

Hyperthyroidism in Children

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Educational Gap

Hyperthyroidism is a rare but potentially serious disorder in childhood with unique effects on growth and development. Clinicians should be aware of the clinical manifestations of this condition, which can be subtle. Timely identification and referral to pediatric endocrinologists can help reduce associated morbidity.

Objectives After completing this article, readers should be able to:

1. Describe the epidemiology and pathogenesis of hyperthyroidism.
2. Identify the various causes of hyperthyroidism.
3. Recognize the signs and symptoms of hyperthyroidism, including neonatal hyperthyroidism.
4. Initiate an appropriate evaluation and know when to refer patients to subspecialty care.
5. Understand the various modalities for treatment of hyperthyroidism and the limitations of each option.

CASE STUDY

An 11-year-old girl with a history of asthma comes to your office with shortness of breath, chest pain, and increased use of her albuterol inhaler for the past 2 weeks. On physical examination, her blood pressure is 135/63 mm Hg and heart rate is 108 beats/min. She appears “jumpy” and anxious and has a tremor of her extremities and tongue. Neck evaluation reveals a diffusely enlarged goiter with a bruit. Laboratory testing documents an undetectable thyrotropin of less than 0.01 mIU/mL (normal range, 0.4–5.0 mIU/mL), free thyroxine of 7.8 ng/dL (100.39 pmol/L) (0.9–1.8 ng/dL [11.58–23.17 pmol/L]), and very high total triiodothyronine of more than 650 ng/dL (10.01 nmol/L) (60–181 ng/dL [0.92–2.79 nmol/L]). On further evaluation, she is diagnosed with Graves’ disease. Following treatment of hyperthyroidism, her symptoms improve, including those of asthma.

AUTHOR DISCLOSURE Dr Srinivasan has disclosed no financial relationships relevant to this article. Dr Misra has disclosed that she received an investigator-initiated grant from Genentech. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

EPIDEMIOLOGY

Hyperthyroidism is less common in children than in adults. Graves’ disease is the most common cause for hyperthyroidism in children. Few studies have prospectively examined the incidence of childhood hyperthyroidism. In a national

prospective surveillance study from the United Kingdom and Ireland in children younger than 15 years of age, the incidence of hyperthyroidism was 0.9 per 100,000. (1) Graves' disease accounted for 96% of cases. The authors reported an increasing incidence of hyperthyroidism with age in both sexes, although girls had a significantly higher incidence than boys in the 10- to 14-year age group. In 2008, approximately 8000 children in the United States were being treated for Graves' disease at any time, with an estimated prevalence of 1 in 10,000 children. (2)

Etiology and Pathogenesis

Graves' disease is the most common cause of hyperthyroidism in children, accounting for more than 95% of cases. Other causes are described in the Table.

The pathogenesis of Graves' disease is not completely understood but is believed to include a complex interaction of genetic, immune, and environmental factors. The contribution of genetic factors is suggested by disease clustering in families and findings from twin studies. A population-based study of Danish twins suggested that nearly 80% of the risk of Graves' disease is attributable to genetic factors. (3) Graves' disease occurs from formation of stimulating antibodies to the thyrotropin (TSH) receptor (TSHR) called TSH receptor-stimulating immunoglobulins (TSIs). These antibodies were previously referred to as the long-acting thyroid stimulators. They bind to and stimulate the TSH receptor on thyroid follicular cells, causing increased vascularity of the gland, follicular hypertrophy and hyperplasia, and excessive synthesis and secretion of thyroid hormone. Graves' ophthalmopathy is also immune-mediated and caused by cross-reactivity of TSI with a TSHR-like protein in retro-orbital tissue and extraocular muscles, leading to local inflammation and infiltration of glycosaminoglycans. The resulting edema, muscle swelling, and increase in intraorbital pressure causes the characteristic features of Graves' ophthalmopathy. Clinical manifestations of ophthalmopathy are typically less severe in children than in adults. A similar mechanism in the dermis may be responsible for Graves' dermopathy, which is rarely seen in children.

Transient hyperthyroidism may result from destruction of thyroid follicular cells by an autoimmune or infectious process, leading to unregulated release of preformed hormone into the circulation. Subacute thyroiditis from an infectious or inflammatory cause usually resolves in a few months, with subsequent normalization of thyroid function. Autoimmune thyroiditis causing hyperthyroidism may be followed by hypothyroidism.

