Graves' disease

Graves' disease can occur at any age but is unusual before puberty and most commonly affects women aged 30–50 years .The most common manifestation is thyrotoxicosis with or without a diffuse goitre. Graves' disease also causes ophthalmopathy and, rarely, pretibial myxoedema .

These extrathyroidal features usually occur in thyrotoxic patients but can arise in the absence of thyroid dysfunction.

Graves' thyrotoxicosis

Pathophysiology

The thyrotoxicosis results from the production of immunoglobulin G (IgG) antibodies directed against the TSH receptor on the thyroid follicular cell, which stimulate thyroid hormone production and proliferation of follicular cells, leading to goitre in the majority of patients. These antibodies are termed thyroid-stimulating immunoglobulins or TSH receptor antibodies (TRAb) and can be detected in the serum of 80–95% of patients with Graves' disease.

The concentration of TRAb in the serum is presumed to fluctuate to account for the natural history of Graves' thyrotoxicosis . Thyroid failure seen in some patients may result from the presence of blocking antibodies against the TSH receptor, and from tissue destruction by cytotoxic antibodies and cell-mediated immunity Graves' disease has a strong genetic component.

A suggested trigger for the development of thyrotoxicosis in *genetically* susceptible individuals may be infection with viruses or bacteria. Certain strains of the *gut organisms* Escherichia coli and Yersinia enterocolitica possess cell membrane TSH receptors and it has been suggested that antibodies to these microbial antigens may cross-react with the TSH receptors on the host thyroid follicular cell. In regions of *iodine deficiency* ,iodine supplementation can precipitate thyrotoxicosis, but only in those with pre-existing subclinical Graves' disease.

Smoking is weakly associated with Graves' thyrotoxicosis but strongly linked with the development of ophthalmopathy.

Management

Symptoms of thyrotoxicosis respond to β-blockade but definitive treatment requires control of thyroid hormone secretion.

Some clinicians adopt an empirical approach of prescribing a course of antithyroid drug therapy and then recommending 131I or surgery if relapse occurs.

Antithyroid drugs :The most commonly used are carbimazole and its active metabolite, methimazole ,the Propylthiouracil is equally effective. These drugs reduce the synthesis of new thyroid hormones by inhibiting the iodination of tyrosine . Carbimazole also has an immunosuppressive action, leading to a reduction in serum TRAb concentrations, but this is not enough to influence the natural history of the thyrotoxicosis significantly.

Antithyroid drugs should be introduced at high doses (carbimazole 40–60 mg daily or propylthiouracil 400–600 mg daily). Usually, this results in subjective improvement within 10–14 days and renders the patient clinically and biochemically euthyroid at 6–8 weeks. At this point, the dose can be reduced and titrated to maintain T4 and TSH within their reference range.

In most patients, carbimazole is continued at 5–20 mg per day for 12–18 months in the hope that remission will occur. Between 50% and 70% of patients with Graves's disease will subsequently relapse, usually within 2 years of stopping treatment. Risk factors for relapse include *younger age, male sex, presence of a goitre, and higher TRAb titres at both diagnosis and cessation of antithyroid therapy*.

Antithyroid drugs can have adverse effects. The most common is a rash. Agranulocytosis is a rare but potentially serious complication that cannot be predicted by routine measurement of white blood cell count but which is reversible on stopping treatment. Patients should be warned to stop the drug and seek medical advice immediately, should a severe sore throat or fever develop while on treatment. Propylthiouracil is associated with a small but

definite risk of hepatotoxicity, which, in some instances, has resulted in liver failure requiring liver transplantation, and even in death. It should therefore be considered second-line therapy to carbimazole and be used only during pregnancy or breastfeeding , or if an adverse reaction to carbimazole has occurred.

