

GRAVES DISEASE

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Abstract

Hyperthyroidism (Graves' disease (GD)), is a relatively rare disease in adults and children. Treatment options for adults and children are antithyroid drugs (ATD), radioactive iodine (RAI), or thyroidectomy, but the risks as well as benefits of each are different.

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Аңдатпа

Гипертиреоз (Грейвс ауруы (ГА)), ересектер мен балаларда салыстырмалы түрде сирек кездесетін ауру. Ересектер мен балалардағы емдеу нұсқалары антитиреоидты препараттар (АТП), радиоактивті йод (РАИ) немесе тиреоидэктомия болып табылады, бірақ әр әдістің қауіп-қатері мен пайдасы әртүрлі.

Болезнь Грейвса

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Аннотация

Гипертиреоз (болезнь Грейвса (БД)), является относительно редким заболеванием у взрослых и детей. Варианты лечения у взрослых и детей – антитиреоидные препараты (АТП), радиоактивный йод (РАИ) или тиреоидэктомия, но риски, а также преимущества каждого способа различны.

Introduction

Graves' disease is an autoimmune disease resulting in generalized hyperfunction of the thyroid gland, i.e., hyperthyroidism.

It is named after Robert Graves, the Irish doctor who described this form of hyperthyroidism about 150 years ago. It occurs 7-8 times more often in women than in men [1].

Etiology

It is generally recognized that Graves' disease has a pronounced hereditary component, implementing a significant role of genetic factors.

Human leukocyte antigen (HLA), CD40, CTLA-4, PTPN22, Tg and TSHR are the main genes contributing to hypertheriosis. Impaired immune response (autoaggression) proteintyrosine phosphatase, non-re-

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Conflict of interest

The authors declare that they have no conflicts of interest

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hyperthyroidism, diffuse toxic goiter, Graves' disease, radioactive iodine, thyroidectomy

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ceptor type 22 (PTPN22). PTPN22 is a strong inhibitor of T-cell activation [2].

In Graves' disease these antibodies (called thyrotropin receptor antibodies (trab) or thyroid stimulating immunoglobulins (TSI) act in the opposite way [3].

Antibodies in Graves' disease bind to receptors on the surface of thyroid cells and stimulate these cells to overproduce and release thyroid hormones [4].

The term "primary hyperthyroidism" is sometimes used to refer to hyperthyroidism that develops as a result of thyroid disease. Secondary hyperthyroidism develops due to pathological processes occurring outside the thyroid gland, such as a TSH-secreting pituitary tumor. The 3 most common causes of thyrotoxicosis are also associated with thyroid hyperfunction:

- Diffuse thyroid hyperplasia associated with Graves' disease (85% of observations);

- hyperfunctional multinodular goiter;
- hyperfunctional thyroid adenoma.

Epidemiology

Iodine deficiency is the most common cause of goiter worldwide, affecting approximately 2.2 billion people. The prevalence and incidence of goiter depend on the degree of iodine deficiency. With mild iodine deficiency, the incidence of goiter is between 5% and 20%. With moderate deficiency, the prevalence increases to 20-30%, and with severe iodine deficiency, the incidence rises to over 30% [5].

Graves' disease is the most common cause of hyperthyroidism, accounting for 60% to 80% of hyperthyroidism cases. The prevalence in the general population is 1% to 1.5%. The incidence is 20 to 30 cases per year per 100,000 population [6].

Classification

Table 1.

According to the degree of enlargement of the thyroid gland (WHO) [7]

Grade	Characteristics
0	>No palpable or visible goitre.
1	A goitre that is palpable but not visible when the neck is in the normal position (i.e. the thyroid gland is not visibly enlarged). Nodules in a thyroid that is otherwise not enlarged fall into this category.
2	A swelling in the neck that is clearly visible when the neck is in a normal position and is consistent with an enlarged thyroid gland when the neck is palpated.

Table 2.

