disease treatment is based on three types of therapies that have been carried out for decades including: pharmacological treatment anti-thyroid drugs, I^{131} therapy and radical treatment — thyroidectomy. The purpose of the treatment is to control symptoms and patient to return to euthyreosis. Treatment of Graves' disease is of great importance because if left untreated, it can lead to long-term harmful effects on the heart, bone and mental well-being of patients.

KEY word: Graves' disease

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Background

Graves' disease is one of the most common autoimmune diseases. It affects around 5% of the population and accounts for 50–80% of cases of hyperthyroidism [1, 2]. The number of cases is about 24 per 100,000 patients per year [3]. The incidence of the disease is similar among White Race and Asians Race, but it is lower among blacks. The greatest risk of developing the disease falls on women aged 40–60 years [4]. In the United States Graves' disease is the most common cause of hyperthyroidism and its occurrence is approx. 1.2% [5]. Genetic and environmental factors (80%: 20%) are responsible for the rise of the disease. Environmental factors include: smoking, stress, pregnancy, sex hormones, infections and adequate consumption of iodine [6–8]. The immunopathogenesis of Graves' disease is complex. Antibodies against the TSH receptor (TRAb) are responsible for hyperthyroidism (TRAB) [8, 9]. These antibodies, on the surface of thyroid cells, link with TSH receptors, causing uncontrolled and continuous stimulation of the thyroid, leading to excessive synthesis of the thyroid hormones: thyroxine (T4) and triiodothyronine (T3) and its hypertrophy. The spontaneous remission of the disease occurs in 30% of patients [8].

Nuclear medicine allows performing both diagnosis and treatment of Graves' disease. The aim of this review is to show the current approach to diagnosis and therapy of Graves' disease, particularly putting the particular emphasis on paying attention to the methods used in nuclear medicine, which may be useful to GP doctors and specialists providing care for patients with Graves' disease.

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Diagnosis of Graves' disease

A full-blown picture of hyperthyroidism is often seen in patients aged 20–50 years. In the elderly, symptoms may be hardly visible, often in the form of thyroid-heart set [10]. Clinical signs and symptoms of the disease are divided into different forms of hyperthyroidism [9, 11]. Graves' disease is associated with beyond thyroid symptoms including symptoms around the eye sock-

ets (Graves' ophthalmopathy) and less common symptoms: skin lesions (thyroid dermopathy), and the swelling around fingers and nails (thyroid acropachia) [10, 12–15]. Orbitopathy is characterized by inflammation of oculomotor muscles and extraocular connective tissue. It occurs in about one-third of patients. It is unique for Graves' disease. Thyrotropin receptors located on orbit fibroblasts and adipocytes are probably responsible for autoimmune features of Graves' ophthalmic [17]. In addition, in Graves' disease vascular goiter can be detected, making it easy to recognize, because the disease occurs rarely without the goiter [10]. When these characteristic symptoms occur in combination with diffuse goiter and hyperthyroidism, the diagnosis of this disease is easy. However, in the case of patients without symptoms of hyperthyroidism or ocular symptoms and lack of goiter, Graves' disease should be differentiated from other causes of hyperthyroidism such as toxic adenoma or toxic multinodular goiter. Larger diagnostic difficulties occur in the elderly, in whom hyperthyroidism occurs in the form of thyroid-heart set and in patients with Graves' ophthalmopathy without symptoms of hyperthyroidism (the so-called euthyreosis in Graves' disease) [8, 9, 16, 18].

Laboratory studies

In 2011 there was a major international survey conducted among members of the Endocrine Society, the American Thyroid Association (ATA) and the American Association of Clinical endocrinologists (AACE) to oversee Graves' disease. The majority of respondents came from North America (63%), while the others were from Europe (12.9%), South America (11.3%), Asia and Oceania (9.5%), Middle East and Africa (3.4 %) [8, 19]. A study showed that 90% of endocrinologists in case of suspicion of hyperthyroidism require the measurement of TSH and FT4 free thyroxine concentration. This approach is consistent with the guidelines of the AACE and ATA in the diagnosis of hyperthyroidism, therefore the finding of reduced levels of TSH and the increase level of FT4 is usually sufficient to diagnose Graves' disease despite the fact that the concentration of FT3 is also often elevated in patients with hyperthyreosis [5, 8]. A study on the level of FT3 was only needed for 40% of endocrinologists involved in the survey (without geographical differences) [19]. However, 2-4% of patients with hyperthyroidism have the correct level of FT4 and increased level of FT3, T3 (i.e. T3 thyrotoxicosis) [8, 11]. Thus, in the initial assessment of status of thyroid in case of patients with suspected hyperthyroidism it is recommended that the measurement of concentration level of TSH, FT4 and FT3 in the serum should take place.

