Thyroid Disorders

Guido Alarcon, MD,* Veronica Figueredo, MD,* Joshua Tarkoff, MD, MBA*

*Nicklaus Children's Hospital, Miami, FL

PRACTICE GAP

Thyroid dysfunction is one of the most common reasons for referral to a pediatric endocrinologist. Understanding thyroid physiology and the etiologies and management of common thyroid diseases can improve clinical practice.

OBJECTIVES *After completing this article, readers should be able to:*

1. Recall the basics of thyroid hormone synthesis and physiology.
2. Describe the etiology and management of common causes of hypothyroidism.
3. Describe the etiology and management of common causes of hyperthyroidism.

INTRODUCTION

The thyroid hormone axis is an endocrine system with many important actions, including growth and development. As a result, the thyroid hormone axis is also a potential cause of myriad signs and symptoms. Thyroid function is routinely checked as part of the annual physical examination despite the lack of clinical evidence for this practice and the resultant increase in health-care costs. (1)(2)(3)(4)

Concern for thyroid dysfunction is one of the most common reasons for referral to a pediatric endocrinologist. As with other endocrine measures, age and clinical status strongly influence what are considered normal values with testing. Although thyroid dysfunction encompasses a wide range of disorders, this review focuses on the most clinically pertinent thyroid disorders: hypothyroidism and hyperthyroidism. In this review, the term *thyroid hormone (TH)* refers to thyroxine (T4) and triiodothyronine (T3).

BIOCHEMISTRY

The clinically relevant THs are T4 and T3. T4 is synthesized exclusively in the thyroid gland, and T3 is generally converted at the target tissue level from circulating T4. The thyroid gland itself is responsible for only 20% of the body's T3 production, (5) with the other 80% coming from deiodination in target cells. The synthesis of T4 begins with the trapping of iodine via the sodium-iodide symporter in the follicular cell. Figure 1 reviews the major steps to TH synthesis.

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ABBREVIATIONS

ATD	antithyroid drug
GD	Graves disease
HT	Hashimoto thyroiditis
PTU	propylthiouracil
T3	triiodothyronine
T4	thyroxine
TBG	thyroxine binding globulin
TFT	thyroid function test
Tg	thyroglobulin
TH	thyroid hormone
THR	thyroid hormone receptor
TPO	thyroid peroxidase
TRH	thyrotropin-releasing hormone
TSI	thyroid-stimulating immunoglobulin

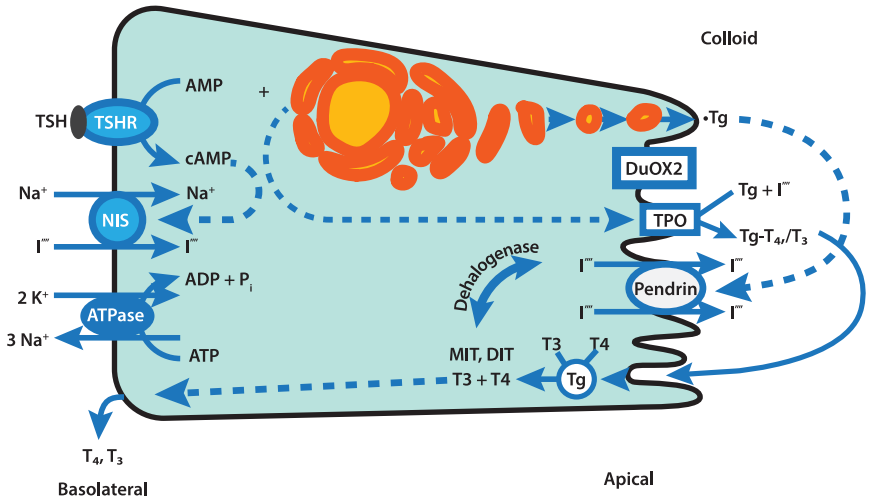

Figure 1. Steps of thyroid hormone synthesis. (1) Iodide (I^-) trapping by the thyroid follicular cells. (2) Diffusion of I^- to the apex of the cells. (3) Transport of I^- into the colloid. (4) Oxidation of inorganic iodide to I^- by thyroid peroxidase (TPO) and incorporation of I^- into tyrosine residues with thyroglobulin (Tg) molecules in the colloid. Dual oxidase 2 (DuOX2) and dual oxidase maturation factor 2 (DuOXA2) are required for generation of hydrogen peroxide, a substrate for TPO. (5) Combination of 2 diiodotyrosine (DIT) molecules to form thyroxine (T4) or of monoiodotyrosine (MIT) with DIT to form triiodothyronine (T3). (6) Uptake of Tg from the colloid into the follicular cell by endocytosis, fusion of the Tg with a lysosome, and proteolysis and release of T4, T3, DIT, and MIT. (7) Release of T4 and T3 into the circulation. (8) Deiodination of DIT and MIT to yield tyrosine. ADP=adenosine diphosphate, AMP=adenosine monophosphate, ATP=adenosine triphosphate, ATPase=adenosine triphosphatase, cAMP=cyclic adenosine monophosphate, K^+=potassium, NA^+=sodium, NIS=sodium-iodide symporter, P_i=inorganic phosphate, TSH=thyrotropin, TSHR=thyrotropin receptor.

Extrathyroidal production of T3 is important to TH physiology. T3 is produced in almost all tissues, with the liver and kidney contributing the most significant amount of deiodinase activity. (6) There are 3 types of deiodinases: types I and II are responsible for producing T3 via outer ring deiodination, and type III produces reverse T3 from T4 via inner ring deiodination (Fig 2).

