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Thyroid Disorders in Children and Adolescents
A Review

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IMPORTANCE Normal thyroid gland function is critical for early neurocognitive development, as well as for growth and development throughout childhood and adolescence. Thyroid disorders are common, and attention to physical examination findings, combined with selected laboratory and radiologic tools, aids in the early diagnosis and treatment.

OBJECTIVE To provide a practical review of the presentation, evaluation, and treatment of thyroid disorders commonly encountered in a primary care practice.

EVIDENCE REVIEW We performed a literature review using the PubMed database. Results focused on reviews and articles published from January 1, 2010, through December 31, 2015. Articles published earlier than 2010 were included when appropriate for historical perspective. Our review emphasized evidence-based management practices for the clinician, as well as consensus statements and guidelines. A total of 479 articles for critical review were selected based on their relevance to the incidence, pathophysiology, laboratory evaluation, radiological assessment, and treatment of hypothyroidism, hyperthyroidism, thyroid nodules, and thyroid cancer in children and adolescents. Eighty-three publications were selected for inclusion in this article based on their relevance to these topics.

FINDINGS The primary care physician is often the first health care professional responsible for initiating the evaluation of a thyroid disorder in children and adolescents. Patients may be referred secondary to an abnormal newborn screening, self-referred after a caregiver raises concern, or identified to be at risk of a thyroid disorder based on findings from a routine well-child visit. Irrespective of the path of referral, knowledge of the signs and symptoms of hypothyroidism, hyperthyroidism, and thyroid nodules, as well as the general approach to evaluation and management, will help the primary care physician complete an initial assessment and determine which patients would benefit from referral to a pediatric endocrinologist.

CONCLUSIONS AND RELEVANCE Early identification and treatment of thyroid disease in children and adolescents is critical to optimize growth and development. The primary care physician plays a critical role in identifying patients at risk. An understanding of risk factors, clinical signs and symptoms, and interpretation of screening laboratories ensures an efficient and accurate diagnosis of these common disorders. Regular communication between the primary care physician and the subspecialist is critical to optimize outcome because the majority of patients with thyroid disorders will require long-term to lifelong medical therapy and/or surveillance.

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Hypothyroidism is defined as a low level or absence of thyroid hormones. It may be present at birth (congenital) or develop later in life (acquired). Primary hypothyroidism, due to defects in the thyroid gland itself, is the most common cause of hypothyroidism. Secondary or central hypothyroidism occurs secondary to defects at the level of the pituitary gland or hypothalamus.

Congenital Hypothyroidism

Background

Congenital hypothyroidism (CH) occurs in 1 in 1500 to 3000 newborns.[1] Early diagnosis and treatment of thyroid hormone deficiency is crucial to ensure normal development and cognition. Screening for CH is part of all newborn screening programs in the United States, as well as most developed countries.[2,3]

The most common cause of primary CH is thyroid dysgenesis, which explains 80% to 85% of all cases, followed by defects in thyroid hormone biosynthesis or secretion known as thyroid dyshormonogenesis (**Figure 1**).[4] Central hypothyroidism occurs less frequently and is often associated with additional pituitary hormone deficiencies. Infants with multiple pituitary hormone deficiencies often present with hypoglycemia, cholestatic hepatitis, microphallus, and ocular abnormalities.[5,6] Exogenous or environmental etiologies of CH include maternal thyrotropin receptor blocking antibodies, antithyroid drug use, and iodine deficiency or excess.[4,7-12]

Congenital hypothyroidism may present as a sporadic disorder or follow a familial pattern of inheritance.[13] Less is known about the familial pattern of inheritance for thyroid dysgenesis; however, there is accumulating evidence for a genetic basis with several monogenic etiologies associated with additional congenital anomalies (termed *syndromic CH*) (**Table 1**).[14,15]

Clinical Presentation

Newborns with CH are typically asymptomatic at birth. Fetuses are protected from the effects of hypothyroidism by the placental transfer of maternal thyroid hormone and because they commonly have some functioning thyroid tissue.[16] Classic symptoms of untreated CH include prolonged jaundice, lethargy, poor feeding, constipation, and a hoarse cry. The most common signs are umbilical hernia, macroglossia, and mottled skin. A physical examination may also reveal bradycardia, wide posterior fontanelle, coarse facies, and hypotonia with delayed reflexes.

Diagnosis

Primary thyrotropin or thyroxine (T_4) testing is the mainstay of newborn screening with heel-prick samples obtained between 2 and 5 days of life.[15] False positives may occur if the newborn screening is performed before 48 hours of life due to the thyrotropin surge that occurs shortly after birth. In high-risk newborns, to include extremely premature infants (<28 weeks' gestation and/or weighing <1500 g) and acutely ill-term newborns, an elevation in thyrotropin is frequently delayed until 2 to 6 weeks after delivery. In these infants, an initial high level of thyrotropin is uncommon but consistent with CH, whereas a low level of thyrotropin should be monitored with serial serum testing to determine the status of the thyroid axis (**Table 2**).[17,18]

> **Key Points**
>
> **Question** What common signs and symptoms should alert primary care physicians to consider a thyroid disorder in a child or adolescent?
>
> **Findings** This systematic review reveals that hypothyroidism and hyperthyroidism may present with altered growth, development, and/or behavior; however, patients with thyroid nodules are often asymptomatic at the time of diagnosis.
>
> **Meaning** The appropriate evaluation and interpretation of readily available laboratory and radiologic test results will help the primary care physician determine which patients will benefit from referral to a pediatric endocrinologist.