According to the severity of clinical manifestations and hormonal disturbances [8]

Subclinical (mild flow)	The clinical picture is absent or mild. TSH content is decreased, T4 and T3 levels are within the reference values.
Manifest (medium flow)	An elaborate clinical picture. The TSH content is significantly decreased, and the concentrations of T4 and T3 are elevated.
Complicated (severe flow)	Thyrotoxicosis and its complications: Atrial fibrillation, heart failure, relative adrenal insufficiency, dystrophic changes in the parenchymatous organs, psychosis, severe weight loss. TSH levels are significantly decreased, with elevated concentrations of T4 and T3 [8].

Diagnosis

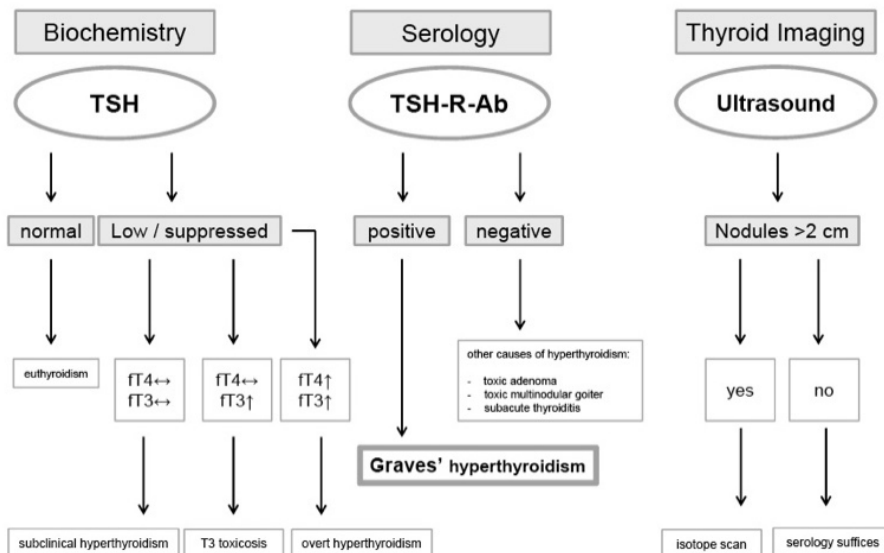
Diagnosis begins with complaints and a general examination of the patient. Laboratory data are the main diagnostic measures for diagnosis. Namely - general blood test and biochemistry, determination of the content of TSH, T3, T4, pituitary hormones, antibody titer to the TSH receptor, "classical" antibodies to

the thyroid gland titer. An ultrasound or MRI scan of the thyroid gland is also important [8].

Serology

Measurement of serum TSH has the highest sensitivity and specificity of any single blood test used in evaluating suspected hyperthyroidism and should be used as an initial screening test (Fig.1) [9].

Figure 1. Serology of Graves disease [9]



As in other autoimmune thyroid diseases, high levels of classical antithyroid antibodies - at-TPO and at-(at least 70-80% of cases) can be determined in HD [10]. Tactics patients management (Fig.2) [9].

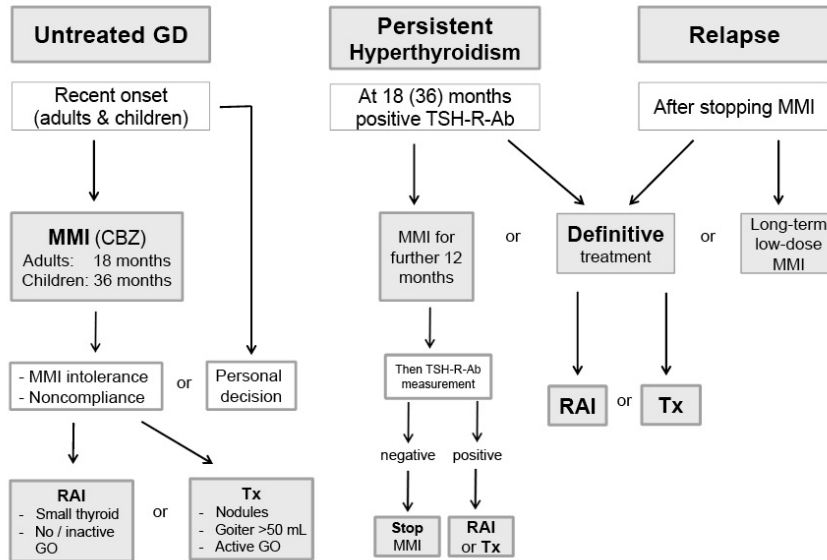


Figure 2. Algorithm for the management of a patient with Graves' hyperthyroidism [9]