To determine whether the cause of hyperthyroidism is Graves' disease, a designation in the serum of the concentration level of antibodies against the TSH receptor (TRAB) is advisable. Due to the fact that antibodies against thyroglobulin (anti-Tg) and thyroid peroxidase (anti-TPO) are found both in patients with the disease of Hashimoto as well as in patients with Graves' disease, modern immunological and biological tests for TRAb with high sensitivity and specificity allow to identify the etiology of hyperthyroidism [8, 20–23]. A designation of antibodies against THS receptor (TRAB) takes place in a short time, because the current automated TRAb tests developed over the last 5–10 years are comparable to tests helping determine the level of antibodies against thyroid peroxidase (TPO) in terms of ease of use and costs of implementation. A meta-analysis published in 2012 showed that the sensitivity of TRAb tests of the third generation is respectively 98.3% and specificity is 98.2%. The probability that the patient has Graves' disease is 1.367–3.420 times higher in the case, when antibody against TSH receptor are positive than negative [8, 24, 25].

In a study from 2011 concentration measurement of TRAb antibodies was practiced by 58.1% of respondents: including in Europe (77.5%), South America (54.3%) and also by 65.3% of respondents from Asia and Oceania [8, 26]. The measurement of TRAb in patients with hyperthyroidism is a helpful test in establishing the diagnosis, which often helps predict the clinical course and response to treatment. This study plays a special role in ambiguous clinical cases, such as: painless thyroiditis, unilateral exophthalmos, Graves' opthalmopathy in the condition of euthyreosis, subclinical hyperthyroidism, hyperthyroidism induced by amiodarone, hyperemesis gravidarum, with a hyperthyroidism and anticipating the risk of neonatal hyperthyroidism in mothers with Graves' disease [27]. Due to the much higher sensitivity, and low cost to measure the concentrations of antibodies against the TSH receptor, this test should be performed in every patient suspected of having Graves' disease, especially in the absence of symptoms beyond thyroid including Graves' ophthalmopathy [8].

Image exploration and the iodine uptake test

Ultrasound examination on thyroid, belonging to the screening examinations, helps in its diagnosis. It is inexpensive, non-invasive, repeatable, which allows diagnosing breast-feeding mothers, pregnant women giving immediate results and documentation in the form of photos of tested thyroid. The ultrasound examination allows assessing echostructure of pulp, highlighting focal lesions, assessing their vasculature by using Color Doppler Ultrasonography, as well as diversifying them into solid and cystic changes [8, 28]. Under the control of ultrasonography a fine needle biopsy can be performed, which determines a type of change we face: mild or cancer change. It is useful in the diagnosis of lumpy version of Graves' disease and autoimmune toxic nodular goiter [8]. In patients with Graves' disease usually an increased hipoechogenicity of pulp is stated during the ultrasound examination.

Among 426 patients with Graves' disease, USG examination made it possible to determine the correct ultrasound diagnosis in 406 patients (95.2%), while scintigraphy led to the correct diagnosis in 415 patients (97.4%) [8, 29].

Image tests used in nuclear medicine include: scintigraphy and the iodine uptake test. Scintigraphy is based on a physiological phenomenon that consists of the ability to actively uptake of iodine. It is due to the presence of proteins in the basal membrane — sodium-iodine thyrocyte symporter [30]. The scintigraphy is performed with a metastable technetium (Tc99m) or by using radioactive iodine. The iodinated isotopes, in the examination, emit gamma radiation that is registered by means of a gamma camera. The intensity of tracer accumulation is proportional to the thyroid. The isotope of iodine which is used in scintigraphic examination is I^{131}. Scintigraphy is based on the assumption that the affected pulp of thyroid has a different ability to uptake technetium radioisotopes and iodine than normal pulp [30, 31]. Improper placement of a given compound indicates the presence of pathological changes in the thyroid gland [31]. The routine scintigraphy is administered intravenously at a dose of 40–60 MBq (1–2 mCi). Radioactive iodine is administered orally at a dose of 2–4 MBq (74–148 μCi) [30, 31].

