



Thyrotoxicosis In Children & Adolescents

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Hyperthyroidism is a relatively rare condition in children

Graves disease accounts for more than 95% of childhood cases of hyperthyroidism

Causes

Transient

- Neonatal thyrotoxicosis
- Infectious : Acute & Sub acute thyroiditis
- Drug – induced: Amiodarone, interferon & interleukin
- Hashitoxicosis (initial stage of Hashimoto's thyroiditis)
- Iatrogenic: over dose of L-Thyroxin

- Permanent causes of thyrotoxicosis in childhood include:

- Graves disease
- Toxic adenoma/ carcinoma
- Toxic nodular goiter
- McCune-Albright syndrome

Pituitary causes of thyrotoxicosis include:

- Pituitary adenoma
- Pituitary resistance to T4

Graves' disease (diffuse toxic goitre)

- Triad of hyperthyroidism, exophthalmos & dermopathy (later is rare in pediatric)
- Incidence 15-50 / 100,000
- Prevalence of Graves disease is approximately 0.02% in childhood
- The most common cause of hyperthyroidism
- Females affected 4-5 times more frequently than males
- Autoimmune disease which has a chronic course of remissions & relapses

- Graves disease is associated with human leukocyte antigen (HLA)-B8 and HLA-DR3 & is more common in some families than in others
- Inheritance is polygenic
- Monozygotic twins show 50% concordance for the disease, suggesting interplay between environmental & genetic factors
- 6-15% general risk to siblings
- Graves disease is more common in patients with trisomy 21 than in patients without trisomy 21

Neonatal Graves disease

- Neonatal Graves disease is rare even among mothers with known hyperthyroidism
- Neonatal Graves disease is caused by the transplacental passage of TSI “Thyroid stimulating immunoglobulin”
- Only 1 in 70 infants of thyrotoxic mothers has clinical symptoms
- A maternal TSI level must be very high (> 5 times normal) to produce clinical disease in the neonate
- The frequency of neonatal Graves disease is equal in males and females

- If the mother is taking antithyroid drugs, infants are usually born asymptomatic
- Signs and symptoms may become manifest when antithyroid medications that have crossed the placenta are cleared from the infant's bloodstream
- Signs are similar to those in older children with thyrotoxicosis
- Signs include tachycardia, wide pulse pressure, irritability, tremor, and hyperphagia with poor weight gain
- The baby may have exophthalmos and goiter

- Neonates have a much higher risk of morbidity and mortality from cardiac disease
- In severe cases, CHF can be observed
- Goiter can occasionally be large enough to cause airway compression
- Long-term effects can include craniosynostosis and developmental delay
- This latter finding occurs even in the face of early diagnosis and treatment, which suggests that prenatal exposure to high levels of thyroid hormone may have early effects that cannot be overcome after birth

Fetal thyrotoxicosis

- Prenatally, the thyroid gland is fully responsive at 28 weeks' gestation
- These babies can be treated with propylthiouracil (PTU) or Methimazole, which is given to the mother
- PTU may be preferable because it binds less to plasma proteins and therefore crosses the placenta more easily
- Risk of cutis Aplasia may be increased in infants born to mothers who have taken Methimazole during pregnancy

Fetal thyrotoxicosis

Consequences

- IUGR
- Premature delivery
- Tachycardia (HR > 160)
- Craniosynostosis
- Mental retardation
- Mortality rate is 16%

Toxic adenomas, toxic nodular goiter, carcinomas

- Isolated toxic adenoma (Plummer disease) & toxic nodular goiter of adulthood are rare in children
- Although follicular or papillary carcinomas can appear as a thyroid mass, they are virtually always nonfunctioning and therefore rarely cause hyperthyroidism

McCune-Albright syndrome

- Hyperthyroidism associated with McCune-Albright syndrome is rare
- McCune-Albright syndrome includes polyostotic fibrous dysplasia, [café-au-lait spots](#) precocious puberty & endocrinopathies
- The most common endocrinopathies is peripheral precocious puberty, but hyperthyroidism also can be observed

Sub acute thyroiditis

- Subacute thyroiditis is generally associated with a viral upper respiratory infection
- Signs and symptoms of hyperthyroidism are mild and generally overshadowed by fever and thyroid tenderness
- The area surrounding the thyroid may be erythematous and warm, and the gland is always tender to touch.
- Hyperthyroidism in these patients is caused by inflammation of the thyroid gland and subsequent release of preformed thyroid hormone
- Laboratory studies reveal elevated thyroid hormones and decreased TSH
- Once the inflammation resolves, thyroid-related symptoms resolve

Hashitoxicosis

- The hyperthyroid phase of chronic lymphocytic thyroiditis (Hashitoxicosis) is self-limited and responds to antithyroid therapy
- Antithyroid antibodies cause destruction of thyroid follicular cells, and hypothyroidism occurs over time
- The duration of the hyperthyroid phase of Hashimoto thyroiditis may be **as long as 6 months**
- One study found that 11.5% of patients with Hashimoto thyroiditis presented with hyperthyroidism

