Thyrotoxicosis

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The term *thyrotoxicosis* refers to all causes of elevated thyroid hormones circulating in the body, whereas the term *hyperthyroidism* describes a disease process caused by the thyroid gland overproducing and secreting excessive amounts of thyroid hormone. A recently published survey suggests a prevalence of thyrotoxicosis in the United States of approximately 0.5%.[1] Thyrotoxicosis causes a wide range of symptoms, including nervousness, palpitations, heat intolerance, diaphoresis, tremor, fatigue, and weight loss.

The most common cause of thyrotoxicosis is Graves' disease, which accounts for approximately 60% to 80% of cases of hyperthyroidism in the United States and in other countries where the population has adequate iodine intake.[2] Iodine-deficient populations have a much lower incidence of Graves' disease (< 50%).[3] Graves' disease is approximately 5 to 10 times more common in women than in men; the incidence is similar among Caucasian and Asian populations but lower among African Americans.[2] Patients younger than age 40 years are at the highest risk for the development of Graves' disease.[4]

Other causes of thyrotoxicosis include toxic multinodular goiter, solitary toxic nodules, and thyroiditis. Treatment for thyrotoxicosis depends on the underlying disorder and may include β-blockers, antithyroid medications, radioactive iodine ablation, and surgery. This article reviews the clinical features of thyrotoxicosis, including behavioral, musculoskeletal, dermatologic, ophthalmologic, cardiovascular, gastrointestinal, and reproductive features. Laboratory findings are briefly discussed, and studies used to establish the etiology of thyrotoxicosis are reviewed. The treatments are presented in context of the specific etiology of thyrotoxicosis.

CLINICAL FEATURES

The clinical features of thyrotoxicosis are diverse and can affect most organ systems. More than 50% of patients with thyrotoxicosis develop symptoms of nervousness, rapid heartbeat or palpitations, heat intolerance, fatigue, and weight loss.[5] Patients with Graves' disease usually present with a diffusely enlarged goiter.[5] The goiter is normally nontender but may be slightly tender to palpation, and, if significantly enlarged, can cause pressure symptoms. Auscultation over the lobes of the thyroid may reveal a characteristic soft bruit, which is virtually diagnostic for Graves' disease.

Behavioral Features

Patients with thyrotoxicosis may complain of emotional lability, anxiety, and difficulty concentrating. Difficulty with sleep patterns in these patients can contribute to symptoms of moderate to profound fatigue throughout the day. Patients with thyrotoxicosis may be restless during the history and physical portions of the medical examination.

Neurologic Features

A fine tremor is commonly seen in thyrotoxicosis. The physician may elicit the tremor by asking the patient to hold the hands outstretched (simultaneously closing the eyes may enhance the tremor) or by sticking out the tongue. Patients may also develop proximal muscle weakness and have difficulty performing ordinary activities, such as climbing a flight of stairs, reaching the arms over the head, or standing from a sitting position without the assistance of one's hands.

Dermatologic Features

Patients with thyrotoxicosis may have unusually smooth skin, especially over the elbow, because of a decrease in the keratin layer.[6] The skin also can be warm and even diaphoretic because thyrotoxicosis can cause an increase in blood flow. This increased warmth is usually associated with heat intolerance, which is a common

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feature of thyrotoxicosis. The fingernails of patients with thyrotoxicosis may be soft and loosened from the nail bed, developing a characteristic onycholysis or "Plummer's nails." More rapid hair shedding occurs in thyrotoxicosis, causing diffuse hair loss and thinning.

In a small subset of patients with Graves' disease, dermopathy may be present, characterized by lymphocytic infiltration of the dermis layer of skin, accumulation of glycosaminoglycans, and edema.[7] Although uncommon, this infiltrative dermopathy or localized myxedema tends to occur in older patients with severe ophthalmopathy.[8] The most frequent area of occurrence is over the anterolateral aspects of the shin (pretibial myxedema) but dermopathy can also occur at other sites, especially after mild trauma. The dermopathy is usually nonpitting, thickened, indurated, and although usually asymptomatic, may be pruritic or painful.

Ophthalmologic Features

Thyrotoxicosis can result in contraction of the eyelid muscles (levator palpebrae) because of increased sympathetic tone that causes both the characteristic stare and "lid lag."[9] Approximately 25% of patients with Graves' disease develop clinically evident ophthalmopathy.[10] These clinical features can even precede the diagnosis of Graves' disease.[2] Ophthalmopathy in Graves' disease is more common in Caucasians than Asians, and older men are at highest risk of severe ophthalmopathy.[11] In addition, ophthalmopathy in Graves' disease appears to be more common and severe in patients who smoke cigarettes.[12] Almost all patients who develop bilateral ophthalmopathy are diagnosed with Graves' disease.

Most of the clinical manifestations of ophthalmopathy associated with Graves' disease are caused by an increase in the volume of retrobulbar tissue.[13] This increase results in the characteristic exophthalmos (proptosis). Ophthalmopathy in Graves' disease is characterized by edema and inflammation of the extraocular muscles and increased orbital connective tissue and fat. The edema is thought to be caused by the hydrophilic action of fibroblast-secreted glycosaminoglycans, whereas the inflammation results from lymphocytic infiltration of the extraocular muscles and orbital connective tissue.[14] Involvement of the extraocular muscles can result in impairment of eye muscle function, leading to diplopia. Exophthalmos occurs in approximately 25% to 30% of patients with ophthalmopathy in Graves' disease; approximately 5% to 10% of these patients develop diplopia.[15] Severe ophthalmopathy may lead to a dry or "gritty" sensation in the eyes and even to the development of corneal ulcerations because of the inability to fully close the eyelids during sleep. Other complications include periorbital edema, conjunctival edema, conjunctival hyperemia, and photophobia.