If the results of a newborn screening are positive (low T_4 level and/or high thyrotropin level), confirmatory serum thyroid hormone samples should be obtained. The sample should include thyrotropin and free T_4 (Table 2). The addition of a thyroglobulin (Tg) level may aid in the diagnosis of thyroid agenesis, although patients with thyroid dyshormonogenesis may also have low Tg levels secondary to mutations in the *TG* gene.[19]

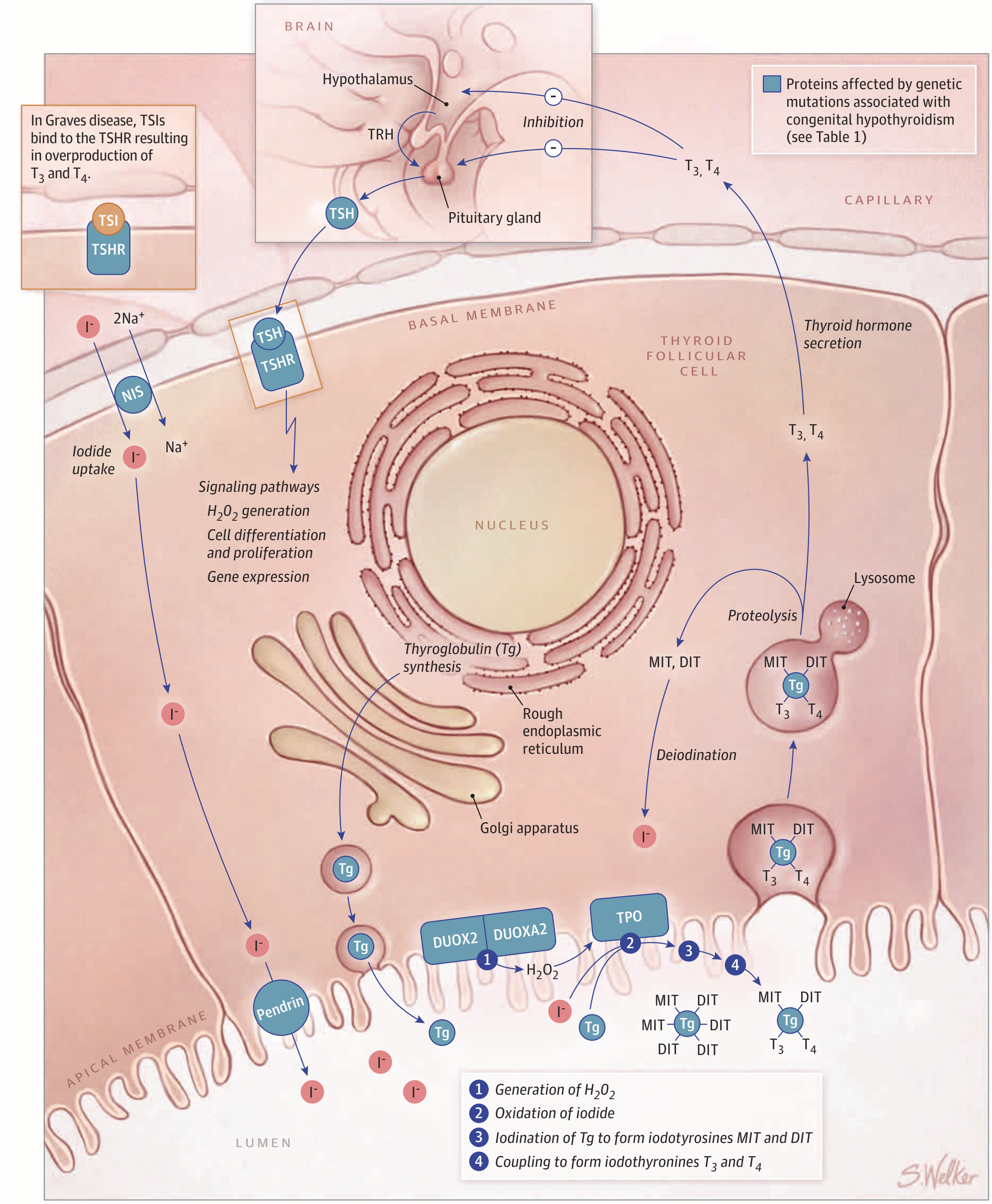
Once the diagnosis has been made, additional testing can be considered to determine the etiology of the hypothyroidism so that the family can receive anticipatory guidance in regard to the potential need for lifelong thyroid hormone replacement therapy.[20,21] A thyroid radionuclide uptake and scan (scintigraphy), administering either iodine 123 or sodium pertechnetate technetium Tc 99m, can demonstrate an ectopic gland or thyroid aplasia (**Figure 2**).[22] Ultrasonography of the thyroid can confirm thyroid hypoplasia or aplasia, but is generally less accurate in identifying ectopic thyroid tissue. Thyroid scintigraphy should be performed within 1 week of initiating thyroid hormone replacement therapy; however, treatment should not be delayed while obtaining these imaging tests.[3] Infants should also undergo a complete physical examination because there is an increased prevalence of renal, cardiac, gastrointestinal, and skeletal anomalies in children who receive a diagnosis of CH.[23]

Treatment

Thyroid hormone replacement should be started no later than the first 2 weeks of life. The goal of therapy is to normalize thyroid hormone levels as early as possible because there is an inverse relationship between the age at diagnosis, the normalization of thyroid hormone levels, and IQ.[3,24] Rapid normalization of thyroid hormone levels and maintenance of euthyroidism during the first 2 to 3 years of life are critical to optimize neurocognitive outcome. Frequent laboratory monitoring can decrease the likelihood of prolonged periods of subphysiologic and supraphysiologic thyroid hormones, both associated with deficits in neurocognitive development.[25,26]

The treatment of choice for CH is levothyroxine at a starting dose of 10 to 15 μg/kg administered once daily.[3] The majority of full-term infants are started on 37.5 μg per day, with short-term higher dosing (50 μg per day) considered for infants with very low pretreatment T_4 levels.[15,21] Brand-name tablets are recommended over generic secondary to increased reliability of the administered dose.[3] The tablet form should be crushed and then administered via a spoon with a few milliliters of water, formula, or breast milk. In the United States, there are no stable suspensions of levothyroxine.

