Advances in Pediatrics 69 (2022) 219–229
ADVANCES IN PEDIATRICS

# Update on Pediatric Hyperthyroidism

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**Keywords**

• Hyperthyroidism in children • Graves' disease • Neonatal hyperthyroidism

**Key points**

- Hyperthyroidism is diagnosed by elevated thyroid hormones (TH), Free T4 and total T3 and suppressed thyroid-stimulating hormone (TSH).
- Graves' disease (GD), an autoimmune disorder makes up 96% of pediatric hyperthyroidism.
- Hyperthyroidism is a hypermetabolic state with cardiovascular, GI, neurologic, dermatologic, and ocular symptoms. Symptoms can also be misleading and point to other systemic disorders and delay diagnosis.
- First line of treatment of GD in children is with methimazole (MMI) while radioactive iodine (RAI) treatment and thyroidectomy offer permanent treatment and render patient hypothyroid.
- Neonates born to mothers with current or past treatment of GD are at risk for neonatal hyperthyroidism (NH).

## AN UPDATE ON HYPERTHYROIDISM IN CHILDREN

Purpose of the review: This review is intended to highlight causes, enable early and accurate diagnosis and management of hyperthyroidism in children and neonates.

## INTRODUCTION

Hyperthyroidism is due to increased production of thyroid hormone (TH) as noted biochemically by elevated TH, Free T4 and T3, and suppressed thyroid-stimulating hormone (TSH). The most common cause of hyperthyroidism is GD which is an autoimmune disorder from TSH receptor stimulation by TSH receptor antibody (TRAb) and makes up for 96% of pediatric

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https://doi.org/10.1016/j.yapd.2022.04.004

hyperthyroidism [1]. GD is more common in females and may occur at any age during childhood, peaking during adolescence. A French population-based study [2] in 2015 identified a total of 670 cases of childhood hyperthyroidism for an annual incidence of 4.58/100,000 person-years showing the rarity of the diagnosis, with a 3.27 F/M ratio. Only 10% were less than 5 years of age. In a study from Sweden [3] incidence rate (IR) was higher from 2000 to 2009 versus 1990 to 1999 (2.8/100,000 vs 1.6/100,000 person-years, $P = .006$), suggesting that at least in some parts of the world the incidence of childhood hyperthyroidism is increasing. There is concern that increasing exposures to endocrine-disrupting chemicals may have caused the increase [2] Hyperthyroidism is a hypermetabolic state with cardiovascular, GI, neurologic, dermatologic and ocular symptoms [4]. Symptoms are gradual, and it may take months before families seek medical attention. Symptoms can also be misleading and point to other systemic disorders and delay diagnosis. It is important that pediatricians be aware of these diverse symptoms to facilitate early screening and referral to a pediatric endocrinologist for treatment.

## CLINICAL MANIFESTATIONS OF HYPERTHYROIDISM

Hyperthyroidism has a myriad of clinical manifestations affecting multiple systems. Cardiovascular effects are pronounced due to an increase in heart rate and cardiac output leading to hyperdynamic circulation and systolic hypertension. Unintentional weight loss is noted despite an increase in appetite. Growth is often accelerated in children while puberty can be delayed and menstrual irregularities such as oligomenorrhea and secondary amenorrhea may appear. Deterioration in school performance, inability to focus, anxiety, emotional lability, and jitteriness may be mistaken for ADHD or a behavioral disorder. Fine hand tremors, brisk deep tendon reflex, and tongue fasciculations are typical signs. Due to cutaneous vasodilation, skin is moist and warm, there is heat intolerance, and hair is fine and brittle. Pretibial myxedema, a very rare Thyroid dermopathy presents as nonpitting edema or plaque-like lesions on the pretibial region due to the accumulation of glycosaminoglycans in the dermis and is thought to be mediated by TSH receptor antibodies [5] Fatigue, proximal muscle weakness, osteopenia from an increase in bone resorption are all systemic effects of hyperthyroidism [4,6,7].