The clinical course of Graves' ophthalmopathy is independent of thyroid status but is usually more severe in patients with poorly controlled hyperthyroidism. The clinical features typically worsen over the initial 12 to 18 months and subsequently stabilize; however, sudden worsening of ophthalmopathy may occur spontaneously and independent of therapy. Spontaneous improvement of mild ophthalmopathy occurs in approximately 60% of patients.[16]

Cardiovascular Features

The hypermetabolic state of thyrotoxicosis leads to an increase in cardiac output manifested by increased heart rate, widened pulse pressure, and decreased peripheral vascular resistance.[17] A flow murmur may be detected during cardiac examination of a patient with thyrotoxicosis. High-output congestive heart failure can occur in patients with severe thyrotoxicosis. A common feature of thyrotoxicosis is the development of cardiac arrhythmia. Atrial fibrillation occurs in up to 20% of patients with thyrotoxicosis and is more common in patients age 60 years or older; other arrhythmias, such as atrial ectopy, also can occur.[18] In more than 50% of patients with thyrotoxicosis-induced atrial fibrillation, the rhythm can spontaneously convert to sinus rhythm when the thyrotoxicosis is treated.[19] The hypermetabolic state increases oxygen consumption, causing some patients to develop symptoms of angina, dyspnea, and chest discomfort.[20]

Gastrointestinal Features

Patients with thyrotoxicosis often become hyperphagic to compensate for their higher metabolic rate. This increase in appetite usually occurs in conjunction with weight loss. Gut motility is increased, causing hyperdefecation (but not necessarily diarrhea), which can lead to malabsorption of nutrients. Additionally, symptoms of obstructive dysphagia can occur when a large goiter is present.

Reproductive System Features

Menstrual irregularities can be the presenting symptom in women with thyrotoxicosis. Oligomenorrhea, the most common menstrual disorder in thyrotoxicosis, is characterized by elevated luteinizing hormone (LH) and follicle-stimulating hormone levels, loss of midcycle LH peak, and consequent anovulation. Excess thyroid hormone increases sex hormone–binding

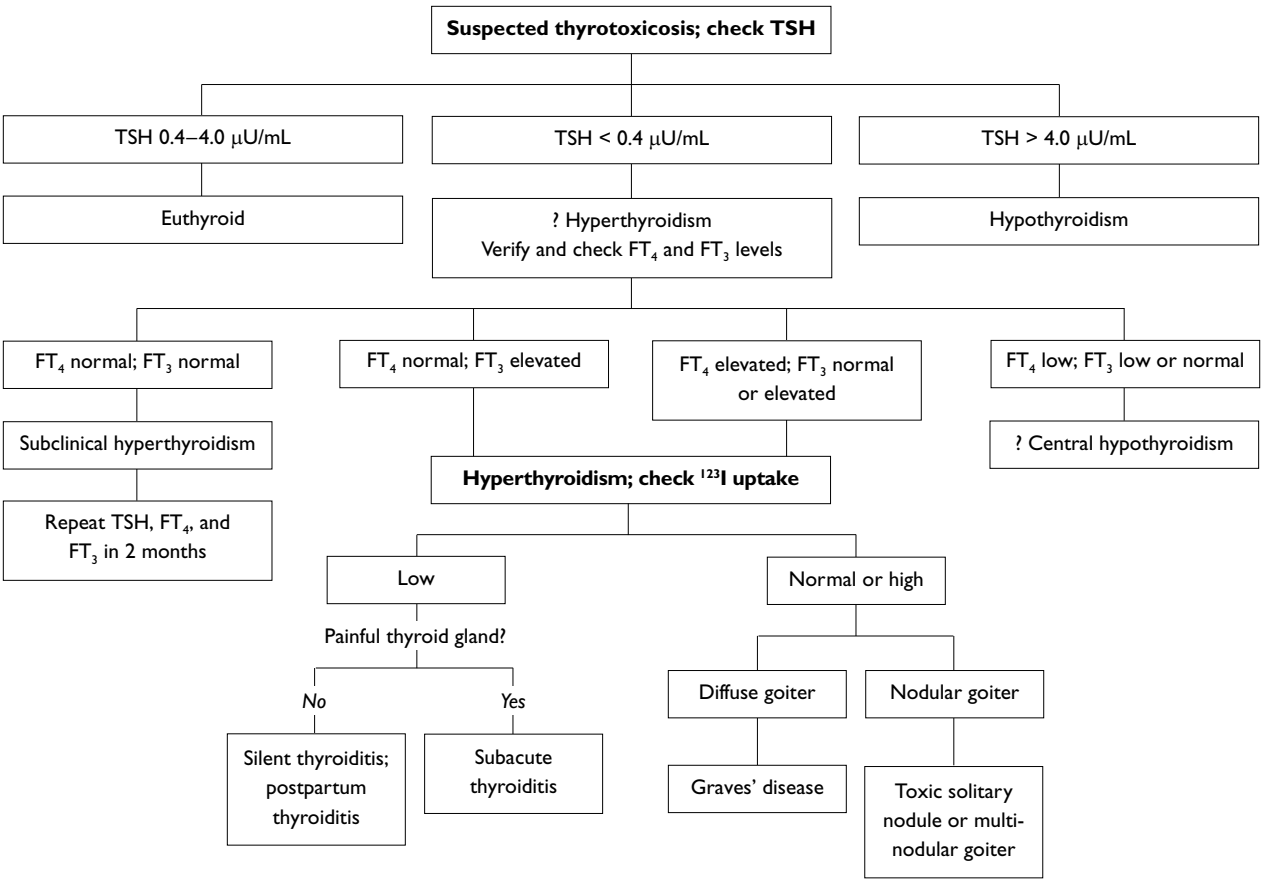

Figure. Algorithm for the diagnosis of hyperthyroidism. FT_3 = free triiodothyronine; FT_4 = free thyroxine; TSH = thyroid-stimulating hormone.

globulin (SHBG) production, thereby increasing serum estrogen and testosterone levels.[21] Whereas the circulating total sex hormone concentrations are increased, the free hormone concentrations are normal or even slightly reduced. Estrogen is metabolized more rapidly because of the hypermetabolic state. This combination of factors reduces the mid-cycle surge of LH secretion, causing oligomenorrhea and, in cases of severe thyrotoxicosis, amenorrhea.[22]