Figure 1. Diagram Summarizing the Biosynthesis of Thyroid Hormone and Correlations With Thyroid Disorders



Thyroid hormone synthesis begins with iodide uptake by thyroid follicular cells via the sodium-iodide symporter (NIS), a protein that is regulated by thyrotropin (thyroid stimulating hormone; [TSH]) as well as iodine status. Iodide is transported across the apical membrane via pendrin and subsequently oxidized by thyroid peroxidase (TPO) using endogenously generated H_2O_2. The TPO-mediated iodination of tyrosine residues on thyroglobulin (Tg) forms mono- and diiodotyrosines (MIT and DIT), which then couple to form T3 (1 MIT plus 1 DIT) or T4 (2 DITs). T3 and T4 attached to Tg are stored as colloid in the follicular lumen. T3 and T4 are released from the thyroid follicular cell after endocytosis and proteolysis of the Tg-bound T3 and T4. Congenital hypothyroidism may be secondary to mutations in multiple genes associated with thyroid hormone biosynthesis. Autoimmune hypothyroidism (Hashimoto thyroiditis) is usually associated with antibodies against TPO and/or TG. These autoantibodies indicate immune activation against the thyroid gland and damage to thyroid follicular cells. In autoimmune hyperthyroidism (Graves disease), thyroid-stimulating immunoglobulins (TSIs) bind to the TSH receptor resulting in dysregulated overproduction of T3 and T4.

Table 1. Molecular Etiology and Phenotype of Inheritable Forms of Congenital Hypothyroidism

Gene	Protein(s)	Chromosomal Localization	Inheritance	Phenotype (Most Severe)
Thyroid dyshormonogenesis				
NIS (OMIM 606765)	Thyroid peroxidase	2p25	Autosomal recessive	Large goiter, multinodular goiter
TG (OMIM 188450)	Thyroglobulin	8q24	Autosomal recessive	Elevated T_3:T_4 ratio with low or undetectable Tg, goiter
SLC5A5 (OMIM 601843)	NIS	19p13	Autosomal recessive	Congenital or postnatal or childhood hypothyroidism, goiter with low or absent radioiodine uptake
SLC26A4 (OMIM 274600)	Pendrin	7q31	Autosomal recessive	Childhood-onset goiter (50%) with congenital, bilateral sensorineural hearing loss (enlarged vestibular aqueduct); Pendred syndrome
DUOX2 (OMIM 606759)	Dual oxidase 2	15q15.3	Autosomal recessive or dominant	Transient and/or mild elevation in thyrotropin level
DUOXA2 (OMIM 612772)	Dual oxidase maturation factor 2	15q21.1	Autosomal recessive	Thyroid dyshormonogenesis 5
Thyroid dysgenesis				
TSHR (OMIM 275200)	Thyroid-stimulating hormone receptor	14q31	Autosomal recessive or dominant	Variable; partial to total resistance to thyrotropin, normal thyroid to severe thyroid gland hypoplasia
NKX2-1 (OMIM 600635)	Thyroid transcription factor 1	14q13	Autosomal dominant	Thyroid hypoplasia with neurologic (hypotonia resulting in benign hereditary chorea) and lung abnormalities (surfactant deficiency, interstitial lung disease, and congenital cystic adenomatoid malformation)
PAX8 (OMIM 218700)	Paired box gene	2q12	Autosomal dominant	Thyroid hypoplasia (at birth or developing during childhood), urogenital malformations
FOXE1 (OMIM 241850)	Thyroid transcription factor 2	9q22	Autosomal recessive	Athyreosis with cleft palate, choanal atresia, spiky hair (Bamforth-Lazarus syndrome)

Abbreviations: T_3, triiodothyronine; T_4, thyroxine.

Table 2. Interpretation of Thyroid Function Testing

Disorder	Thyrotropin Level	T_4 Level[a]	T_3 Level[b]	Comment
Primary hypothyroidism	High	Low		Assess for goiter on examination and elevated antithyroglobulin and antithyroid peroxidase
Subclinical hypothyroidism	High	Normal		Assess for goiter on examination and elevated antithyroglobulin and antithyroid peroxidase
Central hypothyroidism	Low or normal	Low		Evaluate for other pituitary hormone deficiencies and consider CNS imaging
TBG deficiency	Normal	Low		Normal free T_4; males (X-linked)
Prematurity	Low or normal	Low		Normal free T_4; treatment controversial
Nonthyroidal illness (euthyroid sick syndrome or low T_3 syndrome)	Low or normal	Low	Low	T_3 level lower than T_4 level; high reverse T_3 level
Hyperthyroidism	Low	High	High	High TSI or thyrotropin receptor antibody levels; T_3 may be increased prior to T_4 (elevated T_3:T_4 ratio)
Resistance to thyroid hormone	"Inappropriately" normal (nonsuppressed)	High	High	Goiter, ADHD behavior; normal T_3:T_4 ratio
Oral contraceptives	Normal	High		Normal free T_4 level

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CNS, central nervous system; TBG, thyroxine-binding globulin; TSI, thyroid-stimulating immunoglobulin; T_3, triiodothyronine; T_4, thyroxine.

[a] May be measured as free T_4 or total T_4 with T_3 resin uptake. It is redundant to order both.

[b] Not typically measured in patients with hypothyroidism.

Some medications and foods, such as calcium, iron, and soy, are known to interfere with the absorption of levothyroxine and should be administered at a different time of the day, separated by several hours. When an infant with CH is switched to soy formula, thyroid tests should be performed 2 to 3 weeks afterward to determine whether an increase in the levothyroxine dose is needed.

