UAB MEDICINE

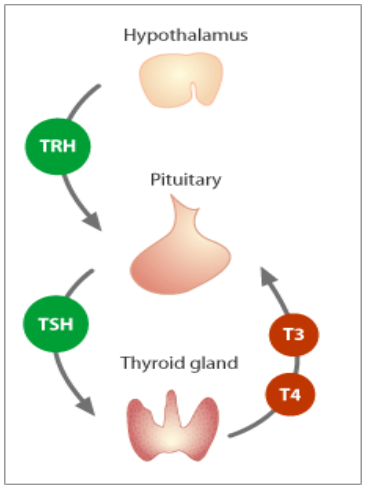
February 2021 Education Newsletter

Grave's Disease: A Review

Introduction:
Graves' disease, also known as toxic diffuse goiter, is the most common cause of hyperthyroidism. It is an autoimmune disorder resulting from the production of TSH-Receptor antibodies (TRab), which stimulate thyroid gland growth (resulting in a goiter) and thyroid hormone synthesis and release (resulting in hyperthyroidism).

Pathogenesis and Autoimmunity:
Autoimmune thyroid diseases (AITD) are the most prevalent organ-specific autoimmune diseases. AITD is primarily composed of Grave's disease and Hashimoto's (among others). Several different antibodies have been implicated in AITD; TRab antibodies are specific for this condition. This is in contrast to other thyroid antibodies such as thyroglobulin antibody (TgAb) and TPO antibody (TPOAb), which can also occur in up to 20% of the general population (*in other words, TRab positivity is always pathologic, though it is not specific for Graves; up to 20% of Hashimoto's patients will be TRab (+) too*).
Genetic susceptibility, infection, stress, smoking, pregnancy, and iodine exposure are all predisposing factors which increase one's risk of developing Graves' Disease. The mechanisms by which these factors result in antibody production are either unknown or beyond the scope of this newsletter, but, ultimately, there is loss of self-tolerance which leads to autoimmunity (remember this same discussion in regards to SLE during our last Noon Report??).

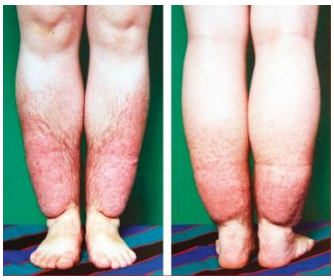
Pathophysiology:
Normal thyroid physiology depends on the hypothalamic-pituitary-thyroid axis. The hypothalamus releases thyrotropin releasing hormone (TRH), which stimulates the anterior pituitary to release TSH, which in turn stimulates the thyroid gland to produce T4 and T3. Through a negative feedback mechanism, T3 and T4, influence the hypothalamus and the pituitary to produce less TRH and TSH. *See image to the right.*
In Graves' disease, however, autoantibodies bind to the TSH receptor on the thyroid gland, chronically stimulating it to produce and release thyroid hormone. This results in an abnormally high production of T3 and T4 and low TSH levels (pituitary release of TSH is suppressed by the excess T3 and T4).



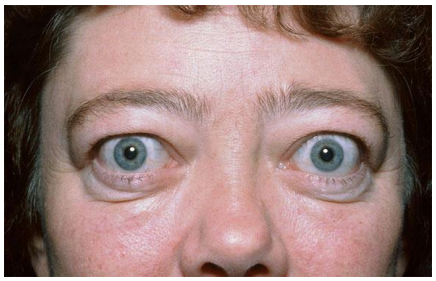
Clinical Presentation:
Clinically, Graves' disease presents with symptoms of hyperthyroidism and goiter, along with organ-specific eye and skin disease - the latter two are unique to Graves'.

- The classic symptoms of hyperthyroidism are protean and include insomnia, hyperactivity, hair loss, excessive sweating, oligomenorrhea, weight loss despite increased appetite, heat intolerance, tremor, palpitations, anxiety, increased frequency of bowel movements, and dyspnea
- Goiter is an enlarged thyroid gland; Graves' disease is the most common cause of diffuse goiter.
- Eye involvement, known as exophthalmos, is due hypertrophy of the extraocular muscles and orbital fat expansion. This occurs because thyroid stimulating hormone receptors are not only found within the thyroid gland, but also within fibroblasts and adipocytes (which are in abundance within the retro-ocular tissues).
- Skin involvement, AKA thyroid dermopathy, AKA pretibial myxedema is a non-pitting edema that results in swelling, scaly thickening, and induration within the skin of the lower legs. Like exophthalmos, thyroid dermatopathy is also related to fibroblast activation within the skin.

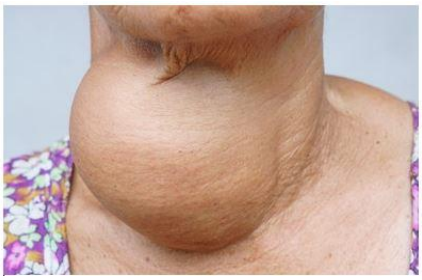
Physical exam findings in Graves' disease:



Pretibial myxedema



Exophthalmos



Goiter

Treatment:

Treatment of Graves' begins with rapidly addressing the hyperadrenergic symptoms caused by excess thyroid hormone. This is usually accomplished with a beta blocker initially. In patients with severe hyperthyroidism or those who are at most risk of complications due to hyperthyroidism (such as patients with severe coronary disease), methimazole, in addition to beta blockade, helps to quickly achieve euthyroidism. Methimazole works by inhibiting the production of *new* thyroid hormone within the thyroid gland (it does not inactivate *circulating* T4 and T3).

Once medical intervention is initiated to address symptom burden, definitive therapy should be undertaken; this is usually accomplished with surgery or radioiodine. A prolonged course of methimazole is also a reasonable alternative to the more invasive therapies. Each treatment has its own advantages and disadvantages. Lastly, be mindful that treatment of pregnant patients is considerably different.

Take Home Pearls:

*** Hyperthyroidism + goiter + exophthalmos + pretibial myxedema = Graves' Disease**
*** TRab antibodies are relatively sensitive and specific for Graves'**
*** Treatment of Graves': quickly initiate medical therapy for symptom burden. Then consider definitive management.**