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Review Article

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HYPERTHYROIDISM IN INFANTS AND CHILDREN

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A. ETIOLOGY

In infants, hyperthyroidism is rare but potentially life-threatening. It develops in fetuses of women with current or prior Graves disease. In Graves disease, maternal autoantibodies against the thyroid receptor for thyroid-stimulating hormone (TSH) overstimulate thyroid hormone production by binding to TSH receptors in the thyroid gland. These antibodies cross the placenta and cause thyroid hyperfunction in the fetus (intrauterine Graves disease), which can result in fetal death or preterm birth due to fetal hyperactivity or tachycardia. Because infants clear the antibodies after birth, neonatal Graves disease is usually transient. However, because the clearance rate varies, duration of neonatal Graves disease varies.

In children and adolescents, Graves disease is the cause of hyperthyroidism in > 90% of cases. There is an increased incidence of Graves disease during puberty, with 80% of cases occurring after 11 years of age. The primary mechanism is stimulating antibodies for the TSH receptor. Other antibodies block the TSH receptor, and the balance between stimulating and blocking determines the severity of Graves disease. Many children with Graves disease have a family history of autoimmune thyroid disease or other autoimmune conditions. Children with trisomy 21 are at increased risk of Graves disease.

Less common causes of hyperthyroidism in children and adolescents include autonomously functioning toxic nodules, transient hyperthyroidism during the early phase of Hashimoto thyroiditis followed by eventual hypothyroidism (hashitoxicosis), or adverse drug effects (eg, amiodarone-induced hyperthyroidism). Occasionally, transient hyperthyroidism can be caused by infections, including bacterial (acute thyroiditis) and viral (subacute thyroiditis) infections; bacterial causes include *Staphylococcus aureus*, *S. epidermis*, *Streptococcus pyogenes*, *S. pneumoniae*, *Escherichia coli*, and *Clostridium septicum*. Predisposing factors for acute thyroiditis in children include congenital anomalies (eg, persistent pyriform sinus fistula) and immunocompromised status.

A. INCIDENCE

It is a rare disease in children, accounting for 1 to 5% of all patients with it. In adults, this disease affects approximately 2% of women and 0.2% of men. In both adults and children, it is much more frequent in female than in male subjects. It may occur at any age during childhood, but it increases in frequency with age, peaking during adolescence. The incidence is thought to be rising and is about 0.1 per 100 000 person-years in young children to 3 per 100 000 person-years in adolescents. A frequency of up to 14 per 100 000 patient-years has been reported in Hong-Kong, with no relationship to differences in iodine nutritional status. It is more frequent in children with other autoimmune conditions and in children with a familial history of autoimmune thyroid disease.

B. TYPES OF HYPERTHYROIDISM

Increased Hormone Production				Increased Hormone Release/Ingestion		
Graves' Disease	Toxic Multinodular Goiter	Toxic Adenoma		Subacute Thyroiditis	Iodine Excess (e.g., amiodarone)	Factitious Hyperthyroidism
Diffusely Enlarged, Nontender	Multiple Nodules	Single Nodule	Palpation	Tender	Normal	Normal
↑	↑	↑	Thyroglobulin	↑	↓	↓
↑	• or ↑	• or ↑	RAIU	↓	↓	↓
Diffuse Uptake	Patchy Uptake	Focal Uptake	Thyroid Scan	Decreased Uptake	Decreased Uptake	Decreased Uptake

C. HYPERTHYROIDISM MALE V/S FEMALE

	%	P
Men		
Euthyroid	96.44	<0.01
Hypothyroid	3.02	<0.01
Hyperthyroid	0.54	<0.01
Women		
Euthyroid	82.9	<0.01
Hypothyroid	10.5	<0.01
Hyperthyroid	1.47	<0.01

