

Hyperthyroidism: What the generalist should know

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Hyperthyroidism is a relatively common problem, particularly among women. Its management can be complex and requires a good understanding of the underlying pathology.

Thyrotoxicosis is one of the more common endocrine disorders and most cases result from hyperactivity of the thyroid gland (hyperthyroidism) (Table I).

Table I. Causes of hyperthyroidism

Common

- Graves' disease
- Toxic multinodular goitre
- Single toxic nodule
- Thyroiditis

Rare

- Struma ovarii
- Thyroid carcinoma
- Trophoblastic disease
- 'Hamburger thyrotoxicosis'
- Syndrome of inappropriate TSH secretion

THYROTOXICOSIS

Younger patients with thyrotoxicosis of any cause may present with palpitations, anxiety, easy fatigability, psychomotor activity, diarrhoea, excessive sweating, heat intolerance, preference for cold, amenorrhoea, and marked weight loss without appetite loss.

However, there is a small group of hyperthyroid patients who describe weight gain at presentation as a result of increased appetite exceeding the increase in basal metabolic rate induced by excess thyroid hormones.

The clinical features of tachycardia, tremor, sweating and lid lag associated with thyrotoxicosis suggest catecholamine

excess. Yet circulating levels of catecholamines are normal and the increased sympathetic activity is accounted for by an increased number of beta-receptors. Thyroid enlargement and muscle weakness may occur.

Elderly patients commonly present with cardiovascular involvement such as atrial fibrillation and develop palpitations and dyspnoea on exertion. Older patients may also present with 'apathetic' hyperthyroidism.

Laboratory findings

Primary hyperthyroidism is confirmed by a suppressed thyroid-stimulating hormone (TSH), with an elevated free T₄ or free T₃ in the case of a normal free T₄.

As the cause of hyperthyroidism may not be evident clinically, further investigation is frequently required, using a technetium thyroid uptake scan.

Therapy

The specific therapeutic modality for hyperthyroidism is dependent upon the underlying cause. Options include antithyroid drug therapy, surgery and radioactive iodine. However, treatment varies according to the cause of hyperthyroidism.

Beta-blockade is an important adjunct to therapy and has greatest value in counteracting the sympathetic overactivity. In asthmatics calcium channel blockers may be used as an alternative to beta-blockers. Calcium channel blockers may successfully block chronotropy but will fail to coun-

Table II. Specific options for management of various causes of hyperthyroidism

Graves' disease	Antithyroid drugs, radioactive iodine, surgery
Toxic multinodular gland*	Radioactive iodine or surgery
Toxic adenoma*	Radioactive iodine or surgery
Thyroiditis	Beta-blocker and in cases of painful subacute thyroiditis aspirin or glucocorticoids, depending on severity

* The primary care physician may wish to stabilise the patient on antithyroid drugs initially, while arranging definitive therapy.

teract the excess sympathetic over-activity (Table II).

GRAVES' DISEASE

Graves' disease is the most common form of thyrotoxicosis. It is an autoimmune condition of unknown aetiology and occurs more commonly in women. There is a strong familial predisposition as 15% of patients have a close relative with Graves' disease and circulating thyroid antibodies are found in 50% of relatives.

Pathogenesis

Graves' disease results from the sensitisation of T lymphocytes to antigens within the thyroid. The subsequent stimulation of B lymphocytes results in the synthesis of antibodies to the TSH receptor on the thyroid cell membrane. These antibodies have the ability to promote thyroid cell growth and function (TSH receptor-stimulating antibodies) and their presence is positively correlated with active disease and relapse. The sensitised lymphocytes release cytokines which cause inflammation of the orbital fibroblasts and orbital muscles, resulting in swollen orbital muscles and proptosis.

Predisposing factors for the development of Graves' disease

In the majority of cases no cause can be identified, but certain factors have been shown to incite the

development of Graves' disease. These include the postpartum period where there is a resurgence of immune-mediated conditions, iodide exposure to patients from iodide-deficient areas, lithium therapy, viral or bacterial infections, glucocorticoid withdrawal and stress.

Clinical features

There are a number of clinical features which are so specific to Graves' disease that diagnosis can be certain once hyperthyroidism is confirmed biochemically. These include: a diffusely enlarged thyroid gland with an obvious bruit, Graves' ophthalmopathy and thyroid dermopathy which consists of thickening of the skin, particularly the lower tibia, due to the accumulation of glycosaminoglycans (Fig. 1).