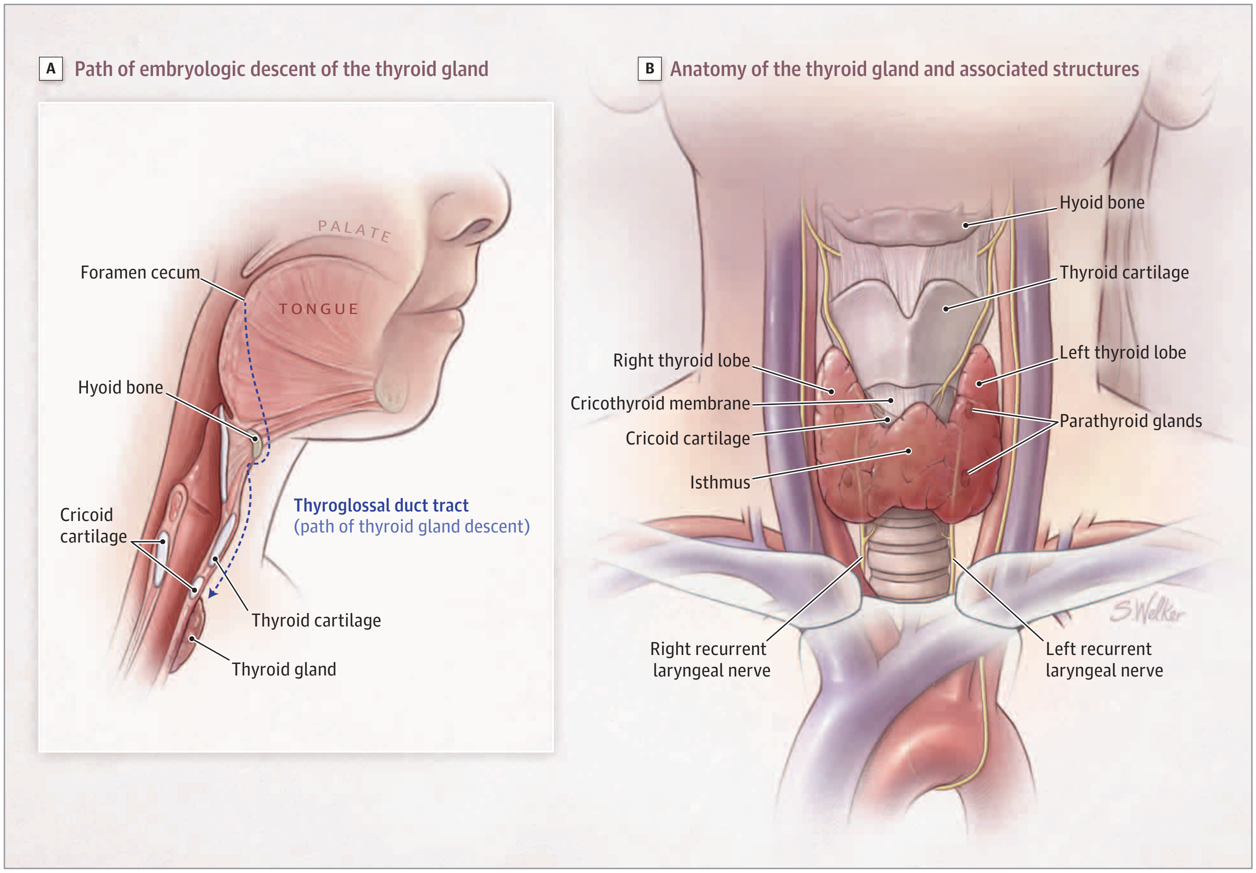
The goal of treatment is to normalize the T_4 level within 2 weeks of starting levothyroxine, to normalize the thyrotropin level within 1 month, and to maintain the T_4 level within the upper half of the normal range during the first year of life.[15] Clinicians should monitor thyroid hormone levels every 2 weeks until the thyrotropin level normalizes, then every 1 to 3 months during the first year of life, and every 2 to 4 months between 1 and 3 years of age.[3] For patients suspected to have transient CH, a reevaluation of treatment with levothyroxine can be considered after they reach 3 years of age.[21]

Acquired Hypothyroidism

Background

Autoimmune hypothyroidism (Hashimoto thyroiditis) is the most common cause of acquired hypothyroidism in children, adoles-

Figure 2. Path of Embryologic Descent of the Thyroid Gland and Postembryonic Neck Anatomy



The thyroid gland develops in the pharyngeal floor, the lateral portion from neural crest cells and the larger median portion from the primitive pharynx. It migrates from the foramen cecum through the thyroglossal duct along a path anterior to the hyoid bone, reaching its mature shape and location inferior to the cricoid cartilage by the seventh week of gestation. Failure to complete migration may be secondary to mutations in several genes (Table 1). Aberrant ectopic thyroid tissue may be found anywhere along the path of descent, including within the tongue (lingual thyroid). Persistence of the inferior portion of the thyroglossal duct results in the formation of the pyramidal lobe of the thyroid. Failure of the thyroglossal duct to involute may be associated with formation of a thyroglossal duct cyst, a structure that may harbor aberrant, and even the only, thyroid tissue.

cents, and adults. The prevalence of autoimmune hypothyroidism in childhood is an estimated 1% to 2% with a 4:1 female predominance.[27] Approximately 50% of cases have a family history of autoimmune thyroid disease. Several syndromes are associated with an increased risk for developing autoimmune hypothyroidism, including Down syndrome and Turner syndrome.[28,29] An additional autoimmune disorder in the same patient is also associated with an increased risk, most commonly diabetes, alopecia, vitiligo, and celiac disease.[30-32]

Other less common etiologies of acquired hypothyroidism occur. Although infrequent in the United States, iodine deficiency is the most common cause worldwide.[33] Hypothyroidism may also occur following radiation therapy to the head and neck for certain cancers, following total-body irradiation in preparation for a bone marrow transplant, as well as secondary to several medications, including lithium carbonate or citrate, amiodarone hydrochloride, antiepileptic drugs, and tyrosine kinase inhibitors.[34-36] Permanent hypothyroidism is also the goal of therapy for patients undergoing definitive treatment for Graves disease and for patients with thyroid cancer.

