Systemic Management of Graves' Disease

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Graves' Disease:

Endocrinopathy or Ophthalmopathy?

Robert James Graves, M.D., FRCS (1796 - 1853)

- Eminent Irish Surgeon
- President of the Royal College of Physicians of Ireland
- Fellow of the Royal Society of London
- Founder of the Dublin Journal of Medical Science
- The uncredited inventor of the second hand on watches.

Graves' Endocrinopathy

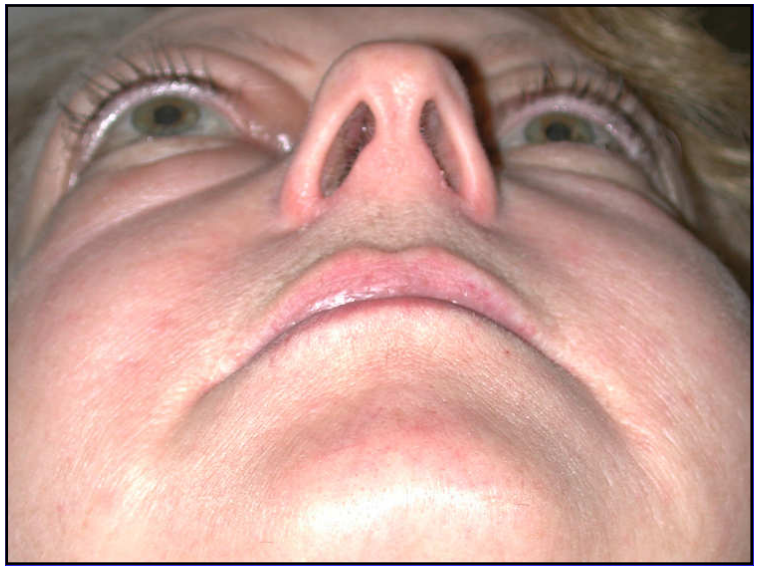
- Most common cause of hyperthyroidism
- Affects 2% of female population
- Female : male – 5-10:1
- 25-30% of patients with endocrinopathy develop ophthalmopathy (thyroid eye disease)

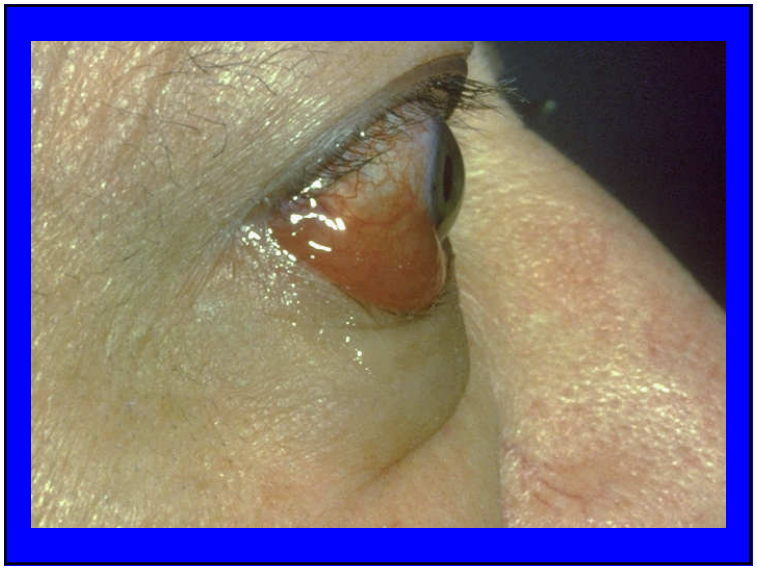
Thyroid Eye Disease (TED)

