THYROTOXICOSIS

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Thyroid disease is the commonest endocrinopathy after diabetes. The physiological role of thyroid hormones ensures a diverse range of pathology involving most body systems including, for example, bone. Thus all clinicians need an understanding of the condition.

THYROID PHYSIOLOGY

The thyroid is particularly good at capturing iodine – as are gastric and salivary glands. Tissue is arranged in follicles of cuboidal epithelium which store thyroid hormones in a central pool of colloid – the appearance and turnover varying with activity. Iodine uptake, all processes leading to the formation, turnover and release of thyroid hormones (Table 1), and growth of the thyroid gland are regulated by the pituitary glycoprotein thyroid stimulating hormone (TSH). Note that T_3 is the active hormone. The hypothalamo-pituitary-thyroid axis is regulated by a classic negative feedback loop with additional input eg from dopamine (Figure 1). Interference at any level may cause disease.

THYROTOXIC DISEASE

Typical symptoms and signs of thyrotoxicosis are given in Table 2. They are, however, non-specific and none is inviolate – so obese people can be thyrotoxic and weight gain

- organification
 - **thyroglobulin** production containing much tyrosine
 - peroxidase for tyrosine iodination → thyroxine + T_3 production in the colloid on thyroglobulin
 - pinocytosis
 - breakdown of **thyroglobulin** and release of T_4 (85%) + T_3 (15%)
- Thyroglobulin** is hardly secreted and can be used as a marker of malignancy.

Table 1 TSH stimulated processes in thyroid hormone production

Symptoms	Signs
<ul style="list-style-type: none">• weight loss• heat intolerance• anxiety and irritability• sweating• increased appetite• lack of energy• loose stool• thirst• palpitations• pruritis	<ul style="list-style-type: none">• tremor• warm and sweaty skin• tachycardia• “jumpy and flighty” presentation• lid retraction• systolic hypertension, wide pulse pressure• atrial fibrillation• muscle weakness• gynaecomastia
<ul style="list-style-type: none">• weight gain• breathlessness	<p>Graves’ disease</p> <ul style="list-style-type: none">• bruit, soft symmetric goitre• eye signs• infiltrative dermopathy• acropachy

Table 2 – Symptoms and signs of thyrotoxicosis

Fig 1 The hypothalamo-pituitary-thyroid axis

may occur. Additional features include shortness of breath, thirst, lethargy and tiredness. Muscle weakness is also common and the elderly may become withdrawn. Remember thyrotoxicosis can be dangerous, causing heart failure and atrial fibrillation leading to embolisation and stroke. Warfarinisation is therefore advisable in either of these situations. Metabolic changes may also occur, particularly hypercalcaemia.

CAUSES OF THYROTOXICOSIS

Thyrotoxicosis may result from inappropriate stimulation of the thyroid gland, autonomous function of the gland, release of stored thyroid hormone from the colloid, or over-medication.

Inappropriate stimulation by TSH may occur, either from a TSH-producing pituitary adenoma or Struma ovarii, but both are extremely rare. TSH-producing adenomas present biochemically with elevated free thyroid hormones and detectable TSH – which need to be distinguished from assay

interference and from thyroid hormone resistance states, one of the few remaining reasons for the thyroid-releasing hormone (TRH) test. Occasional confusion arises because the latest generation of TSH assays are not used locally, and because some drugs (particularly diclofenac) can cause assay interference leading to apparently elevated free T₃ values.

Autoimmune stimulation of the TSH receptor is the basis of Graves' Disease, the commonest thyrotoxic pathology. Occasionally a mixture of stimulating and blocking antibodies is present, the ratio of which, in addition to disease activity, can affect the degree of toxicosis. Rarely, episodes of hypothyroidism occur. There is a 9:1 female predominance, often a positive family history, an association with other disease states, and specific associated autoimmune phenomena may occur. The gland is typically soft and smoothly enlarged, often with a thyroid bruit present. TPO (microsomal) and TSH receptor antibodies are helpful in making the diagnosis, but are not always positive.

We must look out for associated conditions. Ophthalmopathy may start before, during or after a thyrotoxic episode and may be uni- or bi-lateral. If it is uni-lateral, orbital scans may be needed to exclude tumours. There is swelling and later fibrosis of the intraorbital muscles, which push the eye forward (biophthalmos and proptosis). A diagnostic feature is inflammation of the lateral rectus insertion. Other features include impaired eye movement with diplopia particularly on upward gaze due to muscle tethering. Exophthalmos may prevent closure of the lids resulting in exposure keratitis so that artificial tears during the day and ointment (eg: lacrilube) overnight are needed. Surgery may be required. Rarely, marked oedema occurs. In

severe disease the muscles can compress the optic nerve leading to blindness and this is, paradoxically, most often the case when the orbit cannot move forward, so that exophthalmos is less noticable. Monitoring visual accuity and orbital imaging are important in deciding whether steroid treatment, surgical decompression or even orbital radiotherapy are necessary to control the disease. Early referral is advised – once fibrosis has set in, it cannot be reversed. The antigen responsible is unknown, but we know that ophthalmopathy is aggravated by smoking. Many have thought the condition was worsened by destructive thyroid therapy (surgery or radio-iodine), but recent evidence shows that this is unlikely to be the case. Infiltrative dermatopathy (pretibial myxoedema) also occurs and is difficult to treat. Occlusive steroid dressings may help. Thyroid acropachy and osteopathy are other uncommon manifestations.