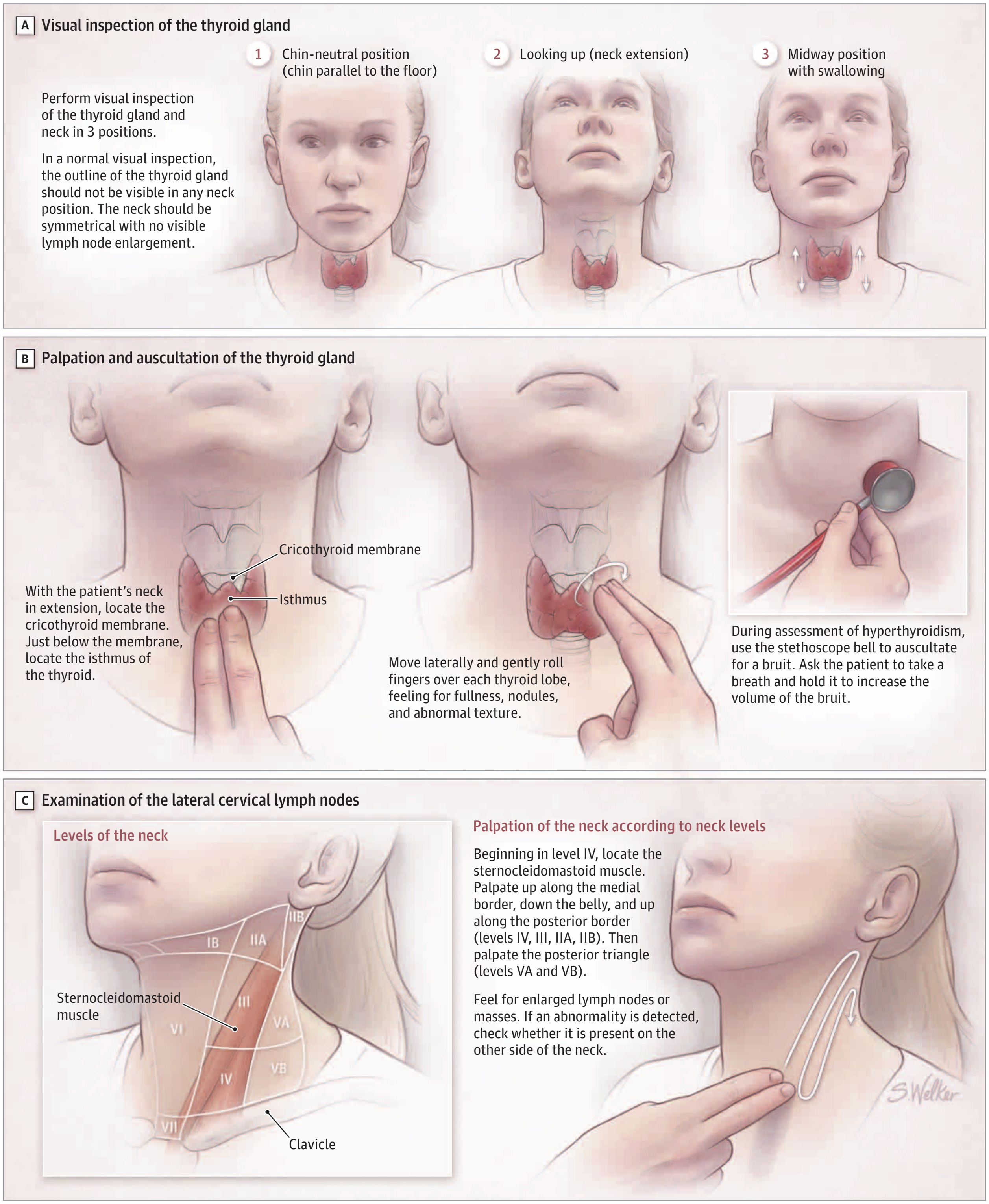
Clinical Presentation

The most common symptoms of hypothyroidism are fatigue, cold intolerance, constipation, and menstrual irregularities.[27] Children may present with pubertal delay or, in cases of severe longstanding hypothyroidism, precocious puberty.[37] A goiter is the most common physical examination finding. Other examination findings include bradycardia, delayed reflexes, and myxedema of the face and extremities. Hypothyroidism causes poor linear growth and/or growth failure and, if undiagnosed, may compromise adult height. However, contrary to common belief, hypothyroidism is rarely the etiology of weight gain. In fact, excess weight gain is associated with mild elevations in thyrotropin (between 5 and 10 mIU/L), with normalization of the thyrotropin level after achieving weight loss.[38]

Diagnosis

An enlarged thyroid (a goiter) is a typical but nonspecific finding of acquired thyroid disease (both hypothyroidism and hyperthyroidism). Visual inspection in the office setting should include 3 positions, and palpation can be performed from either side of the patient (**Figure 3** and https://www.youtube.com/watch?v=Z9norsLPKfU).

Figure 3. Examination of the Thyroid Gland in Pediatric Patients



Examination of the thyroid gland is an important and readily accomplished aspect of a complete pediatric physical examination. The examination follows the important steps of any examination; look (A) and feel and listen (B and C). An enlarged thyroid (goiter) is defined by the ability to visualize the shape of the thyroid gland during physical examination (A and Table 3). Auscultation may be restricted to patients with suspected hyperthyroidism, in which a bruit, a continuous "murmur-like" sound from increased blood flow in the gland, may be appreciated using the bell of the stethoscope. A complete examination of the lateral neck lymph nodes (C) is an important addition to the examination of patients with thyroid nodules because differentiated thyroid cancer frequently metastasizes to lymph nodes in the neck. Palpable symmetric level IIA and IIB lymph nodes are a common finding in pediatric patients but thyroid cancer should be in the differential diagnosis for patients found to have persistent, large, firm lymph nodes in levels III, IV, and V.

Table 3. World Health Organization Classification of Goiter

Grade	Charateristics
0	No visible or palpable goiter
1	Goiter is palpable but not visible in chin-neutral position
2	Goiter is visible and palpable in chin-neutral position

Use of the World Health Organization 3-tiered classification system can aid in the descriptive process of the thyroid size (**Table 3**).[39]

For children with suspected hypothyroidism, serum thyrotropin and T_4 samples should be obtained. Triiodothyronine (T_3) and reverse T_3 levels are rarely helpful in the diagnosis of hypothyroidism, and thus samples should not be obtained from the majority of patients. The levels of thyroid-binding proteins (thyroxine-binding globulin, transthyretin, and albumin) affect total T_4 levels, so a free T_4 level is generally a better measure of thyroid hormone status.

Children with primary hypothyroidism have a high level of thyrotropin and a low level of T_4. An elevated level of thyrotropin and a normal level of T_4 indicate subclinical hypothyroidism (Table 2). A significant percentage of patients with subclinical hypothyroidism convert to normal thyroid status with observation; however, the presence of a goiter and/or positive thyroid antibody levels, in particular antithyroid peroxidase, is associated with an increased risk of progression to overt hypothyroidism (a thyrotropin level above 10 mIU/L).[36]

Central hypothyroidism presents with a low T_4 level and a nonelevated thyrotropin level (Table 2). Children confirmed to have central hypothyroidism should have their central nervous system and pituitary gland screened for mass lesions by use of magnetic resonance imaging.