A diffuse goiter is seen in most forms of hyperthyroidism, but the absence of a goiter does not rule it out. A goiter is best observed by having the patient look up at the ceiling to stretch the skin of the neck. Thyroid enlargement can sometimes be quite large leading to tracheal compression and dyspnea. Palpable nodule should raise concern for a toxic nodule. Ophthalmopathy is seen only in Graves' disease (GD) and is due to inflammatory cell infiltration in the retroocular tissue and extra-ocular muscles. TSH receptors are expressed by orbital adipose cells and fibroblasts. Elevated TSH receptor antibodies in GD not only stimulate thyroid growth and increase TH synthesis but also stimulate the secretion of glycosaminoglycan by orbital adipose cells and fibroblasts leading to proptosis seen in Graves' ophthalmopathy GO [8]. In a study from

2014, 39/80 patients with GD had GO with 81% being females [9]. In another study from i2008, 17 of the 152 children with GD were referred to ophthalmology with most noted to have only mild findings [10] Hyperthyroid symptoms and signs are further elaborated in Table 1.

## DIFFERENTIAL DIAGNOSIS OF HYPERTHYROIDISM AND ITS KEY FEATURES

Aside from GD, other less common causes are autonomous toxic nodule overproducing THs, Hashitoxicosis which is a transient phase of increase in the release of THs, subacute viral thyroiditis, acute suppurative thyroiditis, McCune-Albright syndrome (MAS) as well as germline and somatic gain-of-function mutations of the TSH receptor gene, drug-induced thyrotoxicosis, pituitary TH resistance, rarely from TSH secreting pituitary adenoma, external head and neck radiation and anticancer treatment [1,4,6,7]. This is further illustrated in Table 2.

## LABORATORY DIAGNOSIS OF HYPERTHYROIDISM

All patients suspected of having hyperthyroidism should have TSH, Free T4, and total T3 tested. In hyperthyroidism, TSH is very low, typically less than 0.01 mIU/mL, and Free T4 and T3 are elevated. As GD is the most common cause of pediatric hyperthyroidism, all patients must either have thyroid-stimulating immunoglobulin (TSI) or TRAb tested. TRAb has a faster turnaround time than TSI but cannot differentiate from stimulatory versus blocking antibodies and either test is acceptable. An elevated TSI/TRAb in the setting of elevated THs confirms GD. If the TSI/TRAb are negative, thyroid peroxidase (TPO) and antithyroglobulin antibody should be tested. If they are elevated, suspect Hashitoxicosis especially if hyperthyroidism is mild. Thyroid sonogram and I-123 thyroid uptake scans are reserved for the few cases with antibody-negative hyperthyroidism or if a thyroid nodule is suspected.

## MANAGEMENT OF GRAVES' DISEASE

Antithyroid drug (ATD), radioactive iodine (RAI), and thyroidectomy are available treatment options for GD in children [11,12]. ATD is the preferred initial treatment with the hope that remission is achieved in a few years with the restoration of euthyroid state. Methimazole (MMI) is the drug of choice, and it inhibits the organification and coupling of iodothyronines and lowers TH synthesis. Propylthiouracil (PTU) is no longer used due to frequent side effects and severe hepatotoxicity, and it carries a US Food and Drug Administration (FDA) boxed warning against its use in children [13]. Atenolol, a cardioselective beta-blocker or propranolol can be added as an adjunct for a few weeks to offer symptomatic relief from palpitations and tremors. Propranolol has the advantage of decreasing T4 to T3 conversion but must be dosed 3 to 4 times a day.

Baseline CBC, AST, and ALT are drawn before starting MMI. Mild abnormalities can be seen in the setting of hyperthyroidism and do not exclude MMI

**Table 1**
Hyperthyroid symptoms and signs

| | |
|---|---|
| Thyroid | Generally diffusely enlarged, bruit over the thyroid |
| Cardiovascular | Palpitations, dyspnea, systolic hypertension, wide pulse pressure, bounding pulses, carotid bruit |
| Gastrointestinal | Increase in bowel movements and weight loss |
| Neurologic | Jitteriness, restlessness, anxiety, insomnia, decline in school performance, brisk DTR, tremors, and tongue fasciculations |
| Ocular (Graves' ophthalmopathy) | Tearing, grittiness, photophobia, conjunctival redness, wide-eyed stare, lid lag, proptosis, exophthalmos |
| Muscle | Proximal muscle weakness, fatigue |
| Dermatologic | Heat intolerance, hair loss, friable nails, warm moist skin, rarely pretibial myxedema |