An uncommon cause of hyperthyroidism in children is McCune-Albright syndrome (MAS). MAS is caused by

a somatic-activating mutation of the *GNAS* gene, resulting in increased GS protein signaling that leads to hyperfunction of glycoprotein hormone receptors, autonomous cell proliferation, and hormonal hypersecretion. The thyroid gland is frequently involved and is the second most common endocrinopathy after precocious puberty.

Secondary causes of hyperthyroidism, including TSH-secreting pituitary adenomas and pituitary resistance to thyroid hormone, are exceedingly rare in children and caused by unregulated overproduction of TSH.

Clinical Manifestations

Hyperthyroidism in children can have a wide variety of clinical manifestations, many of which are similar to those seen in adults. However, hyperthyroidism has unique effects on growth and development and may cause pronounced neuropsychological manifestations in children.

Growth and Puberty

During infancy, excess circulating thyroid hormone can lead to premature craniosynostosis. Longstanding hyperthyroidism from Graves' disease may result in growth acceleration and advancement in epiphyseal maturation. Children with Graves' disease are tall for age at presentation and their bone age tends to be advanced. However, in a retrospective Italian study of 101 children with Graves' disease, although bone age was advanced at presentation, there were no adverse effects on subsequent growth, and adult height was consistent with genetic potential. (4) In severe cases of hyperthyroidism, pubertal onset and progression may be delayed. Anovulatory cycles, oligomenorrhea, and secondary amenorrhea are common in postmenarchal girls. Hyperthyroidism causes an increase in plasma sex hormone-binding globulin. As a result, total testosterone and estradiol concentrations are increased, but their unbound fractions are normal or even decreased.

Cardiovascular and Respiratory

Hyperthyroidism causes an increase in heart rate and cardiac output, widening of pulse pressure, and decrease in peripheral vascular resistance. Systolic blood pressure may increase. The classic "water hammer" pulse (a bounding pulse with a rapid upstroke and descent) may be seen in acute stages of thyrotoxicosis. The patient may experience palpitations, and dyspnea is common in severe thyrotoxicosis. Atrial fibrillation occurs in up to 20% of adults with hyperthyroidism but is rare in children. The incidence of mitral valve prolapse is more common in patients with Graves' disease than in the general population.

TABLE. Causes of Hyperthyroidism

INCREASED TSH SECRETION OR TSH-LIKE ACTION

CONDITION	PREVALENCE	THYROID EXAMINATION RESULTS	LABORATORY FINDINGS	ANTIBODIES	RADIOACTIVE IODINE OR TECHNETIUM-99 UPTAKE
TSH-secreting pituitary adenomas	Very rare	Normal	TSH↑ or Normal	Negative	Diffusely ↑
Pituitary thyroid hormone resistance	Very rare	Normal or symmetric goiter	TSH↑ or Normal	Negative	Diffusely ↑
hCG-induced (TSH-like action)	Uncommon in children	Normal	TSH↓ ↑ serum β-hCG	Negative	Diffusely ↑
• Physiologic hyperthyroidism of pregnancy (twin pregnancy)					
• Gestational trophoblastic tumors					
• Familial gestational hyperthyroidism due to TSH receptor mutations					

INCREASED TSH RECEPTOR ACTIVATION OR ACTIVATION OF THE DOWNSTREAM SIGNALING PATHWAY

CONDITION	PREVALENCE	THYROID EXAMINATION RESULTS	LABORATORY FINDINGS	ANTIBODIES	RADIOACTIVE IODINE OR TECHNETIUM-99 UPTAKE
TSH receptor-activating or -stimulating antibodies (Graves' disease)	Most common	Diffuse goiter	TSH↓	+TSI +/- anti-TPO	Diffusely ↑
Activating mutations of the TSH receptor	Very rare	Normal or diffuse goiter	TSH↓	Negative	↑
McCune-Albright syndrome	Very rare	Normal or nodular or diffuse goiter	TSH↓	Negative	↑

AUTONOMOUS THYROID HORMONE SECRETION

CONDITION	PREVALENCE	THYROID EXAMINATION RESULTS	LABORATORY FINDINGS	ANTIBODIES	RADIOACTIVE IODINE OR TECHNETIUM-99 UPTAKE
Toxic adenoma	Less common in children than in adults	Single nodule	TSH↓	Negative	↑ in a single focus; suppressed uptake in the rest of the gland
Toxic multinodular goiter	Uncommon in children	Multinodular goiter	TSH↓	Negative	↑ multifocal uptake

Continued

TABLE (Continued)

INCREASED RELEASE OF PREFORMED THYROID HORMONE (TRANSIENT HYPERTHYROIDISM)