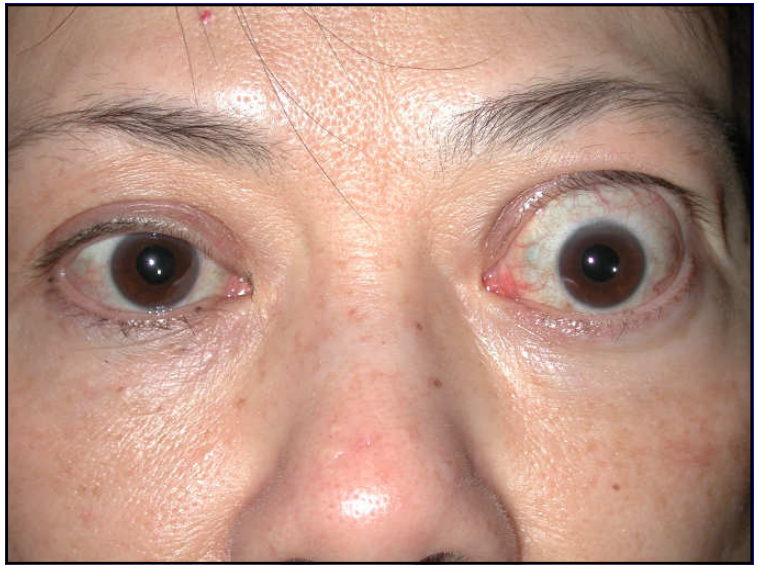
- Graves' ophthalmopathy (TED) is the most common cause of unilateral or bilateral proptosis
- 6X more common in women than in men
- Associated with hyperthyroidism (90%), euthyroidism (6%), hypothyroidism (4%)
- Associated with severe psychosocial stress
- Associated with elevated TSH-R stimulating auto antibodies (TRAb)

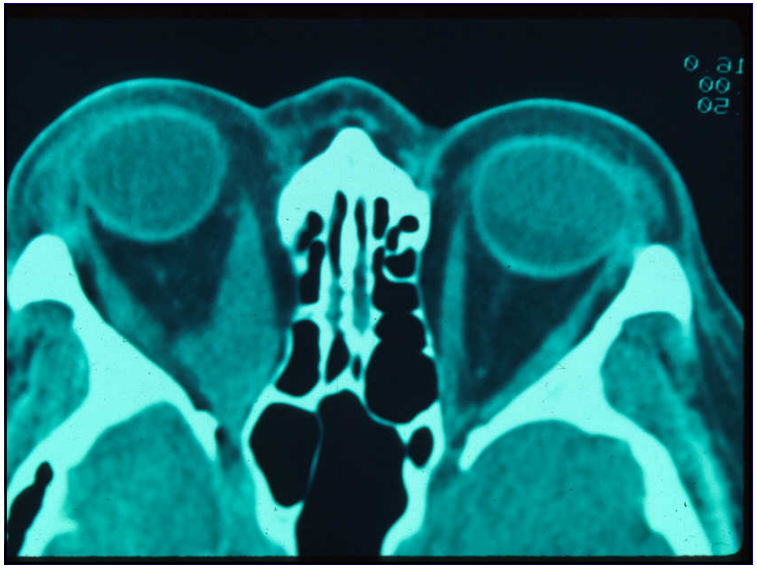
Clinical Features of TED

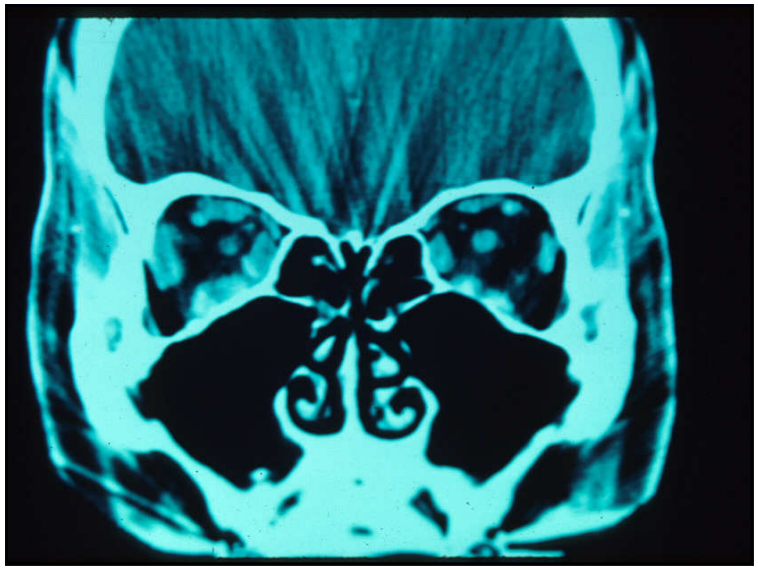
- Eyelid retraction - most common
- Lid lag
- Conjunctival injection, chemosis
- Proptosis
- Restrictive extraocular myopathy-strabismus
- Optic neuropathy









