

Graves' disease

Graves' disease is caused by autoantibodies that bind to the thyrotropin receptor (TSHR-Ab), stimulating growth of the thyroid and overproduction of thyroid hormone. It is by far the most common cause of hyperthyroidism in children. Clinical manifestations of Graves disease include diffuse goiter and symptoms and signs resulting from hyperthyroidism. Graves disease is often associated with ophthalmopathy, which is not found in other etiologies of hyperthyroidism and is not caused by the high serum thyroid hormone concentrations. In children, hyperthyroidism also tends to have effects on growth and development.

Clinical manifestation

General symptoms and signs of thyrotoxicosis — Graves' disease is associated with the following symptoms and signs, which are also seen in other causes of thyrotoxicosis:

- **Cardiovascular** – Patients with hyperthyroidism have an increase in cardiac output, caused by both increased peripheral oxygen needs and increased cardiac contractility. Heart rate is increased, pulse pressure is widened, and peripheral vascular resistance is decreased. Atrial fibrillation, which occurs in 10 to 20 percent of adults with hyperthyroidism, is rare in children. Mitral valve prolapse, which is common in adults with thyrotoxicosis, has also been reported in children.
- **Gastrointestinal** – Failure to gain weight or weight loss, despite an increase in appetite, is common. Weight loss is caused primarily by increased calorigenesis, and secondarily by increased gut motility and associated hyperdefecation and malabsorption.
- **Eyes** – Stare and lid lag occur in many children with hyperthyroidism. "Stare" refers to the patient's widely opened eyes, which give the appearance of staring. Lid lag is evaluated by having the patient follow the examiner's finger as it is moved up and down. The patient has lid lag if the sclera can be seen above the iris as the patient looks downward.
- **Neurologic**
 - **Movement disorders** – Tremulousness and tremor are common in hyperthyroidism. The tremor is best demonstrated from the outstretched hands or the tongue (fasciculations). Deep tendon reflexes are hyperactive.

- Cognitive dysfunction – Among very young children (<4 years), hyperthyroidism may cause neurodevelopmental delay.
- Peripheral nervous system – Proximal muscle weakness may be present, with decreased muscle mass and decreased efficiency of muscle contraction.
- Periodic paralysis – Hypokalemic periodic paralysis (thyrotoxic periodic paralysis) is a rare disorder that may be associated with hyperthyroidism, especially in Asian adolescent boys.

•**Behavioral and psychiatric** – Children with hyperthyroidism tend to have greater mood swings and disturbances of behavior, compared with adults. Their attention span decreases, they are usually hyperactive, they sleep poorly, and their school performance deteriorates. Occasionally, children or adults with hyperthyroidism may experience marked personality changes, agitation, anxiety, depression, mania, or psychosis .

•**Bone** – Thyroid hormone stimulates bone resorption, resulting in increased porosity of cortical bone and reduced volume of trabecular bone. Serum alkaline phosphatase and osteocalcin concentrations are high, indicative of increased bone turnover. The increase in bone resorption may lead to an increase in serum calcium concentrations, thereby inhibiting parathyroid hormone secretion and the conversion of calcidiol (25-hydroxyvitamin D) to calcitriol (1,25-dihydroxyvitamin D). The net effect is osteoporosis and an increased fracture risk in patients with chronic hyperthyroidism.

•**Skin** – The skin is warm in hyperthyroidism because of increased blood flow; it is also smooth because of a decrease in the keratin layer. Sweating is increased because of increased calorogenesis. Onycholysis (loosening of the nails from the nail bed, Plummer's nails) and softening of the nails and thinning of the hair may occur. Vitiligo and alopecia areata can occur in association with autoimmune disorders.

Treatment

The therapeutic approach to Graves' hyperthyroidism consists of both rapid amelioration of symptoms with a beta blocker and measures aimed at decreasing thyroid hormone synthesis with the administration of a thionamide, radioiodine ablation, or surgery . The choice of therapy should

involve active discussion between clinician and patient; it may also be determined by the severity of the patient's hyperthyroidism.

- Assuming there are no contraindications to its use, we recommend using a beta blocker for patients with moderate to severe hyperadrenergic symptoms until euthyroidism is achieved by thionamides, radioiodine, or surgery.

- For patients with significant symptoms of hyperthyroidism, or patients with a significant risk of hyperthyroid complications (eg, older age, cardiovascular disease), we suggest a thionamide in addition to beta blockers to achieve euthyroidism quickly. Methimazole is now used almost exclusively (except during the first trimester of pregnancy and in patients who have minor drug reactions to methimazole who refuse radioiodine or surgery) because of its longer duration of action, allowing for once-daily dosing, more rapid efficacy, and lower incidence of side effects.

- Once patients with more severe hyperthyroidism are euthyroid on methimazole, we suggest definitive therapy with radioiodine or surgery. A one- to two-year course of methimazole or long-term methimazole are both reasonable alternatives. In the absence of moderate to severe orbitopathy, we suggest radioiodine therapy if definitive therapy is desired, given its lower cost and lower complication rate than surgery.

- For patients who are tolerating hyperthyroid symptoms and who are not at risk for complications from hyperthyroidism, radioiodine can be used as initial therapy. Primary antithyroid drug therapy is an alternative option and may be preferable for patients with mild disease and small goiters who are more likely to achieve a remission after a year of treatment.

- For patients with hyperthyroidism due to a very large or obstructive goiter, we suggest surgery. It is also indicated for patients who are allergic to thionamides and are unable to or do not want to receive radioiodine. Surgery may also be preferred in patients with active orbitopathy.

- We advise women desiring to become pregnant in the near future to consider radioiodine or surgery six months in advance of a planned pregnancy to avoid the need for a thionamide during the pregnancy. However, if radioiodine or surgery is not desired, propylthiouracil (PTU) therapy would be the preferred drug during the first trimester of pregnancy and may be continued throughout pregnancy.