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Signs and Symptoms of Thyroid Dysfunction

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The clinical spectrum of thyroid disease varies from asymptomatic subclinical disease detected by laboratory screening to overt thyroid storm and myxedema coma. However, laboratory detection of subclinical or early thyroid disease usually occurs before these overt manifestations of disease develop. The clinician must maintain a high degree of suspicion for thyroid disease as its signs and symptoms can mimic those of other common diseases (eg, fatigue, dyspnea, palpitations associated with anemia). This article reviews the signs and symptoms of thyroid disease and briefly discusses aspects of the laboratory evaluation.

LABORATORY EVALUATION

Thyroid-stimulating hormone (TSH), or thyrotropin, is produced by the pituitary gland in response to thyrotropin-releasing hormone and stimulates production and secretion of thyroid hormones. Measurement of the TSH serum concentration is the initial test of choice for evaluating thyroid function (**Figure 1**). An increased level of TSH points to a diagnosis of hypothyroidism. If the TSH level is low, then free thyroxine (FT_4) should be measured to evaluate for thyrotoxicosis. The FT_4 assay has replaced the older method of determining free thyroxine, known as the FT_4 index, in which the triiodothyronine (T_3) resin uptake method was used. FT_4 is measured rather than total T_4 because 70% to 80% of T_4 is bound to thyroid-binding globulin, making the total T_4 assay susceptible to error due to variations in thyroid-binding globulin.[1] Measurement of free T_3 is helpful in the clinical diagnosis of thyrotoxicosis when the FT_4 values are unexpectedly normal (ie, T_3 thyrotoxicosis).

Radioactive iodine uptake (RAIU) scans are useful in differentiating among the types of thyrotoxicosis. High iodine uptake is seen in diseases that cause increased thyroxine synthesis, including Graves' disease, toxic multinodular goiter, toxic adenoma, and molar pregnancy. Low uptake is seen in diseases that cause inflammation and release of thyroxine, including subacute thyroiditis, thyrotoxicosis factitia, iodine ingestion, and postpartum thyroiditis.

THYROID DYSFUNCTION

- Graves' disease is the most common cause of hyperthyroidism in the United States.
- Common signs and symptoms of hyperthyroidism include nervousness, fatigue, palpitations, weight loss, and heat intolerance.
- Hashimoto's thyroiditis is the most common cause of hypothyroidism in the United States.
- Common signs and symptoms of hypothyroidism include lethargy, cold intolerance, weight gain, constipation, coarse dry skin, hair loss, hoarse voice, bradycardia, and psychomotor retardation.

HYPERTHYROIDISM

Although there is controversy as to the exact definitions, the term *hyperthyroidism* typically is used to describe the disease process in which excessive thyroid hormone is synthesized and excreted (eg, toxic nodular goiter, Graves' disease), whereas the term *thyrotoxicosis* is mainly used to describe conditions in which there is excessive circulatory thyroid hormone (eg, thyroiditis).[2] Causes of thyrotoxicosis are shown in **Table 1**. Graves' disease is the most common cause of hyperthyroidism in the United States, accounting for 60% to 80% of cases of hyperthyroidism.[3] Graves' disease is sometimes associated with other autoimmune disorders, including type 1 diabetes mellitus, Addison's disease, pernicious anemia, celiac disease, collagen diseases, vitiligo, and the autoimmune polyglandular syndromes.

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		TSH		
		Low	**Normal**	**High**
FT_4	**Low**	Secondary hypothyroidism (pituitary disorder) Euthyroid sick syndrome		Primary hypothyroidism
	Normal	Subclinical hyperthyroidism	Normal No further testing Consider repeating test	Subclinical hypothyroidism
	High	Thyrotoxicosis (see discussion of RAIU)	Medications (amiodarone, levothyroxine)	Secondary hyperthyroidism (TSH-secreting pituitary tumor)

Figure 1. Laboratory evaluation of thyroid disease. FT_4 = free thyroxine; RAIU = radioactive iodine uptake; TSH = thyroid-stimulating hormone.