Differential diagnosis

Disease	Distinguishing features
Thyroid-producing pituitary adenoma	«-» TSH reaction to thyrolyberine
Thyroid cancer metastases	Surgical treatment in anamnesis
Iatrogenic thyrotoxicosis	History of taking lithium, interferon, and drugs containing large amounts of iodine
Multinodular toxic goiter	Heterogeneity of scintigraphic pattern [11].

Treatment
 Methods of treatment:
 - Conservative therapy
 - RAI therapy
 - Surgical treatment
 Conservative therapy
 Conducted with antithyroid therapy (ATT). The mechanisms of the drugs are as follows:
 Intrathyroid inhibition:
 - Iodine oxidation.
 - Iodothyrosine compound.
 - Thyroglobulin biosynthesis
 - Follicular cell growth
 Extrathyroid inhibition of T4/T3 conversion (PTU) [9].
 The main ATT drugs are thionamides such as propylthiouracil (PTU), carbimazole (CBZ), and the active metabolite of CBZ, methimazole (MMI)
 The usual daily maintenance doses of ATP in the titration regimen are 2.5-10 mg MMI and 50-100 mg PTU. In addition, daily doses of 30 mg MMI may be given in combination with the addition of levothyroxine (L-T4) (blocking and replacement mode) to avoid medication-induced hypothyroidism [12].
Advantages:
 - Early treatment of the disease
 - Availability
Disadvantages:
 - Frequent relapses
 - Duration of treatment

- Adverse complications (liver cirrhosis, toxic hepatitis, unresponsiveness to ATP) [13].
 Both groups had recurrence of hyperthyroidism after discontinuation of methimazole, according to the results of the study. Secondary key findings were both clinical and subclinical hypo- and hyperthyroidism during methimazole treatment [14].
RAI radioactive iodine therapy
 One of the treatments for Graves' disease is radioactive iodine therapy. The mechanism of action is that radioactive iodine (RAI) exerts its effect when it is absorbed by follicular thyroid cells, emitting beta-rays that further cause permanent local damage to thyroid tissue.
 RAI treatment can predispose patients to irreversible hypothyroidism because it causes permanent destruction of thyroid tissue. Patients may require lifelong thyroxine therapy [15].
 Radioiodine (RAI) therapy is contraindicated in the following cases:
 - Pregnancy
 - Breast-feeding
 - Cancer without iodine absorption
 - Graves' ophthalmopathy (moderate to severe)
 - Severe thyrotoxicosis
 - Vomiting
 - Diarrhea [16].
 Radioiodotherapy worsens the course of ophthalmopathy. This is because radiation, by affecting thyrocytes, leads to a massive release of antigens shared

with the retrobulbar tissue, which in turn stimulates the formation of antibodies that induce the appearance or activation of EOP [17].

- Early complications
- Teratogenicity
 - Bone marrow suppression
 - Radiation-induced thyroiditis
 - Transient thyrotoxicosis
- Late complications
- Bone marrow depression
 - Pulmonary fibrosis
 - Leukemia
 - Hypothyroidism [16].

Radioiodine therapy is an effective treatment for Graves' disease. A high dose of radioiodine provides a high remission rate. The use of radioiodine as a therapeutic agent is simple, safe, effective and cost-effective [18].

Surgical treatment

Thyroidectomy is the most commonly chosen treatment. In recent American and European surveys, surgery is the first-line treatment. However, thyroidectomy is an effective treatment when the thyroid gland is enlarged, when primary hyperparathyroidism or suspected malignant nodules are present, or when the patient wishes to avoid exposure to ATD (Anti Thyroid Drugs) or RAI (radioactive iodine).