treatment. While there is no evidence that neutropenia or liver disease increases the risk of complications from ATDs, the ATA task force recommends reconsidering initiating ATD if the baseline neutrophil count is $< 1000$ or if there is a 5-fold elevation of transaminases [12]. While less common or severe compared with PTU, idiosyncratic neutropenia and hepatitis has been reported with MMI. While on therapy, if a patient develops fever or pharyngitis, a CBC should be drawn and MMI stopped if there is agranulocytosis. If there is jaundice or clinical evidence of liver disease, AST and ALT are measured [12]. Urticaria, myalgia, and arthralgia are other known side effects of MMI.

Unlike adults, remission rates after 2 years of treatment are low, 30% versus 50% in adults, and risk of relapse after stopping therapy is high. There are emerging data over the last 10 years that suggest an increased likelihood of remission with prolonged ATD therapy [14–18]. Remission rates can be increased to 50% after 8 years of treatment and seem to plateau thereafter. It is speculated that the euthyroid state created by ATD treatment and perhaps direct immunosuppressive effect on humoral and cellular immunity may help induce remission [18]. It is also possible that long-term ATD has minimal effect in inducing remission and the remission achieved reflects natural disease progression in these patients. In any case, long-term MMI treatment is proven to be safe without any additional adverse effects noted on prolonged treatment and should be considered in patients with good compliance who can be maintained on a modest dose of MMI.

RAI and thyroidectomy offer permanent treatment of hyperthyroidism with the aim of inducing permanent hypothyroidism. It is felt that hypothyroidism is relatively easier to manage, L-thyroxine therapy for hypothyroidism has no side effects, and the course is predictable compared with hyperthyroidism from autoimmunity. Permanent treatment is considered in well-controlled patients who fail to achieve remission after long-term ATD of 6 to 8 years, are poorly compliant with ATD, have adverse effects from ATD, or are poorly controlled with ATD and remain symptomatic. The choice of RAI versus thyroidectomy depends on several factors and is a joint decision between the

treating endocrinologist and the patient/family and are elaborated in detail in Box 1 under considerations for the management of GD.

## MANAGEMENT OF OTHER FORMS OF HYPERTHYROIDISM

In Hashitoxicosis, hyperthyroidism is self-limiting and can be monitored if there are no significant symptoms or treated briefly with beta-blockers or MMI for symptomatic relief. Toxic thyroid nodules are treated with surgery. Hyperthyroidism from subacute thyroiditis is self-limiting as well and managed with supportive care and anti-inflammatory medications such as NSAID. Suppurative thyroiditis is treated with antibiotics and if it fails to respond to antibiotics, then with surgery. TSH receptor mutations and hyperthyroidism from MAS can be treated with MMI but will not remit and eventually will need total thyroidectomy. A heightened awareness of medications such as amiodarone, lithium, and immune check point inhibitors used in oncology patients, and even rarely external head and neck radiation inducing hyperthyroidism and screening with thyroid levels is important for effective early management of medication or radiation-induced thyroiditis which for the most part are self-limiting or reversible when the medications are stopped.

## THYROID STORM

Thyroid storm is a very rare life-threatening illness in children. There is no specific laboratory or clinical abnormality that is diagnostic of thyroid storm, instead the diagnosis considers several clinical features using a scoring system. The degree of hyperthyroidism is not more severe than in patients without thyroid storm but increased sensitivity to TH and abrupt availability is thought to cause the thyroid storm. There is often a precipitating event, such as acute infection, trauma, surgical procedure, stopping ATD, or very rarely after RAI.

Although there is no pediatric scoring system, the adult clinical scoring system developed by Burch and Wartofsky is widely adopted [19]. Hyperpyrexia, mental status changes, cardiovascular decompensation, GI-hepatic dysfunction, and any precipitant history are scored. A total score greater than 45 is highly suggestive of thyroid storm, 35 to 45 supportive of diagnosis, and less than 25 thyroid storm unlikely. Pediatricians should consider thyroid storm in the differential diagnosis when a patient exhibits both CNS and GI symptoms and clinical signs of hyperthyroidism. Patients who meet the diagnostic criteria of a thyroid storm are best managed in a PICU setting and treated with beta-blockers, ATD, glucocorticoids, inorganic Iodine solutions such as SSKI which rapidly decreases TH synthesis, and supportive care.

