Overview and Initial Management: Hyperthyroidism

42

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The terms "hyperthyroidism" and "thyrotoxicosis" are sometimes used interchangeably to describe conditions that lead to signs and symptoms of thyroid hormone excess. Hyperthyroidism is characterized by increased thyroid hormone synthesis and secretion from the thyroid gland. Thyrotoxicosis more generally describes conditions that lead to increased levels of circulating thyroid hormone (irrespective of the source). This section will review the causes of thyrotoxicosis, focusing on the pathophysiology of hyperthyroidism, and will discuss the management of pediatric Graves' disease and neonatal Graves' disease.

Etiology and Pathophysiology

Hyperthyroidism is an uncommon but serious condition in the pediatric population. The most common cause of hyperthyroidism in children and adolescents is Graves' disease (Table 42.1). While relatively rare in children, accounting for 1–5% of all patients with Graves' disease, it accounts for roughly 95% of hyperthyroidism in the pediatric population [1]. Graves' disease may occur at any age during childhood but increases in frequency with age – especially in postpubertal children, where the incidence is higher in girls than boys.

Graves' disease is an autoimmune disorder in which the body produces thyroid-stimulating hormone (TSH) receptor antibodies that mimic the action of TSH by binding directly to the TSH receptor. This leads to increased thyroid gland vascularity, follicular hyperplasia, and excessive production and secretion of thyroid hormone. The TSH-receptor-stimulating antibodies can also lead to the development of Graves' ophthalmopathy secondary to local inflammation, edema, and muscle swelling [2]. The underlying trigger for Graves' remains unclear, but it is thought to result from a combination of genetic, environmental, and immune factors [3]. Graves' disease is more common in children with other autoimmune conditions and/or family history of autoimmune diseases.

In newborns, the most common cause of hyperthyroidism is neonatal Graves' disease. This condition occurs when maternal TSH-receptor-stimulating antibodies cross the placenta and stimulate the TSH receptors of the neonate, leading

Table 42.1 Causes of thyrotoxicosis

Etiology	Mechanism
Thyrotoxicosis with hyperthyroidism (increased thyroid hormone production)	
Graves' disease	TSH-receptor stimulating antibodies
Neonatal Graves' disease	Maternal TSH-receptor-stimulating antibodies
Functioning adenoma/toxic multinodular goiter	Focus of functional autonomy
McCune–Albright syndrome	*GNAS* gene mutation
TSH-receptor-activating mutation	Activating mutation in TSHR
TSH-secreting pituitary adenoma	Pituitary adenoma
Thyrotoxicosis without hyperthyroidism (release of preformed thyroid hormone)	
Chronic lymphocytic thyroiditis ("Hashitoxicosis")	Thyrotoxic phase of autoimmune process
DeQuervain's thyroiditis (subacute)	Viral
Infectious (acute or chronic)	Bacterial or fungal
Silent thyroiditis	Painless
Drug effects	Drug-induced thyroiditis (amiodarone, lithium, iodine, interferon)
Mechanical insult	Follicle damage from manipulation
Extrathyroidal exposure	Excess exogenous thyroid hormone

Abbreviations: *TSH* thyroid-stimulating hormone, *TSHR* thyroid-stimulating hormone receptor

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to transient neonatal hyperthyroidism. It affects approximately 2% of infants whose mothers have Graves' disease during pregnancy (about 0.2% of all pregnancies), and although antibodies are most prevalent in mothers with active Graves' disease treated with an antithyroid drug, they can also be present in mothers who have been treated for Graves' disease in the past with definitive therapy (i.e., surgery or radioactive iodine) [4]. It is therefore immensely important to obtain a thorough maternal medical history to clarify the underlying etiology of any possible thyroid disease prior to and during pregnancy.