D. CAUSES OF THYROTOXICOSIS IN CHILDREN

- Graves' disease
- Autoimmune neonatal hyperthyroidism (passage of maternal TRAbs across the placenta)
- Thyroiditis
  - Subacute thyroiditis
  - Chronic lymphocytic thyroiditis (Hashimoto's disease)
- Exogenous causes
  - Exogenous thyroid hormone (acute or chronic)
  - Iodine-induced hyperthyroidism (iodine, radiocontrast agents, amiodarone)
- Autonomous functioning nodules
  - Somatic activating mutation of Gsα (McCune-Albright syndrome)
  - Somatic activating mutation of the TSH receptor gene
  - Toxic adenoma
  - Hyperfunctioning papillary or follicular carcinoma
- Congenital activating mutations of the TSH receptor gene (hereditary or *de novo*) (congenital hyperthyroidism)
- Selective pituitary resistance to thyroid hormones
- TSH-secreting pituitary tumours

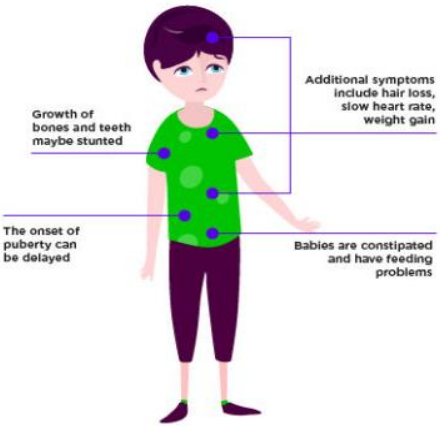
TRAb: thyroid hormone receptor antibody, TSH: thyroid stimulating hormone,

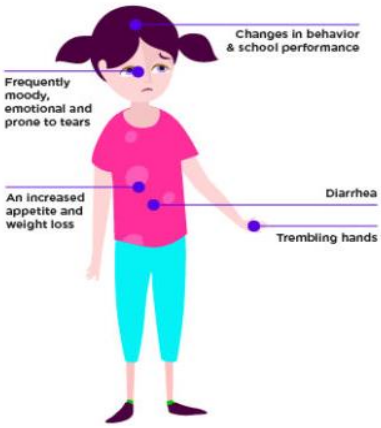
E. PATHOGENESIS

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 immunemediated and caused by cross-reactivity of TSI with a TSHRlike 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 fewmonths, 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 TSHsecreting pituitary adenomas and pituitary resistance to thyroid hormone, are exceedingly rare in children and caused by unregulated overproduction of TSH.

F. 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.

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 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 Y Anti-TPO, and/or antithyroglobulin in most Y Lymphocytic thyroiditis (silent, painless, and postpartum thyroiditis) Rare Firm, nontender TSH Y Anti-TPO in most Y Subacute thyroiditis (painful, postviral, granulomatous, and de Quervain) Rare Tender gland TSH Y [ESR Negative Y 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 Y Negative Y Contrast agents: iodine-induced synthesis of excess thyroid hormone (Jod Basedow effect in an underlying multinodular goiter) Very rare in children Normal TSH Y Negative [OTHERS CONDITION PREVALENCE THYROID EXAMINATION RESULTS LABORATORY FINDINGS ANTIBODIES RADIOACTIVE IODINE OR TECHNETIUM-99 UPTAKE Factitious intake of thyroid hormone Rare Normal TSH Y low serum thyroglobulin Negative Y Dermoid cysts with thyroid tissue Very rare in children Normal TSH Y Negative Y in thyroid Anti-TPO¼antithyroid peroxidase; hCG¼human chorionic gonadotropin; ESR¼erythrocyte sedimentation rate; TSH¼thyroid stimulating hormone (thyrotropin); TSI¼TSH receptor-stimulating immunoglobulin 242 Pediatrics in Review Downloaded from http://pedsinreview.aappublications.org/ by guest on June 13, 2016 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.