Fig. 1. Severe thyroid dermopathy.

Thyroid dermopathy is relatively rare, with an incidence of 2 - 3% of patients with Graves' disease. It is usually associated with ophthalmopathy.

Graves' ophthalmopathy is most commonly bilateral, but may be unilateral (Table III). Where unilateral, the diagnosis may be made once there has been confident exclusion of a unilateral mass lesion behind the proptosed eye (Fig. 2).

A relatively common additional finding is onycholysis where there is separation of the fingernails from their beds. It is easy to recognise because of the accumulation of grime, despite the best intention to keep the nails clean. This on its own is not diagnostic of Graves' disease.

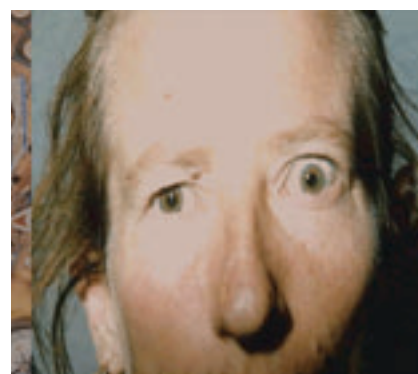


Fig. 2. Unilateral Graves' ophthalmopathy.

Laboratory findings

A suppressed TSH and a normal T_4 mandates the checking of T_3 because it may indicate early Graves' disease. In the absence of any of the characteristic signs of Graves' disease a thyroid uptake scan is required for definitive diagnosis. An elevated, diffuse uptake on scan is diagnostic of Graves' disease.

Therapeutic options for treatment

Options for therapy for Graves' disease include antithyroid drug therapy, surgery and radioactive iodine.

Antithyroid drug therapy

This is most useful in younger patients. Either carbimazole or propylthiouracil may be used. The

Table III. Graves' disease eye signs

- Pain, painful oppressive feeling behind globe
- Pain on attempted up, side or down gaze
- Redness, redness of conjunctiva
- Swelling or chemosis of conjunctiva
- Oedema of eyelids
- Caruncle swelling
- Proptosis*
- Impaired function, decrease in visual acuity/one or more lines
- Decrease of eye movements in any direction $\geq 5^{\circ}$ *

*Increasing proptosis or decreasing eye movements are followed to determine the progression of Graves' eye disease.

normal starting doses of carbimazole are 30 - 45 mg per day and of propylthiouracil 300 - 450 mg per day. The therapy is continued for 12 - 18 months, with drug dosage titration dependent upon the levels of thyroid hormone.

Ideally TSH and T_4 should be monitored at approximately 6-weekly intervals.

An example of dose titration

A patient whose T_4 is 70 pmol/l (normal 11 - 24 pmol/l) would require in the order of 40 mg carbimazole. After 6 weeks of continued therapy the patient with a reasonably good response may have reached a T_4 of 30 pmol/l (Table IV). At this stage one is obliged to reduce the dose to 20 mg even though the patient remains thyrotoxic. Premature withdrawal of carbimazole will result in a higher relapse rate.

Sustained remission of Graves' disease can be predicted by the thyroid gland returning to normal size, if the TSH receptor-stimulating antibody is no longer detectable in serum (Table V), or if the disease can be controlled with a low dose of antithyroid drugs.

A rash may occur in 5% of patients taking antithyroid drugs and can be managed with antihistamines. Unless the rash is severe, it is not

an indication for discontinuing the antithyroid drugs. Agranulocytosis is a serious, potentially life-threatening complication which occurs less frequently, in approximately 0.5% of patients on antithyroid treatment. Agranulocytosis is often heralded by a sore throat and fever but may be asymptomatic. This complication demands the immediate cessation of antithyroid therapy. Other rare complications of antithyroid drugs include cholestatic jaundice, angioneurotic oedema and hepatocellular toxicity.

Surgery

Surgery for Graves' disease is considered when the thyroid gland is very large. In these cases a subtotal thyroidectomy is performed. The patient should be rendered euthyroid with antithyroid drugs before surgery. Potassium iodide is often administered before surgery to reduce the vascularity of the gland. Many centres in South Africa and in the UK preferentially treat Graves' disease with medical therapy, at least until there is failure of antithyroid drugs.