Pituitary adenoma

- Clinical hyperthyroidism and elevated or normal TSH levels in the face of high T3 and T4 indicate inappropriate secretion by the pituitary gland
- This constellation of findings can occur in 2 disorders, TSH-secreting pituitary adenoma and pituitary resistance to thyroid hormone
- TSH-secreting pituitary adenomas are extremely rare
- These tumors may also secrete growth hormone and prolactin
- MRI may reveal a microadenoma or a macroadenoma

Pituitary resistance to T4

- Pituitary resistance to T4 is also very rare
- It can occur as a spontaneous mutation or can be inherited as an autosomal dominant trait
- Because the pituitary gland is not fully inhibited by T4, TSH levels are high, and thyroid hormones continue to be secreted
- Peripheral tissues respond normally to thyroid hormones, thus symptoms and signs of hyperthyroidism result
- Pituitary resistance to T4 is in contrast to the syndrome of generalized resistance to thyroid hormone, which includes both peripheral and pituitary resistance to thyroid hormone
- Patients with generalized resistance to thyroid hormone are clinically hypothyroid or euthyroid but have high concentrations of T3, T4, and TSH

Iodine-induced hyperthyroidism (i.e., Jod-Basedow phenomenon)

- Iodine can be found in radio contrast materials, topical antiseptics such as povidone-iodine, and medications such as Amiodarone
- **Diets very high in iodine may also increase the risk of hyperthyroidism**
- Ingestion can cause hyperthyroidism, especially in patients with previous hyperthyroidism from Graves disease or toxic nodular goiter
- Discontinuation of the offending agent is the treatment of choice
- Symptomatic therapy with an adrenergic beta-blocker can be helpful

hCG-secreting tumors

- Adolescents with hCG-secreting tumors, such as a hydatidiform mole and choriocarcinoma, can present with symptoms of hyperthyroidism
- The hCG directly binds to the TSH receptor and stimulates thyroid hormone release

Clinical manifestations of thyrotoxicosis in children

- May result in significant morbidity, mortality and even death
- **General manifestations:** Hyper metabolic state, heat intolerance, weight loss, nervousness, hair loss and dysphagia
- **Eyes:** proptosis, keratitis, chemosis, lid edema, lid lag, lid retraction, conjunctivitis, enlargement of extraocular muscles, optic atrophy and diplopia
- Prevalence of orbitopathy is increased with smoking in adolescents

Clinical manifestations

- **Heart:** Increased heart rate, contractility and cardiac output
- **Skeletal muscles:** Proximal myopathy, easy fatigability and muscle atrophy
- **Gonads:** Irregular menstrual cycles, impotence
- **Liver:** Low cholesterol LDL and apolipoprotein
- **Bone:** Increased bone turnover, osteoporosis and increased risk of fracture

Diagnosis

- A comprehensive history
- **Examination**
 - Weight, blood pressure, pulse rate and rhythm
 - Thyroid palpation and auscultation
 - Neuromuscular examination
 - Eye examination
 - Dermatological examination
 - Cardiovascular examination
 - Lymph nodes examination

Diagnosis

- Suppressed TSH
- Elevated Free T4, Free T3 levels
- Positive Thyroid Stimulating Antibodies:
 - Thyroid Peroxidase
 - Thyroglobulin
 - Thyroid Stimulating Immunoglobulin

Isotope scan is very important

Graves Disease



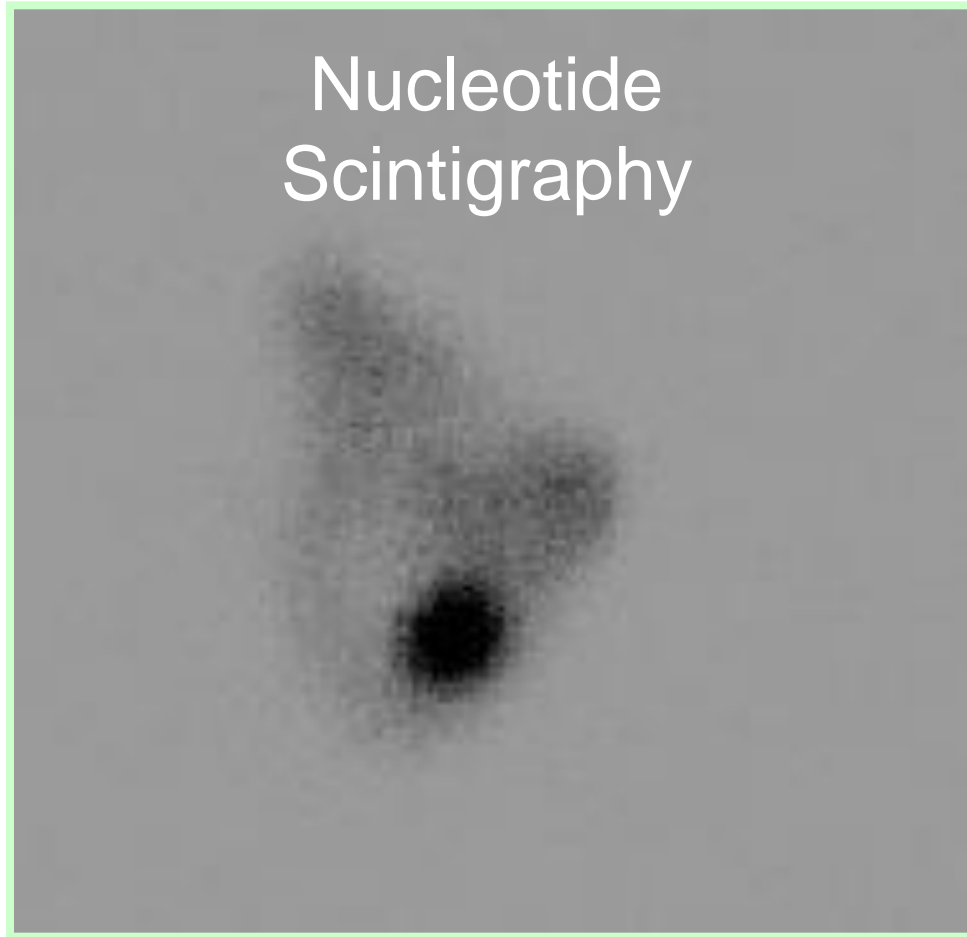
| ^{123}I or $^{99\text{m}}\text{Tc}$ Normal v/s Graves