TH TRANSPORT AND ACTION

More than 99% of THs are bound to thyroxine-binding globulin (TBG), transthyretin, and albumin, with by far the most bound to TBG. It is ultimately the free concentrations of THs that determine their activity. Free T4/T3 are kept in a narrow range via these binding proteins. Therefore, the bound together hormone and protein function as a reservoir for TH to ensure equal distribution to the tissues and organs. (7) T4 and T3 gain entry into cells in a mostly carrier-mediated process via membrane-bound transporters. (8)(9)

TH must get to the cellular nucleus in target tissues to elicit its action. TH action is mediated through the nuclear TH receptor (THR). Only free T4 and T3 are available for transport into cells. T3 is the ligand that binds to the THR, which is either synthesized locally from T4 or is directly transported from the serum. There are 2 genes that encode for the THR: alpha and beta. These can exist as monomers or homodimers. (10)(11) The THR is a steroid hormone receptor that regulates DNA transcription. After binding T3, the THR can affect transcription in a multitude of target tissues.

REGULATION

TH production in the thyroid gland is regulated via thyrotropin, which is released from the anterior lobe of the pituitary gland (Fig 3). The thyrotropin receptor is a G protein–coupled receptor located on thyroid follicular cells. Once bound by thyrotropin, the thyrotropin receptor raises intracellular concentrations of cyclic adenosine monophosphate, which leads to iodine trapping, iodotyrosine synthesis, thyroglobulin (Tg) synthesis, and, finally, TH release.

Thyrotropin secretion is ultimately regulated by thyrotropin-releasing hormone (TRH), which is synthesized in the medial paraventricular nucleus of the hypothalamus, secreted into the portal circulation, and, ultimately, arrives at the anterior pituitary. There it can bind to the TRH receptor, another G protein–coupled receptor, in the thyrotroph (thyrotropin-producing cells in the anterior pituitary). T4 and T3 are negative regulators of thyrotropin and

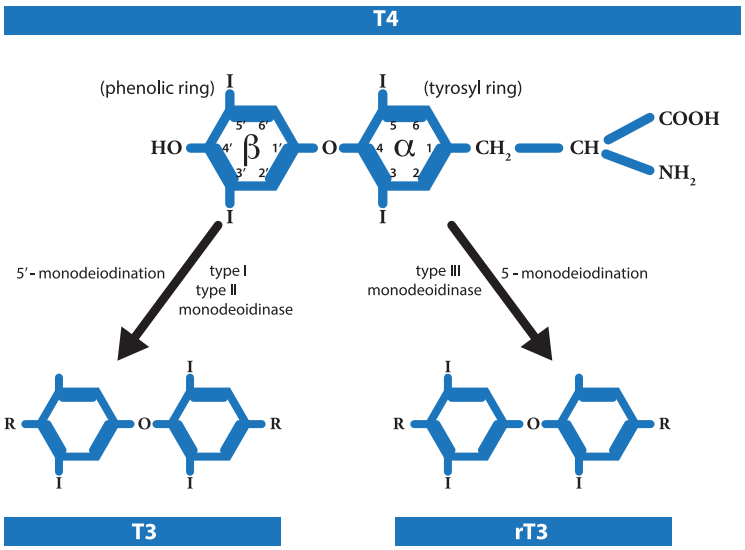

Figure 2. The monodeiodinases. rT3=reverse triiodothyronine, T3=triiodothyronine, T4=thyroxine.

TRH secretion. There is a negative log-linear relationship between circulating TH and thyrotropin, meaning that relatively small changes in TH concentrations produce large changes in thyrotropin. (12)

EVALUATION OF THYROID FUNCTION

The evaluation of thyroid function should begin with the history and physical examination. Children can present with overt signs and symptoms of thyroid disease, with

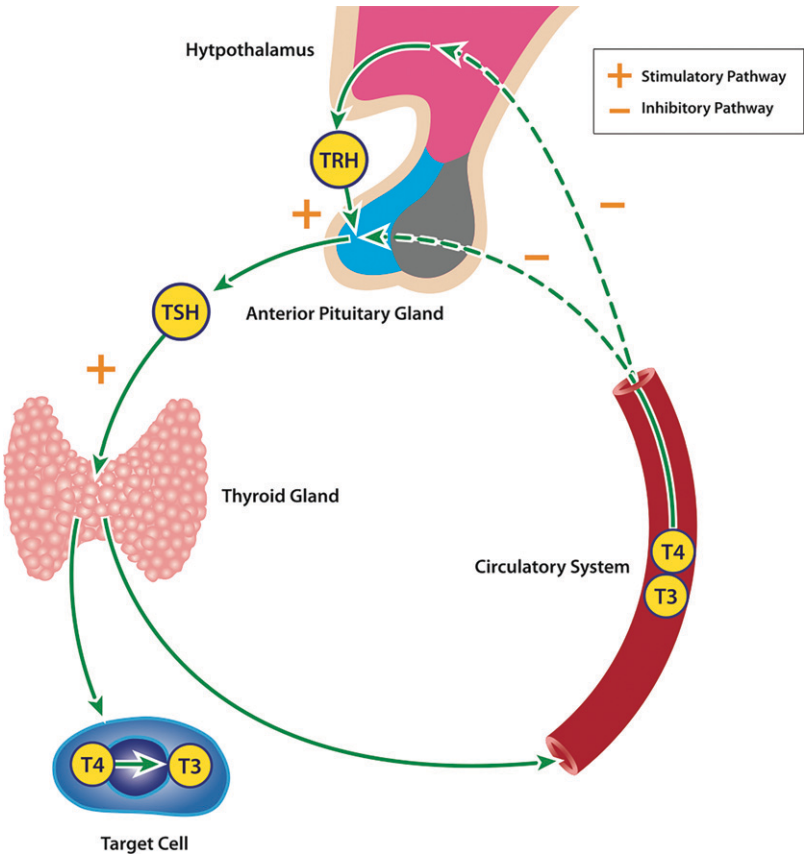

Figure 3. The regulation of thyroid functions. T3=triiodothyronine, T4=thyroxine, TRH=thyrotropin-releasing hormone, TSH=thyrotropin.

