HYPERTHYROIDISM

Thyrotoxicosis: clinical state of inappropriately high levels of thyroid hormones acting on tissues
Hyperthyroidism: thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormones
Subclinical hyperthyroidism: suppression of TSH by normal T4/T3 levels (can have thyrotoxicosis but less severely)

Epidemiology: age 20-40; 5% of all females; female 8x

CAUSES OF THYROTOXICOSIS

COMMON

1. Graves' disease
2. Toxic multinodular goitre (TMG)
3. Toxic adenoma (TA)
4. Thyroiditis (early phase)
5. Thyroxine over-replacement
6. Exogenous iodine excess (diet) *Jod-Basestow effect: iodine-induced hyperthyroidism in pts w/ goitre*
7. Drugs (Amiodarone analogous to T4 and cytotoxic to follicular cells)
8. Thyrotoxicosis factitia

LESS COMMON

9. TSH-secreting tumours (pituitary)
10. hCG-secreting tumours (choriocarcinoma)(pregnancy)
11. Struma ovarii (ovarian teratoma w/ >50% thyroid tissue)
12. Thyroid cancer metastases

GRAVES' DISEASE (DIFFUSE TOXIC GOITRE)

90% have anti-TPO Abs

Autoimmune: thyroid receptor autoantibodies (TRAbs) bind TSH 'ceptors→constitutive stimulation→ thyrotoxicosis
Type V hypersensitivity/associated with other autoimmune diseases/ genetics: HLAB8,DR2,DR3
Similar: *Yersina enterocolita* and *E. coli* have TSH binding sites → molecular mimickry
Macroscopic: symmetrically enlarged/rubbery/beefy red
Microscopic: follicular hyperplasia; absent colloid, columnar epithelium; very vascular

TOXIC MULTINODULAR GOITRE

Disorganised response to hyperstimulation → juxtaposed hyper/hypoplasia
Hyperthyroid from hyperplastic nodules (escape need for TSH stimulation → autonomous) + atrophy of rest of gland
Eventually hypothyroid when hyper plastic nodules atrophy

SOLITARY TOXIC ADENOMA

Somatic mutation of genes regulating thyroid hormone synth → autonomous hormone-producing toxic adenoma (Plummer's adenoma)

THYROIDITIS

CLINICAL FEATURES OF HYPERTHYROIDISM **Increase in BMR and sympathetic tone**
CNS: Restless/hyperaesthestic/hyperkinetic/tremor
MOOD: Irritable/insomnia
ENDO/METABOLIC: Heat intolerance (increased basal metabolic rate → thermogenesis)/Weight loss
CVS: tachycardia, palpitations, sweating *AF/cardiac failure*
GI: appetite increase/vomiting/diarrhoea
SKIN: *only in Graves*; onycholysis, palmar erythema, itching, other Graves' changes
MUSCLES: upper limb wasting/myopathy
EYES: *only in Graves*; see below
GU: loss of libido/oligomenorrhoea and lighter periods/gynaecomastia

Kids: tall stature, behavioural disorders, learning difficulties

FEATURES OF GRAVES'
1. OPTHALMOPATHY (50%, especially if smoker, can precede thyrotoxicosis)
Cytokines in chronic retro-orbital inflammation induce fibroblasts → secrete hydrophilic GAGs → interstitial oedema and fibrosis
a)corneal exposure (proptosis/lid retraction as lev palp sup is overactive/lid lag)
b)exophthalmos with diplopia (oedema and fibrosis of extra-ocular muscles)
c)optic nerve compression → optic atrophy (increased retrobulbar pressure)
d)chemosis (conjunctival oedema due to obstructed venous and lymphatic drainage)

2. PRETIBIAL MIXOEDEMA (10%) *Infiltrative dermopathy: fibroblasts deposit hyaluronic acid in dermis → thickening of skin*
Orange/purple/pink plaques on anterior leg/dorsum of foot (non-pitting)

3. THYROID ACROPACHY (<1%) Clubbing and new bone formation in fingers

Differentiating from anxiety:
(i)Warmth of hands (cold in anxiety, warm in thyrotoxicosis)
(ii)Tachycardia (sleeping tachycardia suggests thyrotoxicosis)
(iii)Other signs ie goitre, proximal myopathy and wasting, extra-thyroid features of Graves'

