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Review Article

Diagnosis and management of Grave's disease: A global overview

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Grave's disease is an organ-specific autoimmune disorder characterized by a variety of circulating antibodies, including common autoimmune antibodies, as well as anti-TPO and anti-TG antibodies.The most important autoantibody is TSI, which is directed toward epitopes of the TSH receptor and acts as a TSH-receptor agonist. Like TSH, TSI binds to the TSH receptor on the thyroid follicular cells to activate thyroid hormone synthesis and release and thyroid gland growth (hypertrophy). This results in the characteristic picture of Grave's thyrotoxicosis, with a diffusely enlarged thyroid, very high radioactive iodine uptake, and excessive thyroid hormone levels compared with a healthy thyroid.The hyperthyroidism is caused by thyroid hypertrophy and stimulation of function, resulting from interaction of anti-TSH-receptor antibodies (TRAb) with the TSH receptor on thyroid follicular cells. Measurements of serum levels of TRAb and thyroid ultrasonography represent the most important diagnostic tests for Grave's disease. Management of the condition currently relies on antithyroid drugs, which mainly inhibit thyroid hormone synthesis, or ablative treatments (^{131}I-radiotherapy or thyroidectomy) that remove or decrease thyroid tissue. None of these treatments targets the disease process, and patients with treated Grave's disease consequently experience either a high rate of recurrence, if receiving antithyroid drugs, or lifelong hypothyroidism, after ablative therapy. Novel agents that might act on the disease process are currently under evaluation in preclinical or clinical studies, but evidence of their efficacy and safety is lacking.

Key Words : autoimmune disorder, exophthalmos, pretibial myxedema, TSH receptors, thyrotoxicosis, antithyroid gland

INTRODUCTION

Grave's' disease, also known as **toxic diffuse goiter** and **Flajani-Basedow-Grave's disease**, is an autoimmune disease[1].Autoimmune thyroid disease has a higher prevalence in patients with human leukocyte antigen (HLA)-DRw3 and HLA-B89. Grave's disease is felt to be an HLA-related, organ-specific defect in suppressor T-cell function. Grave's' disease is one of the most common of all thyroid problems. It is also the leading cause of hyperthyroidism, a condition in which the thyroid gland produces excessive hormones[2]. First described by Sir Robert Grave's in the early 19th century, Grave's' disease occurs in about 0.5% of people. It occurs about 7.5 times more often in women than men. Often it starts between the ages of forty to sixty.[3]

Thyroid hormone levels can be highly elevated in Grave's disease. Clinical findings specific to Grave's disease include thyroid ophthalmopathy (periorbital edema, chemosis [conjunctival edema], injection, or proptosis) and, rarely, dermopathy over the lower extremities. This autoimmune condition may be associated with other autoimmune diseases, such as pernicious anemia, myasthenia gravis, vitiligo, adrenal insufficiency, celiac disease, and type 1 diabetes mellitus.

Once the disorder has been correctly diagnosed, it is quite easy to treat. In some cases, Grave's' disease

goes into remission or disappears completely after several months or years. Left untreated, however, it can lead to serious complications -- even death.Although the symptoms can cause discomfort, Grave's' disease generally has no long-term adverse health consequences if the patient receives prompt and proper medical care.

Causes of Grave's' Disease

Hormones secreted by the thyroid gland control metabolism, or the speed at which the body converts food into energy. Metabolism is directly linked to the amount of hormones that circulate in the bloodstream.[4] If, for some reason, the thyroid gland secretes an overabundance of these hormones, the body's metabolism goes into high gear, producing the pounding heart, sweating, trembling, and weight loss typically experienced by hyperthyroid people. The onset of disease may be triggered by stress, infection, or giving birth. Those with other autoimmune diseases such as type 1 diabetes and rheumatoid arthritis are more likely to be affected. Smoking increases the risk of disease and may make the eye problems worse.[8] Normally, the thyroid gets its production orders through another chemical called thyroid-stimulating hormone (TSH), released by the pituitary gland in the brain. The disorder results from an antibody, called thyroid stimulating immunoglobulin (TSI), that has a similar effect to thyroid stimulating hormone (TSH). Spurred by these false signals to produce, the thyroid's hormone factories work overtime and exceed their normal quota.

