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## HIGHLIGHTS FROM MEDICAL GRAND ROUNDS

### THE DIFFERENT FACES OF THYROTOXICOSIS

**O**FTEN when a physician suspects a patient has thyrotoxicosis, clinical clues will suffice in determining the cause. When the clues are not sufficient, in a patient with a low thyroid-stimulating hormone (TSH) level and a high free thyroxine ( $T_4$ ) level, the radioactive iodine uptake (RAIU) is a useful next step in narrowing the diagnosis.

The different etiologies of thyrotoxicosis can be differentiated by whether they exhibit a high or low RAIU. Hyperthyroidism, a major cause of thyrotoxicosis, is due to increased synthesis and release of thyroid hormone due either to stimulatory substances in the blood or to autonomous thyroid function, and is associated with an elevated thyroid RAIU. Thyrotoxicosis associated with a low thyroid RAIU is due either to inflammatory disorders of the gland or exogenous ingestion of excess thyroid hormone. The thyroiditis results in increased release but not increased synthesis of the thyroid hormones and is, therefore, not true hyperthyroidism. The treatment of subclinical thyrotoxicosis and Graves' disease present special challenges to the clinician.

#### THE PATHOPHYSIOLOGY OF THYROTOXICOSIS AND TSH SCREENING

Control of thyroid function starts with the hypothalamus, which synthesizes and releases thyrotropin-releasing hormone, which in turn stimu-

lates the pituitary to synthesize and release TSH. TSH stimulates the thyroid to release the thyroid hormones  $T_4$  and triiodothyronine ( $T_3$ ). In a negative feedback loop, the pituitary adjusts its TSH output in response to serum levels of free  $T_4$  and  $T_3$ .

In almost all thyroid disorders that can increase serum  $T_4$  and  $T_3$  levels, the serum TSH concentration is low. Thus, the single best screening test is a sensitive TSH assay. If the TSH level is normal, the patient is almost certainly euthyroid; if the TSH level is suppressed, the patient is subclinically or overtly thyrotoxic. Exceptions are thyrotoxic patients who have pituitary tumors (which are rare, and marked by increased levels of the alpha subunit of TSH) and those with pituitary resistance to thyroid hormone (which is even rarer). These patients have normal or elevated serum TSH values. Of note, high doses of dopamine and glucocorticoids inhibit release of TSH, and many patients receiving these drugs may have low serum TSH levels.

#### HIGH RADIOACTIVE IODINE UPTAKE CONDITIONS (TRUE HYPERTHYROIDISM)

##### Graves' disease

Graves' disease, the most common cause of thyrotoxicosis, is an autoimmune disorder in which an IgG immunoglobulin directed against the TSH receptor stimulates the thyroid to make extra hormone. The thyroid is almost always diffusely enlarged. An autoimmune process probably accounts for the characteristic signs of exophthalmos and pretibial myxedema, and in a patient with these hallmark signs, one need only measure circulating levels of TSH,  $T_4$ , and  $T_3$  to make the diagnosis. The course is marked by remissions and relapses. Early in the disease, occasional patients have elevations in  $T_3$  but not in  $T_4$ .

■ Highlights from Medical Grand Rounds present take-home points from selected Cleveland Clinic Division of Medicine Grand Rounds talks and other educational presentations at the Cleveland Clinic.

Some autoimmune disorders sometimes associated with autoimmune thyroid disease are type 1 diabetes mellitus, vitiligo, premature grey hair, pernicious anemia, collagen disease, hypoparathyroidism, Addison's disease, premature ovarian failure, testis failure, and hypophysitis.

### **Trophoblastic tumor, choriocarcinoma, hyperemesis gravidarum**

Human chorionic gonadotropin (HCG) is a weak stimulator of thyroid function, but a sialic acid deficient form of HCG is a more potent stimulator and is present in high levels in patients with trophoblastic tumors, choriocarcinoma, or hyperemesis gravidarum. The resulting thyrotoxicosis abates after these underlying conditions are appropriately treated.

### **Pituitary TSH-secreting tumor**

This unusual cause of hyperthyroidism is due to excess stimulation of the thyroid by TSH produced by the pituitary tumor.

### **Autonomous thyroid function**

Solitary or multiple "hot nodules" account for the excess iodine uptake and hormone production in some forms of thyrotoxicosis. In such cases, the RAIU is usually, but not always, elevated, and the autoimmune aspects of Graves' disease are not present.

### **LOW RADIOACTIVE IODINE UPTAKE CONDITIONS**

As a rule, except for iodine-induced thyrotoxicosis, the low-uptake forms do not require antithyroid drug therapy or surgery, and radioiodine therapy is not effective because the uptake is low. These disorders should be treated symptomatically.

### **Inflammatory diseases**

Inflammatory diseases of the thyroid cause excess release of thyroid hormones—not excess production. After the first 3 or 4 months, as the thyroid is depleted of hormones, the patient may go through several months of hypothyroidism before finally returning to a euthyroid state.

**Silent lymphocytic thyroiditis.** From 5% to 10% of postpartum women have silent lymphocytic thyroiditis. The thyrotoxic phase of this condition is often brief, and is followed by a hypothyroid phase

which is often misdiagnosed as "postpartum blues." These patients have no history of iodine or thyroid hormone intake, and thyroid-stimulating immunoglobulins are absent. The thyroid gland is firm and nontender, and the women almost always have thyroid peroxidase antibodies in their blood, even before pregnancy. Biopsy of the thyroid shows classic lymphocytic infiltration. The condition almost always recurs with subsequent pregnancies.

