Graves' disease

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All about Mary

Mary, 47, is a perimenopausal mother of one. She presented to her family doctor for fatigue.

Mary reported progressive fatigue, hand tremors, and heat intolerance for two months. She had no palpitations, eye symptoms, weight loss, bowel pattern, or appetite changes. She also denied recent neck pain, tenderness, exposure to intravenous dyes or use of lithium, amiodarone, or interferon. Her physical exam is briefed in Table 1. Her biochemical workup is shown in Table 2.

Mary had previously been diagnosed with depression and used citalopram, multivitamins, and an anxiolytic. She is a housewife who quit smoking eight years ago and denies alcohol intake. Family history was significant for hypothyroidism in her mother.

Table 1
Physical exam

- *Blood pressure:* 110/60 mmHg
- *Weight:* 138 lbs
- *Height:* 5'3"
- *Heart rate:* 76 beats per minute regular
- *Eye exam:* No lid lag, retraction, proptosis, chemosis, diplopia, or ocular paresis
- *Thyroid:* Diffusely enlarged about 30 g symmetrical without nodules or bruit on auscultation
- *Chest and heart exam:* Unremarkable
- *Extremities:* No tremors or onycholysis; absent dermopathy; swift ankle reflex relaxation

Graves' disease was discussed with Mary along with treatment options. As expected, she chose radioactive iodine treatment. She received I131 and became hypothyroid in approximately eight weeks. She was started on levothyroxine sodium replacement. She never required a beta blocker since she was not tachycardic. To date, no ocular complications are reported.

What about Graves'?

Robert Graves first identified the association of goiter, palpitations, and exophthalmos in 1835. Graves' hyperthyroidism is an autoimmune disease. It also affects the eyes (Graves' ophthalmopathy) and the skin (localized dermopathy or myxedema), but the causes of these less common components of the disease are not known. It most commonly occurs in people under 40, and is seen up to 10 times more often in women than in men.

The chief risk factor for Graves' disease (female sex) is in part the result of the modu-

Table 2
Investigations

- Suppressed thyroid stimulating hormone: < 0.01 µIU/L
- High free thyroxine (FT4): 29 pmol/L (normal < 23)
- High total T3: 3.7 nmol/L (normal < 2.8)
- Diffuse high 24-hour uptake: 34% (normal < 28)

Table 3
Common manifestations of thyrotoxicosis

Symptoms:	Signs:
Nervousness	Tachycardia
Increased sweating	Atrial fibrillation
Heat intolerance	Fine tremors
Palpitations	Hyperreflexia
Fatigue	Onycholysis
Weight loss	Warm moist skin
Racing heart	Lid lad
Dyspnea	Lid retraction
Weakness	Diffuse goiter
Hyperphagia	Tremors of hands and tongue
Eye complaints	Bruit over thyroid gland
Leg swelling	Dermopathy
Diarrhea	Ophthalmopathy.
Oligomenorrhea	

lation of the autoimmune response by estrogen. Smoking is weakly associated with Graves' hyperthyroidism, and strongly associated with the development of ophthalmopathy.

How do you know it's Graves'?

The term thyrotoxicosis refers to the clinical and biochemical manifestations of exposure to excessive quantities of thyroid hormones, whereas hyperthyroidism implies that these hormones have originated in the thyroid gland (Table 3).

The diagnosis is based on the clinical and biochemical manifestations of hyperthyroidism and on the clinical and laboratory features that confirm the cause.

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Measurement of serum thyrotropin is a useful screening test for the presence of hyperthyroidism, but the diagnosis of hyperthyroidism must be confirmed by the measurement of serum free thyroxine. Patients in the earliest stage of Graves' hyperthyroidism may have only increased secretion of triiodothyronine (T3 Toxicosis); therefore, serum free triiodothyronine should be measured in patients with normal serum free thyroxine concentrations and low serum thyrotropin concentrations. Measurements of serum total thyroxine and triiodothyronine alone are less reliable, because use of certain drugs and increases in thyroid hormone-binding proteins can cause high values. The differential diagnosis of thyrotoxicosis should also be kept in mind (Table 4).