G. DIAGNOSIS

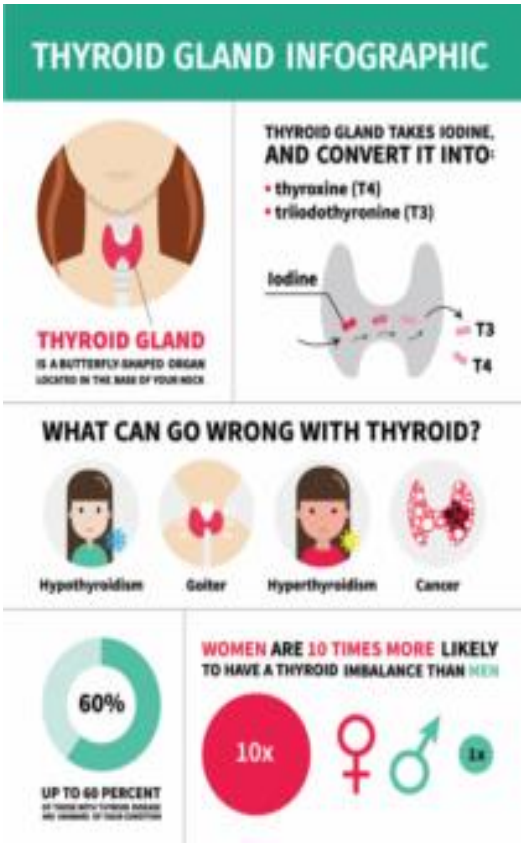
Typically patients will present with a combination of symptoms, an increased heart rate, restlessness, hand tremor, prominent eyes (found in about 1/3 of patients with GD), and an enlarged thyroid. An enlarged thyroid is called a 'goiter' and it may be found in hypothyroidism, hyperthyroidism, and even in some people with normal thyroid hormone levels.

Blood tests will reveal a low level of TSH combined with high levels of T3 and T4. Since there are several different causes of hyperthyroidism, additional tests might be necessary to determine the cause of your hyperthyroidism. Additional blood tests include thyroid auto-antibody levels (thyrotropin receptor antibody (TRAb), thyroid stimulating antibody (TSI). Thyroid imaging may include thyroid ultrasound and/or a nuclear medicine study called thyroid scintigraphy to see if the thyroid is over- or underactive (thyroid uptake) as well as what part of the thyroid is overactive (thyroid scan).

H. MANAGEMENT

There are three options for pediatric hyperthyroidism treatment.

- **Anti-thyroid medicine** called methimazole is given to decrease thyroid hormone levels. We may also use a medicine called a beta-blocker to decrease your child's symptoms until their thyroid levels are closer to the normal range. Anti-thyroid medicine is usually taken for at least two years. Some children may go into remission and be able to end treatment. Remission is when there are no longer any symptoms of hyperthyroidism. Other children will need ongoing treatment. Those who do stop treatment should be monitored, as hyperthyroidism returns in up to 75% of children. There are possible side effects of anti-thyroid medicine, which include skin rash, joint and muscle pain, liver problems and low white blood cell count. Any problems should be checked by your doctor.
- **Radioactive iodine treatment** is a way to permanently treat hyperthyroidism. For this therapy, your child will swallow radioactive iodine. This is safe because their thyroid gland absorbs it. This makes their thyroid gland shrink over time, reducing its hormone production. The radioactive iodine does not harm any other body tissues. Your child may then need to take medicine to replace some of their thyroid hormones and prevent symptoms of hypothyroidism. Hypothyroidism happens when thyroid levels are too low, but it is a safer and easier condition to manage. For families looking for permanent hyperthyroidism treatment, radioactive iodine therapy is our preferred choice. Sometimes we need to perform the treatment more than once, and it can worsen eye problems in Graves' disease.
- **Surgery** is another option for permanent hyperthyroidism treatment. We can use it to remove part or all of your child's thyroid gland, depending on their needs. This surgery is called a thyroidectomy. After surgery, your child may need to take medicine to replace their thyroid hormones.



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