Clinical Presentation

Many organ systems can be involved in the clinical picture of hyperthyroidism (**Table 2**). The most common symptoms of hyperthyroidism include nervousness, fatigue, palpitations, weight loss, and heat intolerance.[4] The symptoms of hyperthyroidism are more common in patients younger than 50 years,[4] except for atrial fibrillation, which is more likely to occur in patients older than 70 years.[5] Thyrotoxicosis is a known cause of a high-output cardiac state.[6] O'Malley and colleagues[7] reported a case that presented solely as heart failure before the more classic manifestations of hyperthyroidism appeared. Severe pulmonary hypertension has also been reported as an atypical sole manifestation of hyperthyroidism.[8] Marvisi and colleagues[9] evaluated 34 patients with hyperthyroidism and found a strong association between lower TSH values and increased pulmonary arterial pressure.

Thyroid storm, the most severe manifestation of hyperthyroidism, results from untreated hyperthyroidism and may be precipitated by infection, trauma, a surgical procedure, and diabetic ketoacidosis. The signs and symptoms include fatigue, fever, tachycardia, dyspnea, restlessness, confusion, psychosis, and coma. Patients with thyroid storm may progress to cardiovascular collapse and shock. Atrial arrhythmias are common. Thyroid storm is a medical emergency and is diagnosed based on clinical symptoms rather than on laboratory hormone values.

Thyrotoxic periodic paralysis is another rare complication of hyperthyroidism. It is seen mainly in Asian men between 20 and 40 years of age, with a male/female ratio of approximately 20:1, despite the higher incidence of hyperthyroidism in women. Thyrotoxic periodic paralysis is a reversible disorder characterized by acute muscle weakness and hypokalemia. The attacks of periodic paralysis are precipitated by hypokalemia that is caused by a transcellular shift rather than total body depletion of potassium. Attacks often are preceded by symptoms of muscle weakness and cramps.[10]

Etiology

Graves' disease. Graves' disease is an autoimmune disease in which antibodies against thyrotropin receptors within the follicular cells of the thyroid gland develop. These thyroid-stimulating antibodies lead to an increase in synthesis and release of thyroid hormone and enlargement of the thyroid gland (goiter; **Figure 2**).[3] Signs and symptoms of Graves' disease include those of hyperthyroidism. Age can strongly influence the clinical findings of Graves' disease. Thyroid enlargement occurs in 90% of patients younger than 50 years but occurs in only 50% of patients older than 70 years.[5,11] Other manifestations specific to Graves' disease include ophthalmopathy (eyelid retraction or lag and periorbital edema) and exophthalmos (**Figure 3**). The ocular findings in patients with Graves' disease are not universal, with clinically apparent Graves' ophthalmopathy occurring in only one third of patients. Graves' dermopathy (also termed pretibial myxedema) is another manifestation, albeit rare. It is characterized by lymphocytic and mucopolysaccharide infiltration of the dermis most commonly located over the pretibial region. The cause of Graves' ophthalmopathy and dermopathy is unknown, but cross-reactivity between antigens of the thyroid gland and other tissues has been suggested.[2]

Toxic solitary or multinodular goiter. A toxic multinodular goiter (Plummer's disease) has at least 2 autonomously functioning nodules that secrete excess thyroid hormone. Toxic nodular goiter is the second most common cause of hyperthyroidism in the United States, although 1 study showed that it is the most common cause of spontaneous hyperthyroidism in patients older that 55 years.[12] Many patients are asymptomatic

Table 1. Summary of Thyrotoxicosis

Cause	Mechanism	Clinical Findings	Laboratory Findings
Primary hyperthyroidism			↓TSH ↑FT_4
Graves' disease	TSH-receptor stimulating antibodies	Ophthalmopathy, goiter with bruit	Diffuse RAIU
Toxic multinodular goiter (toxic adenoma, Plummer's disease)	Multiple autonomous functioning nodules	Multinodular goiter	Multinodular RAIU
Toxic solitary goiter	Solitary hyperfunctioning nodule	Solitary nodule	"Hot" nodule on RAIU
Hashimoto's thyroiditis	Chronic lymphocytic infiltration of thyroid gland	Painless goiter	↓RAIU
Subacute thyroiditis (de Quervain's)	Inflammation leading to leakage of stored hormone	Fever, neck pain, viral infection	↓ RAIU ↑ESR
Postpartum thyroiditis	Inflammation leading to leakage of stored hormone	Small, nonpainful goiter	↓RAIU
Drug induced	Amiodarone Lithium	Goiter (lithium)	↓ RAIU (amiodarone) ↑ RAIU (lithium)
Factitious	Exogenous thyroid hormone ingestion	No goiter	↑FT_4 ↓ RAIU
Secondary hyperthyroidism			
Pituitary tumor	Increased thyrotropin secretion	Goiter	Abnormal MRI ↑TSH ↑FT_4
Molar pregnancy, choriocarcinoma, hyperemesis gravidarum	hCG with TSH-like activity		↑ Serum hCG