INVESTIGATIONS
1. ESTABLISH HYPERTHYROIDISM
TSH: most sensitive/specific thyroid status test; usable in screening
Inverse log linear r'ship between TSH and free T4 (if intact pit-thyroid axis); small Ft4 change → large TSH changes
Overt hyperthyroidism: undetectable TSH + elevated FT4/FT3
Mild hyperthyroidism: detectable low TSH + normal FT4/slightly elevated FT3
Subclinical hyperthyroidism: low TSH + normal FT4/FT3

2. ESTABLISH AETIOLOGY
General 5 step plan: History/examination/TRAbs||thyroid uptake scans (Graves') +USS (hot nodule) *USS only if pregnant*
Graves 2 step plan: extrathyroid symptoms and signs + confirmed by TRAbs → no need to image
Non-Graves' aetiology suspected → thyroid uptake scan + US neck for nodule (US if pregnant; further anatomical info obtained)

Tracer uptake patterns:
Graves: diffuse uptake
TMNG: patchy uptake
TA: focal uptake with suppressing of surrounding thyroid and contralateral lobe
Thyroiditis/thyr factitia/iodine excess have absent uptake

MANAGEMENT

Modes: (i)Symptomatic and (ii)definitive management OR (i)surgical and (ii)non-surgical
Non-surgical management can be definitive or can be in preparation for surgery

GRAVES' DISEASE

3 modalities with equivalent long-term QoL; RAI preferred in USA, ATDs +/- surgery in Europe and Japan

1. ^{131}I (radioactive iodine therapy, RAI) CONTRAINDICATED IF EYE SIGNS

Mechanism: Iodine trapped and organified in thyroid
Use: Must be euthyroid with no drugs 4 days before and 3 days after last dose (inhibited by ATDs and low TSH)
Problems: (i)worsens opthalmopathy (ii)Jod-Basestow effect (lessened with propranolol/carbimazole prior) (iii)hypothyroidism in ensuing 6mths
Outcomes: Most achieve normal TFTs and symptom resolution in 4-8 weeks (long half-life)
Follow-up: monitor clinical features and TFTs +/- T4 replacement vs hypothyroidism

2. Anti-thyroid drugs (ATDs) PREFERRED OPTION IN PREGNANCY AND DOESN'T WANT SURGERY

(a)Carbimazole/methimazole are drugs of choice (dose titration/block and replace)
(b)PTU in T1 pregnancy (carbimazole crosses placenta better than maternal T4)/thyroid storm/major reaction to (a)
Mechanism: carb/meth immunosuppressive, block T4 synths, block de-iodination of T4 to T3; PTU blocks t3/4 synth and TPO
Risks: agranulocytosis, aplastic anaemia (Basal WCC and LFTs before starting these drugs)

3. Total thyroidectomy

6 indications: patient preference/urgent control/compressive goitre/contraindicated ATD or RAI/failed medical treatment
Complications: RLN injury (0.2%), permanent hypo Ca^{2+}(2%), bleeding (2%)

TOXIC MULTINODULAR GOITRE

TTx: recurrence <1% so treatment of choice

TOXIC ADENOMA

Surgery: thyroid lobectomy (<1% recurrence cf ^{131}I= 18%) is treatment of choice
Atrophy of rest of gland so only nodule takes up tracer/^{131}I
Complications: RLN injury (0.1%)

Operative considerations

1. Patient must be euthyroid: (i)**carbimazole** up until night before op (ii)**B-blockers** pre- and continued 7 days post-op)
2. Iodine (Lugol's solution/saturated solution of potassium iodide or inorganic iodine) for 10 days pre-op reduces gland vascularity/make firmer
   steroids can be added in emergency setting requiring rapid preparation
3. Thyroid storm: fever/hyperthermia, delirium, tachycardia, diarrhoea, jaundice; 10% mortality; physiological stress initiates
   treat with iv fluids, iv hydrocortisone, PTU, B-blockers, cooling blankets, sedatives
4. Postoperative hypocalcaemia: bone hunger in severe Graves' requiring large amounts of calcium and calcitriol; measure iPTH and serum calcium post-op as well as magnesium
5. Laryngoscopy: RLN function
6. Serum calcium estimation