Additional causes of hyperthyroidism include an autonomously functioning thyroid nodule ("hot" nodule) or multiple nodules (i.e., toxic multinodular goiter); while these etiologies are more common in the adult population, they are occasionally detected by a physical examination in children as well [5]. Less-common etiologies include McCune–Albright syndrome, which is caused by a somatic mutation of the *GNAS* gene and leads to constitutive activation of affected G-protein coupled receptors. Clinically, it is characterized by a classic triad of café-au-lait macules (with irregular boarders often compared to the "coast of Maine"), skeletal findings secondary to fibrous dysplasia, and peripheral precocious puberty (present in about 85% of cases). Not all elements of the triad may be present, however, and other endocrinopathies can occur, of which hyperthyroidism is the second most common after precocious puberty [6]. Rarely, isolated activating mutations in the TSH receptor gene can lead to familial non-autoimmune hyperthyroidism. Causes of hyperthyroidism associated with elevated TSH levels (i.e., from a brain tumor in pituitary gland making too much TSH, or pituitary resistance to thyroid hormone) are incredibly rare in the pediatric population.

Transient thyrotoxicosis (without hyperthyroidism) may result from the inflammation and subsequent destruction of thyroid follicular cells, perhaps secondary to an autoimmune process, infection, or medication, and leads to excess thyroid hormone leaking into the bloodstream. These symptoms usually resolve in about 2 months, as this is the approximate amount of thyroid hormone reserve that is maintained in the thyroid gland, though the hyperthyroid phase can be of variable duration in children [7]. Ingestion of exogenous thyroid hormone may also result in transient thyrotoxicosis, so it is important to obtain a history of possible exposure to prescription medication or thyroid supplements.

Diagnosis

The clinical signs and symptoms of thyrotoxicosis include stare/lid retraction and lid lag secondary to sympathetic hyperactivity, warm/moist skin, tachycardia, and widened pulse pressures with hyperdynamic precordium, tremor, and hyperreflexia. Children can present with growth changes and weight loss, although it is important to note that many have increased appetite which can cause unchanged or even increased weight [8]. Patients with Graves' disease may present with exophthalmos secondary to antibody stimulation causing inflammation, edema, and muscle swelling behind the eye.

Close examination of the thyroid gland may help in differentiating causes of thyrotoxicosis. In Graves' disease, the thyroid tends to be enlarged (minimally to maximally) and smooth with a spongy texture, and a bruit may be audible over the gland. Patients with a toxic nodule or multinodular goiter will present with palpable nodules. Patients with thyroiditis may have no to modest thyroid gland enlargement and, depending on the etiology, may or may not have pain with palpation.

In cases of primary hyperthyroidism, serum TSH levels are low or suppressed as a result of negative feedback of thyroid hormone levels on the anterior pituitary. Concurrent elevated serum-free T4 and/or total T3 levels help determine the degree of biochemical hyperthyroidism. Overt hyperthyroidism is characterized by low TSH concentrations with raised thyroid hormone concentrations (T4, T3, or both), whereas subclinical hyperthyroidism is characterized by low serum TSH with normal thyroid hormone levels. The ratio of total T3 to total T4 can also help determine the etiology, as a hyperactive thyroid gland produces more T3 than T4, whereas T4 is elevated more than T3 in thyrotoxicosis caused by thyroiditis [9].

Antibody studies further help clarify the underlying etiology of the hyperthyroidism (Table 42.2). TSH receptor antibodies (TRAbs) can be measured by competition assays or bioassays and are important in the diagnosis of Graves' disease. TRAbs measured by competition assay, also known as TSH-biding inhibitory immunoglobulin (or TBII) assays, detect all autoantibodies that compete for the TSH receptor (blocking and stimulating). Bioassays for thyroid-stimulating immunoglobulins (TSI) measure antibody activity that stimulates the TSH receptor. Newer antibody assays (both TBII and TSI) have very good sensitivity and specificity for Graves' disease [10]. Other thyroid autoantibodies, including thyroid peroxidase antibody or thyroglobulin antibody, can help in the diagnosis of autoimmune thyroiditis, though they may also be present in up to 10% of patients with Graves' disease [3].

Additional lab findings that may be present in a thyrotoxic state include abnormal cholesterol levels (low total, LDL, HDL); anemia and leukopenia; high alkaline phosphatase (suggesting increased bone turnover); mild elevation in liver function tests; and elevated glucose.