ESR = erythrocyte sedimentation rate; FT_4 = free thyroxine; hCG = human chorionic gonadotropin; MRI = magnetic resonance imaging; RAIU = radioactive iodine uptake; TSH = thyroid-stimulating hormone.

and are incidentally found to have hyperthyroidism after screening laboratory results are obtained. On physical examination, a goiter may be present with one or more nodules. A toxic solitary thyroid nodule has autonomous function that results in hyperthyroidism. On RAIU scan, the nodule appears "hot" with increased uptake of radioactive iodine when the remainder of the thyroid gland is suppressed.

Thyroiditis. Subacute thyroiditis, also called de Quervain's thyroiditis, is a painful condition of the thyroid gland that manifests with tenderness in the neck and low-grade fever. It is sometimes confused with pharyngitis. Patients frequently have a history of a prior viral upper respiratory tract infection. On physical examination, the thyroid is enlarged, firm, and tender. Hyperthyroidism occurs early in the disease due to inflammatory destruction of the thyroid gland and the release of preformed thyroid hormone, resulting in decreased uptake on RAIU scan. Subacute thyroiditis is a self-limited process characterized by a clinical course of hyperthyroidism, hypothyroidism, and return to normal thyroid function. Laboratory findings early in the disease include an increase in T_4 and T_3, a decrease in TSH, and a high erythrocyte sedimentation rate.

Table 2. Manifestations of Hyperthyroidism

General	Fatigue, heat intolerance, sweating, weight loss
Dermatologic	Pruritus, warm moist skin
Ophthalmologic	Ophthalmopathy (eyelid lag or retraction, exophthalmos) of Graves' disease
Neck	Goiter
Pulmonary	Dyspnea, tachypnea, signs of pulmonary hypertension
Cardiac	Palpitations, tachycardia, atrial fibrillation, high-output cardiac state
Gastrointestinal	Increased stool frequency
Genitourinary	Menstrual disorders, infertility
Neuromuscular	Muscular weakness, fine tremor, hyperreflexia, periodic paralysis (Asian men)
Psychiatric	Anxiety, nervousness

Shortly after pregnancy, women are at risk for postpartum thyroiditis and Graves' disease. Postpartum thyroiditis presents with a nonpainful goiter, usually 1 to 6 months after childbirth. Differentiating between the 2 diseases with an RAIU scan can be difficult in the

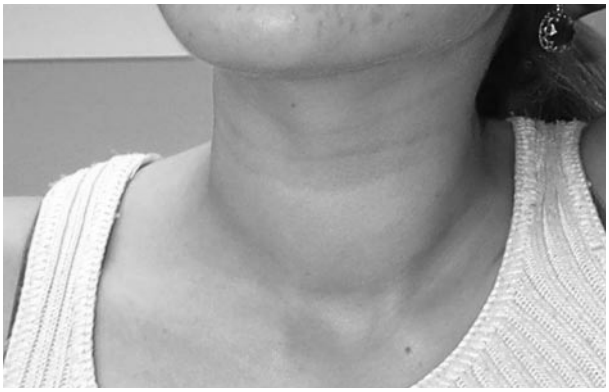

Figure 2. Goiter of Graves' disease.

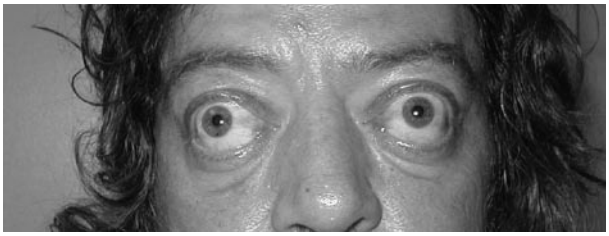

Figure 3. Graves' ophthalmopathy.

postpartum period if the patient is breast feeding because the radioactive iodine is secreted into the breast milk.