In men, gynecomastia and sexual dysfunction as features of thyrotoxicosis have been well established. The frequency of gynecomastia in men with thyrotoxicosis has been reported to be up to 40%.[23] Gynecomastia as the initial presentation is uncommon but has been reported.[24,25] As previously described, SHBG production is increased in thyrotoxicosis. SHBG binds both androgens and estrogens but has a higher affinity for androgens; therefore, the level of free androgen relative to estrogen is lower, leading to increased estrogen bioactivity.[26] Also, enhanced aromatization of testosterone in the periphery occurs, which also contributes to increased estrogen levels.[24,27]

Bone Health

A high level of thyroid hormone stimulates bone resorption, thereby causing a loss of both cortical and trabecular bone (a higher degree of cortical bone loss than trabecular bone loss occurs).[28] The higher rate of bone resorption may lead to hypercalcemia. Overall, untreated thyrotoxicosis is a significant risk factor for the development of osteoporosis and fractures.[29]

LABORATORY FINDINGS

The diagnosis of thyrotoxicosis may be evident based on clinical findings and subsequently confirmed biochemically. Thyroid-stimulating hormone (TSH) concentrations are suppressed because of the high levels of circulating thyroid hormone. The most cost-effective initial test to diagnose thyrotoxicosis is a serum TSH concentration alone (**Figure**). The clinician should be

aware that a suppressed TSH measurement is adequate for diagnosing primary hyperthyroidism but does not rule out central causes of thyrotoxicosis. Once a low TSH value is obtained, both free triiodothyronine (T_3) and free thyroxine (T_4) levels should be measured. Patients with Graves' disease may have a greater ratio of serum T_3 to T_4 because of a disproportionate increase in T_3 secretion and increased extrathyroidal conversion of T_4 to T_3.[30] Overt thyrotoxicosis is usually characterized by complete suppression of TSH and high free T_3 and free T_4 concentrations.

Subclinical hyperthyroidism is characterized by a partially suppressed TSH and normal free T_3 and free T_4 concentrations.[31] Patients with subclinical hyperthyroidism usually have no symptoms of excess thyroid hormone production. A low but incompletely suppressed TSH value may indicate suppression of the pituitary-thyroid axis prior to development of clinically evident thyrotoxicosis. In subclinical disease, free T_3 and free T_4 levels may be in the reference range but elevated for a specific patient. This small increase in free thyroid hormone levels causes negative feedback to the pituitary gland, which responds by decreasing TSH secretion.

ETIOLOGY AND TREATMENT

Once the diagnosis of thyrotoxicosis has been established based on clinical and biochemical data, the etiology must be determined. Treatment of thyrotoxicosis is based on the etiology.

Determining the Etiology

Several tests are commonly used to determine the etiology of thyrotoxicosis: a 24-hour radioactive iodine thyroid uptake, thyroid scintigraphy, the presence of thyroid-stimulating immunoglobulin, and the presence of thyroid peroxidase antibody; in addition, determination of the serum T_3 to T_4 ratio is sometimes helpful. A 24-hour radioiodine thyroid uptake is frequently necessary to aid in the diagnosis of Graves' disease or exclude other causes (Figure). Graves' disease is the most common cause of thyrotoxicosis, but various other disorders can also cause thyrotoxicosis. These disorders can be classified based on the degree of radioactive iodine uptake as noted in **Table 1**. High or normal radioactive iodine uptake indicates de novo synthesis of thyroid hormone. Low radioactive iodine uptake indicates either inflammatory destruction of the thyroid gland resulting in transient release of preformed thyroid hormone from the injured gland, use of excess exogenous thyroid hormone medication, or iodine administration. The usual progression of destructive thyroiditis is a thyrotoxic state followed by hypothyroidism as thyroid hormone stores become depleted. Biochemically, serum T_4 concentrations are proportionally higher than T_3 concentrations in destructive thyroiditis, a state that reflects the physiologic ratio of stored thyroid hormone within the thyroid gland.[30] This T_3 to T_4 ratio is contrary to the T_3 to T_4 ratio in Graves' disease and in toxic multinodular goiters, both disease states in which serum concentrations of T_3 are preferentially elevated.[30]

Table 1. Underlying Disease in Thyrotoxicosis Classified by Radioactive Iodine Uptake

Normal or high radioactive iodine uptake
Graves' disease
Toxic multinodular goiter
Toxic solitary thyroid nodule
Thyroid stimulating hormone–producing pituitary tumor
Human chorionic gonadotropin–induced thyrotoxicosis*
Hyperemesis gravidarum
Molar pregnancy
Choriocarcinoma
Low radioactive iodine uptake
Destructive thyroiditis
de Quervain's thyroiditis (subacute thyroiditis)
Postpartum thyroiditis
Silent thyroiditis
Amiodarone-induced thyroiditis, type II
Amiodarone-induced thyroiditis, type I
Exogenous intake of thyroid hormone (factitious thyrotoxicosis)
Struma ovarii†
Metastatic thyroid cancer†

*Radioactive iodine is contraindicated in pregnancy.

†The degree of radioactive iodine uptake is low in the neck but high elsewhere in the body.

Thyroid scintigraphy reveals the distribution of activity in the thyroid gland and may be useful in determining the etiology of thyrotoxicosis. Thyroid scintigraphy utilizes either technetium or iodine 123 (^{123}I). In Graves' disease, the scan typically demonstrates diffuse uptake of the radioisotope, whereas a hyperfunctioning nodule or toxic multinodular goiter will show foci of hyperactivity and suppression of activity in the remainder of the gland.