Importantly, some lab patterns may appear initially concerning for thyrotoxicosis, but are not secondary to hyperthyroidism (see also Chap. 25). These include binding protein abnormalities (i.e., in pregnancy or inherited forms like thyroxine-binding globulin (TBG) deficiency), or

Table 42.2 Diagnosis of hyperthyroidism

Diagnosis	Specific labs	TSH	Free T4	RAI/Tc99 uptake	Physical exam findings
Thyrotoxicosis with hyperthyroidism (increased thyroid hormone production)					
Graves' disease or neonatal Graves' disease	+TRAb (TBII/TSI)	↓	↑	Uniform ↑	Diffusely enlarged gland +/− eye findings
Functioning adenoma/toxic multinodular goiter		↓	↑	Focal or multifocal ↑	Palpable nodule(s)
McCune–Albright syndrome		↓	↑	↑	Variable thyroid; café au lait macules, fibrous dysplasia
TSH-receptor-activating mutation		↓	↑	↑	Normal thyroid or mildly enlarged
TSH-secreting pituitary adenoma		↑ or normal	↑	↑	Normal thyroid
Thyrotoxicosis without hyperthyroidism (release of preformed thyroid hormone)					
Autoimmune/chronic lymphocytic thyroiditis "Hashitoxicosis"	+TPO and/or thyroglobulin antibody	↓	↑	↓	Firm goiter
DeQuervain's thyroiditis (subacute) or infectious (acute or chronic)		↓	↑	↓	Painful to palpation
Silent thyroiditis	Occasional +TPO antibody	↓	↑	↓	Painless
Drug effects or mechanical insult		↓	↑	↓	Normal thyroid
Extrathyroidal exposure	Low thyroglobulin	↓	↑	↓	Normal thyroid

Abbreviations: *RAI* radioactive iodine, *Tc99* technetium, *TBII* TSH binding inhibitory immunoglobulin, *TPO* thyroid peroxidase, *TRAb* TSH receptor antibody, *TSI* thyroid-stimulating immunoglobulins

laboratory assay interference from heterophile antibodies or medications (most notably high-dose biotin, which is found in hair, skin, and nail supplements). TSH levels can also be low in the setting of critical illness (i.e., non-thyroidal illness or sick euthyroid) from a compensatory decrease in the hypothalamic–pituitary–thyroid axis, with concurrent normal or low thyroid hormone levels. It is vital to recognize the underlying clinical context in these scenarios, and if there is ever any question of the underlying etiology behind an abnormal lab pattern, discussion and review with a pediatric endocrinologist is appropriate.

If there remains any doubt about the causes of thyrotoxicosis, the use of thyroid scintigraphy may be helpful (see Chap. 38). Increased uptake in the setting of a suppressed TSH suggests increased thyroid hormone production. Additional isotope imaging is useful to differentiate between diffuse uptake as seen in Graves' disease versus focal uptake in the setting of one (or multiple) toxic adenomas. Low uptake is typically consistent with thyroiditis, as the thyrotoxicosis is secondary to the passive release of preformed thyroid hormone.

Initial Management of Hyperthyroidism

The initial approach to treating a child with hyperthyroidism consists of symptom control and measures aimed at decreasing thyroid hormone synthesis.

Symptom Control

Many of the systemic clinical features of hyperthyroidism (including tachycardia, hypertension, palpitations, and tremor) are secondary to the beta-adrenergic effects of catecholamines [11]. Accordingly, beta-blockers are effective in managing the symptoms present in a hyperthyroid state (including tachycardia and hypertension), especially because antithyroid medications may take several weeks to normalize thyroid hormone values. Assuming there are no contraindications to its use, a beta-blocker should be started in patients with thyrotoxicosis and symptoms of adrenergic overactivity as soon as the diagnosis is made. Atenolol can be administered once daily, and given its cardioselectivity, it is preferred in children with reactive airway disease; typical dosing ranges from 0.5 to 2 mg/kg/day. Propranolol can also be considered, as it has the potential benefit of decreasing T4 to T3 conversion; typical dosing ranges from 0.5 to 2 mg/kg/day divided three or four times daily.