HYPOTHYROIDISM

Hypothyroidism is the most common pathological hormone deficiency.[13] It is more common in women and its incidence increases with age. Worldwide, the most common cause of hypothyroidism is iodine deficiency, while in the United States the most common cause is Hashimoto's thyroiditis, followed by post-ablation hypothyroidism after radioactive iodine therapy for hyperthyroidism. Other causes include thyroidectomy and pituitary dysfunction (**Table 3**).

Hashimoto's thyroiditis is the most common cause of goiter in the United States and is also the most common type of thyroiditis.[14] Early Hashimoto's thyroiditis is associated with a firm goiter, but later in the disease process a shrunken fibrotic hypofunctioning thyroid gland develops. The disease is characterized by the presence of high concentrations of serum thyroid antibody. The most frequently detected antibodies are antithyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg). In its initial phase, Hashimoto's thyroiditis (autoimmune chronic lymphocytic thyroiditis) can cause hyperthyroidism that presents as a painless goiter caused by lymphocytic infiltration of the thyroid gland.

Subclinical Hypothyroidism

The term subclinical hypothyroidism refers to a hypothyroid condition in which patients are asymptomatic or mildly symptomatic with mild TSH elevations but have normal serum FT_4 and free T_3 concentrations. As hypothyroidism is the most common pathological hormone deficiency, many expert groups recommend screening women for thyroid disease after age 50 years. Because of widespread screening, the prevalence of subclinical hypothyroidism has risen. Although the US Preventive Services Task Force has determined that there is insufficient evidence to support or recommend against routine screening,[15,16] 3 expert groups (the American Association of Clinical Endocrinologists [AACE], the American Thyroid Association [ATA], and the Endocrine Society) have formulated a consensus statement on screening for early thyroid dysfunction stating that the potential benefits of early detection and treatment of subclinical thyroid dysfunction significantly outweigh the potential side effects that could result from early detection.[17] This expert group therefore recommended routine screening for subclinical thyroid dysfunction in adults without specifying age and frequency. Individually, the ATA recommends screening both men and women beginning at age 35 years and every 5 years thereafter, while the AACE recommends screening "older" patients, especially women.

Clinical Presentation

Manifestations of hypothyroidism can range from asymptomatic subclinical detection to overt myxedema, which is rarely seen due to widespread screening for thyroid disease. The manifestations of hypothyroidism result from hypometabolism and involve many organ systems (**Table 4**). Common signs and symptoms include lethargy, cold intolerance, weight gain, constipation, coarse dry skin, hair loss, hoarse voice, bradycardia, and psychomotor retardation. The onset of signs and symptoms may be subtle. In 1 study of patients with suspected hypothyroidism, the findings most likely to occur were bradycardia, abnormal ankle reflexes, and coarse skin.[18]

Neuromuscular involvement in hypothyroidism is evidenced by muscle weakness and a prolonged relaxation phase of the ankle jerk.[19] Patients with thyroid dysfunction should be questioned about musculoskeletal complaints. Musculoskeletal problems include adhesive capsulitis, carpal tunnel syndrome, Dupuytren's contracture, fibromyalgia syndrome, and trigger finger.[20] Finally, it is important to note that no single sign can identify the patient with hypothyroidism, nor can

Table 3. Summary of Hypothyroidism

Cause	Mechanism	Clinical Findings	Laboratory Findings
Primary hypothyroidism			↑TSH ↓FT_4
Cretinism	Iodine deficiency	Large goiter	
Hashimoto's thyroiditis	Lymphocytic infiltration	Painless goiter	
Post-radiation therapy	Post-ablation	History of Graves' disease	
Neck surgery	Thyroidectomy	Surgical scar	
Secondary hypothyroidism			↓TSH ↓FT_4
Pituitary dysfunction	Infarction, tumor, infiltration (sarcoidosis)	Panhypopituitarism	

FT_4 = free thyroxine; TSH = thyroid-stimulating hormone.

the physical examination exclusively confirm or rule out hypothyroidism, hence the need to evaluate thyroid function.

The most extreme form of hypothyroidism is myxedema coma, a life-threatening complication of long-standing hypothyroidism that is characterized by coma with extreme hypothermia, areflexia, bradycardia, and respiratory depression with hypercapnia. Precipitating factors include exposure to cold, illness, infection, trauma, and use of sedative medications in hypothyroid patients.