Autonomous thyroid function occurs with adenomas (hot nodules) and toxic multinodular goitres (TMG). Cancer is rarely thyrotoxic. Why bother to discriminate between Graves' Disease and autonomous function? Because both hot nodules and TMG are progressive conditions and therefore need longterm or definitive therapy. If untreated, patients become increasingly toxic. Treatment is needed when the patient becomes toxic – which may be after the TSH has been suppressed. Clinical examination and negative antibodies, sometimes with pertechnate scanning, aid diagnosis and management.

Release of stored hormones from the colloid occurs in acute thyroiditis, which may be silent or have local symptoms of discomfort or pain. This is an inflammatory condition that causes transient toxicosis but also suppresses the gland. Thus,

Visit	Graves' Disease: Tablets		Post-RAI	Radio-iodine	Hypothyroid	
	Time	Action	Time	Action	Time	Action
1	0	Carbimazole (CBZ) 10-20 mg BD, ? β -blocker, see 1 month	0	? β -blocker, Book RAI * See in 8-10 weeks	0	Usually start 50 or 100 μ g T ₄ daily. See 2 month
2	1m	↓ CBZ 20mg ? stop β -blocker, see 2 months	6w	? stop β -blocker, ? hypothyroid - treat. No – see 6 weeks	2m	? Euthyroid – annual check. No – adjust T ₄
3	3m	↓ CBZ 10mg see 4 months	12w	Not hypothyroid? See 6 weeks	6m	? Euthyroid - annual check. No – adjust T ₄
4	7m	? adjust CBZ see 6 months*, 1 month after stopping CBZ	18w	Not hypothyroid? See 6 weeks, etc	10m	As above.
5	13m	? relapse ? RAI	6m	Not hypothyroid? ? more RAI if toxic		
6	15m	? relapse ? RAI	9m	Not hypothyroid?		
7	19m	? relapse ? RAI	12m	Not hypothyroid?		
8	25m	? relapse ? RAI No – annual check	18m	Not hypothyroid?		
9			24m	Not hypothyroid? No – annual check		

Table 3 – Usual management schedules of some thyroid disease

note: this is only a rough guide and some of the Graves' patients may need different doses and more frequent visits eg *.

* RAI is currently provided at the Christie Hospital, but all the facilities and licences for outpatient therapy are available in Lancaster through Dr Walmsley. It is expected that the Royal Lancaster Infirmary will be able to offer the service in the near future subject to agreement of funding transfer with the health authority.

if suspected, a radio-iodine isotope scan is useful as it will be cold. Specific treatment is not warranted, although beta-blockade will help toxic symptoms. A period of hypothyroidism, transient or permanent, follows. Patients with autoantibodies are particularly likely to develop subsequent hypothyroidism and need replacement therapy. All should be on longterm follow-up, even if euthyroidism has returned.

TREATMENT OF THYROTOXICOSIS

Non-selective beta-blockers are effective for symptomatic control.

Carbimazole, methimazole and propylthiouracil block the peroxidation and organification of iodine. They have a lag effect until T₄ and T₃ reserves are released. They also increase the proportion of T₃ secreted. Unlike the other two, propylthiouracil in large doses inhibits T₄ to T₃ conversion, although the shorter half-life leads to more frequent dosing regimes. There is an immunosuppressive effect so that after control of the toxicosis, the reduced dose is maintained for 12-18 months to try to prevent recurrence. Nonetheless over half of the patients will relapse, most within nine months. This has not been shown to be reduced by the higher dose "block and replacement" regimens, so that it is my practice to tailor dose to thyroid activity (Table 3). Thyroid activity is monitored by free thyroid hormone levels rather than TSH during treatment because the TSH may take many weeks to rise, even when the patient has become overtly hypothyroid. These drugs tend to be used for autoimmune thyrotoxicosis, as lifelong therapy is needed for autonomous conditions. As the relapse rate for Graves' Disease increases the second time round, radioiodine or occasionally surgery for large glands is then used. Men have increased relapse rates. Treatment in pregnancy is a more specialist area, needing care to avoid abortions and to monitor for potential neonatal difficulties.

- Treatment failure for Graves' disease (any cause)
- Second or third relapse of Graves' disease
- Consider in first attacks of older Graves' patients with poor prognostic signs
- Toxic multinodular goitre
- Toxic adenoma (hot nodule)

Table 4 – Indications for low dose (outpatient) radio-iodine therapy

Treatment of amiodarone-induced thyrotoxicosis is a special case because the peripheral conversion of T₄ to T₃ is also blocked. High dose carbimazole with replacement triiodothyronine two or three times daily is usually required. Radioiodine is a very useful therapy (Table 4), but is contraindicated in pregnancy. After a dose, patients must avoid potentially pregnant women as well as children for a time. This will affect therapeutic decisions. Radioiodine is being used in younger patients more frequently. Outcome varies with dose, but about 95% of cases are effectively treated with a single dose. With time, a gradually increasing percentage of cases develop hypothyroidism, necessitating longterm follow-up and therapy. This is not the case for toxic adenoma where the rest of the gland is suppressed. Therapy is therefore targeted at the adenoma with a considerably lower risk of long term sequelae. Controversial areas remain the dose of radioiodine to use and risk of malignancy. No good evidence of an increased thyroid malignancy rate exists. The situation remains under review. The risk of stomach cancer is less well researched, although patients treated with high-dose radioiodine for differentiated thyroid cancer seem to live longer than the normal population!

Surgery is as effective as radio-iodine for toxic adenoma, but has the risk of damage to the recurrent laryngeal nerve and hypoparathyroidism – both rare with an experienced surgeon.