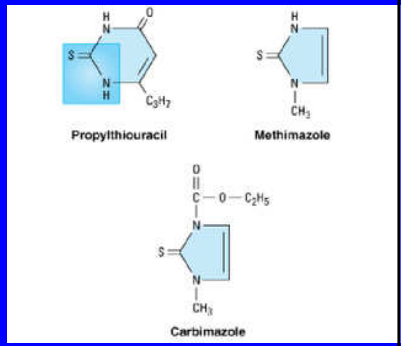


Treatment of Graves' Endocrinopathy

- Antithyroid drugs
- Steroids
- Biologics
- RAI
- Surgery

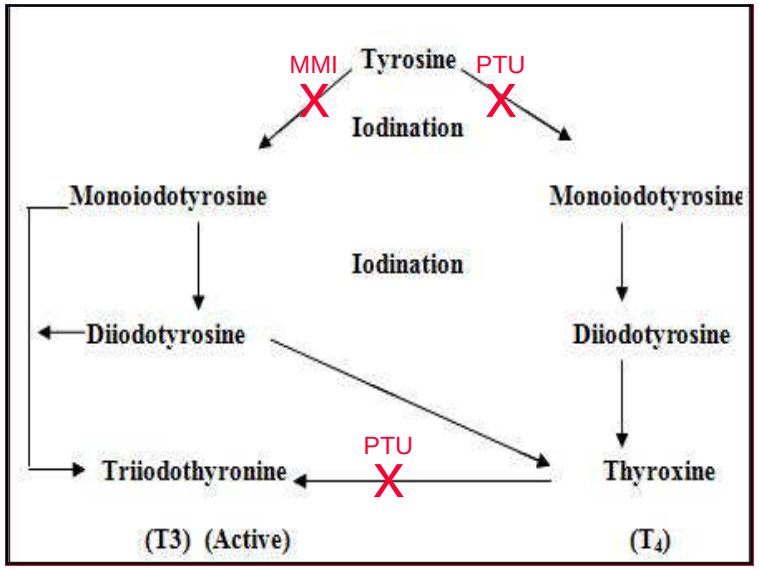
Antithyroid Drugs

- **Thionamides**- introduced in the 1940s
  - Methimazole- Tapazole (USA)
  - Propylthiouracil (USA)- ↑ risk of liver failure
  - Carbimazole- pro drug of MMI (UK)



Mechanism of Action of Thionamides

- Inhibit thyroid hormone synthesis by interfering with thyroid peroxidase mediated iodination of tyrosine residues in thyroglobulin
- PTU blocks conversion of T4 → T3
- Possible immune suppression with ↓ TSHRAb, IL2, IL 6
- ↓ HLA class II expression



Characteristic	Methimazole	Propylthiouracil
Relative potency	10-50	1
Administration	Oral	Oral
Absorption	Nearly complete	Nearly complete
Binding to serum proteins	Negligible	80-90%
Serum half-life (hr)	4-6	1-2
Vol of distrib (L)	40	20
Inhib T4→T3	No	Yes
Dosing	10-40 mg ÷ 1-2 times/d	300-600 mg ÷ 2-3 times/d

Characteristic	Methimazole	Propylthiouracil
Met during liver ds	Decreased	Normal
Met during renal ds	Normal	Normal
Transplacental pass	Low	Even lower
Levels in breast milk	Low	Even lower

Indications for Use of Thionamides

- To achieve a euthyroid state
- Pre intervention control (I^{131}, surgery)
- Treatment of choice in pregnancy, childhood, adolescence, presence of ophthalmopathy
  - I^{131} exacerbates eye disease, requires steroid cover

Methodologies for Administration

- Dose titration
- Block and replace
  - ATD and Levothyroxine replacement
- Treatment duration - 14-18 months
- Recurrence rate - 50-60% within 3-6 months of discontinuing ATD
- May require long term low dose tx

Factors Associated with Relapse

- Severe hyperthyroidism
- High serum T3/T4 ratio
- High TSHRAb levels initially or at end of therapy
- Young age
- Male sex
- Smoking
- Presence of ophthalmopathy