CONDITION	PREVALENCE	THYROID EXAMINATION RESULTS	LABORATORY FINDINGS	ANTIBODIES	RADIOACTIVE IODINE OR TECHNETIUM-99 UPTAKE
Thyrotoxic phase of chronic lymphocytic thyroiditis (Hashitoxicosis)	Rare	Firm goiter	TSH ↓	Anti-TPO, and/or antithyroglobulin in most	↓
Lymphocytic thyroiditis (silent, painless, and postpartum thyroiditis)	Rare	Firm, nontender	TSH ↓	Anti-TPO in most	↓
Subacute thyroiditis (painful, postviral, granulomatous, and de Quervain)	Rare	Tender gland	TSH ↓ ↑ ESR	Negative	↓

DRUG-INDUCED (EXAMPLES)

CONDITION	PREVALENCE	THYROID EXAMINATION RESULTS	LABORATORY FINDINGS	ANTIBODIES	RADIOACTIVE IODINE OR TECHNETIUM-99 UPTAKE
Amiodarone-induced destructive thyroiditis	Very rare in children	Normal	TSH ↓	Negative	↓
Contrast agents: iodine-induced synthesis of excess thyroid hormone (Jod Basedow effect in an underlying multinodular goiter)	Very rare in children	Normal	TSH ↓	Negative	↑

OTHERS

CONDITION	PREVALENCE	THYROID EXAMINATION RESULTS	LABORATORY FINDINGS	ANTIBODIES	RADIOACTIVE IODINE OR TECHNETIUM-99 UPTAKE
Factitious intake of thyroid hormone	Rare	Normal	TSH ↓ low serum thyroglobulin	Negative	↓
Dermoid cysts with thyroid tissue	Very rare in children	Normal	TSH ↓	Negative	↓ in thyroid

Anti-TPO=antithyroid peroxidase; hCG=human chorionic gonadotropin; ESR=erythrocyte sedimentation rate; TSH=thyroid stimulating hormone (thyrotropin); TSI=TSH receptor-stimulating immunoglobulin

Ocular

Children with hyperthyroidism may have lid retraction due to increased adrenergic tone of the ocular muscles that can lead to a prominent stare and lid lag ("adrenergic stare"). Lid lag is assessed by asking the child to follow the examiner's finger as the finger moves downward in front of the eye. In the case of lid lag, the upper eyelid lags behind the globe as the child's gaze shifts slowly downward. True ophthalmopathy in Graves'

disease is characterized by inflammatory infiltrates and edema of retro-orbital tissue and extraocular muscles, resulting in proptosis and impairment of ocular muscle function. Although 50% to 75% of children with Graves' disease may have minor features of Graves' ophthalmopathy, such as pain, a foreign body sensation in the eyes, or diplopia, symptoms are much milder than in adults, and orbital disease severe enough to compromise vision is extremely rare. In a retrospective review

of 152 children with Graves' disease over a 3-year period, only 17% were referred to ophthalmology for prominent ophthalmic manifestations. (5) Following resolution of hyperthyroidism in children, the initial lid retraction or stare from increased adrenergic tone resolves quickly. However, true proptosis from Graves' ophthalmopathy tends to persist or regress only slightly.

Gastrointestinal

Hyperthyroidism in children causes an increase in appetite. However, weight loss occurs despite increased food intake because of thyroid hormone-induced calorigenesis (heat production). There is also an increased frequency of bowel movements, although diarrhea does not occur. In children, weight recovers with treatment of hyperthyroidism.

Muscle and Bone

Hyperthyroidism can cause fatigue. More specifically, hyperthyroidism may cause proximal muscle weakness and difficulty climbing stairs or combing hair. Thyrotoxic periodic paralysis is a complication of hyperthyroidism that is characterized by muscle palsy and hypokalemia. Although hyperthyroidism is more common in females, thyrotoxic periodic paralysis primarily affects males of Asian descent. Severe hyperthyroidism increases osteoclastic bone resorption and the risk of fractures. Bone density improves with treatment of hyperthyroidism.

Neuropsychological

Neuropsychological manifestations can be severe in children. Nervousness, sleep disturbances, and emotional lability are common. Children may have trouble focusing on tasks that can result in a decline in school performance, prompting an evaluation for attention-deficit/hyperactivity disorder. Neurologic examination reveals brisk reflexes, and a fine tremor of the hands and/or tongue may be seen.