little to no signs or symptoms, or sometimes with only a goiter. Biochemically, it is important to remember that normal values for thyroid functions vary significantly by age. In general, thyrotropin and T4/T3 levels tend to peak shortly after birth and fall over time. Applying adult normal values to children can lead to erroneous interpretation of results. For example, the upper limit of normal for thyrotropin in an otherwise healthy child or adolescent can be as high as 7 mU/mL versus 4.5 to 5 mU/mL in adults. (13)(14) The reference range varies by laboratory, and it is, therefore, extremely important to pay attention to your laboratory's reference ranges and age cutoffs.

Overall thyroid function is best evaluated by thyrotropin level because it is exquisitely sensitive to circulating THs. In addition, given advances in thyrotropin assays, a normal thyrotropin value is generally evidence of a euthyroid state. (15) However, checking only the thyrotropin level can lead to missing the diagnosis of central hypothyroidism, which should be considered when free T4 levels are low in the face of a low, an inappropriately normal, or even mildly elevated thyrotropin level. (16)(17)(18)

In general, elevated thyrotropin concentrations indicate hypothyroidism, and suppressed thyrotropin levels indicate a hyperthyroid state. Potentially confusing TH function results can occur in disorders that affect TH binding, which can lead to a diagnosis of thyroid dysfunction when one does not exist. The measurement of free T4 should be included to minimize confusion and to not miss these rare disorders. For the general evaluation and differential diagnosis of abnormal thyroid functions, see Fig 4.

Although rare, TH resistance and thyrotropin-producing adenomas must be considered with elevated TH levels along with elevated or inappropriately normal thyrotropin levels. Clinical clues such as goiter with hyperactivity suggest TH resistance. (19) Visual field defects with other pituitary hormonal derangements are suggestive of a pituitary adenoma.

Finally, interfering substances, such as biotin, can lead to falsely elevated TH levels along with low thyrotropin and even positive thyrotropin receptor–binding inhibitor immunoglobulins, imitating the laboratory findings of Graves disease (GD), or autoimmune hyperthyroidism. (20) This occurs because biotin limits antibody complex formation in sandwich assays and, thus, falsely lowers thyrotropin levels, and in competitive assays that are used to measure free T4/T3 and thyrotropin receptor–binding inhibitor immunoglobulin, biotin competes with the biotinylated labeled analyte and, thus, falsely raises its perceived concentration. In asymptomatic patients with laboratory values suggesting GD, one should inquire about biotin ingestion and repeat testing after withholding biotin supplementation.

Endocrinology referral should generally be reserved for patients with overt hypothyroidism or hyperthyroidism, goiter, or persistent/worsening thyroid functions over time.

HYPOTHYROIDISM

Hypothyroidism is defined as partial or complete deficiency of THs. It is classified as primary when the defect is in the thyroid gland itself or as secondary (also known

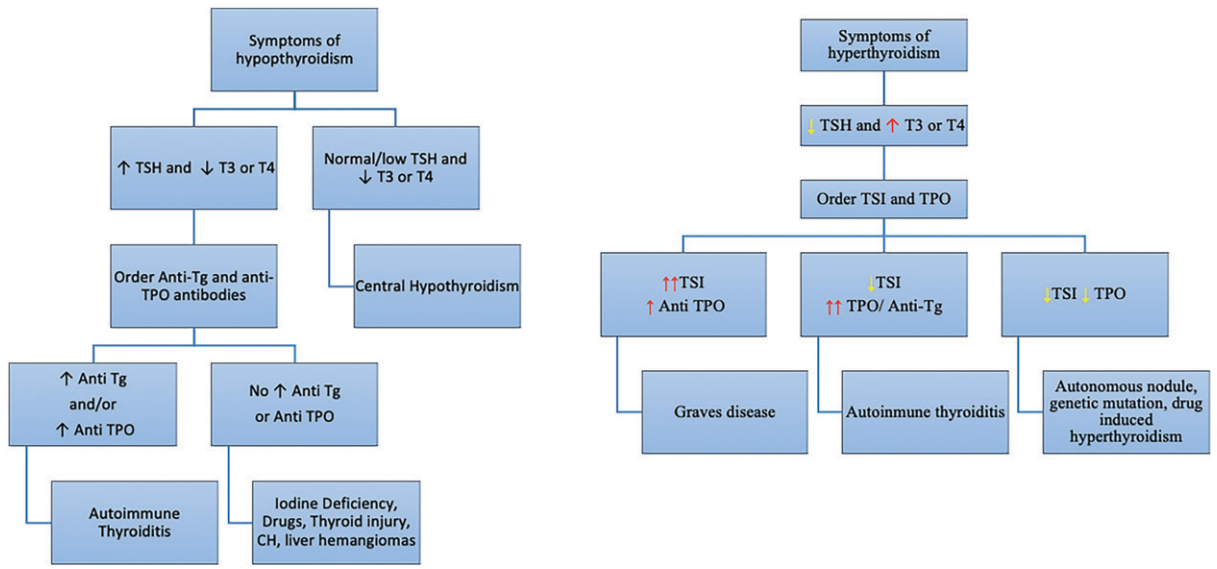

Figure 4. Abnormal thyroid function evaluation. CH=congenital hyperthyroidism, T3=triiodothyronine, T4=thyroxine, Tg=thyroglobulin, TPO=thyroid peroxidase, TSH=thyrotropin, TSI=thyroid-stimulating immunoglobulin.

as central) when it is due to defects in the hypothalamus or the pituitary gland. The most common etiologies of primary hypothyroidism are congenital and autoimmune hypothyroidism.