In Graves' disease equally increased radiotracer uptake by the thyroid gland is reported. Due to the increased turnover of iodine and increased hormone synthesis, you can observe greater radiotracer uptake after 4–6 hours, and after 24 hours [8, 30]. According to the current guidelines of AACE and ATA, the uptake of radioactive iodine by the thyroid should be measured in patients with symptoms of hyperthyroidism; however it does not prove Graves' disease [8].

Treatment of Graves' disease

The ideal therapy for Graves' disease should restore the proper function of the thyroid gland, prevent the recurrence of hyperthyroidism, avoid development of hypothyroidism and not allow progression of Graves' ophthalmopathy. Unfortunately, current therapies do not meet the above criteria. Each patient, therefore, should be aware of their advantages and disadvantages. Treatment of Graves' disease is based on three types of therapies that are carried out for decades including: pharmacological treatment anti-thyroid drugs, I^{131} therapy and radical treatment — thyroidectomy. The purpose of the treatment is to control symptoms and patient to return to euthyreosis [32]. In the United States the most common treatment for Graves' disease chosen by doctors is I^{131} therapy, while in Europe and Japan, there is a greater preference for medical and radical treatment [5]. Treatment of Graves' disease is of great importance because if left untreated it can lead to long-term harmful effects on the heart, bone and mental well-being of patients [32, 33].

Pharmacotherapy

The most commonly used group of anti-thyroid drugs in patients with Graves' disease are thionamides which were introduced in 1943 by Astwood [34]. This group includes: methimazole (MMI), propylthiouracil (PTU) and carbimazole (CBZ); they are the basis of anti-thyroid therapy. Their main effect is to inhibit the synthesis of thyroid hormone by blocking the action of thyroid peroxidase as a consequence of incorporation of iodine to thyroglobulin, which is an important step in the synthesis of triiodothyronine (T3) and thyroxine (T4) [34, 35].

Anti-thyroid drugs which do not belong to thionamides group, nowadays rarely used, is also potassium perchlorate recommended in hyperthyroidism induced by amiodarone [8].

Among the thyrostatic drugs the following are the most frequently applied in practice: propylthiouracil (Thyrosan®) and thiamazole (Thyrozol®: 5, 10, 20 mg, Metizol® 5 mg). Anti-thyroid drug therapy is continued for a period of 9 to 12 months, but in appropriate cases from 18 to 24 months [36]. The current ATA and AACE guidelines indicate that methimazole should be taken for a period of approximately 12–18 months and then that dose should be reduced or discontinued if TSH at this time is normal. Note that the anti-thyroid drugs do not cure Graves' hyperthyroidism, however in the case of suitable doses this drug may be very effective what enables to control hyperthyroidism and allows for the euthyreosis [5]. Anti-thyroid drugs can inhibit the production of thyroid hormone, but they also have topical immunesuppressive activity as a result of which a decrease in the concentration of anti-TSHR occurs [10].

Pharmacological treatment of Graves' disease starts with a full dose of thyrostatic drug gradually decreasing it according to the results of the concentration of free hormones in the serum and the clinical condition of the patient. In case of the correct drug reaction after 2–3 weeks of treatment an improvement is noticed, whereas after 4–6 weeks euthyreosis appears. In cases of non-radioiodine therapy or surgery in 20% of patients have a permanent remission of the disease, while after about 6–9 months after treatment 50% of patients are still in euthyrosis [36]. Higher doses of anti-thyroid drugs allow obtaining euthyroid state faster, however, they do not increase the chance of securing a lasting remission and their use increases the risk of side effects [10].

The current AACE and ATA guidelines suggest that methimazole should be used in all cases of patients eligible for anti-thyroid treatment, except for women in the first trimester of pregnancy [5, 8]. Furthermore, doctors should prescribe pregnant women propylthiouracil (PTU) due to the risk of embryopathy associated with taking methimazole and carbimazole [5, 8].

A study published in 2010 by Emiliano et al. [37] shows that methimazole is the most commonly prescribed anti-thyroid drug since 1996 in the United States. There is a growing popularity of it as nowadays doctors prescribe it 9 times more frequently [8, 37].

Supportive therapy involves the administration of sedatives, and β-adrenolytics. If necessary in the initial stage of Graves' disease and in case of leucopenia, prednisone can be prescribed for patient at a dose 10–20 mg per day [36]. Supportive therapy is mainly used in the initial phase of anti-thyroid treatment to reduce the symptoms of hyperthyroidism [8]. If the patient after completion of treatment with methimazole falls again in hyperthyroidism this qualifies him to radioiodine therapy or thyroidectomy.