Additional laboratory measurements also can help to differentiate Graves' disease from other causes of thyrotoxicosis. Thyroid-stimulating immunoglobulins are positive in approximately 80% of patients with Graves' disease at the time of diagnosis and tend to decline over time. Thyroid-stimulating immunoglobulin

Table 2. Comparison of Treatment Options for Graves' Disease

Treatment Modality	Definitive Treatment	Permanent Hypothyroidism	Pregnancy	Side Effects
Medical therapy (thionamides)	Lower probability	Unlikely	Risk of fetal goiter or hypothyroidism (if dose is too high)	Rash/hives, arthralgias, anorexia, nausea, abnormal taste
Radioactive iodine	Yes	Likely	Contraindicated	Possible radiation-induced thyroiditis or worsened ophthalmopathy
Surgery	Yes	Definite	Possible in second or third trimester	Increased risk for hypoparathyroidism, recurrent laryngeal nerve damage, hemorrhage

measurements can be helpful in differentiating Graves' disease from toxic multinodular goiter in older patients who have none of the usual signs of Graves' disease. Thyroid peroxidase antibodies are present in many patients with Graves' disease and can also be useful in differentiating Graves' disease from toxic multinodular goiter. For cases in which radioiodine uptake and thyroid scintigraphy are contraindicated (eg, pregnant patients), laboratory measurement of serum T_3 to T_4 ratio may sometimes be helpful. A serum T_3 to T_4 ratio greater than 20 would favor Graves' disease.[32]

Graves' Disease

Graves' disease is an autoimmune disease caused by production of antibodies to the TSH receptor. Graves' disease shares many immunologic features with Hashimoto's thyroiditis (chronic lymphocytic thyroiditis), which is the most common cause of hypothyroidism. These shared features of disease include high serum concentrations of antibodies against thyroglobulin and thyroid peroxidase.[33] Thyroid-stimulating immunoglobulins cause enlargement of the thyroid follicles, which results in the characteristic diffuse goiter and overproduction of thyroid hormone.[34] Although thyroid-stimulating immunoglobulins are the cause of Graves' disease, the titers can be very low or even undetectable in this disease.[35]

Treatment should be directed at the amelioration of the symptoms of hyperthyroidism via the use of β-blockers, antithyroid medications, radioactive iodine ablation, or surgery (**Table 2**).[36] Whichever option is selected, monitoring the patient clinically and biochemically is important to determine the point at which the patient becomes euthyroid or hypothyroid or if the patient remains hyperthyroid.

β-Blockers. Thyrotoxicosis is associated with increased sympathetic activity, causing various symptoms including palpitations, anxiety, tremors, and heat intolerance. Therefore, the earliest relief patients can receive during initial treatment of their symptoms is from β-blockers. β-Blockers offer a beneficial adjunctive therapy to antithyroid medications. Treatment should be initiated early during the diagnostic evaluation of thyrotoxicosis because it does not interfere with further diagnostic testing. It is important to remember that, although β-blockers alleviate symptoms, these drugs do not work to reduce thyroid hormone production. (Of note, propranolol has some ability to decrease the conversion of T_4 to T_3 in peripheral tissue). Most β-blockers are equally as effective, but the preferred medications are those with a longer duration of action. Several preparations of β-blockers are long acting, either because of a long half-life (atenolol) or a sustained-release preparation (metoprolol and propranolol). Initially, higher doses may be required until a euthyroid state is achieved; appropriate titration should then be performed. Patients with congestive heart failure or asthma should be followed closely when β-blockers are added to their regimen.

Antithyroid medications. Medical therapy with antithyroid drugs, thionamides (propylthiouracil [PTU] or methimazole), is a valid option for Graves' disease. Both PTU and methimazole (when converted to its active metabolite carbimazole) act to inhibit thyroid peroxidase, thereby inhibiting thyroid hormone synthesis.[36] PTU has a secondary action of blocking the extrathyroidal deiodination of T_4 to T_3. This additional action may more quickly improve symptoms by rapidly reducing serum T_3 concentrations. Most physicians prefer methimazole to PTU because methimazole has a longer duration of action that allows for dosing 1 to 2 doses/d versus 2 to 4 doses/d with PTU. In the pregnant patient, PTU is preferred for treatment of thyrotoxicosis because the risk of aplasia cutis is slightly increased with methimazole.

When initiating therapy with thionamides, the starting dose should be the lowest dose necessary to obtain a euthyroid state; that dose varies according to the severity of the hyperthyroidism. The dose is lower in patients with smaller thyroid glands and lower initial radioiodine

Adverse Reactions	Laboratory Monitoring	Cost
Agranulocytosis or lupus-like syndrome	Frequent	Lower cost
Requires radiation safety precautions after treatment	Within 2 to 3 months	Higher cost
Risks associated with general anesthesia	Within 2 months	Higher cost

uptakes and, conversely, higher in patients with large goiters and higher radioiodine uptakes. Thyroid function tests should be rechecked 4 to 6 weeks after initiation of therapy, and doses should be adjusted as needed to achieve and maintain a euthyroid state and to avoid hypothyroidism. Initially, focus should be on the free T_3 and free T_4 levels when trying to achieve a euthyroid state because patients with Graves' disease may have low or suppressed TSH levels for up to several months after peripheral thyroid hormone levels have been normalized. The thyroid function of patients receiving therapy with thionamides should be assessed at 4- to 6-week intervals until the function is stable.

Medical therapy for Graves' disease has distinct advantages. It offers a chance for remission while avoiding radioactive treatments or surgery. In addition, medical therapy costs less than other treatment options.[37] Medical therapy has several disadvantages, however, that must be discussed with the patient. Several prospective randomized studies have demonstrated that treatment with thionamides should only be used for 1 to 2 years because longer treatment offers no additional benefit.[38–40] The chance of permanent remission after cessation of therapy is approximately 35% to 50% versus definitive treatment with radioactive iodine or surgery.[41] In approximately 15% of patients with Graves' disease, autoimmune hypothyroidism develops 10 to 15 years after medical treatment.[42] Additionally, the side effect profile of thionamides complicates long-term therapy. Side effects include rash, hives, arthralgias, and gastrointestinal problems. Thionamides also have a low incidence (reported 0.2%–0.5%) of agranulocytosis.[43] If the patient develops fever or signs of upper respiratory infection, a complete blood count must be performed to ensure that the patient is not neutropenic.[44]

Radioactive iodine. Radioactive iodine 131 (^{131}I) is the therapy of choice for most patients with Graves' disease in the United States.[45] Iodine 131 is rapidly concentrated in thyroid tissue and ablates the thyroid usually within 6 months after the administration.[46] Radioactive iodine can be given as an initial therapy to patients with mild to moderate hyperthyroidism; however, patients with severe hyperthyroid states, elderly patients, or patients with underlying heart disease should be pretreated with a thionamide and β-blockers to achieve a euthyroid state prior to radioactive iodine treatment. Radioactive iodine therapy is contraindicated in pregnant women.