CONGENITAL HYPOTHYROIDISM

Epidemiology

Congenital hypothyroidism is the most common cause of preventable intellectual disability in the world. (21) Early detection and appropriate treatment are crucial due to the well-known association between later age at treatment onset and lower IQ later in life. (22) Congenital hypothyroidism screening efforts in the United States were initiated in the mid-1970s and have been largely successful, detecting 1 in 4,000 newborns annually. (23) Most cases of congenital hypothyroidism are sporadic; however, girls are 2 times more affected than boys. (24)

Etiology

The most frequent cause of permanent congenital hypothyroidism is embryologic defects in thyroid gland development that accounts for 85% of cases, including dysgenesis, agenesis, and ectopic thyroid gland. (24) Approximately 2% of patients with thyroid dysgenesis have an underlying genetic mutation such as mutations in *PAX8, TSHR, FOXE1, NKX2.1,* and *NXK2.5*. (25) The second most common cause is a defect in TH synthesis, known as dyshormonogenesis. Most of the latter has an identifiable genetic mutation affecting any of the steps shown in Fig 1. (26) Transient congenital hypothyroidism accounts for up to 30% of the cases and resolves during the first few months or years of life. (27) It is secondary to transplacental passage of antithyroid drugs (ATDs) such as propylthiouracil (PTU) or methimazole, maternal thyrotropin receptor–blocking antibodies (as can be seen in infants born to mothers with autoimmune thyroid disease), iodine excess or deficiency, and large hepatic hemangiomas. Hepatic hemangiomas produce type 3 iodothyronine deiodinase, which is the enzyme that is the main inactivator of T4 and T3.

Worldwide, iodine deficiency remains the main cause of transient congenital hypothyroidism, particularly in preterm infants. The incidence is higher in areas where maternal dietary iodine intake is deficient. (27) In areas where iodine consumption is sufficient, common causes include exposure to high doses of iodine or exposure to maternal ATDs such as PTU, the preferred treatment for hyperthyroidism during pregnancy. ATDs can decrease fetal production of TH synthesis, which can last up to 2 weeks after birth. (24) Furthermore, maternal antithyroid antibodies can cross the placenta and block the thyrotropin receptor in the newborn thyroid. In this case, the transient congenital hypothyroidism can last up to 6 months after birth, after which time maternal antibody levels fall to the point where they no longer affect the infant's thyroid function.

Clinical Presentation

Newborns with congenital hypothyroidism are typically asymptomatic at birth; therefore, newborn screening is of paramount importance. The reason most cases are asymptomatic is due to the maternal protection provided by the placental transfer of some maternal T4. Classic symptoms that can develop during the first few months of life in untreated infants include somnolence, hoarse cry, feeding problems, constipation, and coarse facies. Physical examination might show umbilical hernia, macroglossia, and mottled skin. Other findings include wide-open fontanelles, jaundice, hypotonia, delayed reflexes, flat nasal bridge, pseudohypertelorism, and short extremities.

Many infants with congenital hypothyroidism may have associated congenital malformations, with cardiac defects being the most common. (28) Other associated malformations include spiky hair, cleft palate, neurologic abnormalities, and genitourinary malformations. Also, the incidence of congenital hypothyroidism is increased in patients with Down syndrome.

Diagnostic Evaluation

Newborn screening for congenital hypothyroidism is routine in the United States, Western Europe, Australia, and parts of Eastern Europe, Asia, South America, and Central America. (29)

For full-term infants, a sample is usually collected 24 hours after birth, ideally by 2 to 4 days of age. For preterm infants, most newborn screening programs obtain a routine second specimen at 10 to 14 days after birth due to developmental changes in thyroid physiology and higher rates of false-positive and false-negative results on the initial screen. For babies born before 32 weeks of gestation, many programs will also obtain a third specimen at 4 to 6 weeks of age or before discharge, whichever comes first. (30)

Most newborn screening in the United States consists of thyrotropin with reflex testing of total T4, which means that the T4 level is measured automatically if the thyrotropin level is abnormal. This approach can potentially miss central hypothyroidism when the thyrotropin level is inappropriately normal. Certain states use T4 as the primary

test and reflex test thyrotropin and can miss infants who have delayed elevations in thyrotropin levels but can pick up TBG deficiency (normal thyrotropin level with a low total T4 level but normal thyrotropin and free T4 levels on confirmatory testing). The ideal test includes both thyrotropin and total T4 levels; however, this obviously raises the costs of the screening program. In general, caretakers of infants with thyrotropin values greater than 40 mIU/L must be immediately contacted by the responsible physician who was notified of the abnormal results by the state health department. (31) Clinical evaluation and follow-up testing with venous blood sampling should be performed to verify the diagnosis. Confirmatory serum thyrotropin and free T4 concentrations are tested.

Primary hypothyroidism is diagnosed by the finding of a low free T4 level and an elevated thyrotropin level in serum. Additional laboratory and imaging testing may be necessary to determine the etiology, including antibody levels, radionuclide scan, and thyroid ultrasonography, but such investigation should not delay treatment.