Each patient during drug therapy should be informed of side effects of anti-thyroid drugs. Patient should inform your doctor immediately if he/she experiences jaundice, rashes, joint pain, abdominal pain, dark colored urine, fever, nausea, fatigue or sore throat. Before starting treatment, you should also inform the patient to immediately stop taking the medicines and report to their doctor if symptoms suggesting agranulocytosis or liver damage develop [5]. Also when cutaneous allergic symptoms are observed antihistamine may be included in order to relieve these. Cross-reaction between propylthiouracil and thiamazole occurs in approximately 50% of cases. Alternatively, a lithium or inorganic iodine can be used [36].

Anti-thyroid treatment is recommended especially in patients with a high likelihood of remission (especially women with mild disease with low crop and the negative or low titer of TRAb). Pharmacological treatment is also advised in the elderly with underlying conditions that increase the risk of surgery, patients living in nursing homes and other care facilities, as preparation for radioiodine administration, which reduces the need for daily administration of thyreostatics [5].

The main disadvantage of pharmacological treatment is a high rate of relapse of Graves' disease. It varies from 30 to 70% in different studies [38, 39]. Factors that are associated with a high likelihood of relapse after treatment with anti-thyroid are: young age, sex, smoking, postnatal period as well as severe hyperthyroidism. The increased risks of relapse are also encountered in patients who at the end of the treatment have the increased level of TRAb antibodies, but recurrence can also happens to a lesser extent in patients with normal levels of antibodies against the TSH receptor [8].

New therapeutic options

Because of autoimmune etiopathogenesis of Graves' disease immunomodulatory therapy has been recently attempted. High

hopes were placed in the use of rituximab (anti-CD20). Unfortunately, the first results of clinical studies indicate its limited effectiveness which at high cost and aggressiveness of therapy does not encourage its use [36].

Surgical treatment — thyroidectomy (thyroidectomy)

Thyroidectomy is an effective way to treat hyperthyroidism, however, is less common than radioiodine therapy [40–42]. It can be implemented only in patients treated with anti-thyroid [8, 43, 44]. Thyroidectomy should be considered in the following cases: patients with a large goiter, patients not responding to treatment with anti-thyroid drugs or patients, who refuse radioiodine therapy. Such a phenomenon is often observed in Asian countries [45]. Thyroidectomy should be also performed in women in the second trimester of pregnancy, after failure of treatment with anti-thyroid drugs, in the period in which radioiodine therapy is contraindicated, as well as in cases where there is a fear of progress and ophthalmic resulting from the treatment of I^{131}. The treatment should also be considered in any patient with nodular form of Graves' disease, in which fine-needle biopsy of the nodule indicates the presence of malignant thyroid and in scintigraphy a "cold nodule" is stated [46]. The incidence of hypothyroidism is associated with a range of treatment. It is considered that hypothyroidism occurs in approximately 50% of patients after age of 25 [40, 46]. In some centers in patients with low crop without suspicion of cancer the macroscopic visual treatments using an endoscope are implemented, which cause less operative trauma compared to conventional open access [8, 47]. Specific complications after thyroidectomy are as the following: recurrent laryngeal nerve damage and post-surgical wound infection [8, 46]. These complications are inversely correlated with the experience of the surgeon and the annual number of such procedures [48]. The advantage of thyroidectomy is above all the fast relief of hyperthyrodism, while the disadvantages are as the following: general anesthesia, complication among 1–2% of patients such as recurrent laryngeal nerve palsy, hypoparathyroidism [46].

A preparation for surgery usually involves the administration of anti-thyroid drugs to restore euthyreosis and providing a solution of potassium iodide in 10–14 days to reduce congestion thyroid thereby reducing the intra-operative blood loss. Thyroidectomy seems to have no impact on the natural course of Graves' ophthalmopathy, but in its aftermath, cannot be ruled out beneficial effect of treatment due to a decrease in the serum antibody levels of TRAb. The results of a randomized prospective study show that the decline in the level of TRAb antibodies in the serum does not prevent the development of eye diseases. In case of 16 out of 191 patients with Graves' ophthalmopathy mild symptoms were observed over the next 5 years [8, 49].