## PREDICTORS AND MANAGEMENT OF NEONATAL HYPERTHYROIDISM

It is estimated that 2% of children born to mothers with active or past GD develop transient neonatal hyperthyroidism (NH). This is due to the transplacental transfer of TSH receptor antibodies (TRAb) [20]. Elevated TRAb can persist for several years after ablation with a risk of 5.5% in the first 2 years

**Table 2**
Etiology of hyperthyroidism, pathogenesis and diagnostic features

| Etiology | Pathogenesis | Key features | Diagnosis |
|---|---|---|---|
| Graves' disease | Autoimmune disorder due to TSH receptor antibodies stimulating thyroid hormone synthesis and thyroid enlargement | Symptomatic hyperthyroidism, Goiter, GO | TSH ↓<br>Free T4 and T3↑<br>TSI/TRAB ↑<br>Diffuse ↑ in thyroid uptake scan |
| Hashitoxicosis | Transient increase in thyroid hormone release in the setting of autoimmune thyroiditis | Asymptomatic or mildly symptomatic, Goiter, no GO, may progress t o hypothyroidism or revert to euthyroid state | TSH ↓<br>Free T4 and T3 mild ↑or Nl<br>TSI/TRAB negative<br>TPO/Anti-TG Ab ↑<br>↓ uptake on thyroid scan |
| Toxic nodule | Autonomous hypersecretion | Asymptomatic or mildly symptomatic, +'/- palpable thyroid nodule depends on size, no GO | TSH ↓<br>Free T4 and T3 mild ↑ or Nl<br>TSI/TRAB/TPO/ AntiTG Ab Nl<br>Thyroid nodule on sonogram<br>Focal ↑uptake on thyroid scan |
| Subacute thyroiditis | Viral/postviral inflammation | Tender goiter, Transient hyperthyroidism (few weeks) sometimes followed by hypothyroidism before normalizing. | TSH ↓, ESR ↑<br>Free T4 and T3 Nl mild ↑ or Nl<br>TSI/TRAB/TPO/Anti TG Ab Nl<br>↓uptake on thyroid scan |
| Acute suppurative thyroiditis | Bacterial infection | Fever, toxic looking, tender thyroid | Mostly euthyroid but rarely can be hyperthyroid. Sonogram shows abscess |
| McCune Albright Syndrome | Activating the mutation of the gene for the Gs protein | Precocious puberty, fibrous dysplasia, café au lait macules | TSH ↓<br>Free T4 and T3↑<br>TSI/TRAB Nl<br>Diffuse ↑ in thyroid |

(*continued on next page*)

**Table 2 (*continued*)**

| Etiology | Pathogenesis | Key features | Diagnosis |
|---|---|---|---|
| | | Goiter often multinodular<br>Persistent hyperthyroidism | uptake scan<br>Sonogram heterogenic gland with multinodularity |
| TSH receptor activating mutation | Autosomal dominant inheritance | Goiter, can be multinodular, permanent hyperthyroidism | TSH ↓<br>Free T4 and T3↑<br>TSI/TRAB negative<br>↑ in thyroid uptake scan |
| Drug-induced thyroiditis | Amiodarone induced HT type 1 from ↑ production and type 2 due to destructive thyroiditis<br>Lithium ↑ release of TH<br>Immune check point inhibitors cause destructive thyroiditis | Usually, no goiter and often transient | TSH ↓<br>Free T4 and T3↑<br>Thyroid antibodies often negative<br>Diffuse ↑ in thyroid uptake scan in Amiodarone induced type 1 HT |
| Thyrotoxicosis factitia | Thyroid hormone ingestion | No goiter | TSH ↓<br>Free T4 ↑<br>Thyroglobulin ↓ |

*Abbreviations:* AntiTG, Ab; Antithyroglobulin, antibody; GO, Graves' ophthalmopathy; HT, Hyperthyroidism; Nl, normal; TPO, Thyroid peroxidase antibody; TRAb, TSH receptor antibody; TSI, thyroid-stimulating Immunoglobulin.

after RAI [20]. Early diagnosis and treatment of the fetus and neonates is the key to preventing significant adverse effects in the form of premature births, IUGR, microcephaly, cardiac arrhythmias, and failure [20]. Clinical manifestations of neonatal thyrotoxicosis include irritability, 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, and in severe cases congestive heart failure. NH typically resolves in 3 to 12 weeks [4].