Treatment

It is crucial to start treatment during the first 2 weeks after birth because delays will result in impaired neurocognitive outcome. (32)(33) TH is critical for normal brain development during the first 2 to 3 years after birth, so appropriate therapy and follow-up are critical during this period.

Oral levothyroxine is the treatment of choice, at a starting dose of 10 to 15 μg/kg per day, which is consistent with most prominent pediatric health recommendations. Tablets are preferred and should be crushed and mixed with 1 to 2 mL of human milk, formula, or water before administration. Levothyroxine sodium oral solution (Tirosint-SOL, IBSA Pharma Inc, Parsippany, NJ; Thyquidity, Vertice Pharma, New Providence, NJ) is a liquid preparation recently approved by the Food and Drug Administration (FDA) that is administered directly from a single-use pack or mixed with a small amount of water. An acidic pH in the stomach, as occurs during fasting conditions, seems to be important for subsequent absorption in the jejunum and ileum. (34) Co-administration of levothyroxine with soy formula, iron or calcium preparations, antacids, or simethicone can reduce drug absorption. Therefore, co-administration of the previously mentioned substances should be avoided or these substances should be administered appropriately spaced apart from each other. (35)

The treatment goals are to keep serum free T4 or total T4 levels in the upper range of normal during the first year of life, and serum thyrotropin should be kept to less than 5 mIU/L. TH levels should be monitored 2 and 4 weeks after treatment initiation, then every 1 to 2 months in the first 6 months after birth, every 3 to 4 months from 6 months to 3 years of age, every 6 to 12 months until growth is completed, and 4 weeks after any dosage change. (31)

CENTRAL HYPOTHYROIDISM

Central hypothyroidism, which occurs in 1 in 50,000 newborns, is caused by defects in thyrotropin production due to either hypothalamic or pituitary dysfunction. (36) Central hypothyroidism should be suspected when an infant presents with hypoglycemia, jaundice, micropenis, and/or midline facial anomalies because central hypothyroidism is often associated with other pituitary hormone deficiencies. In central hypothyroidism, the T4 level is low and the thyrotropin level is low, inappropriately normal, or mildly elevated.

TBG DEFICIENCY

TBG is the carrier protein for 70% to 80% of plasma TH. The remainder is bound to albumin (10%–15%) and transthyretin (10%–15%). TBG deficiency is an X-linked disorder that occurs in approximately 1 in 4,000 to 1 in 10,000 newborns, predominantly males. (37) Affected infants present with low serum total T4, low or normal serum free T4, and normal thyrotropin concentrations. The diagnosis is confirmed by measuring TBG concentration. Infants born with TBG deficiency are euthyroid and do not require treatment. However, it can potentially cause confusion in the interpretation of thyroid function tests (TFTs) in the newborn period, resulting in incorrectly labeling these infants as having hypothyroidism.

ACQUIRED HYPOTHYROIDISM

In developed countries, Hashimoto thyroiditis (HT) is the most common cause of acquired hypothyroidism and goiter in children and adolescents. (38) In contrast, iodine deficiency is the most common cause of acquired hypothyroidism worldwide.

Epidemiology

HT, also known as chronic lymphocytic thyroiditis, is ten times more common in females and white people compared with males and African American people. (39) The estimated prevalence in children is 1% to 2%. (40) The prevalence increases with age, and, therefore, this condition is more commonly diagnosed in adolescence compared

with childhood. Certain chromosomal abnormalities and autoimmune disorders increase the risk of autoimmune thyroiditis, including Down syndrome, Turner syndrome, Noonan syndrome, type 1 diabetes mellitus, celiac disease, Klinefelter syndrome, and polyglandular autoimmune syndrome type 2.

Etiology

Approximately 70% of patients with HT have an underlying genetic predisposition that is triggered by environmental factors. Individuals with HT develop antibodies against thyroid peroxidase (anti-TPO) and Tg (anti-Tg), leading to defective production of THs, lymphocyte infiltration, and progressive fibrosis. Other causes of hypothyroidism are listed in the Table.

Clinical Presentation

Patients with HT can initially be euthyroid or even hyperthyroid; however, most forms ultimately progress to frank hypothyroidism. Although most patients are asymptomatic, some may present with declining growth velocity, which often results in short stature. This finding may be present for several years before other symptoms of hypothyroidism occur. Children may also present with poor school performance, decreased energy, or abnormal pubertal development. More classic symptoms of HT include weight gain, dry skin, brittle nails, hair thinning or loss, constipation, macroglossia, cold intolerance, depression, diffuse muscle pain, and menstrual irregularities.

On physical examination, the thyroid gland is often diffusely enlarged, nontender, firm, and rubbery, although the thyroid gland may be normal at diagnosis, or even atrophied in a few patients. Other findings may include facial edema, particularly periorbital edema, as well as nonpitting edema involving the hands and feet, bradycardia, delayed relaxation phase of tendon reflexes, elevated blood pressure, slow speech, and ataxia.