Although the advantage of radioactive iodine therapy is the permanent elimination of hyperthyroidism at minimal inconvenience to the patient, there are some disadvantages. The most significant disadvantage is that almost all patients with Graves' disease treated with radioactive iodine become hypothyroid. Another disadvantage occurs in patients with Graves' ophthalmopathy. Via a mechanism that is not clearly understood, there is a risk of worsening the ophthalmopathy in those patients treated with radioiodine, especially in the patients who smoke.[47] Patients with significant Graves' opthalmopathy should be treated with glucocorticoids at the time of radioactive iodine ablation for a minimum of 1 month.[48]

Patients receiving radioactive therapy must follow certain precautions for 3 to 4 days after the administration of ^{131}I. These precautions include avoiding contact with young children and pregnant women, avoiding close contact with other people (ie, maintaining a distance of more than 3 ft except for short periods of time), and ensuring proper hygiene to avoid ^{131}I in bodily secretions from affecting other people. Rarely, symptomatic radiation thyroiditis may develop. Patients should be cautioned about the possible exacerbation of thyrotoxic symptoms following the dose administration because thyroid hormone is released from the damaged thyroid tissue.

Surgery. Surgery is infrequently performed today as a treatment for Graves' disease, given the enormous success and safety of radioactive iodine. Surgical intervention may be offered to pregnant women with Graves' disease who have experienced a severe adverse reaction to antithyroid medication. Surgery is also indicated for patients who have experienced a severe adverse effect to antithyroid medication and refuse radioactive iodine therapy; as well as those who have had a 1- to 2-year trial of antithyroid medication, have not gone into remission, and refuse radioactive iodine therapy. Surgical intervention may also be offered to patients with Graves' diseases who have a suspicious nodule within the gland or to those who have very large goiters and in whom medical therapy is unsuccessful because in such cases, radioactive iodine may be

less effective and repeated doses may have to be administered for successful treatment. Surgery can offer a permanent cure of the hyperthyroid state in patients with Graves' disease.[49] Complications associated with surgical removal of the thyroid may be the induction of hypothyroidism, increased risk for hypoparathyroidism, recurrent laryngeal nerve damage, or complications surrounding general anesthesia.

Toxic Multinodular Goiter

The exact mechanism for an autonomous functioning nodule or nodules is not fully understood but is believed to involve a mutation of the TSH receptor or of the Gs α-subunit resulting in the activation of the TSH receptor.[50] Similar to Graves' disease, patients with a toxic multinodular goiter usually present with features of thyrotoxicosis; however, examination of the thyroid usually discloses multiple palpable nodules versus the smooth gland found in Graves' disease. When radioactive iodine uptake and scintigraphy are performed in cases of toxic multinodular goiter, a heterogeneous pattern is seen with many regions of hyperactivity ("hot" areas) noted on the scan relating to the regions of autonomous overproduction of thyroid hormone interspersed with hypoactive regions. Given the mixed pattern of activity, the overall uptake of the thyroid gland may be lower than that in Graves' disease, in which the entire gland is overactive. Toxic multinodular goiters occur more commonly in the elderly and in populations who have low iodine intake.[51]

The treatment of a toxic multinodular goiter in the United States is usually with radioactive iodine ablation. Given that the overall uptake of the gland may be lower, higher doses of radioactive iodine are necessary; however, the cure rates are similar to those described with Graves' disease.[52] Antithyroid medications can be used in toxic multinodular goiter but are not appropriate for long-term use because, unlike Graves' disease, there is no possibility of remission. Thyroidectomy can be offered to patients with a toxic multinodular goiter that produces compressive symptoms because the decrease in the size of the gland after radioactive iodine is often minimal.

Toxic Solitary Nodules

Solitary adenomas occur sporadically and similarly to toxic multinodular goiters: autonomous production of thyroid hormone occurs and is likely a result of activating mutations in the TSH receptor or Gs alpha subunit.[50] However, the single adenoma causes suppression of the remaining thyroid gland. The adenoma tends to be a large nodule (≥ 3 cm) and usually can be palpated on physical examination.[53] Treatment can be surgery, particularly in young patients, or radioactive iodine ablation, especially in older patients. The patients who choose to undergo radioactive iodine ablation usually have a lower incidence of post-ablation hypothyroidism because the radioactive iodine is usually concentrated within the solitary hyperfunctioning adenoma rather than affecting the entire gland as in Graves' disease.

Iodine-Induced Thyrotoxicosis

Iodine-induced thyrotoxicosis is a relatively uncommon disorder that has increased in incidence over the past several decades. Iodine-induced thyrotoxicosis has been shown to develop after a patient has received iodine for a radiologic procedure (eg, computed tomography or angiography) or when a patient has received amiodarone, which has a high iodine content, resulting in amiodarone-induced thyrotoxicosis type 1 (as noted later in this discussion).[54,55] The course of iodine-induced thyrotoxicosis is usually self-limited after the source of iodine is removed. However, in the case of amiodarone use, the effect can be prolonged because amiodarone is stored in fat and has a half-life of months.

Thyroid-Stimulating Hormone–Producing Pituitary Adenoma

A TSH-producing pituitary adenoma is extremely rare. These tumors are usually large (macroadenomas) at the time of diagnosis because the progression of the disease is so indolent. Frequently, the presenting symptoms are caused by the mass effect of the macroadenoma.[56] This disorder is characterized by an elevation of free T_4 in conjunction with a serum TSH value that is inappropriately elevated or within the normal range. In this situation, treatment should be removal of the pituitary tumor.

Human Chorionic Gonadotropin–Induced Thyrotoxicosis

Human chorionic gonadotropin (hCG) shares an identical α-subunit with TSH and can (with a low affinity) stimulate thyroid hormone production. In healthy pregnant women, during the first trimester of pregnancy when the levels of β-hCG are elevated, results of thyroid function tests can be outside the standard reference range used for the healthy nonpregnant patient. These pregnant women may have low or suppressed TSH levels and normal free T_4 levels and generally do not have clinical features of thyrotoxicosis. This condition is very similar to subclinical hyperthyroidism.