Treatment

The approach to treatment of acquired hypothyroidism is similar to that of CH. Levothyroxine tablets are the treatment of choice, administered once daily, 15 to 30 minutes prior to food consumption, avoiding coadministration with calcium, iron, and soy products. Levothyroxine dosing is based on body surface area (100 μg/m^2/d) or on age and weight following the general pattern: 4 to 6 μg/kg/d for patients 1 to 3 years of age, 3 to 5 μg/kg/d for patients 3 to 10 years of age, 2 to 4 μg/kg/d for patients 10 to 16 years of age, and 1.6 μg/kg/d for patients 17 years of age or older.[36] Additional thyrotropin and T_4 samples should be obtained 6 to 8 weeks after initiating therapy. Once a therapeutic dose has been established, the clinician should check thyroid function every 4 to 6 months until the child achieves final height or every 6 to 8 weeks following a change in levothyroxine dose. The goals of treatment are to maintain clinical and biochemical euthyroidism and to ensure normal linear growth and development throughout childhood and adolescence.

Hyperthyroidism

Background

Hyperthyroidism accounts for 15% of pediatric thyroid disorders, with most cases attributable to autoimmune hyperthyroidism, known by the eponym Graves disease.[40,41] The incidence of Graves disease among pediatric patients is 0.1 to 3 cases per 100 000 children,[40] with geographic variance in the prevalence of disease from 1 case per 10 000 children in the United States[42] to 1 case per 100 000 children in the United Kingdom and Ireland.[43] Graves disease is more common among females, with a peak incidence between 10 and 15 years of age,[43] and is associated with other autoimmune diseases within the family or in the same patient, such as type 1 diabetes, celiac disease, Addison disease, systemic lupus erythematosus, Hashimoto thyroiditis, and pernicious anemia, as well as with other syndromes, such as Down syndrome and Turner syndrome.[44,45] In pediatrics, Graves disease accounts for the majority of cases; however, less-common etiologies of hyperthyroidism, including genetic, infectious, or drug-induced (amiodarone-induced) etiologies, may occur (**Table 4**).[43,46]

Hyperthyroidism is characterized by increased production of T_3 and T_4, with an increased T_3:T_4 ratio, a suppressed thyrotropin level (Table 2), and characteristic clinical symptoms (Table 4). The pathogenesis is due either to the destruction of thyroid follicles causing the release of supraphysiologic levels of T_3 and T_4 (resulting in hashitoxicosis, amiodarone-induced thyroiditis, subacute viral thyroiditis, or acute suppurative thyroiditis) or the inappropriate production of thyroid hormones from a nondestructive process (including Graves disease, toxic multinodular goiter, or an autonomously functioning thyroid nodule). Resistance to thyroid hormones, which is caused by mutations in the nuclear thyroid hormone receptor gene, is unique in that it is the only disorder for which the thyrotropin level is not suppressed.[47]

The pathogenesis of Graves disease includes infiltration of lymphocytes into the thyroid gland, concomitant loss of tolerance to multiple thyroid antigens (including the thyrotropin receptor), and production of thyroid-stimulating immunoglobulins (TSIs), antibodies that bind to and mimic the action of thyrotropin.[48,49] Elevated levels of TSI result in the unregulated, increased production and release of thyroid hormones and the increased growth of the thyroid gland. In addition to TSIs, neutral and inhibitory thyroid antibodies are produced, and alterations in their levels and affinity to the thyrotropin receptor can result in alternating clinical symptoms and thyroid hormone levels.[50]

Clinical Presentation

Fetal hyperthyroidism, most commonly occurring secondary to the transplacental transfer of maternal TSIs, may be associated with the restriction of intrauterine growth, nonimmune fetal hydrops, craniosynostosis, and intrauterine death.[51] The signs and symptoms of Graves disease in children and adolescents are similar to those in adults; however, there is often a delay in diagnosis secondary to considerations of a behavioral disorder (anxiety or attention-deficit/hyperactivity disorder), respiratory disease (exercise-induced asthma), or primary cardiac arrhythmia rather than consideration of hyperthyroidism as the etiology.[49,52] Common physical examination findings include restlessness or fidgetiness, warm moist skin, fine hand tremor noted with arm extension, proximal muscle weakness, and an enlarged thyroid (goiter) with a bruit (Figure 3). Graves ophthalmopathy occurs in up to one-third of pediatric patients; however, in contrast to adults, it is typically mild, without risk to loss of vision, and most frequently improves if the child with Graves disease achieves remission.[53] Children and adolescents may also present with alterations in growth, including growth acceleration and advanced bone age; however, puberty is often delayed rather than precocious.[54,55]

Table 4. Differential Diagnosis of Hyperthyroidism

Diagnosis	Etiology	Signs and Symptoms	Evaluation
Graves disease	Autoimmune; cluster in families with nonmendelian pattern of inheritance	Anxiety, decreased ability to focus, moodiness, increased appetite; tachycardia, proptosis, goiter, tremor, proximal muscle weakness	Elevated T_3 and T_4 levels, suppressed thyrotropin level (<0.1 mIU/L),[a] elevated TSI or thyrotropin receptor antibody levels; heterogeneous tissue, hypoechoic, with increased blood flow (detected by ultrasonography); thyroid scintigraphy with >30% uptake at 24 h
Autonomously functioning nodule	Somatic mutation in *TSHR* or *GNAS*; sporadic	Mild symptoms	Elevated T_3 and T_4 levels, suppressed thyrotropin level[a]; asymmetric thyroid on physical examination and/or a thyroid nodule detected by ultrasonography
Familial, nonautoimmune hyperthyroidism	Germline mutation in *TSHR* (OMIM 609152); autosomal dominant	Severe, congenital hyperthyroidism to typical autoimmune hyperthyroidism	Elevated T_3 and T_4 levels, suppressed thyrotropin level[a]; negative antithyroid antibody testing results; positive uptake detected by scintigraphy; analysis positive for mutation
McCune-Albright syndrome	Somatic, mosaic mutation in *GNAS* (OMIM 174800); sporadic	Café au lait macule (coast of Maine, respects midline; follow the lines of Blaschko); polyostotic fibrous dysplasia of legs, arms, and skull; endocrine hormone excess (cortisol, estrogen, and growth hormone)	Elevated T_3 and T_4 levels, suppressed thyrotropin level[a]; negative for TSIs and thyrotropin receptor antibodies; assess for other endocrine hormone abnormalities
Resistance to thyroid hormone	Germline mutation in *THRB* (OMIM 190160); autosomal dominant or recessive	Decreased ability to focus, goiter, tachycardia, short stature	Elevated T_4 level with nonsuppressed thyrotropin level
Suppurative thyroiditis	Infection, viral and/or bacterial	Fever, pain, sudden onset of swelling, often unilateral; left thyroid lobe more commonly affected than the right thyroid lobe; preceding URI	Elevated WBC count, ESR, and CRP level; enlarged, heterogeneous lobe with central necrosis detected by ultrasonography
Subacute viral thyroiditis	Viral infection	Mild to asymptomatic (silent)	Triphasic laboratories with initial suppressed, then elevated, and then normal thyrotropin level (over 3-6 mo); elevated ESR during the active, hyperthyroid phase
Fictitious hyperthyroidism	Intentional or inadvertent ingestion of thyroid hormone	Similar to other forms of hyperthyroidism except thyroid is not enlarged and no nodule(s)	Elevated T_3 level (if ingesting T_3) or elevated T_3 and T_4 levels (if ingesting T_4) with suppressed thyrotropin level; thyroglobulin level is low, and 24-h RAI uptake is very low (<5%)

