Review Article

All Thyrotoxicosis is not Graves' Disease

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All cases of thyrotoxicosis are not due to Graves' disease. This review describes a pragmatic approach to the differential diagnosis of this condition. It uses a hierarchical approach, based on symptoms, signs, biochemical anomalies and imaging results, to reach the correct diagnosis.

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Thyrotoxicosis is a condition characterized by presence of excess thyroid hormones in the blood. Though the terms hyperthyroidism and thyrotoxicosis are often used interchangeably, it is critical to understand the difference between the two because the management is different. Thyrotoxicosis is a broader term used to define any condition where serum thyroxine (T4) and triiodothyronine (T3) levels are elevated. Hyperthyroidism refers to subgroup of thyrotoxicosis which results from increased production of thyroid hormones from the thyroid gland. Graves' disease (GD), toxic multinodular goiter (MNG), and toxic adenoma are the most commonly encountered causes of hyperthyroidism. Administration of excess exogenous thyroid hormones and thyroiditis are examples of thyrotoxicosis but not hyperthyroidism.

Approach to a Patient with Thyrotoxicosis:

In clinical practice, when a patient presents with clinical and biochemical features of thyrotoxicosis the etiology of the condition should be identified before instituting therapy. History, physical examination, laboratory tests, imaging and radionuclear studies can provide important clues to establish the diagnosis. Table 1 summarizes a suggested therapeutic approach to a patient presenting with thyrotoxicosis.

Graves' Disease :

GD is the most common cause of hyperthyroidism[1]. The clinical symptoms of thyrotoxicosis like weight loss, increased appetite, excess sweating, anxiety, restlessness, palpitations, tremulousness, increased stool frequency, etc. are usually present in GD and are not different from other thyrotoxic states. The distinctive features of GD are commonly a diffuse goiter often associated with a bruit, occasionally Graves' ophthalmopathy (GO) and rarely pretibial myxedema. Some eye signs like lid lag and stare can be due to sympathetic overactivity arising from other thyrotoxic conditions like toxic MNG and do not always indicate GO.

Laboratory tests reveal elevated serum T4 and T3 levels along with a suppressed serum thyroid stimulating hormone (TSH). Antibody to thyroid peroxidase is present in 80% and antibody to thyroglobulin (Tg) in 50-60% of individuals with GD[2]. These antibodies are only markers of thyroid autoimmunity and their presence do not establish the diagnosis of GD. On the other hand, TSH receptor antibodies (TRAb) using third-generation assays, have a

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Table 1 — *Diagnostic Approach to a Patient of Thyrotoxicosis*

1. Clinical and biochemical confirmation of thyrotoxicosis
2. Overt thyroid ophthalmopathy or pretibial myxedema – start ATD
3. Non-pregnant or non-lactating individuals:
   Thyroid scintigraphy if above features not present
   - Diffuse increased uptake – Confirms GD – start ATD
   - Multiple areas of focal increased and suppressed uptake – Confirms toxic MNG – ATD/ surgery
   - Hot nodule – Confirms toxic adenoma - Radioiodine ablation/ATD
   - Absent or low uptake – Confirms thyroiditis – Observe, consider glucocorticoid when necessary
4. Pregnancy, lactation, scintigraphy not interpretable (recent iodine exposure)
   TSH receptor Antibody
   - Positive – Confirms GD – start ATD
   - Negative – rules out GD
5. Thyroid ultrasound and doppler studies
   - Multinodular goiter (usually apparent on physical examination) – ATD/surgery
   - Solitary nodule with increased blood flow – suggests toxic adenoma – Confirm by scintigraphy, consider FNAC if toxic adenoma ruled out
   - Increased blood flow – Suggests GD – start ATD
   - Decreased blood flow – Suggests thyroiditis - Observe, consider glucocorticoid when necessary

GD- Graves' disease, ATD – Antithyroid drug (thionamides), MNG – Multinodular goiter

sensitivity and specificity of 97 and 99% for detecting GD and their presence is pathognomic[3]. The test most commonly employed to confirm diagnosis of GD is thyroid scintigraphy using iodine-123 or technetium-99m. In India iodine-131 is used as iodine-123 is not available. Thyroid scintigraphy can also establish the diagnosis of toxic MNG and toxic adenoma.

Thyroiditis :

Thyroid scintigraphy can also be utilized for identifying thyroiditis, the most common differential diagnosis of GD in clinical practice. Unlike hyperthyroidism, where radioiodine or technetium uptake is increased, thyroiditis is characterized by very low or absent uptake in scintigraphic studies. Thyroiditis refers to inflammation of the thyroid gland where thyrotoxicosis ensues due to damage to thyroid follicular cells and consequent unregulated release of thyroid hormones from the gland. Painful thyroiditis along with a tender often enlarged thyroid gland is termed as subacute thyroiditis. The painless variety is designated as silent thyroiditis and thyroiditis occurring in the postpartum phase is called postpartum thyroiditis.