Factors Associated with Relapse

- Family history of autoimmune disease
- Certain genetic markers
- Large initial goiter
- Increasing goiter size during tx
- Thyroid nodularity, hypoechogenicity by imaging
- High intrathyroidal blood flow at end of ATD tx
- Long delay from start of symptoms to initiation of tx
- Problems in coping with daily life

Side Effects of Thionamides

- Incidence 5%
- MMI dose related, PTU less so
- Ok to switch meds, 50% cross over
- Urticaria, pruritis, arthralgia, fever-rx antihistamine
- Gastrointestinal complaints, abnormalities of taste and smell
- Arthritis
- Transient granulocytopenia

Serious Side Effects

- Agranulocytosis - 0.35%
- Equal frequency MMI-PTU
- Risk of pseudomonas aeruginosa sepsis
- Hepatotoxicity - 0.1-0.2%
- Vasculitis (PTU>MMI)- lupus like
- Hypoprothrombinemia
- Hypoglycemia
- Pancreatitis

- MMI somewhat better side effect profile than PTU

β-Adrenergic Antagonist Drugs

- Ameliorate symptoms - sweating, anxiety, tremor, palpitation, tachycardia
- Mildly inhibits the conversion of T4 to T3
- Avoid in patients with COPD

- Propranolol

Inorganic Iodide

- Decreases T4 and T3 synthesis by inhibiting iodide oxidation and organification (Wolff-Chaikoff effect).
- Blocks the release of T4 and T3 by inhibiting thyroglobulin proteolysis.
- Lugol's solution (8 mg iodide per drop)
- Saturated solution of potassium iodide (SSKI 50 mg iodide per drop)
- Dose : 24-50 mg/day

Glucocorticoids

- Blocks the conversion of T4 to T3 in a similar fashion to beta-blockers
- Use only in patients with ophthalmopathy due to side effects

Supplementary Agents

- Oral cholecystographic agents (e.g., sodium iopanoate, sodium ipodate) inhibit T4-deiodinase activity. Acutely lower serum T3 levels.
- Potassium perchlorate is a competitive inhibitor of iodide transport.
- Lithium acts by inhibiting T4 and T3 release from the thyroid. Dose - 900 mg q d

Novel Biologics

- Rituximab - more later
- anti-B-cell maturation factor
- anti-B-cell maturation antigen receptor (anti-BAFF)
- anti-B-cell maturation antigen (anti-BCMA)
- blockade of the CD40-CD154 (CD40-ligand)
- abatacept (CTLA-4/Ig);

Radioactive Iodine (RAI)

- Introduced in the 1940s (MIT, Berkeley)
- I^{131} concentrated, oxidized, organified by follicular thyroid cells
- Ionizing effect of β particles (path length of 1 to 2 mm) destroys thyroid follicular cells and promotes vascular occlusion
- Induces hypothyroidism

I^{131} Dosing

- No consensus – induce hypothyroidism or retreat
- Incidence of hypothyroidism independent of dose: 2-3% annually
- Dose (mCi) = 80-200 microCi I^{131}/g thyroid x estimated thyroid gland weight (g)/24hour radioiodine uptake
- Typical activities - 5 to 15 mCi I^{131}
- Corresponds to 185-555 MBq = absorbed radiation dose of 50 to 100 Gy.

Becquerel

- The becquerel (Bq) is the SI derived unit of radioactivity. One Bq is defined as the activity of a quantity of radioactive material in which one nucleus decays per second. The Bq unit is therefore equivalent to s-1. The becquerel is named for Henri Becquerel, who shared a Nobel Prize with Pierre and Marie Curie for their work in discovering radioactivity.

Scan of thyroid 24 h after intake of I^{131}

I^{131} Influence on Thyroid Function

- 50-70% euthyroid within 6-8 weeks
- 10 to15 mCi (370–555 MBq) range, 80% to 90% of patients become euthyroid or hypothyroid after one dose of I^{131}.
- 10-20% require a second dose

Carcinogenicity

- Avoid use of I^{131} in children and adolescents
- Avoid use in pregnant or breastfeeding women