Table IV. Predictors of a good response to medical therapy in Graves' disease

- Small thyroid gland
- Only mildly elevated T_4 levels
- Female gender
- Age less than 50 years

Radioactive iodine

In the USA radioactive iodine is the preferred initial management in most patients over the age of 21 years. Usually the gland will shrink after administration of radioactive iodine. Patients with coexistent heart disease or severe thyrotoxicosis should preferably be treated with antithyroid drugs initially to achieve euthyroidism, and when euthyroid should be treated with radioactive iodine. The antithyroid drugs should be discontinued 5 - 7 days prior to administering radioactive iodine and recommenced 3 days after the radioactive iodine.

Ultimately hypothyroidism develops in 80% or more Graves' disease patients treated with radioactive iodine. Radioactive iodine may initially induce radiation thyrotoxicosis, with worsening of the thyrotoxicosis. This complication is fortunately rare and can be minimised by treating patients with very high levels of T_4 with antithyroid drugs before therapy with radioactive iodine. Radioactive iodine may worsen Graves' ophthalmopathy. Consequently, any patient with ophthalmopathy requires careful evaluation and consideration for steroid cover if radioactive iodine is to be administered.

TOXIC MULTINODULAR GOITRE

Typically thyrotoxicosis arises in older patients who have had a longstanding multinodular goitre.

Pathogenesis

Thyrotoxicosis results from the development of functional autonomy of some of the nodules over time. The precise mechanism of these changes is not known. However in some individuals thyrotoxicosis may be precipitated after excess iodine uptake, for example radio contrast material.

Table V. Predictors of sustained remission in Graves' disease

- If the thyroid gland returns to normal size
- Disease can be controlled with a relatively low dose of antithyroid drugs
- If the TSH receptor Ab (stim) is no longer detectable in the serum

Clinical features

The extent of overproduction of thyroid hormone in a toxic multinodular goitre is usually less dramatic than in Graves' disease. It usually occurs in patients over the age of 50 years. Cardiac manifestations of atrial fibrillation and tachycardia with or without cardiac failure tend to predominate. The nervous system manifestations are less apparent. As the gland may enlarge quite substantially, obstructive symptoms may result.

Laboratory investigations

In any patient with a multinodular goitre, it is essential to determine whether there is coexisting thyrotoxicosis. The laboratory findings consistent with this diagnosis are a suppressed TSH, often strikingly high T₃ and an increased T₄. Patchy uptake on technetium or radioiodine uptake scans, normal or elevated in quantity, suggests a toxic multinodular goiter.

Therapy

The treatment of choice for this condition is radioactive iodine, but surgery may be employed for larger glands. As many patients with this disorder are elderly and have underlying heart disease, medical therapy should be initiated to achieve euthyroidism before administration of radioactive iodine. The antithyroid therapy is temporarily withdrawn 5 days before the radioactive iodine and resumed 3 days after the administration of radioactive iodine.

TOXIC ADENOMA

A toxic adenoma, also referred to as Plummer's disease, is a less common cause of hyperthyroidism.

Pathogenesis

Pathogenically, this condition results from an adenoma which progressively gains autonomy and elaborates excessive amounts of thyroid hormone. A substantial proportion are caused by gain of function mutations in the TSH receptor gene. The progression of this condition can sometimes be visualised on thyroid scan. It commences as a hot nodule which slowly increases in size and gradually suppresses the other thyroid lobe. These adenomas are almost never malignant.

Clinical features

Toxic adenomas occur in younger patients, with a peak incidence in the 30 - 40-year age group. The nodule is felt as a smooth, well-defined round mass that moves on swallowing. Usually there is a history of a slow-growing lump in the neck, but thyrotoxicosis results when these lesions exceed 2.5 - 3.0 cm. These adenomas may undergo central necrosis and haemorrhage. Once again the peripheral manifestations are milder than in Graves' disease.

Laboratory tests

Once thyrotoxicosis supervenes the TSH is suppressed, the T₄ levels are occasionally normal, while only the T₃ is increased. Toxic adenoma is a frequent, known cause of T₃ toxicosis, although the usual scenario is for both T₃ and T₄ to be elevated.