Scintigraphy is contraindicated during lactation and cannot be employed to differentiate postpartum thyroiditis from GD in mothers who are nursing their baby. Other than TRAb, ultrasound doppler studies can be utilized to distinguish thyroiditis in such situation. Thyroiditis is characterized by decreased blood flow to thyroid gland in contrast to GD where it is increased[4]. Elevated erythrocyte sedimentation rate and increased serum Tg levels are other indirect markers of thyroiditis. The above three varieties of thyroiditis are usually self-limited and resolve in two to three months. Persistence of thyrotoxic phase beyond this period is unusual and other possibilities should be considered in such a situation. Subacute thyroiditis is sometimes associated with severe pain and fever warranting short term glucocorticoid therapy. Response to glucocorticoid is another characteristic feature of thyroiditis and the diagnosis should be reconsidered if the pain and fever does not settle with in four to five days of starting glucocorticoid. Anti-thyroid drugs (thionamides) have no role in treatment of thyroiditis. Table 2 depicts the salient distinguishing features of GD and thyroiditis.

Other rare varieties of thyroiditis include Reidel's thyroiditis and infectious thyroiditis. Another entity which is being increasingly observed these days is drug induced thyroiditis. The drugs implicated are amiodarone, interferon alpha, interleukin 2, tyrosine kinase inhibitors like imatinib and sunitinib; and checkpoint inhibitor immunotherapy like ipilimumab, and nivolumab[5,6].

Other Causes of Thyrotoxicosis :

Iodine induced hyperthyroidism or Jod Basedow phenomenon mostly occurs in the setting of underlying nodular thyroid disease with areas of autonomy in regions where iodine deficiency is prevalent. Iodine exposure usually results from administration of iodinated radiocontrast agent or amiodarone. Dilution of radiotracer by exogenous iodine source will result in low radioiodine uptake despite presence of hyperthyroidism.

TSH producing pituitary adenoma is a rare cause of hyperthyroidism. High levels of human chorionic gonadotropin from hydatidiform mole, choriocarcinoma or germ cell tumors may cause stimulation of the TSH receptor and induce hyperthyroidism. Struma ovarii is another unusual condition where mature thyroid tissue in an ovarian teratoma can cause thyrotoxicosis.

Thyrotoxicosis factitia refers to surreptitious ingestion of thyroid hormone. Outbreaks of thyrotoxicosis in community were traced to hamburger contaminated with animal thyroid extracts[7].

Subclinical Thyrotoxicosis :

In contrast to overt thyrotoxicosis, T4 and T3 levels remain normal in the setting of low TSH in patients with subclinical thyrotoxicosis. The etiology is similar to overt thyrotoxicosis common causes being GD, toxic MNG, toxic adenoma, thyroiditis and exogenous thyroxine administration. Endogenous subclinical hyperthyroidism is associated with increased risks of total mortality, coronary heart dis-

Table 2 — *Distinguishing features between Graves' disease and thyroiditis*

	Graves' Disease	Thyroiditis
Duration of thyrotoxic symptoms	Variable, can be long duration (months)	Usually short duration (weeks)
Severity of thyrotoxic symptoms	Mild to severe	Mild
Graves' Ophthalmopathy*	Diagnostic if present	Absent
Pretibial myxedema*	Diagnostic if present	Absent
Other autoimmune disease	Can be present	Usually absent
Neck pain	Absent	Can be present
Thyroid morphology	Diffusely enlarged	Variable - diffuse enlargement, nodular (transient) or normal
Thyroid Bruit	Can be present	Absent
Thyroid scintigraphy*	Increased diffuse uptake	Low or absent uptake
TSH Receptor Antibody*	Present	Absent
Ultrasound Doppler blood flow*	Increased	Decreased
ESR	Normal	Elevated
Serum Thyroglobulin	Normal	Elevated
Response to glucocorticoids	Minimal	Characteristic improvement in pain and fever
Treatment	Anti-thyroid drugs	Observation, glucocorticoids if pain persists and/or severe

*Diagnostic, TSH – Thyroid stimulating hormone, ESR – erythrocyte sedimentation rate

ease (CHD) mortality, and incident atrial fibrillation (AF), with highest risks of CHD mortality and AF occurring with a TSH level lower than 0.1 mU/L.8 Treatment with thionamides is recommended if TSH is persistently below 0.1 mU/L in all individuals more than 65 years of age; in patients with cardiac risk factors, heart disease or osteoporosis; in postmenopausal women who are not on estrogens or bisphosphonates; and in individuals with hyperthyroid symptoms[9].

Conclusion :

Hyperthyroidism refers to the subgroup of thyrotoxicosis where the source of excess thyroid hormone is due to hyperfunctioning of thyroid gland. GD remains the most common cause of hyperthyroidism. Thyroiditis is a common differential in clinical practice and should be ruled out by scintigraphic studies or TRAb assay before instituting therapy with thionamides. Unusual causes of thyrotoxicosis should be suspected in appropriate clinical situations.

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