Skin and Hair

The most characteristic change of hyperthyroidism is warm, moist skin that results from cutaneous vasodilatation and excessive sweating. This also causes heat intolerance. Hair becomes fine and friable, and hair loss may increase. Nails may become soft and friable. Graves' dermopathy, which is classically associated with Graves' disease in adults, involves bilateral nonpitting edema with associated thickening and induration of the skin, typically seen over the ankles and feet. This manifestation is rare in children.

DIAGNOSIS

The history, physical examination, and results from thyroid function tests (TSH, free thyroxine [T₄], and total triiodothyronine [T₃]) contribute to the diagnosis of hyperthyroidism.

In children with primary hyperthyroidism, the serum TSH concentration is suppressed and T₄ and T₃ values are elevated. Once the diagnosis of hyperthyroidism is confirmed biochemically, evaluation should be undertaken to determine the underlying cause, which may affect the choice of treatment. The thyroid examination, serum thyroid antibody measurements, and radionuclide uptake scan help differentiate the causes of hyperthyroidism (Table).

In Graves' disease, examination of the neck usually reveals a smooth, diffusely enlarged goiter without palpable nodularity. Often, a thyroid bruit is heard on auscultation due to increased vascularity of the gland. The diagnosis is confirmed by measurement of TSI, which is positive in up to 90% of cases. For children with negative TSI results or when the diagnosis is unclear, a radionuclide uptake scan can aid in differentiating conditions of increased thyroid hormone production (such as Graves' disease) from conditions of increased release of preformed hormone (such as subacute thyroiditis or the early phase of autoimmune thyroiditis). A radionuclide uptake is performed with radioactive iodide (¹²³I) or 99m-technetium (^{99m}Tc) pertechnetate. The use of ^{99m}Tc pertechnetate is preferred for diagnosing Graves' disease because it is less expensive, is a faster test, and involves less total body radiation exposure. The radionuclide uptake scan shows diffusely increased uptake throughout the gland in Graves' disease, whereas conditions of increased release of preformed hormone are associated with reduced uptake. This differentiation becomes important in determining the appropriate therapeutic strategy.

In addition to TSI, endocrinologists often measure concentrations of other antibodies such as thyroid peroxidase antibodies, which are helpful for diagnosis of autoimmune thyroiditis and may be positive in up to 10% of patients with Graves' disease. Additional tests include liver function tests and assessment of the absolute neutrophil count in anticipation of treatment with antithyroid medications.

MANAGEMENT

Treatment options for Graves' disease in children include antithyroid drugs, radioactive iodine therapy, and surgical thyroidectomy. Although thyroidectomy leads to permanent cure and subsequent hypothyroidism, it is typically not used as first-line therapy because of associated morbidity and expense. Radioactive iodine therapy often leads to permanent cure and also hypothyroidism, but it is not recommended for very young patients. Lasting remission after antithyroid medications does not occur in most patients with pediatric Graves' disease, even after years of treatment. However, because some children experience remission over

time, antithyroid medications are still considered first-line treatment. In the initial period, patients often require therapy with β -blockers for management of tachycardia and hypertension because antithyroid medications may take several weeks to normalize thyroid hormone values. Eventually, many pediatric patients require either radioactive iodine or surgery.

Antithyroid Medications

The thionamides methimazole and propylthiouracil (PTU) are used to treat Graves' disease. Methimazole is considered first-line antithyroid treatment for children with Graves' disease. PTU has the unacceptable risk of hepatotoxicity in children; there are reports of fulminant hepatic necrosis and liver failure that may require liver transplantation or may be fatal. Therefore, the Endocrine Society and the American Thyroid Association in conjunction with the American Association of Clinical Endocrinologists (AACE) (6) strongly recommend against use of PTU as first-line treatment for Graves' disease in children and the US Food and Drug Administration has issued a black-box warning regarding use of PTU, noting at least 32 (22 adult and 10 pediatric) cases of serious liver injury with PTU use.

The dose of methimazole is 0.2 to 0.5 mg/kg per day, with a range of 0.1 to 1.0 mg/kg per day (maximal dose typically does not exceed 30 mg/day). Methimazole is available as 5- and 10-mg tablets, and the dose is rounded off accordingly. A higher dose is required at the initiation of treatment, and the dose is reduced by 50% or more after thyroid hormone values normalize to maintain the euthyroid state. Alternatively, some physicians add levothyroxine to attain normal thyroid hormone values, a practice referred to as "block and replace." However, this regimen does not increase the likelihood of sustained remission, and because of a possible higher risk of dose-related complications with methimazole, this practice is no longer recommended, except in special circumstances. PTU is reserved for children who are allergic to or who develop an adverse effect from methimazole that necessitates drug discontinuation or when radioactive iodine or surgery is not a suitable option. PTU is still used in life-threatening thyroid storms because of its ability to act rapidly and inhibit the peripheral conversion of T₄ to T₃ and in women in the first trimester of pregnancy due to the risk of embryopathy, including aplasia cutis, with use of methimazole.