Since Grave's' disease is an autoimmune disease which appears suddenly, often quite late in life, a viral or bacterial infection may trigger antibodies which cross-react with the human TSH receptor (a phenomenon known as antigenic mimicry, also seen in some cases of type I diabetes).[8]

One possible culprit is the bacterium *Yersinia enterocolitica* (a cousin of *Yersinia pestis*, the agent of bubonic plague).[9]It has also been suggested that *Yersinia enterocolitica* infection is not the cause of auto-immune thyroid disease, but rather is only an associated condition; with both having a shared inherited susceptibility.

Predisposing factors for Graves' disease*

- Genetic susceptibility (including HLA alleles)
- Stress (negative life events)
- Smoking (especially associated with ophthalmopathy)
- Female sex (sex steroids)
- Postpartum period
- Iodine (including amiodarone)
- Lithium
- Rare factors:
  - Interferon- α therapy
  - Highly active antiretroviral therapy (HAART) for HIV infection

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Signs and Symptoms

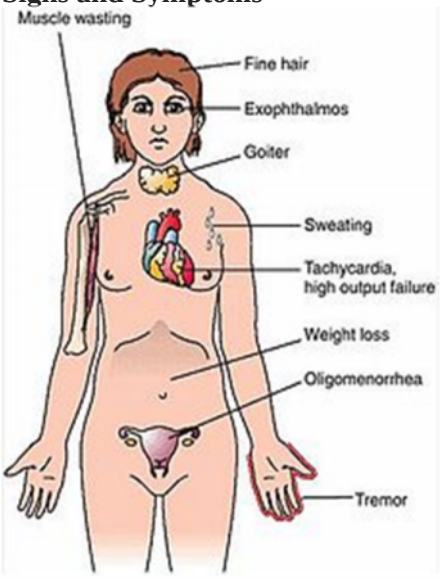
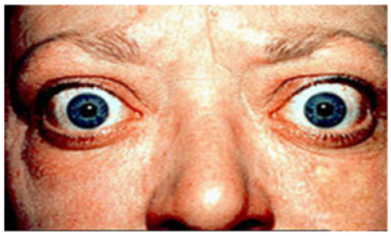


Fig. 1 Sign & symptoms

- Grave's' ophthalmopathy



Grave's ophthalomopathy

- goitre
- pretibial myxedema (which are caused by the autoimmune processes of the disease).
- insomnia
- hand tremor
- hyperactivity[5]
- hair loss
- excessive sweating
- shaking hands
- itching
- heat intolerance
- weight loss despite increased appetite
- diarrhea
- frequent defecation
- palpitations
- muscle weakness
- a diffusely enlarged (usually symmetric), nontender thyroid
- lid lag
- excessive lacrimation due to Grave's' ophthalmopathy
- arrhythmias of the heart, such as sinus tachycardia, atrial fibrillation
- premature ventricular contractions
- hypertension[5]
- psychosis
- mania
- anxiety[6]
- agitation
- depression[6]

In severe cases of exophthalmos, which are rare, swollen eye muscles can put tremendous pressure on the optic nerve, possibly leading to partial blindness.[7] Eye muscles weakened by long periods of inflammation can lose their ability to control movement, resulting in double vision.

Rarely, people develop a skin condition known as pretibial myxedema. It is a lumpy reddish thickening of the skin on the shins. It is usually painless and is not serious. Like exophthalmos this condition does not necessarily begin with the onset of Grave's' nor Does it correlate with the severity of the disease.