Indications	Contraindications
Large goitre Thyreostatic allergy Ineffectiveness of conservative therapy	Chronic diseases in the acute stage Contraindication of RAI [19].

The advantages of thyroidectomy include no radioactive iodine risk, rapid control of hyperthyroidism and no detrimental effects on ophthalmopathy.

Advantages and disadvantages of total thyroidectomy for Graves' hyperthyroidism:

Advantages	Disadvantages
No recurrent hyperthyroidism No radiation risk Rapid control of hyperthyroidism No evidence of harmful effects on the course of Graves' ophthalmopathy	Risk of postoperative hypoparathyroidism Risk of recurrent laryngeal nerve palsy Persistent hypothyroidism Risks related to anaesthesia or surgery Hospitalisation Postoperative scarring

To minimize the risk of complications, surgery must be performed by a qualified surgeon. To minimize the risk of intra- or postoperative exacerbation of thyrotoxicosis, hyperthyroidism must be adequately controlled with ATD treatment before surgery. The use of saturated potassium iodide solution (SSKI) is useful in the immediate preoperative period (10 days) to reduce thyroid vascularisation and intraoperative blood loss (9).

Complications:

1. Post-operative bleeding (up to 6%)
2. Defeat of the recurrent laryngeal nerve and dysphonia (10%)
3. Hypoparathyroidism (20%) (20).

Despite all the variety of drug treatments for patients with hypertheriosis, it has lost its "predominant role" in the choice of treatment. As studies show, 50%

of patients experience a relapse and 30% of patients are ineffective [21].

Predictors of relapse

Potential predictors of recurrence: marked thyroid enlargement, young age, high levels of TSH-R-Ab, and the presence of thyrotoxicosis complications [22].

Conclusion

After reviewing all treatment methods, comparing the advantages and disadvantages of each, we have concluded that surgical treatment is currently the "leading" treatment for Graves' Disease. Thanks to advances in surgery, surgical thyroid removal has been made safer by the development of new surgical, haemostatic and other techniques such as intraoperative monitoring of the recurrent laryngeal nerve. Thereby lowering the rate of complications in patients.

References

1. 2017 the American Thyroid Association <https://www.thyroid.org/graves-disease/>
2. Graves, disease in clinical perspective Margret Ehlers1,* , Matthias Schott1, Stephanie Allelein1 Published: 1 January 2019 IMR Press [https://pubmed.ncbi.nlm.nih.gov/30468646/#:~:text=Graves'%20disease%20\(GD\)%20is%2C%20however%2C%20also%20been%20described.](https://pubmed.ncbi.nlm.nih.gov/30468646/#:~:text=Graves'%20disease%20(GD)%20is%2C%20however%2C%20also%20been%20described.)
3. Graves Disease Binod Pokhrel; Kamal Bhusal. June 22, 2022., StatPearls <https://www.ncbi.nlm.nih.gov/books/NBK448195/>
4. Serikbaeva A.A., Tauesheva Z.B., Kultanov B.J., Turmukhambetova A.A., Dosmagambetova R.S., Shcherbakova L.V., Rymar O.D. Indicators of thyroid function in women of fertile age from the Aral Sea region of Kazakhstan. Clinical and Experimental Thyroidology. 2020;16(1):28-37.