The adverse effect profile of methimazole and PTU is similar. However, adverse effects tend to occur more often and are more severe with PTU. Minor effects include a skin rash, arthralgias, myalgias, nausea, and an abnormal taste sensation. In children who develop a minor adverse effect, the drug should be discontinued for a few days until the symptom subsides and then may be restarted. Major adverse effects

include agranulocytosis, vasculitis with a lupus-like syndrome, hepatitis, and liver failure. Major adverse effects occur in fewer than 2% of patients. Adverse effects to methimazole usually occur within the first 6 months of starting therapy but can develop later. In contrast to PTU, liver toxicity with methimazole usually manifests as cholestatic jaundice. The overall rate of both minor and major adverse effects for antithyroid drugs in children is reported to be 6% to 35%. Patients should be given written information regarding adverse effects of antithyroid drugs before initiating therapy.

Before initiating antithyroid drug therapy, clinicians should obtain a baseline absolute neutrophil count (ANC) and liver function tests because the disease process itself can cause a decrease in ANC and elevation in liver enzymes before medications are started. After initiation of methimazole therapy, thyroid function tests are generally repeated in 2 weeks and then monthly until values normalize. Depending on disease severity, thyroid function tests may not normalize for several months. After normalization of thyroid hormone concentrations, thyroid function tests should be monitored every 3 to 4 months. As indicated previously, a potential dangerous complication of antithyroid drug treatment is agranulocytosis. For this reason, antithyroid medication should be discontinued immediately and the ANC measured in children who develop fever, mouth sores, or pharyngitis during treatment. Agranulocytosis (<500/mm³) is a contraindication for future antithyroid drug treatment; the patient should be considered for radioactive iodine or surgery.

The rate of remission of Graves' disease in children varies from 25% every 2 years to 40% over 8 or more years based on different series of reports. (7) If methimazole is chosen as first-line treatment for Graves' disease, clinicians should attempt to reduce or discontinue the dose after 2 years to assess for remission. Children with Graves' disease not in remission following 2 years of methimazole therapy should be considered for treatment with radioactive iodine or thyroidectomy, although they may also be continued on antithyroid drugs. Some of the predictors of remission include older age, lesser disease severity at presentation, small goiter size, higher body mass index Z-score, post-pubertal status, and a decrease in TSI over time. (8)

Once remission occurs, the relapse rate in children varies from 3% to 47%, based on different studies. Most relapses occur within 1 year of treatment discontinuation, but later relapses do occur. Risk of relapse is higher in non-Caucasians, younger patients, and those who have higher initial free T₄ concentrations at presentation. TSI is also a useful predictor of outcome: positive antibodies after discontinuation of treatment are associated with relapse.

β-blockers

β-blockers such as propranolol are recommended for children who have palpitations and tremors, when the heart rate exceeds 100 beats/min, and in those with hypertension. β-blockers limit β-adrenergic activity and inhibit peripheral T₄-to-T₃ conversion. In addition, because propranolol is highly lipid-soluble and readily crosses the blood-brain barrier, it may be beneficial in those with neurologic symptoms. However, cardioselective β-blockers such as atenolol should be used in children with reactive airway disease. In acute settings such as thyroid storm and during surgery, intravenous β-blockers such as esmolol are preferred due to their rapid onset of action.

Glucocorticoids

Glucocorticoids inhibit peripheral conversion of T₄ to T₃ and reduce thyroid hormone secretion. They are used in severe cases of hyperthyroidism and for treatment of thyroid storm.

Radioactive Iodine Therapy

Treatment with ¹³¹I is an effective therapy for Graves' disease and may be considered for children not in remission after at least 1 to 2 years of treatment with antithyroid drugs or in those who have had a major adverse effect to these medications. Children with severe Graves' disease (total T₄ >20 μg/mL [341.88 nmol/L] and free T₄ >5 ng/dL [64.36 pmol/L]) should be pretreated with β-adrenergic blockade and methimazole until thyroid hormone values are near normal before proceeding with radioactive iodine therapy because of concern for thyroid storm based on rare reports. The present guidelines state that the goal of ¹³¹I therapy for Graves' disease is to induce hypothyroidism rather than euthyroidism with a single adequate dose, based on a possible increased risk for development of thyroid neoplasm in the residual partially irradiated thyroid and poor remission rates with low doses of ¹³¹I.