Diagnosis

Thyroid function tests for hyperthyroidism are as follows:

- Thyroid-stimulating hormone (TSH)
- Free thyroxine (FT_4) or free thyroxine index (FTI—total T_4 multiplied by the correction for thyroid hormone binding)
- Total triiodothyronine (T 3)
- Thyroid function study results in hyperthyroidism are as follows:
- Thyrotoxicosis is marked by suppressed TSH levels and elevated T 3 and T 4levels
- Patients with milder thyrotoxicosis may have elevation of T 3 levels only
- Subclinical hyperthyroidism features decreased TSH and normal T 3 and T 4levels
- Autoantibody tests for hyperthyroidism are as follows:
- Anti–thyroid peroxidase (anti-TPO) antibody
- Thyroid-stimulating immunoglobulin (TSI)
- Autoantibody titers in hyperthyroidism are as follows:
- Grave's disease – Significantly elevated anti-TPO, elevated TSI
- Toxic multinodular goiter- Low or absent anti-TPO
- Toxic adenoma – Low or absent anti-TPO
- Patients without active thyroid disease may have mildly positive anti-TPO[10]
- If the etiology of thyrotoxicosis is not clear after physical examination and other laboratory tests, it can be confirmed by scintigraphy: the degree and pattern of isotope uptake indicates the type of thyroid disorder. Findings are as follows:
- Grave's disease – Diffuse enlargement of both thyroid lobes, with uniform uptake of isotope and elevated radioactive iodine uptake
- Toxic multinodular goiter -- Irregular areas of relatively diminished and occasionally increased uptake; overall radioactive iodine uptake is mildly to moderately increased
- Subacute thyroiditis –Very low radioactive iodine uptake[10].

Pathophysiology

Normally, the secretion of thyroid hormone is controlled by a complex feedback mechanism involving the interaction of stimulatory and inhibitory factors.[10]Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the pituitary to release TSH.

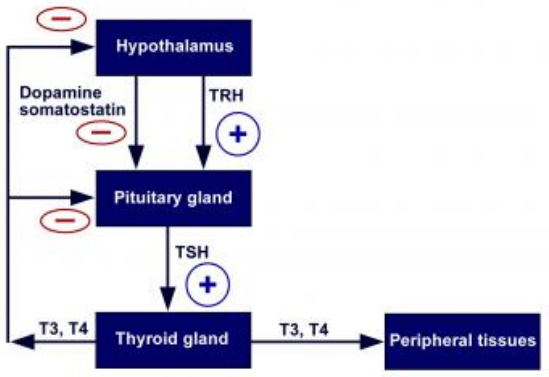


Fig 2: Hypothalamic-pituitary-thyroid axis feed - back. Schematic representation of negative feedback system that regulates thyroid hormone levels. TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

Binding of TSH to receptors on the thyroid gland leads to the release of thyroid hormones—primarily

T_4 and to a lesser extent T_3. In turn, elevated levels of these hormones act on the hypothalamus to decrease TRH secretion and thus the synthesis of TSH.

Synthesis of thyroid hormone requires iodine. Dietary inorganic iodide is transported into the gland by an iodide transporter, converted to iodine, and bound to thyroglobulin by the enzyme thyroid peroxidase through a process called organification. This results in the formation of monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are coupled to form T_3 and T_4; these are then stored with thyroglobulin in the thyroid's follicular lumen. The thyroid contains a large supply of its preformed hormones.

Thyroid hormones diffuse into the peripheral circulation. More than 99.9% of T_4 and T_3 in the peripheral circulation is bound to plasma proteins and is inactive. Free $T_3$is 20-100 times more biologically active than free T_4. Free T_3 acts by binding to nuclear receptors (DNA-binding proteins in cell nuclei), regulating the transcription of various cellular proteins.[10]

Any process that causes an increase in the peripheral circulation of unbound thyroid hormone can cause thyrotoxicosis. Disturbances of the normal homeostatic mechanism can occur at the level of the pituitary gland, the thyroid gland, or in the periphery. Regardless of etiology, the result is an increase in transcription in cellular proteins, causing an increase in the basal metabolic rate. In many ways, signs and symptoms of hyperthyroidism resemble a state of catecholamine excess, and adrenergic blockade can improve these symptoms.