One common entity in which the diagnosis of thyrotoxicosis may be confusing is hyperemesis gravidarum. Women with hyperemesis gravidarum usually present with nausea and vomiting caused by the unusually high levels of β-hCG, and some of these patients may have clinical symptoms of thyrotoxicosis, termed *hCG-induced thyrotoxicosis*. These patients usually have a suppressed TSH and elevated serum free T_3 and free T_4 measurements correlating with the elevation of serum hCG concentrations. Examination of the thyroid gland usually does not reveal a significantly large goiter. Unlike Graves' disease, the symptoms of thyrotoxicosis tend to subside once the vomiting improves, usually by the second trimester. If the symptoms persist, a diagnosis of Graves' disease must be considered, and treatment may be necessary. Other conditions that may result in hCG-induced thyrotoxicosis include molar pregnancies and choriocarcinoma.[57,58]

Destructive Thyroiditis

The term *thyroiditis* refers to a group of disorders in which an insult to the thyroid gland results in the release of preformed thyroid hormones. Four types of thyroiditis are reviewed in the following discussion: de Quervain's thyroiditis, postpartum thyroiditis, silent thyroiditis, and amiodarone-induced thyrotoxicosis type II.

de Quervain's thyroiditis. Also termed *subacute granulomatous thyroiditis*, de Quervain's thyroiditis is associated with a painful thyroid gland, fever, myalgias, and malaise and is usually precipitated by a viral syndrome, although no specific virus has been isolated. The laboratory hallmark of de Quervain's thyroiditis is a markedly elevated erythrocyte sedimentation rate. The course of disease is typically mild thyrotoxicosis followed by the possible development of hypothyroidism in the recovery phase. Ultimately most patients revert to a euthyroid state within several weeks to several months; however, a small percentage of patients remain hypothyroid.[30] The disease course is usually self-limited. Antithyroid medication has no role because increased synthesis of thyroid hormone does not occur. Therapy should be directed at symptomatic relief. Nonsteroidal anti-inflammatory drugs may be initiated but usually a course of glucocorticoids proves to be necessary and results in a prompt resolution of symptoms. β-Blockers may offer symptomatic relief for those patients with tremor or palpitations.

Postpartum thyroiditis. Postpartum thyroiditis occurs in up to 10% of women in the United States within the first few months after delivery.[59] The hyperthyroid phase typically begins 1 to 6 months after delivery and is self-limited, usually lasting up to 2 months. The thyrotoxic phase may be followed by a hypothyroid phase. Although permanent hypothyroidism may develop in approximately 25% of these women, most women recover normal thyroid function within 1 year.[60]

Most women with postpartum thyroiditis have a small, nontender, firm goiter. Laboratory assessment typically reveals elevated serum titers of thyroid peroxidase antibodies and normal erythrocyte sedimentation rates. Radioactive iodine is secreted in breast milk, therefore a radioactive iodine uptake test with ^{123}I should only be performed in patients when the diagnosis is unclear. ^{123}I has a half-life of 13 hours; a nursing mother must be willing to pump and discard milk for at least 2 to 3 days after the test. (^{131}I is not used because of its longer half-life.) Treatment during the hyperthyroid phase usually is not warranted; however, if necessary, treatment with β-blockers can be utilized. Again, antithyroid medications have no role.

Silent thyroiditis. Silent thyroiditis is a rare form of thyrotoxicosis that accounts for approximately 1% of all cases of thyrotoxicosis and has a clinical course similar to postpartum thyroiditis; however, the symptoms of silent thyroiditis are usually more mild and only 20% of patients have residual chronic hypothyroidism.[61] In approximately 50% of these patients, a small, nontender, very firm, diffuse goiter may be palpated and high serum thyroid peroxidase antibody titers are present.[62]

Amiodarone-induced thyrotoxicosis. Amiodarone-induced thyrotoxicosis has been shown to occur in up to 20% of patients receiving amiodarone.[63] Two types of amiodarone-induced thyrotoxicosis may occur while a patient is receiving treatment with amiodarone. Type I amiodarone-induced thyrotoxicosis occurs in patients with an underlying multinodular goiter and is characterized by the synthesis and release of excessive thyroid hormone, inducing hyperthyroidism. In type II, the direct toxic effect of the drug creates an inflammatory response within the follicular cells of the thyroid gland, causing the release of preformed thyroid hormone from the damaged, inflamed thyroid gland.

Distinction between the two forms of amiodarone-induced thyrotoxicosis can be difficult and some patients may have both types. A new approach to distinguish between these two forms of disease is the use of color-flow Doppler ultrasonography, which shows hypervascularity in type I disease versus vascularity that is frequently reduced in type II disease.[64]

Medical treatment is often necessary for patients with amiodarone-induced thyrotoxicosis. Antithyroid medications are used for the treatment of type I disease. If the thyrotoxicosis is severe, the addition of potassium perchlorate may be necessary in order to prevent further

uptake of iodine by the thyroid. Lithium also has been suggested as an alternative therapy for the type I disease. Given the inflammatory nature of type II disease, high-dose corticosteroids are the treatment of choice. Surgical intervention with thyroidectomy may be required if control of severe cases of amiodarone-induced thyrotoxicosis cannot be obtained with medical management. In those patients who have developed hypothyroidism while undergoing treatment with amiodarone, treatment with levothyroxine is indicated if the amiodarone cannot be discontinued.

Factitious Thyrotoxicosis

Clinical exogenous thyrotoxicosis can be seen in various settings.[65] For unknown reasons, patients without history of a thyroid disorder may intentionally ingest thyroid hormone. In addition, some patients who do have a thyroid disorder self-manage their disease by taking inappropriately large amounts of thyroid hormone. Cases also have been described of patients taking thyroid hormone to aid in weight management or treat depression. Once the cause of identified exogenous thyrotoxicosis is identified, these patients should discontinue the thyroid hormone.