After biochemical analysis, the most sensitive and specific test to differentiate Graves' from most forms of thyroiditis is the measurement of iodine uptake by the thyroid gland being high. This test is performed after oral ingestion of fixed small dose of radioactive iodine.

What's the treatment?

Although some beta blockers impair T4-to-T3 conversion, it is unlikely that this effect is of clinical significance. The use of propranolol preferably (long-acting or once daily), long-acting ß1-selective antagonists, such as atenolol or metoprolol, is recommended.

Two thionamide drugs, methimazole (Tapazole) and propylthiouracil (PTU) are available for therapy of Graves' disease. Both

drugs act by inhibiting thyroid hormone synthesis and, additionally, PTU in high concentration blocks the 5'-deiodinase enzyme that converts thyroxine to triiodothyronine. PTU is usually initiated at a dose of 100 mg to 150 mg every 8 hours, and the dose reduced to 50 mg three times daily (tid) or twice daily (bid) after a euthyroid state is reached. Methimazole is usually started at 5 mg to 15 mg bid, but up to 30 mg bid in patients who are very toxic, with maintenance doses of 5 mg to 10 mg daily. Some thyroid specialists prefer to give a fixed dose of antithyroid drug (*e.g.,* methimazole, 30 mg) along with thyroxine to prevent hypothyroidism (the block-replace regimen versus the titration regimen). Common complications of thionamide drug treatment include abnormal sense of taste, pruritus, urticaria, fever, and arthralgias.

Radioiodine is administered orally as iodine 131 in solution or as a capsule. Radioiodine is rapidly incorporated into the thyroid and, via its ß-emissions, produces radiation thyroiditis and fibrosis resulting in euthyroidism usually within six to 18 weeks. Radioactive iodine is contraindicated in pregnant women and those who are breast-feeding, and it can induce or worsen ophthalmopathy, particularly in smokers. The worsening of ophthalmopathy is often transient and may be prevented by glucocorticoid therapy. Patients are advised not to become pregnant for three to six months following treatment.

Subtotal thyroidectomy is preferred by some patients with Graves' hyperthyroidism, especially those with a large goiter, and it may be indicated in patients with a coexistent thyroid nodule whose nature is unclear. The patient should be treated with an antithyroid drug until euthyroidism is achieved; inorganic iodide is also usually administered for seven days before surgery.

Current treatments for Graves' hyperthyroidism are effective, but often result in iatrogenic hypothyroidism, whereas the treatment of ophthalmopathy remains unsatisfactory. Further understanding of the immunologic processes involved should allow the development of better diagnostic methods and treatments. CME

Table 4
Differential diagnoses of thyrotoxicosis

Graves' disease
Solitary toxic adenoma
Toxic multinodular goiter
Thyroid carcinoma
Thyroid-stimulating hormone secreting pituitary adenoma
Hyperemesis gravidarum
Silent thyroiditis
Drug-induced thyroiditis
Subacute thyroiditis
Exogenous thyroid hormone ingestion
Ectopic thyroid tissue

References:
1- Weetman AP: Graves' Disease. NEJM 2000; 343(17):1236-48.
2- Ginsberg J: Diagnosis and management of Graves' Disease. CMAJ 2003; 168(5):575-85.
3- Bartalena L, Pinchera A, Marcocci C: Management of Graves' Ophthalmopathy: Reality and Perspectives. Endocrine Reviews 2000; 21(2):168-99.
4- Fisher JN: Management of thyrotoxicosis. South Med J 2000; 95(5):493-505.
5- Larsen PR, Davies TF, Hay ID: The thyroid gland. Williams Textbook of Endocrinology. Wilson JD, Foster DW, Kronenberg HM, et al (eds). Philadelphia, WB Saunders Co, 9th Ed, 1998, pp 389-51.