In Grave's disease, circulating auto antibodies against the thyrotropin receptor provide continuous stimulation of the thyroid gland. These antibodies cause release of thyroid hormones and thyroglobulin, and they also stimulate iodine uptake, protein synthesis, and thyroid gland growth.

Ophthalmopathy

The underlying pathophysiology of Grave's ophthalmopathy (also called thyroid-associated orbitopathy) is not completely characterized. It most likely involves an antibody reaction against the TSH receptor that results in activation of T cells against tissues in the retro-orbital space that share antigenic epitopes with thyroid follicular cells.

These immune processes lead to an active phase of inflammation, with lymphocyte infiltration of the orbital tissue and release of cytokines that stimulate orbital fibroblasts to multiply and produce mucopolysaccharides (glycosaminoglycans), which absorb water. In consequence, the extraocular muscles thicken and the adipose and connective tissue of the retro-orbit increase in volume.[10]

Notable cases

- Ayaka, Japanese singer[11,12]
- George H. W. Bush, U.S. president[13]
- The president's wife Barbara Bush[13]
- Rodney Dangerfield, American comedian and actor [14]
- Missy Elliott, Hip-hop rapper[15]
- Marty Feldman, British comedian[15]
- SiaFurler, singer and song writer[16]
- Heino, German folk singer[17]
- Barbara Leigh, an American former actress and

fashion model [17]

- Sir Cecil Spring Rice, British ambassador to the United States during the First World War [18]
- Maggie Smith, a British actress [20]

Management of grave's' disease

The treatment goals for Grave's' disease are to inhibit the production of thyroid hormones and to block the effect of the hormones on the body. Some treatments include:[21]

- **Radioactive iodine therapy**

With this therapy, radioactive iodine, or radioiodine is taken up by mouth. Because the thyroid needs iodine to produce hormones, the radioiodine goes into the thyroid cells and the radioactivity destroys the overactive thyroid cells over time. This causes thyroid gland to shrink, and symptoms lessen gradually, usually over several weeks to several months. [23]

Radioiodine therapy may increase the risk of new or worsened symptoms of Grave's' ophthalmopathy. This side effect is usually mild and temporary, but the therapy may not be recommended if one already have moderate to severe eye problems.

Other side effects may include tenderness in the neck and a temporary increase in thyroid hormones.

Radioiodine therapy isn't used for treating pregnant or nursing women. Because this treatment causes thyroid activity to decline, you'll likely need treatment later to supply your body with normal amounts of thyroid hormones.

- **Anti-thyroid medications**
- Anti-thyroid medications interfere with the thyroid's use of iodine to produce hormones.

These prescription medications include:[21,22]

Carbimazole (in UK)

Propylthiouracil

Methimazole(Tapazole).

When these two drugs are used alone, a relapse of hyperthyroidism may occur at a later time. Taking the drug for longer than a year, however, may result in better long-term results. Anti-thyroid drugs may also be used before or after radioiodine therapy as a supplemental treatment.

Side effects of both drugs include rash, joint pain, liver failure or a decrease in disease-fighting white blood cells. Methimazole isn't used to treat pregnant women in the first trimester because of the slight risk of birth defects. Therefore, propylthiouracil is the preferred anti-thyroid drug during the first trimester for pregnant women. These drugs also cross the placenta and are secreted in breast milk. Lugol's iodine may be used to block hormone synthesis before surgery.[22]

- **Beta blockers**

These medications don't inhibit the production of thyroid hormones, but they do block the effect of hormones on the body. They may provide fairly rapid relief of irregular heartbeats, tremors, anxiety or irritability, heat intolerance, sweating, diarrhea, and muscle weakness.[21,24]

Beta blockers include:

- ✓ Propranolol (Inderal)
- ✓ Atenolol (Tenormin)
- ✓ Metoprolol (Lopressor, Toprol-XL)
- ✓ Nadolol (Corgard)

Beta blockers aren't often prescribed for people with asthma, because the drugs may trigger an asthma

attack. These drugs may also complicate management of diabetes.