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RAI, radioactive iodine; TSI, thyroid-stimulating immunoglobulin; T_3, triiodothyronine; T_4, thyroxine; URI, upper respiratory tract infection; WBC, white blood cell.

[a] Below the lower detection limit (<0.1 mIU/L).

Diagnosis

All patients suspected of having hyperthyroidism should have their levels of thyrotropin, T_4, T_3, and thyroid antibodies (specifically TSIs or thyrotropin receptor antibodies) measured. In Graves disease, the thyrotropin level is suppressed with elevated T_3 and T_4 levels (Table 2). In contrast to the evaluation for hypothyroidism, obtaining a T_3 level is essential because early Graves disease may be associated with isolated elevation in T_3 levels prior to increases in T_4 levels.[49] Thyrotropin receptor antibodies may be substituted for TSIs because the newer assays have a high sensitivity, faster turnaround times for results, and are less expensive than the older assays. However, in contrast to TSI testing, thyrotropin receptor antibody testing is not a functional assay and does not provide specific, quantitative data on the level of stimulatory antibodies. Ultrasonography and scintigraphy (using iodine 123 or sodium pertechnetate technetium Tc 99m) of the thyroid can aid in the diagnosis for a small percentage of patients who are negative for thyrotropin receptor antibodies and TSIs.[46,48]

In Graves disease, the severity of the signs and symptoms may not correlate with the degree of elevation in T_3 or T_4 level. However, as a general rule, other forms of hyperthyroidism frequently present with mild or subclinical physical features (Table 4).

Treatment

With rare exception, the majority of pediatric patients with Graves disease initially start antithyroid drug therapy. Methimazole is the only antithyroid drug approved for treatment of hyperthyridism in children and adolescents in the United States after the US Food and Drug Administration issued a safety alert against the use of propylthiouracil secondary to an increased risk of drug-induced fulminant hepatic necrosis in children and adolescents.[56,57] Temporary use of a cardioselective beta-blocker should also be considered for patients with significant signs and symptoms pending normalization of T_3 and T_4 levels by use of methimazole. The most common adverse effect of methimazole is rash, which occurs in approximately 20% of patients, and the most severe adverse events are bone marrow suppression and liver toxicity, which occur in less than 1% of patients.[58] Thus, any patient receiving methimazole who presents with fever or sore throat should have his or her complete blood cell count checked for evaluation of neutropenia, and any patient receiving methimazole with right upper quadrant abdominal pain should undergo a liver function test. Most adverse events from methimazole occur in the first 3 to 6 months of treatment; however, patients may experience adverse events more than 2 years after the start of antithyroid drug therapy.[58,59]

Patients should be considered for definitive therapy if they experience recalcitrant adverse effects of therapy (eg, hives), if they experience an adverse event, or if they have not achieved biochemical remission from Graves disease 5 to 6 years after initiation of antithyroid drug therapy.[46,49,58] Patients may also consider elective definitive therapy if they have persistent symptoms despite normalization of thyroid hormone levels, if the management of hyperthyroidism interferes with their activities of daily

Box. Selection Criteria for Definitive Treatment of Graves Disease

Radioiodine ablation
- Age >10 y
- Goiter <3-4 times enlarged
- No thyroid nodule
- No access to a high-volume pediatric thyroid surgeon (<30 thyroidectomies/y)
- Minimal or no eye disease
- Patient/family choice
  - 1- to 3-mo window to achieve hypothyroid state
  - Desire to not have a scar

Total thyroidectomy
- Age <10 y
- Goiter >3-4 times enlarged
- Thyroid nodule
- Access to a high-volume pediatric thyroid surgeon
- Significant proptosis with active eye disease
- Patient/family choice
  - Desire for rapid achievement of hypothyroidism
  - No concern over having a scar

living, and/or if they are at a transition time in life (moving away, starting a job, or attending college). Overall, only 35% of pediatric patients will ultimately achieve remission, which is defined as the lack of recurrence 12 months or longer after discontinuing antithyroid drug therapy.[58]

The goal of definitive therapy, either radioiodine ablation or thyroidectomy, is permanent hypothyroidism. The benefit of pursuing definitive therapy includes the relative ease and low risk associated with thyroid hormone replacement therapy, as well as the more predictable course of disease and less-frequent laboratory surveillance. A general approach to the selection between these 2 options is listed in the Box.