There are few adverse effects from ¹³¹I therapy other than lifelong hypothyroidism, the goal of therapy. Permanent hypothyroidism develops 2 to 3 months after treatment, at which time levothyroxine administration is necessary in replacement doses. Mild tenderness can occur over the thyroid in the first few days after therapy from radiation-induced thyroiditis, which responds well to treatment with nonsteroidal anti-inflammatory agents. There are rare reports of thyroid storm occurring in children after radioactive iodine treatment.

Radioactive iodine is excreted in saliva, urine, and stool, and significant radioactivity is retained within the thyroid for several days. Therefore, children should follow local radiation

safety recommendations following treatment, which include absence from school for 1 week, not sharing cups or utensils with others, and not kissing or sitting next to pregnant women and babies for this duration.

Concern for thyroid malignancy from use of ¹³¹I therapy is based on the increased incidence of thyroid neoplasms in children after the nuclear disasters at Hiroshima and Chernobyl. However, those exposures were to external ionizing radiation and are not directly applicable to the use of radioactive iodine in Graves' disease. It is notable that thyroid cancer rates were not increased among 3,000 children exposed to only ¹³¹I from the Hanford nuclear reactor site (9) or in 6,000 children who received ¹³¹I for diagnostic scanning. (10) Further studies have not revealed an increased risk of thyroid cancer, leukemia, or other cancers. There has also not been an increase in the rate of infertility, spontaneous abortions, or congenital anomalies in offspring of patients treated with radioactive iodine. However, because of the relatively small number of young children treated with radioactive iodine and for theoretical cancer risk concerns, the American Thyroid Association and AACE recommend that ¹³¹I therapy be avoided in very young children (<5 years) and that the dose be limited to 10 mCi in children who are 5 to 10 years of age. (6)

Surgery

Based on current guidelines, thyroidectomy is the preferred treatment in children younger than 5 years of age when definitive therapy is required and in children with large goiters who experience major adverse effects to antithyroid drugs because the response to ¹³¹I may be poor in these cases. If surgery is planned, the patient should be pretreated with β-blockers and antithyroid drugs or inorganic iodine. Use of inorganic iodine for 7 to 10 days reduces the vascularity of a large goiter and is particularly important when antithyroid drugs cannot be used because of their adverse effects. Near-total or total thyroidectomy is the recommended procedure for management of Graves' disease to reduce the risk of persistent hyperthyroidism. Surgery must be performed by a highly experienced surgeon to reduce the rate of complications, which include postoperative hemorrhage, wound infection, transient or permanent hypoparathyroidism, and vocal cord paralysis from injury to the recurrent laryngeal nerve.

Management for Other Causes of Hyperthyroidism

The management of other causes of hyperthyroidism in children, such as the various forms of thyroiditis (autoimmune thyroiditis and subacute thyroiditis), does not involve specific treatments other than observation, symptomatic treatment if necessary, and monitoring of thyroid function

tests. Symptomatic treatment is rarely required because symptoms are mild and short-lived. β -blockers can be used in children with palpitations, tremors, significant tachycardia, and hypertension. In subacute thyroiditis, nonsteroidal anti-inflammatory agents or glucocorticoids are used for pain and tenderness, if present. Thyroid function tests are monitored to assess for the resolution of hyperthyroidism and to detect subsequent transient or permanent hypothyroidism.

Methimazole can be used to control biochemical effects of hyperthyroidism in MAS and activating mutations of the TSH receptor. However, this is a temporary measure; radioactive iodine or surgery is eventually necessary for permanent treatment. Treatment options for toxic adenomas and toxic multinodular goiters include radioactive iodine or surgery, although surgery is preferred in children. Therapies for TSH-secreting pituitary adenomas are directed at treatment of the pituitary tumor.