Diagnostic Evaluation

The diagnosis of hypothyroidism is based on clinical symptoms in addition to low free T4 levels and elevated thyrotropin levels. The diagnosis of HT relies on the demonstration of circulating antibodies, specifically anti-TPO and anti-Tg. Approximately 85% to 90% of children with HT have positive serum anti-TPO titers, and 30% to 50% have positive anti-Tg titers. (41) If a patient is euthyroid but has positive thyroid antibodies, as can occur approximately 10% of the time, follow-up with TFTs should occur every 6 months. (42)(43) Ultrasonography should be performed when a thyroid nodule is palpable, or with large goiter that makes palpation of nodules difficult, because there is evidence of a higher incidence of malignancy in HT. (44)(45)

Treatment

Levothyroxine is the recommended treatment for children with primary or central hypothyroidism. Patients should be treated early to restore normal growth and development and to ensure good cognitive outcome. The doses tend to decrease with increasing age. (43) The goal is to keep the serum thyrotropin level less than 5 mIU/L, to maintain serum free T4 or total T4 levels within the upper half of the age-specific reference range, and to eliminate symptoms and signs of hypothyroidism. Once treatment is initiated or a dose has been modified, thyrotropin and free T4 levels should be measured 6 to 8 weeks later, and then every 6 to 12 months. (46) A high thyrotropin level in a patient taking levothyroxine requires adjustment of the dose once noncompliance is excluded.

EUTHYROID SICK SYNDROME

Euthyroid sick syndrome constitutes a complex mix of physiologic adaptation and pathologic response that can occur in critically ill patients. Patients with this condition are thought to be euthyroid; however, there is recent

Table. Causes of Thyroid Dysfunction in Children and Adolescents

CATEGORY	HYPOTHYROIDISM	HYPERTHYROIDISM
Autoimmune	Hashimoto thyroidosis	Graves disease
		Hashitoxicosis[a]
Congenital	Thyroid dysgenesis	Thyrotropin receptor–activating mutations
	Dyshormonogenesis	
Drugs/external	Radiation/radioactive iodine	Iodine contrast[a]
	Infiltrative disease (sarcoidosis, histiocytosis)	Kelp, seaweed
	Iodine deficiency	Toxic adenoma
	Phenytoin, phenobarbital, valproate	
Others	Liver hemangioma	McCune-Albright syndrome
	Secondary hypothyroidism	

[a]Transient hyperthyroidism.

evidence indicating that some may have acquired transient central hypothyroidism. (47)

In this syndrome, the patient has low total and free T3, normal or low total T4, low to normal or high free T4, and normal thyrotropin levels. The serum reverse T3 level is high due to decreased activity of types I and II deiodinase and increased activity of type III deiodinase (Fig 2).

TFT should not be performed in seriously ill patients unless there is a strong suspicion of thyroid disease. (48) Treatment should be directed to the primary illness, and TH replacement is generally not necessary.

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is defined as a mild elevation of thyrotropin levels (<10 mIU/L) with normal T3 and T4 levels and no clinical signs of hypothyroidism. In adults, there are recommendations for treating subclinical hypothyroidism in certain situations because subclinical hypothyroidism may increase mortality due to cardiovascular diseases; however, this has not been proved in children. (49)(50) The American Thyroid Association recommends that this not be treated. (35) In fact, the finding of subclinical hypothyroidism in children is more likely to be the result of transient thyroid laboratory changes that may occur after recovery from an illness. (51) Therefore, when subclinical hypothyroidism is detected in children, the recommendation is to repeat TFTs in 3 to 6 months. (52)

HYPERTHYROIDISM

Hyperthyroidism is defined by an elevated T4 and/or T3 level along with a suppressed thyrotropin level, except for secondary hyperthyroidism, which is rare in children. The most common symptoms of hyperthyroidism in children include weight loss (64%), fatigue (54%), and behavioral changes (50%). The most common signs are diffuse enlarged goiter (78%), fine tremors (58%), and often an audible thyroid bruit (25%). (53)

Diagnostic Evaluation

Once the definition of hyperthyroidism is met, the following sequential evaluation should occur (Fig 4):

Determination of Hyperthyroidism Etiology. One should obtain thyroid antibodies, including thyroid-stimulating immunoglobulin (TSI), which are positive in GD. Anti-TPO or anti-Tg are usually also positive in GD. Other diagnoses for hyperthyroidism that should be considered based on these laboratory results include the hyperthyroid phase of autoimmune thyroiditis or "Hashitoxicosis," where anti-TPO is positive with negative TSI. If the etiology is not found, one should consider performing a radionucleotide uptake, preferably with technetium-99m because this requires less radiation compared with radioactive iodide ^{123}I. (54) The radionucleotide scanning will show diffuse increased uptake in GD. With a hyperfunctioning nodule, uptake is focal. In contrast, low uptake will be seen in thyroiditis. The Table includes other causes of hyperthyroidism.

Complementary Laboratory Testing. A complete blood cell count and liver function tests are generally included in the initial evaluation of hyperthyroidism in anticipation of possible use of ATDs that may cause agranulocytosis and hepatic failure. Furthermore, a hyperthyroid state per se can cause a mild decrease in white blood cell count and elevated liver function test results.

GRAVES DISEASE

Epidemiology

GD accounts for most hyperthyroidism in children. (55) It is more common in females compared with males (3:1), and the peak age at presentation is during adolescence. (56) Concomitantly, 3% of GD cases are associated with other disorders, including most commonly type 1 diabetes mellitus and Down syndrome. (57)

Etiology

The etiology is not completely understood and is likely attributable to genetics, immunity, and environmental factors, leading to the formation of antibodies. (58)(59) Patients with GD produce TSIs that bind to the thyrotropin receptors and mimic thyrotropin function, which causes hyperplasia and hypertrophy of the thyroid gland, ultimately leading to increased production of TH.