Ectopic Thyroid Production

Ectopic thyrotoxicosis occurs rarely and may be caused by struma ovarii and metastatic thyroid cancer. Patients with struma ovarii have functioning thyroid tissue within an ovarian tumor. The treatment is the removal of the ovarian tumor. In cases of metastatic thyroid cancer, treatment is varied and includes medical therapy, radioactive iodine ablation, and surgical therapy.

CONCLUSION

The term *thyrotoxicosis* refers to excess levels of circulating thyroid hormone. Thyroid dysfunction affects almost all organ systems of the body. The most common cause of thyrotoxicosis is Graves' disease; other causes include thyroid nodules and thyroiditis. It is imperative to properly characterize the etiology of thyroid dysfunction because the treatment modalities differ for each disorder. Treatments include β-blockers, antithyroid medication, radioactive iodine, and surgery. Continued follow-up is critical to monitor the patient's thyroid function. **HP**

REFERENCES

1. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T_4, and thyroid antibodies in the United States population (1988–1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489–99.
2. Weetman AP. Graves' disease. N Engl J Med 2000;343: 1236–48.
3. Laurberg P, Bulow Pedersen I, Knudsen N, et al. Environmental iodine intake affects the type of nonmalignant thyroid disease. Thyroid 2001;11:457–69.
4. Davies TF, Larsen PR. Thyrotoxicosis. In: Williams RH, Larsen PR, Kronenberg HM, et al editors. Williams textbook of endocrinology. 10th ed. Philadelphia: Saunders; 2003:379.
5. Nordyke RA, Gilbert FI, Harada AS. Graves' disease: influence of age on clinical findings. Arch Intern Med 1988;148:626–31.
6. Heymann WR. Cutaneous manifestations of thyroid disease. J Am Acad Dermatol 1992;26:885–902.
7. Fatourechi V, Pajouhi M, Fransway AF. Dermopathy of Graves' disease (pretibial myxedema). Medicine (Baltimore) 1994;73:1–7.
8. Peacey SR, Flemming L, Messenger A, Weetman AP. Is Graves' dermopathy a generalized disorder? Thyroid 1996;6:41–5.
9. Bilezikian JP, Loeb JN. The influence of hyperthyroidism and hypothyroidism on alpha- and beta-adrenergic receptor systems and adrenergic responsiveness. Endocrine Rev 1983;4:378–88.
10. Burch HB, Wartofsky L. Graves' ophthalmopathy: current concepts regarding pathogenesis and management. Endocr Rev 1993;14:747–93.
11. Perros P, Crombie AL, Matthews JN, Kendall-Taylor P. Age and gender influence the severity of thyroid-associated ophthalmopathy: a study of 101 patients attending a combined thyroid-eye clinic. Clin Endocrinol (Oxf) 1993;38: 367–72.
12. Prummel MF, Wiersinga WM. Smoking and risk of Graves' disease. JAMA 1993;269:479–82.
13. Small RG. Enlargement of levator palpebrae superioris muscle fibers in Graves' ophthalmopathy. Ophthalmology 1989;96:424–30.
14. Heufelder AE. Pathogenesis of Graves' ophthalmopathy: recent controversies and progress. Eur J Endocrinol 1995;132:532–41.
15. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy [published erratum appears in Clin Endocrinol (Oxf) 1997;47:632]. Clin Endocrinol (Oxf) 1997;47:9–15.
16. Perros P, Crombie AL, Kendall-Taylor P. Natural history of thyroid associated ophthalmopathy. Clin Endocrinol 1995;42:45–50.
17. Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system: from theory to practice [editorial]. J Clin Endocrinol Metab 1994;78:1026–7.
18. Sawin CT, Geller A, Wolf PA, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994;331:1249–52.
19. Nakazawa HK, Sakurai K, Hamada N, et al. Management of atrial fibrillation in the post-thyrotoxic state. Am J Med 1982;72:903–6.