THYROID STORM

Thyroid storm is a rare and life-threatening condition that is an extreme manifestation of hyperthyroidism and an endocrine emergency. In adults, thyroid storm is estimated to occur in fewer than 1% of patients with hyperthyroidism, and the incidence in children is not clear. Thyroid storm is characterized by multisystem organ failure and clinical features that include nausea, vomiting, diarrhea, tachycardia, hyperpyrexia, hepatic dysfunction, hypotension, arrhythmias, and congestive heart failure. Among the neuropsychiatric manifestations are agitation, delirium, psychosis, stupor, and coma. Factors that can precipitate thyroid storm include abrupt cessation of antithyroid drugs, thyroid or nonthyroid surgery in a patient with unrecognized or inadequately treated hyperthyroidism, radioactive iodine therapy, and acute illnesses such as diabetic ketoacidosis. In children, thyroid storm has also been reported after inadvertent or purposeful ingestion of levothyroxine. (11)

A high index of suspicion for thyroid storm should be maintained in children with hyperthyroidism who demonstrate evidence of systemic decompensation. Guidelines from the American Thyroid Association and AACE suggest a multimodality treatment approach with close monitoring in an intensive care unit. Treatment should include β -adrenergic blockade with propranolol or esmolol (parenteral therapy is usually necessary), antithyroid drug therapy with PTU, inorganic iodine solutions for acute inhibition of thyroid hormone secretion and synthesis, and corticosteroid therapy. Supportive measures include aggressive cooling with cooling blankets, use of acetaminophen, volume resuscitation, and respiratory support.

NEONATAL THYROTOXICOSIS

Neonatal thyrotoxicosis is almost always the result of neonatal Graves' disease caused by transplacental passage of maternal TSI antibodies. This condition is transient and self-limiting but can have severe clinical manifestations and long-term sequelae. Graves' disease occurs in approximately 0.2% of women, and neonatal thyrotoxicosis occurs in approximately 1% to 5% of infants born to affected mothers. Based on these data, the incidence of neonatal Graves' disease is estimated to be 1 in 25,000 neonates. The likelihood of neonatal Graves' disease is related to the titer of maternal TSI, with hyperthyroidism most likely when the maternal TSI titer exceeds 500%. Neonatal thyrotoxicosis typically occurs in infants of mothers with active Graves' disease but can also occur in infants of mothers with a history of Graves' disease previously treated with radioactive iodine or surgery due to the persistence of TSI.

During pregnancy, fetal thyrotoxicosis is monitored by assessing for the presence of a fetal goiter on ultrasonography and for fetal tachycardia. Intrauterine growth restriction can cause small-for-gestational age births, and preterm births may occur. Very severe cases can lead to intrauterine heart failure, fetal hydrops, and intrauterine demise. Clinical manifestations of neonatal thyrotoxicosis include irritability, hyperactivity, restlessness, poor sleep, diarrhea, and poor weight gain. Physical examination may reveal warm and moist skin, tachycardia with bounding pulses, arrhythmias, frontal bossing with triangular facies, hepatosplenomegaly, a diffuse goiter, and an adrenergic stare. Severe neonatal thyrotoxicosis may be complicated by congestive heart failure.

The time of onset and severity of symptoms vary, depending on whether the mother received treatment with antithyroid drugs during pregnancy. Infants born to mothers not treated with antithyroid drugs during pregnancy can exhibit hyperthyroidism at birth. Infants of mothers treated with antithyroid drugs may be euthyroid or even hypothyroid at birth from transplacental passage of the antithyroid drug and may become hyperthyroid several days later, after the antithyroid drug clears from the neonate's circulation. Thyroid function tests should be obtained in infants born to mothers with Graves' disease after birth and additionally if symptomatic. If neonatal thyrotoxicosis is detected, treatment should be initiated promptly.

For the management of severe cases of neonatal thyrotoxicosis, inorganic iodine (such as Lugol solution) is administered in pharmacologic doses to inhibit organification of iodide and thyroid hormone release. The advantage of inorganic iodine over methimazole is its rapid onset of action. Effects of inorganic iodine wear off after 4 to 6

weeks, but neonatal Graves' disease is usually in the process of resolving by this time. Treatment options also include β -blockers and sometimes methimazole. As mentioned, there is a black-box warning against the use of PTU for treatment of Graves' disease in children. Glucocorticoids are used in severe cases, and digoxin is helpful if heart failure occurs. Transient hypothyroidism rarely occurs from prolonged suppression of TSH that persists even after thyroid hormone secretion has decreased. Affected infants may require a short duration of levothyroxine replacement therapy until TSH concentrations normalize.

Neonatal Graves' disease typically resolves spontaneously 3 to 12 weeks after birth, although it occasionally persists for a longer period. Long-term sequelae include poor growth, craniosynostosis, hyperactivity, developmental and behavioral problems, and very rarely persistent hypothyroidism.

Summary

- On the basis of strong research evidence, hyperthyroidism is a rare (1) but potentially serious disorder in childhood that, if uncontrolled, can lead to a wide range of complications, including effects on growth and development.
- On the basis of strong research evidence, Graves' disease is the most common cause of hyperthyroidism in children, accounting for greater than 95% of cases. (2) It is caused by stimulating antibodies to the thyroid-stimulating hormone receptor.