Thyroid surgery: Patients should be rendered euthyroid with antithyroid drugs before operation. Oral potassium iodide, 60 mg three times daily, is often added for 10 days before surgery to inhibit thyroid hormone release and reduce the size and vascularity of the gland, making surgery technically easier. Traditionally, a 'subtotal' thyroidectomy is performed, in which a portion of one lobe of the thyroid is left in situ, with the aim of rendering the patient euthyroid. While complications of surgery are rare and 80% of patients are euthyroid, 15% are permanently hypothyroid and 5% remain thyrotoxic. As a consequence, many endocrine surgeons now opt to perform a 'near-total' thyroidectomy, leaving behind only a small portion of gland adjacent to the recurrent laryngeal nerves. This strategy invariably results in permanent hypothyroidism and is probably associated with a higher risk of hypoparathyroidism, but maximises the potential for cure of thyrotoxicosis.

Radioactive iodine 131I is administered orally as a single dose and is trapped and organified in the thyroid . 131I emits both β and γ radiation and, although it decays within a few weeks, it has long-lasting inhibitory effects on survival and replication of follicular cells. The variable radio-iodine uptake and radiosensitivity of the gland means that the choice of dose is empirical. This regimen is effective in 75% of patients within 4–12 weeks.

If thyrotoxicosis persists after 6 months, a further dose of 131I can be given. The disadvantage of 131I treatment is that the majority of patients eventually develop hypothyroidism.

131I is usually avoided in patients with Graves' ophthalmopathy and evidence of significant active orbital inflammation. It can be administered with caution in those with mild or 'burnt-out' eye disease, when it is customary to cover the treatment with a 6-week tapering course of oral prednisolone. In women of reproductive age, pregnancy must be excluded

before administration of 131I and avoided for 6 months thereafter; men are also advised against fathering children for 6 months after receiving 131I.

18.14 Comparison of treatments for the thyrotoxicosis of Graves' disease

Management	Common indications	Contraindications	Disadvantages/complications
Antithyroid drugs (carbimazole, propylthiouracil)	First episode in patients <40 years	Breastfeeding (propylthiouracil suitable)	Hypersensitivity rash 2% Agranulocytosis 0.2% Hepatotoxicity (with propylthiouracil) – very rare but potentially fatal >50% relapse rate usually within 2 years of stopping drug
Subtotal thyroidectomy[1]	Large goitre Poor drug adherence, especially in young patients Recurrent thyrotoxicosis after course of antithyroid drugs in young patients	Previous thyroid surgery Dependence on voice, e.g. opera singer, lecturer[2]	Hypothyroidism (~25%) Transient hypocalcaemia (10%) Permanent hypoparathyroidism (1%) Recurrent laryngeal nerve palsy[2] (1%)
Radio-iodine	Patients >40 years[3] Recurrence following surgery Irrespective of age Other serious comorbidity	Pregnancy or planned pregnancy within 6 months of treatment Active Graves' ophthalmopathy[4]	Hypothyroidism: ~40% in first year, 80% after 15 years Most likely treatment to result in exacerbation of ophthalmopathy[4]

[1]A near-total thyroidectomy is now the favoured operation for Graves' thyrotoxicosis in many institutions and is associated with a higher risk of some complications, including hypothyroidism (nearly 100%), but a reduced risk of persistent or recurrent thyrotoxicosis. [2]It is not only vocal cord palsy due to recurrent laryngeal nerve damage that alters the voice following thyroid surgery; the superior laryngeal nerves are frequently transected and this results in minor changes in voice quality. [3]In many institutions, ^{131}I is used more liberally and is prescribed for much younger patients. [4]The extent to which radio-iodine exacerbates ophthalmopathy is controversial and practice varies; some use prednisolone to reduce this risk.

Thyrotoxicosis in pregnancy

Thyrotoxicosis in pregnancy may be associated with significant maternal and fetal morbidity.