This self-limited disorder can be treated symptomatically with beta blockers during the thyrotoxic phase. If the hypothyroid phase lasts for more than a few weeks, it can be treated with levothyroxine short-term (4 to 6 months).

**Subacute painful thyroiditis** is also frequently misdiagnosed—as a sore throat or otitis media. In addition to a tender, enlarged thyroid, symptoms include fever, acute viral symptoms, and those of thyrotoxicosis. Serum thyroglobulin levels are elevated, as is the sedimentation rate. A nonsteroidal anti-inflammatory drug such as aspirin or ibuprofen may help. In more protracted and severe cases, I almost always use a short course of prednisone for 6 weeks, stopping the medication when the RAIU returns to normal.

### **Thyrotoxicosis factitia**

Overtreatment with thyroid hormone is the most common cause of thyrotoxicosis factitia, although an outbreak in Minnesota was traced to consumption of hamburgers that contained bovine thyroid tissue. Goiter is absent, thyroglobulin levels are normal or low, and thyroid peroxidase antibodies are absent.

### **Metastatic thyroid cancer**

Rarely, patients who have had their thyroids removed for the treatment of cancer may develop thyrotoxicosis, resulting from widespread small areas of metastases (often in the lungs) that continue to produce thyroid hormone. The RAIU is low because there is little if any thyroid tissue left after the thyroidectomy.

### **Iodine-induced thyrotoxicosis**

Iodine-induced thyrotoxicosis is most commonly seen in elderly patients given iodine who already have a nodular goiter. These patients have elevated urine iodine excretion. Excess iodine exposure is usually iatrogenic, due to amiodarone, cough mixtures, povidone iodine, or radiographic contrast



agents. I strongly suggest examining the thyroid prior to using contrast agents, to identify patients with goiter who are at greater risk of developing iodine-induced thyrotoxicosis.

#### TREATMENT ISSUES

##### What to do about subclinical thyrotoxicosis

Subclinical thyrotoxicosis—in which the TSH level is low but the  $T_4$  and  $T_3$  levels are normal—poses a dilemma for the clinician. The prevalence is about 1.5% in elderly patients, and most have a multinodular goiter. Such patients are at two to three times greater risk of atrial fibrillation than those with normal serum TSH values, but it is not clear whether to give them antithyroid therapy to prevent atrial fibrillation. The most common cause of subclinical thyrotoxicosis is excess administration of levothyroxine for hypothyroidism.

##### Treatment of Graves' disease

Treatment of Graves' disease is not standardized. I recommend radioactive iodine therapy in older patients, or antithyroid drugs in younger patients. Patients with extremely large goiters may require surgery. I prefer methimazole to propylthiouracil because the former can be given once daily, compared with two to three times a day for the latter, assuring better patient compliance.

Patients must be made euthyroid before thyroid surgery. A regimen that can accomplish this in 5 to 7 days when urgent surgery is necessary is dexamethasone (1 mg every 12 hours), iopanoic acid (0.5 g every 12 hours), propranolol (120 mg daily), and large doses of propylthiouracil (600 mg daily) or methimazole (40 mg daily).

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#### SUGGESTED READING

Braverman LE. Evaluation of thyroid status in patients with thyrotoxicosis. *Clin Chem* 1996; 42:174–178.

Braverman LE, Utiger RD, eds. *The thyroid*, 6th edition. Philadelphia: JB Lippincott, 1991.

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## CONTEMPORARY ISSUES IN COST-EFFECTIVE DRUG THERAPY

**M**ANY FACTORS influence a physician's decision to prescribe a particular drug. Now, in addition to considering the efficacy of the drug therapy they prescribe, physicians are increasingly being asked to consider its cost-effectiveness.

Although cost is a factor in selecting drugs, it should not be the deciding factor. Efforts to control pharmacy costs involve preventing medication errors (which lead to preventable hospitalizations), using the least-expensive drug that is appropriate, and using the most cost-effective drug to reduce overall health care costs.

#### PREVENTING DRUG ERRORS

Pharmacists and physicians can collaborate to reduce health care costs by minimizing adverse drug effects, which are common and costly. By one estimate, each adverse drug event costs an average of \$2000, excluding legal repercussions.<sup>1</sup> Extended stays due to inappropriate antibiotic use cost an average of \$5300. Overall, adverse drug events cost the US health care system an estimated \$76 billion per year.<sup>2</sup>

Statistics vary, but according to one study, adverse drug events are responsible for 11% of all hospital admissions (28% to 35% of these admissions are of patients older than age 65), and 28% of hospitalized patients experience an adverse drug event.<sup>3</sup> Another study found an incidence of 6.5 adverse drug events per 100 admissions, of which 1% were fatal, 12% were life-threatening, and 30% were serious.<sup>4</sup> The investigators considered 28% of all the drug events preventable, as were 42% of the life-threatening and serious events. Of the preventable events (ie, errors), 56% occurred during ordering, 34% occurred during administration, 6% occurred during transcription, and 4% occurred during dispensing.

The latter study points out the need to provide physicians more information when they prescribe, perhaps in the form of computer systems or information pharmacists. At one hospital, use of such a computer system resulted in a decrease in antibiotic use, a decrease in costs per treated patient, fewer adverse events, and a lower mortality rate.<sup>5</sup>