SPECIAL CONSIDERATIONS

Euthyroid Sick Syndrome

The term euthyroid sick syndrome refers to abnormal findings on thyroid function tests in patients with severe illnesses not caused by primary thyroid or pituitary dysfunction. Conditions associated with euthyroid sick syndrome include malnutrition, anorexia nervosa, trauma, myocardial infarction, chronic renal failure, diabetic ketoacidosis, cirrhosis, and sepsis. Patients with the euthyroid sick syndrome have suppressed or normal levels of serum TSH, making it difficult to determine whether the patient has secondary hypothyroidism or the euthyroid sick syndrome. The measurement of other pituitary hormones may be useful in differentiating between sick euthyroid syndrome and secondary hypothyroidism in rare cases. There is no role for levothyroxine treatment in sick euthyroid syndrome.[21]

Gestational Thyrotoxicosis

Gestational thyrotoxicosis is a transient increase in thyroid secretion leading to thyrotoxicosis of varying degrees of severity that can occur when human chorionic gonadotropin (hCG) levels are very high. As hCG is a thyroid stimulator, a state of hyperstimulation of the thyroid gland is common in early pregnancy. hCG values are higher in women with hyperemesis gravidarum, molar pregnancy, and choriocarcinoma. Gestational thyrotoxicosis is closely associated with hyperemesis gravidarum, a state of persistent severe vomiting during pregnancy in the first trimester.[22]

Table 4. Manifestations of Hypothyroidism

General	Fatigue, weight gain, anemia, cold intolerance
Dermatologic	Dry coarse skin, brittle hair, hair loss, nonpitting peripheral edema
Ears, eyes, throat	Hearing loss, hoarse voice, periorbital edema, facial puffiness
Neck	Goiter
Pulmonary	Dyspnea, pleural effusions, hypoventilation, sleep apnea
Cardiac	Bradycardia, congestive heart failure, pericardial effusions
Gastrointestinal	Anorexia, constipation
Genitourinary	Menstrual disorders, decreased libido, impotence, infertility
Neuromuscular	Muscle weakness, delayed ankle jerk relaxation phase
Psychiatric	Depression, psychomotor retardation, coma

Adapted with permission from Felz MW, Forren AC. Profound hypothyroidism—a clinical review with eight recent cases: is it right before our eyes? South Med J 2004;97:491.

Medication Effects

Thyrotoxicosis factitia results from the ingestion of excess amounts of thyroid hormone, which leads to hyperthyroidism in the absence of a goiter. In thyrotoxicosis factitia, the serum level of thyroglobulin is not elevated and is generally low in contrast to other causes of hyperthyroidism.

Medications can effect thyroid function or alter the

levels of thyroid-binding globulin, leading to altered findings on thyroid function tests. A full discussion of all medications that effect thyroid function is beyond the scope of this article. However, 2 medications, lithium and amiodarone, require special attention as they both can cause hyperthyroidism and hypothyroidism through complex effects on the thyroid gland.[23] Lithium is frequently used in the treatment of bipolar manic-depressive disorder. This drug inhibits thyroid hormone release and has been associated with the development of goiter as the normal thyroid gland attempts overcome this effect. Lithium generally causes hypothyroidism but rarely can cause thyrotoxicosis. Amiodarone is a commonly used antiarrhythmic drug with a high iodine content. Amiodarone can cause thyrotoxicosis via an iodine-induced increase of thyroid hormone synthesis (type 1) or cytotoxic damage of the thyroid gland (type 2). Amiodarone can also cause hypothyroidism.

CONCLUSION

Thyroid disease can mimic a variety of common complaints. Early detection of thyroid disease is important to prevent progression to life-threatening manifestations that include thyroid storm and myxedema coma. TSH serum concentration is the initial test of choice for evaluating thyroid function. RAIU scans are used to differentiate among the types of thyrotoxicosis. Subclinical hypothyroidism is quite common, and an expert group recently has recommended routine screening for subclinical thyroid dysfunction in adults. Because the symptoms and signs of hypothyroidism can be subtle, clinicians cannot rely exclusively on physical examination to confirm or rule out hypothyroidism. **HP**

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