Clinical Presentation

Typical hyperthyroid symptoms include tachycardia, increased appetite, weight loss, increased frequency of bowel movements, fatigue, moist skin due to capillary vasodilatation, and hair loss. Growth and development in children may be affected, with growth acceleration and advancement in epiphyseal maturation; however, growth potential is conserved. (60) Severe cases of hyperthyroidism can result in delayed pubertal onset, anovulatory cycles, or amenorrhea. Furthermore, patients may present with neuropsychological manifestations such as anxiety, depression, sleep disturbances, and/or trouble focusing.

Treatment

In children, the first line of treatment is an ATD, preferably methimazole over PTU because the latter carries an unacceptable risk of hepatotoxicity. The addition of a ß-blocker is often required due to its rapid onset of action of blocking peripheral conversion of T4 to T3. In contrast, methimazole effects are often appreciated several weeks later. More importantly, ß-blockers are more effective at ablating signs and symptoms such as tachycardia, tremors, or neuropsychological disturbances in the short term compared with ATDs. Atenolol or metoprolol are the preferred ß-blockers to start because they are more cardioselective, but if there is no history of asthma, propranolol can also be considered. (61) More than 25% of patients achieve remission 2 to 5 years after treatment. However, relapse is not uncommon. (62) PTU is another less commonly used ATD and currently has few indications, such as first trimester of pregnancy, thyroid storm, and allergic reaction to methimazole when radical therapy is not an option. (62)

Radical therapy, which includes radioactive iodine and thyroidectomy, is indicated for patients who have no evidence of remission despite prolonged treatment with ATDs (2 years), have severe disease, or have adverse effects from ATDs. (63) Patients undergoing radioactive iodine therapy should be recommended to have a low-iodine diet before the treatment and isolate themselves after the treatment for 1 week, especially from pregnant women and other children because radioactive material is excreted via saliva, urine, and stools. (64)(65) Furthermore, there is a theoretical dose-dependent increased risk of cancer with radioactive iodine when radiation received is greater than 100 mCi, although treatment for GD requires 10 to 15 mCi. (66)(67) However, radioactive iodine is generally avoided in younger kids (<5 years old), and doses are attenuated for those aged 5 to 10 years. (62) Lastly, if the decision is to perform a thyroidectomy, the patient should be referred to a high-volume thyroid surgeon so as to decrease complications. (68)

Monitoring is particularly important to assess for response and potential adverse effects related to treatments for GD. Thyrotropin, free T4, and total T3 levels should be measured 4 to 6 weeks after initiating treatment, keeping in mind that the thyrotropin concentration is generally suppressed months after free T4 and total T3 levels have normalized. Typically, once free T4 and total T3 levels have normalized, the dose of methimazole can be reduced and ß-blockers can be discontinued. Feared, although rare, adverse effects of methimazole are agranulocytosis and liver failure. Therefore, patients should be aware of signs such as mucositis, jaundice, fatigue, acholic stools, or abdominal pain. (69) There is not enough evidence to encourage or discourage routine checkups for liver function testing and a complete blood cell count unless the patient is symptomatic. (62) Last, if minor adverse effects appear, such as urticaria, myalgias, and arthralgias, the ATD can be stopped for a few days and later resumed unless there is a minor rash that can be treated with antihistamines. (54)

NEONATAL GD

The major culprit for neonatal thyrotoxicosis is maternal TSIs that cross the placenta. (70) Less than 10% of infants born to mothers with GD develop neonatal thyrotoxicosis. The development of neonatal thyrotoxicosis is proportionally related to the maternal TSI concentration, which is generally greater than 3 times above the upper limit of normal to cause problems. (70)(71) Fortunately, this disease is transient (3–12 weeks), but it can lead to severe symptoms such as sustained tachycardia (with heart rates >160 beats/min), diarrhea, lid lag, heart failure, jaundice, diaphoresis, premature craniosynostosis, and intrauterine growth retardation. (72) The treatment goal for neonatal thyrotoxicosis is to block the thyroid gland function. A combination of a ß-blocker and methimazole is typically initiated after the diagnosis is confirmed. Potassium iodide (Lugol solution) is another treatment option that can be considered, but its effectiveness is generally limited to a few weeks. It is important to remember that all newborns born to a mother with GD should undergo thyroid testing (free T4, total T3, and thyrotropin concentrations) at delivery, 3 to 5 days later, and 10 to 14 days after birth. TSI should preferably be measured in the cord blood if this is available, otherwise it can be measured in serum. (73)

THYROID STORM/THYROTOXICOSIS

Thyrotoxicosis is a rare life-threatening condition that is an exaggeration of hyperthyroidism symptoms. This differs from compensated hyperthyroidism in that the patient presents with hyperpyrexia, cardiovascular dysfunction, and, more importantly, altered mental status. (74) It is often triggered by abrupt cessation of ATDs or acute illness. Fast-acting medication that prevents T4 toT3 conversion should be given, such as PTU and ß-blockers. Lugol solution is often administered to quickly block the release of TH, as well as glucocorticoids that potentiate the inhibition of T4 to T3 conversion.

OTHER CAUSES OF HYPERTHYROIDISM

Non-GD causes of hyperthyroidism include transient thyroiditis, genetic mutations, medications, certain types of food, and laboratory error. Transient hyperthyroidism occurs as the result of thyroid follicle destruction generally due to autoimmune causes (Hashitoxicosis) or infectious thyroiditis, which leads to release of TH into the bloodstream. Treatment for these causes is directed toward blunting symptoms and includes the use of ß-blockers for cardiovascular symptoms and/or nonsteroidal anti-inflammatory drugs/corticosteroids for pain and inflammation symptoms. Iodine may induce transient hyperthyroidism, which is relevant to consider in patients undergoing imaging with iodinated contrast media such as computed tomography. (75) Certain foods, such as kelp and seaweed, have been associated with the development of hyperthyroidism. (76) Furthermore, there are rare genetic causes that can lead to hyperthyroidism, including McCune-Albright syndrome, which is an activating mutation of the *GNAS* gene that increases G stimulating protein signaling and leads to hyperfunction of glycoprotein hormone receptors (follicle-stimulating hormone, luteinizing hormone, thyrotropin, corticotropin, and growth hormone–releasing hormone receptors).