Thyroid Nodules

Background

The incidence of thyroid nodules and thyroid cancer has increased significantly over the last several decades.[60] The majority of patients have neither known risk factors for the development of a thyroid nodule or cancer, nor the opportunity for prevention. The one exception is exposure to ionizing radiation, either environmental or, more commonly, secondary to diagnostic imaging and/or medical therapy for a nonthyroid malignant neoplasm. Within this cohort, a younger age at the time of exposure, female sex, iodine insufficiency, and lower doses of radiation (increased risk up to 30 Gy) are all independently associated with increased risk.[61-64] Additional diagnoses associated with an increased risk of developing thyroid nodules and thyroid cancer include a history of autoimmune thyroid disease[65,66]; several familial tumor predisposition syndromes, including multiple endocrine neoplasia (MEN) type 2 (MEN2A [OMIM 171400] and MEN2B [OMIM 162300]), associated with an increased risk of medullary thyroid carcinoma[67]; and several syndromes associated with an increased risk of differentiated thyroid cancer, both papillary thyroid cancer and follicular thyroid cancer: *PTEN* hamartoma tumor syndrome (OMIM 601728), *DICER1* pleuropulmonary blastoma syndrome (multinodular goiter and differentiated thyroid cancer [OMIM 606241]), Carney complex (multinodular goiter and differentiated thyroid cancer [OMIM 160980]), and familial adenomatous polyposis (papillary thyroid cancer [OMIM 175100]).[68] A family history of isolated multinodular goiter and differentiated thyroid cancer (papillary thyroid cancer and follicular thyroid cancer) is also associated with increased risk; however, to date, there are no known molecular markers of disease, and the pattern of penetrance and expression of multinodular goiter and familial nonmedullary thyroid cancer is quite variable.[69]

Clinical Presentation

The majority of patients with a thyroid nodule or thyroid cancer are asymptomatic at the time of diagnosis, with the thyroid mass discovered incidentally on routine physical examination, during unrelated head and neck imaging, or during evaluation of persistent cervical neck lymphadenopathy.[70] The prevalence of thyroid nodules increases with age; however, in contrast to adults, there is a higher rate of malignancy for nodules diagnosed in a patient younger than 19 years of age (20%-25% vs 10%-15%, respectively).[71,72]

Papillary thyroid cancer is the most common form of thyroid cancer in both adults and pediatric patients.[73] Because papillary thyroid cancer metastasizes via the lymphatic system, metastasis to cervical neck lymph nodes occurs commonly and is found in approximately 70% of pediatric patients.[73] For patients with lateral neck lymph node metastasis (neck levels II, III, IV, and V [Figure 3]; see consensus statement on cervical lymph node location[74]), there is also a 15% risk of pulmonary metastasis, typically diffuse, micronodular disease.[75] In contrast to papillary thyroid cancer, follicular thyroid cancer metastasizes hematogenously, most commonly to bone; however, for pediatric patients, follicular thyroid cancer often follows a less-invasive course, typically confined to the thyroid gland (minimally invasive disease).[68]

Medullary thyroid carcinoma may be sporadic or familial. In pediatrics, medullary thyroid carcinoma is most frequently associated with a family history of MEN2A, and children typically receive the diagnosis in the presymptomatic phase secondary to a family history of a known *RET* mutation transmitted in an autosomal dominant pattern of inheritance.[67] Patients with de novo mutations have an increased risk of metastasis secondary to a delay in diagnosis, and, unfortunately, de novo mutations are more common in MEN2B, the disorder associated with a more aggressive form of medullary thyroid carcinoma. Heightened clinical awareness of the disorder is associated with improved outcome.[76]

Diagnosis

A thorough history screening for personal and family risk factors, along with a complete physical examination, is the foundation of the diagnostic process. The history and physical examination should specifically look for findings associated with familial tumor predisposition syndromes, including macrocephaly, lipoma, and freckling of the glans penis (*PTEN* hamartoma tumor syndrome)[77]; lentigines of epicanthal folds, lips, and oral mucosa (familial adenomatous polyposis[78] and Carney complex[79]); and a marfanoid body habitus with elongated facies, mucosal neuromas (lips and tongue), everted eyelids with a history of alacrima (lack of tears), and constipation (pseudo–Hirschsprung disease or intestinal ganglioneuromatosis; MEN2B).[80,81]

The thyroid examination includes visual inspection and palpation (Figure 3) combined with ultrasonography of the thyroid for patients with a suspected thyroid nodule and/or cervical lymphadenopathy. Ultrasonography provides information on the size, number, centricity (focal or multicentric), laterality (unilateral or bilateral), and characteristics of the nodule (solid vs cystic vs mixed), as well as thyroid parenchyma echotexture (normal or consistent with thyroiditis). For patients with a confirmed thyroid nodule, ultrasonography of the lateral neck to assess for the presence of abnormal lymph nodes must be a formal part of the study and report.[82] A serum thyrotropin level is the only other prereferral test that should be performed because a suppressed thyrotropin level increases the likelihood of an autonomously functioning nodule, a thyroid mass associated with a lower risk of malignancy.[68]

Patients with a thyroid nodule either suspected by a physical examination and/or confirmed by ultrasonography should be referred to a pediatric endocrinologist. The endocrinologist will obtain and/or review the ultrasonographic images, decide if a fine-needle aspiration (FNA) is warranted, complete preoperative staging if surgery is recommended, and then refer the patient to a high-volume pediatric thyroid surgeon with a recommended operative plan. With rare exception, all patients with a thyroid nodule should undergo FNA prior to surgery. The use of conscious sedation, ultrasonographic guidance, bedside confirmation of sample adequacy, and interpretation of the FNA sample by an experienced cytopathologist using the Bethesda System for Reporting Thyroid Cytopathology aids in a nontraumatic experience and allows for informed stratification of surgical management.[68,83]

Treatment

Although the overall risk of a malignant thyroid nodule diagnosed in a pediatric patient is approximately 20% to 25%, the majority of nodules are benign.[72] The ultrasonographic characteristics help stratify which patients should undergo FNA, and the results of the FNA direct which patients may benefit from surgery. Guidelines for the evaluation and management of thyroid nodules and differentiated thyroid cancer in children and adolescents,[68] as well as guidelines for the management of medullary thyroid carcinoma,[67] are available to clinicians as well as patients and families (http://www.thyroid.org). When possible, patients should be referred to a pediatric thyroid center with a multidisciplinary team that regularly evaluates and cares for pediatric patients with thyroid nodules and thyroid cancer to ensure optimal outcome and reduce the risk of medical and surgical complications.[68]

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