Radioiodine therapy (I^{131})

A treatment of Graves' disease with radioactive iodine was introduced in 1940 in order to provide an alternative to surgical treatment of hyperthyroidism. In Poland, therapy with I^{131} is routinely carried out in the treatment of hyperthyroidism, including Graves' disease since 1950. Since that time, it has become widely used in the treatment of thyroid diseases making gradual necrosis of the thyroid cells [17, 50]. Loss of functional thyroid tissue after treatment with radioiodine in the majority of patients ultimately leads to its hypo-function, which is the desired effect of treatment with I^{131} [8, 17]. The use of low doses of this isotope is to restore the euthyroid state, but it is associated with a high rate of relapse of hyperthyroidism [5].

I^{131} is available in the form of sodium iodide (NaI) for oral administration in the form of capsules or liquid. The most commonly used forms are capsules, because the use of fluid is associated with a higher risk of contamination. They are supplied by the manufacturer in a variety of activities depending on demand. Under the current rules, capsules are transported and stored in containers with a capacity to absorb beta and gamma radiation. I^{131} capsules are administered to the individual via the respective applicators for reducing or eliminating the risk of direct contact with the skin of the capsule and its drop.

The effectiveness of the treatment of Graves' disease largely depends on the therapeutic activity of the I^{131}. The selection of optimal activity is difficult, high therapeutic doses give the highest cure rates, but relatively often cause hypothyroidism. On the other hand, the low activity less likely lead to hypothyroidism, but their effectiveness is poor. In addition, as shown by many years of experience, the effectiveness of radioiodine therapy of Graves' disease is influenced by a number of factors, many of which are immeasurable and they cannot be all included in one chart. Currently, there are two methods of determining therapeutic activity: solid dosage and method based on individual calculation of the dose. Recommended current activities of I^{131} were selected empirically. Activity of I^{131} (A) is calculated by taking into account the desired absorbed dose (D), the target tissue mass (m) and a maximum of thyroid iodine uptake (U), according to the following formula:

$$A\ [MBq] = 27.2\ \frac{m\ [g] \times D\ [Gy]}{U\ [\%] \times T\ [d]}$$

In order to achieve euthyroid it is recommended that the desired absorbed dose is 40–80 Gy, whereas for ablation of thyroid tissue 200–300 Gy. Activities used in practice range from 3 to 30 mCi (111–1110 MBq). The method does not require a fixed dose of the above calculations and establishes the administration of doses depending on the size of the thyroid, and the severity of symptoms of hyperthyroidism. The advantage of this method is a smaller percentage of patients with early hypothyroidism and lower total absorbed dose. A survey conducted among professionals in Britain showed that 70% of respondents recommended a fixed dose. High doses (≥ 0.78 GBq) with I^{131} are associated with higher rates of treatment success and cure than with low-dose of I^{131} (≤ 0.56 GBq). The method of applying fixed dose showed higher relapse rates of hyperthyroidism as well as the prevalence of hypothyroidism of the following treatment [8, 51–54].

I^{131} treatment effect in patients with Graves' disease is not immediate, temporary restoration of anti-thyroid treatment after administration I^{131} is indicated in the elderly or in patients with severe comorbidities especially with circulatory system diseases. A quick check of hyperthyroidism allows you to specify both lithium carbonate and I^{131} [8].

I^{131} treatment of patients with Graves' disease is associated with risk of developing or worsening of thyroid orbitopathy. On this complication, patients are exposed to smoking and high levels of antibodies of TRAb. In order to prevent symptoms, it

is recommended to cover the steroid prednisone in the form of doses of 0.4–0.5 mg/kg of body weight per day, ranging from 1–3 days before treatment with I^{131}. These doses are maintained for 2–4 weeks and then reduced over the next month to settle. In cases of mild orbitopathy it is possible to use lower doses of the casing (approximately 0.2 mg/kg of body weight per day for 6 weeks). Hypothyroidism is a major and frequent undesirable effect. It occurs at different frequencies depending on the population and the selection of the dose. Hypothyroidism can occur at various times after I^{131} treatment from a few weeks to several years. Therefore, these patients require periodic checks of TSH levels throughout life. In case of TSH increase it is recommended to administer L-thyroxine in substitute doses. In some patients with severe Graves' disease and accompanied by hypothyroidism, thyroid orbitopathy after treatment with high "ablative" doses of I^{131} is the expected effect of therapy. Of course, as in every case it requires using substitution of L-thyroxine [51, 52, 59–64].