20. Ayres J, Rees J, Clark TJ, Maisey MN. Thyrotoxicosis and dyspnoea. Clin Endocrinol (Oxf) 1982;16:65–71.
21. Kalro BN. Impaired fertility caused by endocrine dysfunction in women. Endocrinol Metab Clin 2003;32:573–92.
22. Ridgway EC, Maloof F, Longcope C. Androgen and oestrogen dynamics in hyperthyroidism. J Endocrinol 1982;95:105–15.
23. Carlson HE. Gynecomastia. NEJM 1980;303:795–9.
24. Chan WB, Yeung VT, Chow CC, et al. Gynaecomastia as a presenting feature of thyrotoxicosis. Postgrad Med J 1999;75:229–31.
25. Ho HK, Loh KC. Hyperthyroidism with gynaecomastia as the initial complaint: a case report. Ann Acad Med, Singapore 1998;27:594–6.
26. Braunstein GD. Gynecomastia. N Engl J Med 1993;328: 490–5.
27. Santen RJ. Gynecomastia. In: Degroot LJ, Jameson JL, editors. Endocrinology. 4th ed. Philadelpia: Saunders; 2001:2340.
28. Ross DS. Hyperthyroidism, thyroid hormone therapy, and bone. Thyroid 1994;4:319–26.
29. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 1995; 332:767–73.
30. Pearce EN, Farwell AP, Braverman LE. Thyroiditis [published erratum appears in N Engl J Med 2003;349:620]. N Engl J Med 2003;348:2646–55.
31. Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. Standards of Care Committee, American Thyroid Association. JAMA 1995;273:808–12.
32. Amino N, Yabu Y, Miki T, et al. Serum ratio of triiodothyronine to thyroxine, and thyroxine-binding globulin and calcitonin concentrations in Graves' disease and destruction-induced thyrotoxicosis. J Clin Endocrinol Metab 1981;53:113–6.
33. Weetman AP, DeGroot L. Autoimmunity to the thyroid gland. In: Thyroid disease manager. Chicago: Endocrine Education; 1999:112–6. Available at www.thyroidmanager.org/Chapter7/7-frame.htm. Accessed 19 Jan 2005.
34. Marcocci C, Chiovato L. Thyroid-directed antibodies. In: Braverman LE, Utiger RD, editors. Werner and Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2000:414–31.
35. Chazenbalk GD, Wang Y, Guo J, et al. A mouse monoclonal antibody to a thyrotropin receptor ectodomain variant provides insight into the exquisite antigenic conformational requirement, epitopes and in vivo concentration of human autoantibodies. J Clin Endocrinol Metab 1999;84:702–10.
36. Cooper DS. Antithyroid drugs. N Engl J Med 1984;11: 1353–62.
37. Ljunggren J-G, Törring O, Wallin G, et al. Quality of life aspects and costs in treatment of Graves' hyperthyroidism with antithyroid drugs, surgery, or radioiodine: results from a prospective, randomized study. Thyroid 1998;8:653–9.
38. Maugendre D, Gatel A, Campion L, et al. Antithyroid drugs and Graves' disease—prospective randomized assessment of long-term treatment. Clin Endocrinol (Oxf) 1999;50:127–32.
39. Allannic H, Faucher R, Orgiazzi J, et al. Antithyroid drugs and Graves' disease: a prospective randomized evaluation of the efficacy of treatment duration. J Clin Endocrinol Metab 1990;70:675–9.
40. Weetman AP, Pickerill AP, Watson P, et al. Treatment of Graves' disease with block-replace regimen of antithyroid drugs: the effect of treatment duration and immunogenetic susceptibility on relapse. QJM 1994;87:337–41.
41. Solomon BL, Evaul JE, Burman KD, Wartofsky L. Remission rates with antithyroid drug therapy: continuing influence of iodine intake? Ann Intern Med 1987;107:510–2.
42. Tamai H, Kasagi K, Takaichi Y, et al. Development of spontaneous hypothyroidism in patients with Graves' disease treated with antithyroidal drugs: clinical, immunological, and histological findings in 26 patients. J Clin Endocrinol Metab 1989;69:49–53.
43. Cooper DS. Antithyroid drugs for the treatment of hyperthyroidism caused by Graves' disease. Endocrinol Meta Clin North Am 1998;27:225–47.
44. Risk of agranulocytosis and aplastic anaemia in relation to use of antithyroid drugs. International Agranulocytosis and Aplastic Anaemia Study. BMJ 1988;297:262–5.
45. Solomon B, Glinoer D, Lagasse R, Wartofsky L. Current trends in the management of Graves' disease. J Clin Endocrinol Metab 1990;70:1518–24.
46. Franklyn JA. The management of hyperthyroidism [published erratum appears in N Engl J Med 1994;331: 559]. N Engl J Med 1994;330:1731–8.
47. Bartalena L, Marcocci C, Tanda ML, et al. Cigarette smoking and treatment outcomes in Graves' ophthalmopathy. Ann Intern Med 1998;129:632–5.
48. Bartalena L, Marcocci C, Bogazzi F, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998;338:73–8.
49. Chou FF, Wang PW, Huang SC. Results of subtotal thyroidectomy for Graves' disease. Thyroid 1999;9:253–7.
50. Holzapfel H, Fuhrer D, Wonerow P, et al. Identification of constitutively activating somatic thyrotropin receptor mutations in a subset of toxic multinodular goiters. J Clin Endocrinol Metab 1997;82:4229–30.
51. Laurberg, P, Pedersen, KM, Vestergaard, H, et al. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs. high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. J Intern Med 1991; 229:415.
52. Allahabadia A, Daykin J, Sheppard MC, et al. Radioiodine treatment of hyperthyroidism-prognostic factors for outcome. J Clin Endocrinol Metab 2001;86:3611–17.
53. Hamburger JI. Solitary autonomously functioning thyroid lesions. Diagnosis, clinical features and pathogenic

considerations. Am J Med 1975;58:740–8.
54. Conn JJ, Sebastian MJ, Deam D, et al. A prospective study of the effect of nonionic contrast media on thyroid function. Thyroid 1996;6:107–10.
55. Martin FI, Tress BW, Colman PG, Deam DR. Iodine-induced hyperthyroidism due to non-ionic contrast radiography in the elderly. Am J Med 1993;95:78–82.
56. Beck-Peccoz P, Brucker-Davis F, Persani L, et al. Thyrotropin-secreting pituitary tumors. Endocr Rev 1996;17: 610–38.
57. O'Reilly S, Lyons DJ, Harrison M, et al. Thyrotoxicosis induced by choriocarcinoma a report of two cases. Irish Med J 1993;86:124–7.
58. Ngowngarmratana S, Sunthornthepvarakul T, Kanchanswat S. Thyroid function and human chorionic gonadotropin in patients with hydatidiform mole. J Med Assoc Thailand 1997;80:693-9.
59. Muller AF, Drexhage HA, Berghout A. Postpartum thyroiditis and autoimmune thyroiditis in women of childbearing age: recent insights and consequences for antenatal and postnatal care. Endocr Rev 2001;22:605–30.
60. Premawardhana LD, Parkes AB, Ammari F, et al. Postpartum thyroiditis and long-term thyroid status: prognostic influence of thyroid peroxidase antibodies and ultrasound echogenicity. J Clin Endocrinol Metab 2000; 85:71–5.
61. Nikolai TF, Coombs GJ, McKenzie AK. Lymphocytic thyroiditis with spontaneously resolving hyperthyroidism and subacute thyroiditis: long-term follow-up. Arch Intern Med 1981;141:1455–8.
62. Woolf PD. Transient painless thyroiditis with hyperthyroidism: a variant of lymphocytic thyroiditis? Endocr Rev 1980;1:411–20.
63. Harjai KJ, Licata AA. Effects of amiodarone on thyroid function. Ann Intern Med 1997;126:63–73.
64. Eaton SE, Euinton HA, Newman CM, et al. Clinical experience of amiodarone-induced thyrotoxicosis over a 3-year period: role of colour-flow Doppler sonography. Clin Endocrinol (Oxf) 2002;56:33–8.
65. Cohen JH, Ingbar SH, Braverman LE. Thyrotoxicosis due to ingestion of excess thyroid hormone. Endocr Rev 1989; 10:113–24.