Hyperthyroidism

The coexistence of pregnancy and thyrotoxicosis is unusual, since anovulatory cycles are common in thyrotoxic patients and autoimmune disease tends to remit during pregnancy, due to suppression of the maternal immune response. Thyroid function tests must be interpreted in the knowledge that thyroid-binding globulin, and hence total T4 and T3 levels, are increased in pregnancy and that the normal range for TSH is lower. Despite this, a fully suppressed TSH is usually indicative of Graves' disease. When thyroid disease during pregnancy is being dealt with, both mother and fetus must be considered, since maternal thyroid hormones, TSH receptor antibodies (TRAb) and antithyroid drugs can all cross the placenta to some degree, exposing the fetus to the risks of thyrotoxicosis, iatrogenic hypothyroidism and goitre. Moreover, poorly controlled thyrotoxicosis can result in fetal tachycardia, intrauterine growth retardation, prematurity, stillbirth and possibly even congenital malformations.

Antithyroid drugs are the treatment of first choice for thyrotoxicosis in pregnancy. Newly diagnosed hyperthyroidism during pregnancy can be treated with *β-adrenoceptor antagonists (β-blockers)* in the short term, followed by antithyroid drugs. *Propylthiouracil (PTU)* is the preferred antithyroid drug because treatment with carbimazole during the first trimester has been associated with the occurrence of choanal atresia and aplasia cutis. Hyperthyroid women who become pregnant while taking carbimaole or PTU should be advised to continue their current drug in pregnancy, with close monitoring. Both carbimazole and PTU cross the placenta and are effective in treating thyrotoxicosis in the fetus caused by transplacental passage of TRAb. To avoid fetal hypothyroidism, which can affect brain development and cause goitre, it is important to use the smallest dose of antithyroid drug (typically < 150 mg PTU or 15 mg carbimazole per day) that will maintain maternal free T4, T3 and TSH concentrations within

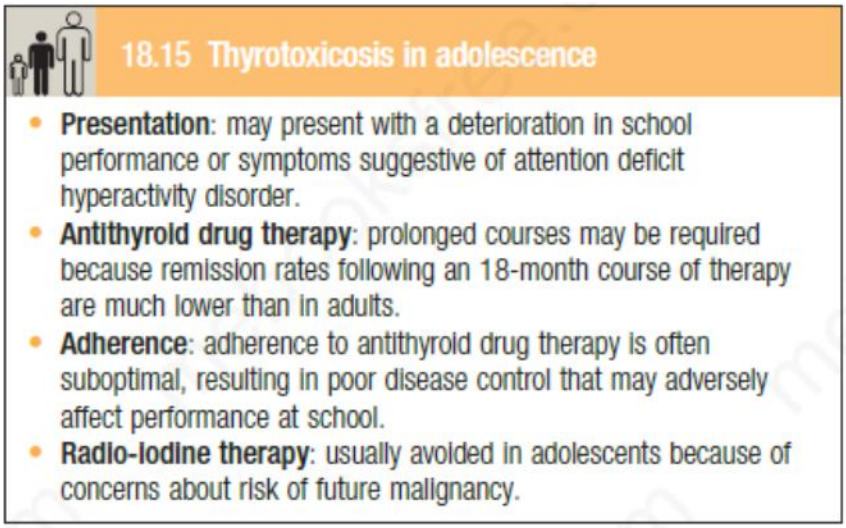
their respective reference ranges. Thyroid surgery is sometimes necessary because of poor drug adherence, drug hypersensitivity or failure of medical treatment and is most safely performed during the second trimester. Radioactive iodine is *absolutely contraindicated* throughout pregnancy, as it invariably induces fetal hypothyroidism. Frequent review of mother and fetus (monitoring heart rate and growth) is important during pregnancy and in the puerperium. Serum TRAb levels can be measured in the third trimester to predict the likelihood of neonatal thyrotoxicosis. PTU is the drug of choice in the breastfeeding mother, as it is excreted in the milk to a much lesser extent than carbimazole. Thyroid function should be monitored periodically in the breastfed child.