Maternal TRAb levels greater than 500% of normal values in French study [21] and levels greater than 5.9 IU/L (n:<2IU/L) in another study [22] predicted NH and negative maternal TRAb is associated with no risk for NH underscoring the importance of maternal TRAb measurement and cut off values requiring close monitoring of fetus and neonates. When maternal TRAb is elevated, fetal thyroid ultrasound, fetal bone maturation, and fetal heart rate (greater than 160/min) can all be used to determine fetal

**Box 1: Considerations for the management of GD**

ATD is the first line of treatment

- Methimazole 0.25–1 mg/kg/d divided twice a day, first-line therapy
- Atenolol 1 to 2 mg/kg/d daily or Propranolol 0.5 to 2 mg/kg/d in 3 to 4 divided doses for a few weeks
- Thyroid function tests (free T4, total T3, TSH) are obtained at 2 to 6 weeks, the dose is adjusted if indicated, and again at 4 to 6 weeks, and then every 2 to 3 months once the dose is stabilized.
- Can be continued for up to-8 years if tolerated to increase the chance of remission
- Side effects: Urticaria, Idiosyncratic neutropenia, hepatoxicity less common

Permanent treatment with RAI with I-131

- Indication: Failure to achieve remission after prolonged ATD, side effect, poor compliance, poor control
- Contraindicated in thyroid nodule or severe GO
- Offered for children greater than 10 years of age
- Outpatient procedure
- Stop methimazole 5 days before RAI
- Posttreatment isolation for a week
- About 2 months to achieve hypothyroidism
- Persistent hyperthyroidism a year after RAI denotes treatment failure and need for repeat RAI therapy

Permanent treatment with thyroidectomy

- Indication: Failure to achieve remission after prolonged ATD, side effect, poor compliance, poor control
- Offered if there is thyroid nodule, very enlarged thyroid gland, compressive symptoms, severe GO
- Offered for Children less than 10 years of age
- Pretreatment with MMI, beta-blockers to achieve euthyroid state
- SSKI ( Potassium Iodide) for 7 days before surgery
- Low complication rate in high volume centers
- Permanent hypoparathyroidism in some studies reported up to 10%
- Permanent neck scar Next line please add Immediate hypothyroidism

hyperthyroidism and the need for treatment. Fetal hyperthyroidism can be treated by administering ATDs to the mother.

Neonates at risk for NH come to medical attention at different stages and while knowing the maternal TRAb status is ideal, there are occasions when the status is not known. A 2016 review by Van der Kay and colleagues [23] gives excellent insight to the approach and management of NH when maternal TRAb levels are known and unknown. Measurement of cord or neonatal

TRAb, TSH, and Free T4 in the neonates offers additional understanding toward the risk for NH.

## A SIMPLIFIED GUIDE AND INTERPRETATION ARE AS FOLLOWS

1. If maternal TRAb is unknown or positive, the neonate is considered at high risk. Check cord/neonatal TRAb. If negative, no risk for NH
2. If maternal TRAb/cord TRAb/neonatal TRAb is unknown or maternal/cord/neonatal TRAb is positive, check TSH and free T4 on days 3 to 5 of life, day 10 to 14 of life and clinical follow-up with PCP until 2 to 3 months of age. Check thyroid levels immediately at any point if neonate is symptomatic
3. If NH diagnosed at any point in time, MMI is the treatment of choice; β-blockers can be added for sympathetic hyperactivity. In refractory cases, potassium iodide may be used in conjunction with MMI

Continuation of breastfeeding is safe and should be encouraged in hyperthyroid mothers taking ATDs. Experts currently recommend using low-to-moderate MMI doses as a first-line therapy in lactating mothers. MMI dose of less than 20 mg per day, or a PTU dose of less than 300 mg per day has no adverse effects. ATD should be administered in divided doses immediately following each feeding [24,25].