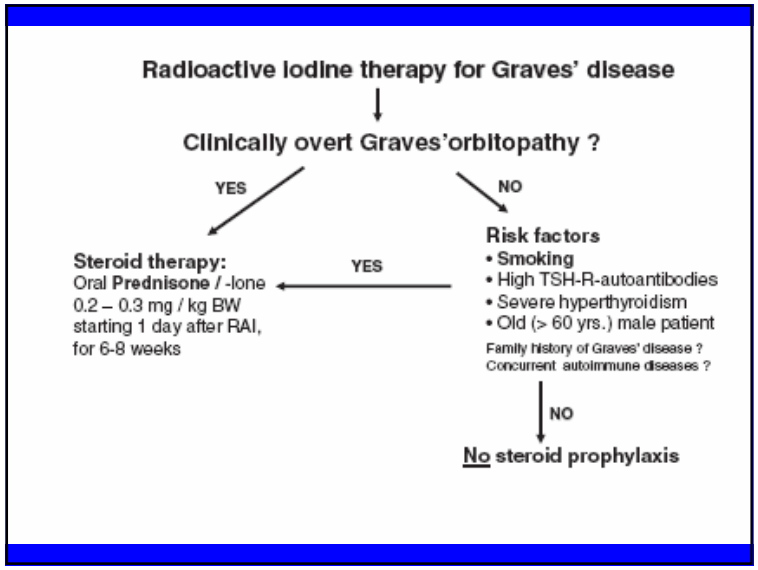
Factors that Increase Risk of TED

- Smoking
- High levels of pretreatment serum T3 (twice the upper limit of normal)
- A high TSH-receptor antibody titer

RAI and TED

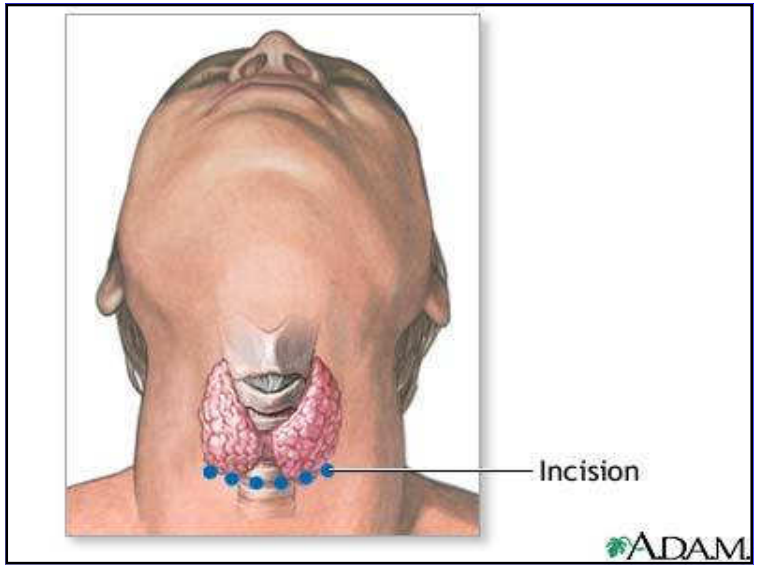
- RAI is associated with increased risk of ophthalmopathy compared with antithyroid drugs.
- The risk of developing new or worsening ophthalmopathy is ~ 20% after radioiodine and ~ 5% after antithyroid drugs.
- Post radioiodine hypothyroidism ↑ risk of TED

- Post radioiodine hypothyroidism should be treated promptly.
- Patients with mild pre-existing ophthalmopathy, should be pretreated with prednisone to prevent progression.
- Routine use of prophylactic steroids in all RAI pts is not indicated at present- but should be considered in pts at higher risk of TED (e.g. smokers).



Surgery

- Children, adolescents, pregnant women
- Large goiters (pressure symptoms, cosmesis)
- Suspicion of thyroid malignancy
- Graves' ophthalmopathy especially those not responsive to ATD.



Complications of Thyroidectomy

- Permanent damage to the recurrent laryngeal nerve and hypoparathyroidism - (1-2% up to 5-10%)
- Transient hypocalcemia, bleeding, wound infections, keloids.
- Hypothyroidism (12- 80% during the first year and at a rate of 1-3% annually)
- Subtotal thyroidectomy associated with recurrent hyperthyroidism in 5-15%

Choices?

- Preference for ATD, I^{131} or surgery should be discussed with patient and endocrinologist on an individualized level.
- Stop smoking!

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Thank you