- <https://doi.org/10.14341/ket11222>
5. Goiter StatPearls, Ahmet S. Can; Anis Rehman. Last Update: June 5, 2022. <https://www.thyroid.org/graves-disease/>
 6. Graves' Disease: Can It Be Cured? *Endocrinol Metab.* 2019;34(1):29-38. DOI: <https://doi.org/10.3803/EnM.2019.34.1.29>
 7. Zimmermann, M. B., Hess, S. Y., Adou, P., Toresanni, T., Wegmüller, R., & Hurrell, R. F. (2003). Thyroid size and goiter prevalence after introduction of iodized salt: a 5-y prospective study in schoolchildren in Côte d'Ivoire. *The American journal of clinical nutrition*, 77(3), 663–667. <https://doi.org/10.1093/ajcn/77.3.663>
 8. Davies, T., Burch, H. (2020). Treatment of Graves' orbitopathy (ophthalmopathy). UpToDate. Retrieved February 11, 2021, from <https://www.uptodate.com/contents/treatment-of-graves-orbitopathy-ophthalmopathy>
 9. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism <https://pubmed.ncbi.nlm.nih.gov/30283735/>
 10. <https://cyberleninka.ru/article/n/bolezni-greivsa-klinicheskaya-lektsiya/viewer>)
 11. Douglas S. Ross, Henry B. Burch, David S. Cooper, M. Carol Greenlee, Peter Laurberg, Ana Luiza Maia, Scott A. Rivkees, Mary Samuels, Julie Ann Sosa, Marius N. Stan, and Martin A. Walter. American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis, 2016. *THYROID*, Volume 26, Number 10, 2016, P. 1369-1421.
 12. Current Diagnosis and Management of Graves' Disease Imam Subekti 1 , Laurentius Aswin Pramono 2018 April <https://pubmed.ncbi.nlm.nih.gov/29950539/>
 13. Control of Graves' hyperthyroidism with very long-term methimazole treatment: a clinical trial Fereidoun Azizi 2021 Jan 14 <https://pubmed.ncbi.nlm.nih.gov/33446181/>
 14. Long-term Methimazole Therapy in Juvenile Graves' Disease: A Randomized Trial Fereidoun Azizi, Miralireza Takyar 2019 May <https://pubmed.ncbi.nlm.nih.gov/31040197/>
 15. Treatment of post-radioactive iodine relapse of hyperthyroidism: comparison of long-term methimazole and radioactive iodine treatment <https://pubmed.ncbi.nlm.nih.gov/35610532/>
 16. Radioactive Iodine Therapy Inderbir S. Padda, Minhthao Nguyen. Treasure Island (FL): StatPearls Publishing; 2022 Jan. 2022 May 29. <https://pubmed.ncbi.nlm.nih.gov/32491673/>
 17. Effect of radioactive iodine treatment on the course of endocrine ophthalmopathy A.V. Dreval1, A.F. Tsyb, O.A. Nechaeva, I.V. Komerudus, O.V. Perepelova, B.Y. Drozdovsky, P.I. Garbuzov, T.N. Guseva <https://cyberleninka.ru/article/n/vliyanie-lecheniya-radioaktivnym-yodom-na-techenie-endokrinnoy-oftalmopatii>
 18. Irathérapie dans la maladie de Basedow: place et efficacité Ali Sellem, Wassim Elajmi, Rania Ben Mhamed, Nesrine Oueslati, Haroun Ouertani, Hatem Hammami *Pan Afr Med J.* 2020 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7603816/>
 19. 2022 European Thyroid Association Guideline for the management of pediatric Graves' disease. in *European Thyroid Journal* Authors: Christiaan F Mooij, Timothy D Cheetham, Frederik A Verburg, Anja Eckstein, Simon H Pearce, Juliane Léger, and A S Paul van Trotsenburg <https://etj.bioscientifica.com/view/journals/etj/11/1/ETJ-21-0073.xml>
 20. Overview of Thyroid Surgery Complications 2020 Juraj Lukinović and Mario Bilić <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8212606/>
 21. Comparison of Morbidity After Total Thyroidectomy Among Adult Patients With and Without Preoperative Hyperthyroidism Maxime Gerard, Antoine Hamy, Jean-Christophe Lifante, François Pattou, Niki Christou, Claire Blanchard, Eric Mirallié 2021 June <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7974829/>
 22. Pesheva E.D., Morgunova T.B., Fadeev V.V. (2022). Current approaches to the management of patients with Graves' disease. *Medicine*, (1), 48-56. DOI: 10.24412/2071-5315-2022-12487