## SUMMARY

Hyperthyroidism leads to cardiovascular, neurologic and GI symptoms which can be misleading and point to other systemic disorders or referral to other specialists and therefore being aware of the different symptoms and early screening will facilitate prompt treatment. Hyperthyroidism is diagnosed based on suppressed TSH, elevated Free T4 and T3. TSI is elevated in GD which is an autoimmune disorder. Thyroid sonogram and I-123 thyroid uptake scan can be reserved for rare instances when a thyroid nodule is suspected. GD constitutes 96% of pediatric hyperthyroidism and is managed initially with MMI. Remission of GD in children is low at about 30% after 2 years of ATD treatment and can be improved to 50% or more after 8 years of treatment with no increase in adverse effects. Therefore, in children with good control on modest dose of MMI, long-term treatment should be offered.

RAI with I-131 offers definitive treatment and results in permanent hypothyroidism. Thyroidectomy should be offered as a definitive treatment of younger patients less than 10 years of age and those with persistently poor control and is sometimes preferred over RAI and carries the low risk of complications if conducted by high-volume surgeons.

Thyroid storm is a rare life-threatening condition and should be suspected in the presence of overwhelming cardiovascular decompensation, altered mental status, hyperpyrexia, and GI decompensation. Pediatricians and emergency medicine providers must be aware of this presentation. Neonates born to mothers with active or past GD are at risk for transient NH.

## CLINICS CARE POINTS

1. Hyperthyroidism is due to increased production of thyroid hormone (TH) as noted biochemically by elevated THs, Free T4, and total T3 and suppressed thyroid-stimulating hormone (TSH). The most common cause of hyperthyroidism is GD which is an autoimmune disorder from TSH receptor stimulation by TSH receptor antibody (TRAb) and makes up for 96% of pediatric hyperthyroidism [1].
2. Hyperthyroidism is a hypermetabolic state resulting in unintentional weight loss and has cardiovascular, GI, neurologic, dermatologic, and ocular symptoms. Symptoms can be misleading and point to other systemic disorders and delay diagnosis. Pediatricians should be aware of these symptoms and signs to make an early diagnosis and referral to a pediatric endocrinologist.
3. All patients suspected to have hyperthyroidism should have thyroid-stimulating hormone (TSH), Free T4, and total T3 tested. In hyperthyroidism, TSH is very low and typically less than 0.01 mIU/mL and Free T4 and T3 are elevated. As GD is the most common cause of pediatric hyperthyroidism, all patients must either have thyroid-stimulating immunoglobulin (TSI) or TRAb tested [12]. Thyroid sonogram and I-123 thyroid uptake scans are reserved for the few cases with antibody-negative hyperthyroidism or if a thyroid nodule is suspected.
4. Methimazole (MMI) is the first line of therapy for pediatric Graves' disease (GD) [12]. Propylthiouracil (PTU) should not be used in children and carries an FDA boxed warning against its use due to hepatotoxicity (12). Long-term MMI use for up to 8 years increased the chance of remission in children. Radioactive iodine (RAI) and Thyroidectomy offer permanent treatment resulting in hypothyroidism.
5. Thyroid storm is a rare life-threatening condition resulting in hyperpyrexia, altered mental status, cardiovascular and GI decompensation and needs immediate care in an ICU setting and treated with MMI, beta-blockers, SSKI, glucocorticoids, and supportive care [19]. Pediatricians should be aware of this presentation.
6. Neonates born to mothers with active or past GD develop transient neonatal hyperthyroidism (NH), which typically self resolves in 2 to 3 months. This is due to the transplacental transfer of TSH receptor antibodies (TRAb) [20]. A robust screening of maternal TRAb and if unavailable, cord or neonatal TRAB and screening TSH and Free T4 in neonate [23] can result in proper identification and treatment of children with NH.

### Disclosure

The authors have nothing to disclose.

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