- **Surgery**

Surgery to remove all or part of thyroid (thyroidectomy or subtotal thyroidectomy) is also an option for the treatment of Grave's' disease. After the surgery, one will likely need treatment to supply the body with normal amounts of thyroid hormones.[24,25]

Risks of this surgery include potential damage to vocal cords and the tiny glands located adjacent to thyroid gland (parathyroid glands).

- **Grave's' ophthalmopathy**

Mild symptoms of Grave's' ophthalmopathy may be managed by using over-the-counter artificial tears during the day and lubricating gels at night. If the symptoms are more severe, doctor may recommend:

- **Corticosteroids.** Treatment with prescription corticosteroids, such as prednisone, may diminish swelling behind the eyeballs. Side effects may include fluid retention, weight gain, elevated blood sugar levels, increased blood pressure and mood swings.
- **Prisms.** One may have double vision either because of Grave's' disease or as a side effect of surgery for Grave's' disease. Though they don't work for everyone, prisms in glasses may correct double vision.
- **Orbital decompression surgery.** In this surgery, doctor removes the bone between the eye socket (orbit) and sinuses — the air spaces next to the orbit. This gives eyes room to move back to their original position.This treatment is usually used if pressure on the optic nerve threatens the loss of vision. Possible complications include double vision.
- Orbital radiotherapy. Orbital radiotherapy was once a common treatment for Grave's' ophthalmopathy, but the benefits of the procedure aren't clear. Orbital radiotherapy uses targeted X-rays over the course of several days to destroy some of the tissue behind your eyes. Doctor may recommend orbital radiotherapy if eye problems are worsening and prescription corticosteroids alone isn't effective or well-tolerated.

Grave's' ophthalmopathy doesn't always improve with treatment for Grave's' disease. Symptoms of Grave's' ophthalmopathy may even get worse for three to six months. After that, the signs and symptoms of Grave's' ophthalmopathy usually stabilize for a year or so and then begin to get better, often on their own.[21, 24, 23]

Lifestyle and home remedies

If one have Grave's' disease, make mental and physical well-being a priority;

- **Eating well and exercising** can enhance the improvement in some symptoms while being treated and help feel better in general. For example, because thyroid controls metabolism, one may have a tendency to gain weight when the hyperthyroidism is corrected. Brittle bones can also occur with Grave's' disease and weight-bearing exercises can help maintain bone density.

- Easing stress as much as you can. This may be helpful, as stress may trigger or worsen Grave's' disease. Listening to music, taking a warm bath or walking can help relax oneself and put one in a better frame of mind.[22]

For Grave's' ophthalmopathy

These steps may make your eyes feel better if you have Grave's' ophthalmopathy:

- **Apply cool compresses to your eyes.** The added moisture may soothe your eyes.
- **Wear sunglasses.** When your eyes protrude, they're more vulnerable to ultraviolet rays and more sensitive to bright light. Wearing sunglasses that wrap around the sides of your head will also lessen the irritation of your eyes from the wind.
- **Use lubricating eye drops.** Eye drops may relieve the dry, scratchy sensation on the surface of your eyes. A paraffin-based gel, such as Lacri-Lube, can be applied at night.
- **Elevate the head of your bed.** Keeping your head higher than the rest of your body lessens fluid accumulation in the head and may relieve the pressure on your eyes.
- **Don't smoke.** Smoking worsens Grave's' ophthalmopathy.[22]

For Grave's' dermopathy

If the disease affects your skin (Grave's' dermopathy), use over-the-counter creams or ointments containing hydrocortisone to relieve swelling and reddening. In addition, using compression wraps on your legs may help.[22]

Summary

Graves' disease is a complex disease affecting multiple organ systems. A high level of suspicion is required for the diagnosis in all except the obvious patient. Because all available treatments have serious drawbacks, extensive discussion with the patient about therapeutic options is key to disease control and persistent long-term health. It is hoped that further understanding of the underlying pathogenesis will lead to new therapies capable of restoring the immunological milieu to normal.

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