- On the basis of some research evidence and consensus, history, physical examination, and thyroid function tests help diagnose hyperthyroidism. The condition is characterized by suppressed serum thyrotropin and elevated serum triiodothyronine and thyroxine. Radioactive iodine (or technetium-99) uptake and serum thyroid antibody measurements help determine the cause of hyperthyroidism. (6)
- On the basis of some research evidence and consensus, treatment options for Graves' disease in children include antithyroid medications, radioactive iodine, and surgery. Antithyroid medications are commonly used as the first-line therapy in children. However, because of the low rates of spontaneous remission, (7) most children eventually require permanent treatment with radioactive iodine or surgery. Of the available antithyroid medications, current guidelines recommend use of methimazole and not propylthiouracil because of the unacceptable risk of hepatotoxicity associated with propylthiouracil. (6)
- On the basis of strong research evidence, thyroid storm is a rare life-threatening endocrine emergency that should be suspected in children with hyperthyroidism who demonstrate evidence of systemic decompensation.
- On the basis of strong research evidence, neonatal hyperthyroidism can occur in infants born to mothers with a history of Graves' disease due to transplacental passage of TSH receptor stimulating antibodies.

References for this article are at <http://pedsinreview.aappublications.org/content/36/6/239.full>.

Parent Resources from the AAP at HealthyChildren.org

- <http://www.healthychildren.org/English/health-issues/conditions/chronic/Pages/Thyroid-Disorders-Treatment.aspx>

PIR Quiz

1. Which of the following thyroid examination findings, thyroid function tests, serum thyroid antibody measurements, and radionuclide uptake scan results are most commonly seen in patients with Graves' disease?
 - A. Diffuse goiter, decreased thyrotropin (TSH), positive serum thyroid antibody, diffusely increased radionuclide uptake.
 - B. Firm goiter, decreased TSH, positive serum thyroid antibody, decreased radionuclide uptake.
 - C. Multinodular goiter, decreased TSH, negative serum thyroid antibody, increased multifocal radionuclide uptake.
 - D. Normal thyroid examination, decreased TSH, negative serum thyroid antibody, diffusely increased radionuclide uptake.
 - E. Tender thyroid gland, decreased TSH, negative serum thyroid antibody, decreased radionuclide uptake.
2. Graves' disease results from:
 - A. Autonomous thyroid hormone secretion.
 - B. Excessive production of thyrotropin-releasing hormone in the hypothalamus.
 - C. Formation of stimulating antibodies to the TSH receptor.
 - D. Increased release of preformed thyroid hormone.
 - E. Increased TSH secretion.
3. A 13-year-old girl comes to your office for a routine health supervision visit. During the physical examination, you palpate a firm thyroid gland. You also notice a tremor of her extremities and tongue. Because of these physical examination findings, you order laboratory tests. Results include: TSH <0.01 mIU/L (normal, 0.4–5.0 mIU/L), free thyroxine 5 ng/dL (64.36 pmol/L) (normal, 0.9–1.8 ng/dL [11.58–23.17 pmol/L]), and triiodothyronine 350 ng/dL (5.39 nmol/L) (normal, 60–181 ng/dL [0.92–2.79 nmol/L]). Which of the following additional physical examination findings best supports the diagnosis of hyperthyroidism?
 - A. Bilateral ptosis.
 - B. Hepatomegaly.
 - C. Muscle weakness.
 - D. Decreased pulse pressure.
 - E. Truncal obesity.
4. Methimazole is used as first-line antithyroid treatment for children with Graves' disease because propylthiouracil has an unacceptable risk of hepatotoxicity associated with its use. However, liver toxicity is a major adverse effect of methimazole. Liver toxicity with methimazole usually manifests as:
 - A. Cholestatic jaundice.
 - B. Fulminant hepatic necrosis.
 - C. Hepatitis.
 - D. Hepatoblastoma.
 - E. Steatosis.
5. A new admission to the newborn nursery is an infant who was born to a mother with Graves' disease. When reviewing the mother's chart, the presence of which of the following findings on prenatal ultrasonography would be most concerning for fetal thyrotoxicosis?
 - A. Adrenergic stare.
 - B. Craniosynostosis.
 - C. Edema of the lower extremities.
 - D. Fetal tachycardia.
 - E. Frontal bossing.

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Pediatrics in Review 2015;36:239
DOI: 10.1542/pir.36-6-239

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