Summary

- Based on some research evidence and consensus, free thyroxine (T4) is generally preferred over total T4 because of the possibility that thyroid hormone binding protein abnormalities can lead to the appearance of spurious results. (15)
- There is lack of evidence that supports checking thyroid function tests (TFTs) in otherwise healthy children.
- Based on strong evidence, TFT normal values are age dependent and are particularly different in the first few months after birth.
- Based primarily on consensus, TFTs should not be routinely checked on sick patients because values might be abnormal transiently and then recover once the underlying illness is treated (euthyroid sick syndrome).
- Based on moderate-quality evidence, treatment for congenital hypothyroidism needs to be started within the first 2 weeks after birth to avoid intellectual disability. (33)
- Based on moderate-quality evidence, hypothyroidism should be treated with levothyroxine tablets. Brand levothyroxine is preferred in the treatment of infants, especially if severe. (33)
- Based on high-quality evidence, the treatment goal for hypothyroidism should be to aim for a T4 level in the upper half of normal and a thyrotropin level in the low half of normal. (33)(34)
- Based on low-quality evidence, the patient should be informed, preferably in writing, about the adverse effects of antithyroid drugs (ATDs) and should be alerted to stop taking medication if symptoms are suggestive of agranulocytosis or hepatic injury. (61)(69) Based on low-quality evidence but strongly recommended, patients with febrile pharyngitis on ATDs should have a differential white blood cell count. (77)
- There is not enough evidence to encourage or discourage routine monitoring of white blood cell counts while taking ATDs. (77)
- Based on moderate-quality evidence, if surgery is chosen to treat Graves disease, the patient should be referred to a high-volume thyroid surgeon. (67)

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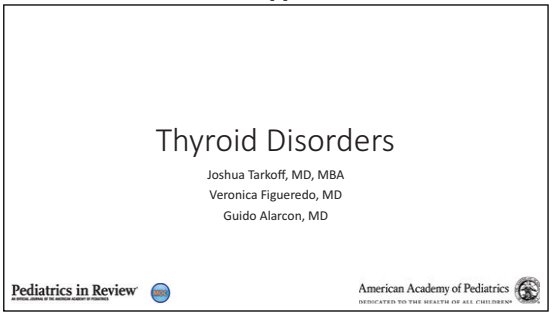
References for this article can be found at http://pedsinreview.aappublications.org/content/42/11/604.

***To view teaching slides that accompany this article, visit* https://pedsinreview.aappublications.org/content/42/11/604/tab-supplemental.**



PIR QUIZ

1. You are discussing thyroid hormone levels with a medical student. When you mention that thyroxine (T4) is produced exclusively in the thyroid gland, the student asks where triiodothyronine (T3) is produced. You explain that the main source of T3 includes which of the following organs?

   A. Large and small intestines.
   B. Liver and kidney.
   C. Parathyroid glands.
   D. Skeletal muscles.
   E. Thyroid gland.

2. A 15-year-old girl presents for follow-up of overweight (BMI, 90th percentile) and abnormal thyroid function test results (thyrotropin level, 0.05 mIU/L; free T4 level, 6.2 ng/dL [79.8 pmol/L]; and T3 level, 5.8 ng/dL [0.09 nmol/L]). She reports that she has been taking a vitamin supplement since reading on the internet that this might help her lose weight. Her review of systems is otherwise normal. On physical examination, vital signs include blood pressure, 112/64 mm Hg; heart rate, 72 beats/min. She has no tremors, and her thyroid is not palpable. High-dose supplementation of which of the following could explain these findings?

   A. B_1 (thiamine).
   B. B_2 (riboflavin).
   C. B_6 (biotin).
   D. B_{12}.
   E. Folate.

3. A pediatric resident is about to see a 2-year-old boy with congenital hypothyroidism who is brought to the clinic by his parents for follow-up. The child was born in the United States, was diagnosed immediately after birth on newborn screen, and has been maintained on thyroid hormone supplementation since his diagnosis. The resident reviews the child's medical and family histories looking for potential contributing causes for this condition in this child. Which of the following represents the most common potential cause of congenital hypothyroidism to look for?

   A. Maternal Graves disease.
   B. Maternal iodine deficiency.
   C. Maternal iodine excess.
   D. Prematurity.
   E. Thyroid dysgenesis.

4. A full-term infant has an elevated thyrotropin level and a low free T4 level on newborn screening, confirmed by repeated studies at a hospital laboratory. Which of the following is the most appropriate immediate next step in this infant's management?

   A. Oral iodine.
   B. Oral levothyroxine.
   C. Radionuclide thyroid scan.
   D. Thyroid autoantibody levels.
   E. Thyroid ultrasonography.

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5. A 4-month-old boy with congenital hypothyroidism taking levothyroxine is seen for follow-up of gastroesophageal reflux and colic. His mother asks if she needs to be concerned about interactions between levothyroxine, his diet, and other ingested substances. You respond that levothyroxine may be safely co-administered with which of the following products?

   A. Human milk.
   B. Iron.
   C. Ranitidine.
   D. Simethicone.
   E. Soy formula.