Post-partum thyroiditis

Post-partum thyroiditis typically presents 3–4 months after delivery. The maternal immune response, which is modified during pregnancy to allow survival of the fetus, is enhanced after delivery and may unmask previously unrecognised subclinical autoimmune thyroid disease. However, symptomatic thyrotoxicosis presenting for the first time within 12 months of childbirth is likely to be due to post-partum thyroiditis and the diagnosis is confirmed by a negligible radio-isotope uptake. The clinical course and treatment are similar to those of painless subacute thyroiditis .Post-partum thyroiditis tends to recur after subsequent pregnancies, and eventually patients progress over a period of years to permanent hypothyroidism.

Thyrotoxicosis in adolescence

Thyrotoxicosis can occasionally occur in adolescence and is almost always due to Graves' disease. The presentation may be atypical and management challenging.



18.15 Thyrotoxicosis in adolescence

- **Presentation**: may present with a deterioration in school performance or symptoms suggestive of attention deficit hyperactivity disorder.
- **Antithyroid drug therapy**: prolonged courses may be required because remission rates following an 18-month course of therapy are much lower than in adults.
- **Adherence**: adherence to antithyroid drug therapy is often suboptimal, resulting in poor disease control that may adversely affect performance at school.
- **Radio-iodine therapy**: usually avoided in adolescents because of concerns about risk of future malignancy.

Graves' ophthalmopathy

This condition is immunologically mediated but the autoantigen has not been identified. Within the orbit (and the dermis) there is cytokine-mediated proliferation of fibroblasts that secrete hydrophilic glycosaminoglycans. The resulting increase in interstitial fluid content, combined with a chronic inflammatory cell infiltrate, causes marked swelling and ultimately fibrosis of the extraocular muscles and a rise in retrobulbar pressure. The eye is displaced forwards (proptosis, exophthalmos) and in Ophthalmopathy, like thyrotoxicosis , typically follows an episodic course and it is helpful to distinguish patients with active inflammation (periorbital oedema and conjunctival inflammation with changing orbital signs) from those in whom the inflammation has 'burnt out'. Eye disease is detectable in up to 50% of thyrotoxic patients at presentation, but active ocular inflammation may occur before or after thyrotoxic episodes (exophthalmic Graves' disease). It is more common in cigarette smokers and is exacerbated by poor control of thyroid function, especially hypothyroidism.

The most frequent presenting symptoms are related to increased exposure of the cornea, resulting from proptosis and lid retraction. There may be excessive lacrimation made worse by wind and bright light, a 'gritty' sensation in the eye, and pain due to conjunctivitis or corneal ulceration. In addition, there may be reduction of visual acuity and/or visual fields as a consequence of corneal oedema or optic nerve compression. Other signs of

optic nerve compression include reduced colour vision and a relative afferent pupillary defect . If the extraocular muscles are involved and do not act in concert, diplopia results. The majority of patients require no treatment other than reassurance.

Smoking cessation should be actively encouraged. Methylcellulose eye drops and gel counter the gritty discomfort of dry eyes, and tinted glasses or side shields attached to spectacle frames reduce the excessive lacrimation triggered by sun or wind. In patients with mild Graves' ophthalmopathy, oral selenium (100 μg twice daily for 6 months) improves quality of life, reduces ocular involvement and slows progression of disease; the mechanism of action is not known but may relate to an antioxidant effect. More severe inflammatory episodes are treated with glucocorticoids (e.g. pulsed intravenous methylprednisolone) and sometimes orbital radiotherapy. There is also an increasing trend to use alternative immunosuppressive therapies, such as rituximab and ciclosporin. Loss of visual acuity is an indication for urgent surgical decompression of the orbit. In 'burnt-out' disease, surgery to the extraocular muscles, and later the eyelids, may improve diplopia, conjunctival exposure and cosmetic appearance.

Pretibial myxoedema

This infiltrative dermopathy occurs in fewer than 5% of patient with Graves' disease and has similar pathological features as occur in the orbit. It takes the form of raised pink-coloured or purplish plaques on the anterior aspect of the leg, extending on to the dorsum of the foot . The lesions may be itchy and the skin may have a 'peau d'orange' appearance with growth of coarse hair; less commonly, the face and arms are affected. Treatment is rarely required but in severe cases topical glucocorticoids may be helpful.