I^{131} treatment can cause a temporary increase in FT4 and FT3 in a few days at the therapeutic dose. For initially high concentrations of these hormones is the possibility of worsening of symptoms, including heart failure, the appearance of atrial fibrillation, and even relapse of the thyroid. These patients prior to administration of a therapeutic dose of I^{131} require the preparation using beta-blockers and anti-thyroid drugs. In the case of contraindications to the use of anti-thyroid drugs (for example, agranulocytosis, damage to the liver Official Journal of the Ministry of Health — 52 — Pos. 82 52) you can administer I^{131} under the cover of β-adrenolytics drugs and steroids provided that you conduct close monitoring of systematic clinical evaluation hormone levels (preferably in a hospital). Patients with a large goiter that causes narrowing of the trachea should be treated with fractionated doses of I^{131} to prevent transient swelling of thyroid tissue, which can lead to respiratory failure and the need for tracheostomy. Rarely after administration of higher doses of therapeutic radiation we can observe symptoms of thyroiditis that require a non-steroidal anti-inflammatory drugs. Due to the very low mass of the iodine contained in a dose of I^{131} drug (about 1/1,000 of the daily supply of iodine) this treatment does not cause hypersensitive response even in patients with allergy to iodine. The increase of risk of cancer, including cancer of the thyroid gland in patients treated with I^{131} has not been clearly shown [51, 52, 64].

Conclusion

To sum up, the key role in monitoring and diagnosis of Graves' disease plays the level of hormones of free thyroxine and triiodothyronine. Helpful is an ultrasound of the thyroid scintigraphy which, due to its functional character, is a valuable complement morphological study and plays an important role in the diagnosis and therapy in patients with Graves' disease. Due to its low cost and much greater sensitivity to measure the concentrations of antibodies against the TSH receptor, this test should be performed in every patient suspected of having Graves' disease, especially in the absence of beyond thyroid symptoms including Graves' ophthalmopathy.

There is no perfect treatment for Graves' disease. The reason for this is the absence of therapy directed against primary pathogenic mechanisms. Currently available treatments need to be thoroughly discussed during the first visit with a specialist, because the patient's awareness about the selection of a treatment constitutes a vital role in the success of therapy. Anti-thyroid drugs represent conservative treatment option in which the thyroid tissue is not removed [8, 55–57]. Their use is generally safe; however, they may be adopted for a period of two years. The main disadvantage of using anti-thyroid drugs is too large proportion of relapse of hyperthyroidism. Large doses of anti-thyroid drugs allow getting euthyreosis faster, but they do not increase the chance of securing a lasting remission, but their use increases the risk of side effects [10].

Treatment with therapeutic doses of I^{131} has many advantages. The therapy is convenient because it is based on the oral administration of radioactive sodium iodide in capsule form. The dose is absorbed within one hour due to the rapid absorption of sodium iodide to the blood in the upper small intestine.

The previous observation suggests that radioactive iodine treatment is safe and free of complications which are connected with surgical treatment, for example: vocal cord paralysis, hypothyroidism or the occurrence of tetany [58].

Treatment with therapeutic doses of I^{131} can be performed on an outpatient basis what makes this method inexpensive and does not require long rehabilitation period comparing to surgery and a long-time administration of pharmacological drugs. The exact calculation of therapeutic activity of I^{131}, taking into account the absorbed dose and carried out in a timely checkups, reduces the number of patients with hypothyroidism and hyperthyroidism relapse.

All these advantages make the I^{131} treatment of Graves' disease being used more often.

Thyroidectomy should be considered in patients with a large goiter and in patients not responding to treatment with anti-thyroid drugs or patients who do not give their consent to the administration of a therapeutic dose of I^{131}. Thyroidectomy should also be performed in women in the second trimester of pregnancy, after failure of treatment with anti-thyroid drugs as well as when there is a fear of progress and ophthalmic resulting from radioiodine therapy.

Criteria for the review

The search for original work was conducted in MEDLINE from 1997 to 2015 that are focused on Graves' disease. The search conditions included: "Graves", "hyperthyroidism", "anti-thyroid drugs", "methimazole", "carbimazole", "propylthiouracil", "radioiodine therapy" and "thyroidectomy". Other relevant sources were also used, such as the American Thyroid Association guidelines, the American Association of Clinical Endocrinologists and chapters from books shown in the bibliography.

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