Clinical Key:
For patients with newly diagnosed thyrotoxicosis who have hypertension and/or tachycardia, treatment with a beta-blocker can be initiated in the primary care setting and does not interfere with further diagnostic testing.

Decrease Thyroid Hormone Synthesis

For patients diagnosed with Graves' disease, there are three treatment options: medical therapy (i.e., antithyroid drugs or thionamides), radioactive iodine therapy, or surgery. All three options present distinct advantages and disadvantages, and the optimal approach depends on patient preference and clinical factors. However, most endocrinologists prefer a trial of antithyroid drugs as first-line therapy in pediatric patients.

Medical Therapy with Antithyroid Drugs

Thionamides inhibit thyroid peroxidase (TPO) oxidization of iodide (I-) to iodine (I2). In the United States and Canada, only methimazole (MMI, or Tapazole) is approved for the treatment of children and adolescents, as there is a black box warning for propylthiouracil (PTU) due to reports of fulminant hepatic necrosis and liver failure [12]. Starting doses of methimazole, depending on the level of severity of the hyperthyroidism, range from 0.25 to 1.0 mg/kg/day (maximal dose typically does not exceed 40 mg/day). It is available as 5 and 10 mg tablets. While administered doses are sometimes divided twice daily, there is improved compliance with daily dosing in adults [10]. Thyroid function tests should be followed closely (i.e., every 4 weeks at first), as dose reductions are often required as thyroid hormone values normalize to maintain a euthyroid state – though, importantly, TSH normalization may lag behind the normalization of circulating thyroid hormone by weeks/months [13].

Prior to initiation of antithyroid drug therapy, all adverse effects should be discussed at length with patients and their families and documented in the medical record. Minor side effects of methimazole include skin reactions (i.e., urticarial/macular rashes), arthralgias, and gastrointestinal complaints including reflux and nausea. These typically begin within the first few weeks of starting therapy and are usually dose-related. Mild rashes may resolve with continued therapy or with antihistamines but can be severe enough to require drug discontinuation.

Major side effects are rare but can be significant [14]. Agranulocytosis (i.e., absolute neutrophil count of <500/mm^3) can occur in 0.1–0.5% of patients, is dose-related to MMI, and, while it tends to present within the first 90 days of treatment, can reoccur upon re-exposure. A typical clinical presentation is fever with severe pharyngitis. All patients should be advised to seek medical attention if these symptoms develop and to have a complete blood count with differential checked in the setting of a fever. Hepatotoxicity, while more common with PTU (causing hepatocellular injury including fulminant hepatic failure), can also be seen with patients on MMI (more often cholestatic in nature). The overall frequency of hepatic dysfunction ranges from 0.1% to 0.2%, and usually occurs within the first few days to months of drug initiation with transaminase levels rising to over five times the normal limits. Importantly, as both leukopenia and transaminitis can be manifestations of Graves' disease, clinicians often obtain baseline white blood cell counts with an absolute neutrophil count, and liver function tests prior to starting therapy; however, monitoring labs throughout the disease process is more controversial. An ANCA vasculitis presenting as polyarthritis, renal dysfunction, and/or vasculitic rash can also be seen with medical treatment, more frequently after months to years of therapy, and again more commonly with PTU than MMI. Prompt drug discontinuation is of utmost importance if a patient presents with any major side effect, followed by a discussion with a pediatric endocrinologist about other treatment options. Lastly, adolescent females should be counseled about the risks of birth defects reported with antithyroid drug use during the first trimester of pregnancy, which include cutis aplasia, congenital heart defects, and omphalocele [15].