Toxic Multinodular Goiter (TMG)



Toxic Adenoma

Nucleotide
Scintigraphy



Treatment

- Three modalities for more than last 50 years
- Radioactive iodine, anti-thyroid drugs & surgery
- None is optimal
- None interrupts the autoimmune process
- Each has a drawbacks
- No other research options so far

Treatment choices

Clinical considerations

- Age of the patient
- Goiter size
- RAI by the thyroid
- Physician preference
- Patient and family preferences

Treatment	Advantage	Disadvantage	For who?
¹³¹ I	Definitive, Safe	Lifelong T4 Rx	Most patients
Antithyroid Drugs	May need life long medication	Side effects, frequent visits, lower rate of remission, compliance	Pre RAI Rx, mild disease small goiter
Surgery	Definitive, rapid	Side effects, life long T4 Rx	Toxic nodule, allergy to drugs, large goiter, ? CA

Antithyroid Drugs

- Methimazole (MZT) and propylthiouracil (PTU) have been used since the 1940's
- Some endocrinologists prefer antithyroid drug therapy in childhood as a first line treatment
- Both have immunosuppressive effects, some centers use “Block and Replace” regimen (Add thyroxin replacement to antithyroid drugs during maintenance)
- Duration for a period of 18– 24 months
- Adverse reactions: Skin rashes and, in rare instances, agranulocytosis and hepatitis

Antithyroid Drugs

Thionamide group

- **Methimazole**

Fewer doses / day (once daily), no bad taste, no compliance problems, cutis aplasia if used during pregnancy

- **Propylthiouracil**

More doses /day, bad taste, no side effects during pregnancy / lactation and compliance problems

Antithyroid Drugs

High risk factors of relapse in children if:

- Large goiter
- History of previous relapse
- High TRAB titer
- Ophthalmopathy
- T3 predominant grave's disease
- Low doses or short duration (31% remission rate for 6 m. treatment and 82% for 2 years)

I^{131} Radioactive iodine

- Some endocrinologists are hesitant to use radioactive iodine to treat patients of childbearing age
- Recommended age in children is above 10 years of age
- There is no evidence to suggest that such therapy has any adverse effects
- No effect on fertility
- No increased incidence of congenital malformations
- No increase risk of cancer in-patients treated with radioactive iodine or in their offspring

I^{131} Radioactive iodine

- Possible deterioration in ophthalmopathy, if was present before treatment

Ophthalmic treatment using:

- Lubricants (artificial tears)
- Diuretics
- Head elevation at night
- Steroids
- Stop smoking (Adolescence)

Surgical treatment

Subtotal thyroidectomy is the most common procedure

Indications

- Large goiter
- Severe thyrotoxicosis
- Failure of medical therapy
- Subtotal thyroidectomy is the most common procedure

Surgical treatment

Complications

- Post- treatment hypothyroidism (42%)
- Recurrent hyperthyroidism (10%)
- Vocal cord paralysis (1.2%)
- Hypoparathyroidism (2%)
- Bleeding (0.2%)
- Infection
- Anesthesia complications
- Mortality (0.1%)

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Key Points

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- Graves disease accounts for more than 95% of childhood cases of hyperthyroidism
- Neonatal Graves disease is rare even among mothers with known hyperthyroidism
- Only 1 in 70 infants of thyrotoxic mothers has clinical symptoms
- Treatment options depending on age of the patient, goiter size, urgency of treatment, RAIU by the thyroid, physician preference & patient choice
- Radio-active Iodine therapy is safe in children with thyrotoxicosis

Thanks شكرا "لكم