Newborns presenting with significant biochemical hyperthyroidism and/or clinical symptoms of neonatal Graves' disease may similarly require treatment with methimazole and/or beta-blockade to avoid complications. Potassium iodide therapy may also be used in conjunction with MMI in severe or refractory neonatal Graves'. Complications of neonatal Graves' include cardiac failure more acutely, and craniosynostosis and intellectual impairment in the long term. Because this is a transient process that usually resolves 1–3 months after birth, very close follow-up with a pediatric endocrinologist is encouraged. Typical starting doses of methimazole are 0.2–0.5 mg/kg/day divided twice daily, estimating 0.625 mg twice daily (0.4 mg/kg/day for a 3 kg newborn) [16]. Notably, transient hypothyroidism may also occur from prolonged TSH suppression, and in some situations, infants may require a short course of levothyroxine supplementation until TSH concentrations normalize.

Clinical Key:
Monitoring asymptomatic neonates in the context of maternal Graves'

- Most infants of mothers with Graves' disease will not have neonatal hyperthyroidism; however, neonates born to mothers with positive or unknown maternal TRAb levels in the second or third trimester should be considered high risk.
- Newborn screen should be sent as usual. For high-risk neonates, TRAb levels should be sent as soon as possible after birth if assay is available. Additionally, TSH and free T4 should be sent to a clinical laboratory between 3 and 5 days of life.
- In infants who remain asymptomatic, it is generally recommended to check TSH and free T4 once more at approximately 2 weeks of life.
- Because of waning antibody titers, infants of mothers with Graves' who do not present within the first few weeks of life are not likely to subsequently develop neonatal Graves'. Nonetheless, infants who develop possible signs or symptoms of hyperthyroidism at any point during the first 3–6 months of life should have TSH and free T4 checked urgently.

Thyroid Storm

Thyroid storm is a life-threatening condition and serious complication of hyperthyroidism that may be precipitated by an acute event. It is exceedingly rare in the pediatric population but is critical to recognize. The diagnosis is based on biochemical evidence of hyperthyroidism with severe symptoms including fevers, altered mental status, cardiovascular dysfunction, and gastrointestinal manifestations [17]. If there is ever any clinical suspicion for thyroid storm, immediate referral to an emergency room is recommended, as supportive therapy may be required in an intensive care unit.

Chronic Management and Considerations for Referral

After normalization of thyroid hormone levels and stabilization of ATD doses, labs (i.e., TSH and FT4) should be monitored every 3–4 months. Continuing on antithyroid drugs allows for a chance for permanent remission; however, the appropriate length of treatment of ATDs for children with Graves' disease remains a topic of controversy. Pediatric Graves' disease is more persistent than adult disease with remission rates estimated to be only 20–30% after 2 years of treatment [10] and reported relapse rates vary from 3% to 47% based on different studies [3]. Predictors of remission include older age, lower thyroid hormone levels at the time of diagnosis, and more rapid achievement of euthyroid status [18].

While long-term therapy with antithyroid drugs is possible, some patients elect for permanent therapy with either radioactive iodine (RAI) or surgery. The goal of both treatments is to induce hypothyroidism, which is then chronically treated with levothyroxine. RAI therapy has few acute adverse effects, and local radiation safety recommendations should be followed. While there are no long-term concerns about future infertility or congenital anomalies, there remain questions about the risk for secondary malignancy. Historically, these concerns have been based on increased incidence of thyroid neoplasms seen in children after natural disasters; more recently, however, there have been additional questions raised about the increased risk for secondary malignancies after RAI treatment in adults [19]. Surgical therapy is preferred for younger children <5 years of age, in addition to patients with toxic adenomas or multinodular goiters who are thyrotoxic. For patients with Graves' disease, a total or near-total thyroidectomy is recommended, and referral to an experienced pediatric thyroid surgeon is most important to reduce the risk of complications, which include transient or permanent hypoparathyroidism and vocal cord paralysis. Additional discussion about these definitive therapies, and the risks and benefits of each, should take place with a pediatric endocrinologist.

Conclusion

The clinical features of hyperthyroidism are important to recognize in children. The underlying etiology can be further clarified with an astute physical examination and the help of biochemical and antibody testing. Initial management of thyrotoxicosis consists of symptom control with beta-blockers, and for pediatric patients with Graves', medical treatments aimed at decreasing thyroid hormone synthesis. Definitive therapy should be reviewed with families as treatment options, with referral to an experienced pediatric endocrinologist for more in-depth discussions.

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