Therapy

Smaller nodules are best managed by radioactive iodine therapy, while larger ones are best managed by surgical excision. Euthyroidism must be instituted medically before surgery.

THYROID CRISIS

A thyroid storm or thyroid crisis, as it is preferentially known, is a clinical syndrome where there is marked exaggeration of the thyrotoxicosis. It is an uncommon but serious complication. The clinical settings predisposing to the development of a thyrotoxic crisis or thyroid storm are shown in Table VI.

Table VI. Precipitants of thyrotoxic crisis (thyroid storm)

- Occurs after surgery
- Radioactive iodine
- Parturition
- Uncontrolled diabetes
- Trauma
- Acute infection
- Myocardial infarction
- Severe drug reaction

Pathogenesis

Although the pathogenesis of a thyroid crisis is uncertain, interestingly thyroid hormone levels are not higher than in patients with thyrotoxicosis without a thyroid storm. The fundamental difference is that the number of binding sites for catecholamines increases, so that the heart and nerves have increased sensitivity to catecholamines. There is also simultaneous decreased binding of T₃ and T₄ to thyroid binding globulin, resulting in increased free T₃ and free T₄.

Clinical features

Noticeably the hyperpyrexia that occurs with a thyroid storm is out of keeping with the other clinical features and may be accompanied

by profuse sweating. Marked tachycardia may be associated with congestive cardiac failure frequently manifesting with pulmonary oedema. At the outset of the crisis tremor and restlessness are characteristic, but as this disorder progresses apathy and coma may supervene. A late feature is the finding of hypotension. If the thyroid crisis is not recognised and not appropriately managed, it is invariably fatal.

Therapy

Therapy is aimed at correcting the severe thyrotoxicosis and the precipitating illness. Large doses of antithyroid drugs are given by mouth or nasogastric tube. Potassium iodide is then administered. In theory, it is desirable to administer antithyroid drugs before initiating potassium iodide therapy to prevent the release of preformed thyroid hormone. Large doses of dexamethasone may also be used as adjunctive therapy as it has the advantage of inhibiting the formation of T_3 from T_4 . A beta-blocker should be given in the absence of cardiac dysfunction or asthma to reduce the sympathetic effects of a thyroid crisis, and salicylates must be avoided. Addressing the thyrotoxicosis alone is insufficient and aggressive management of the underlying medical condition is warranted.

THYROIDITIS

Thyroiditis represents a group of heterogeneous disorders of which a common feature is an inflammatory infiltrate. Subacute or chronic thyroiditis are two groups of conditions that may give rise to hyperthyroidism. These patients present with acute release of preformed thyroid hormone-producing symptoms of mild to severe thyrotoxicosis. These illnesses can be distinguished from other causes of thyrotoxicosis by the markedly reduced

radioactive iodine uptake on thyroid scan. In addition, the natural tendency is for the symptoms to subside spontaneously over a period of weeks or months.

Subacute thyroiditis (De Quervain's thyroiditis)

This is an acute inflammatory disorder of the thyroid gland caused by a viral infection, and a prominent symptom is one of pain of the anterior part of the neck. Importantly, this occurs in the absence of erythema. Thyrotoxic features may be present and are usually accompanied by laboratory values consistent with thyrotoxicosis. The erythrocyte sedimentation rate is frequently greater than 100 mm per hour. For the most part only symptomatic treatment is necessary and a short course of aspirin or glucocorticoids may be necessary to reduce inflammation. Usually this results in spontaneous resolution of inflammation and restoration of euthyroidism. A variation of subacute painful thyroiditis is a painless form without elevated inflammatory markers. This occurs commonly in the postpartum period.

Chronic thyroiditis

Although this condition may manifest with hyperthyroidism, the vast majority of cases progress to hypothyroidism due to the relentless destruction of the thyroid gland. As this disease entity is associated with lymphocytic infiltration and high levels of circulating antibodies, it may coexist with other autoimmune conditions. These include type 1 diabetes, hypoadrenalism, premature ovarian failure and pernicious anaemia, among others. In keeping with its autoimmune character high titres of thyroid antibodies are helpful in clinching the diagnosis, but low titres of these antibodies do not exclude this disease especially in younger patients.

RARE FORMS OF THYROTOXICOSIS (TABLE I)

Thyrotoxicosis factitia

Thyrotoxicosis factitia is a psychoneurotic condition that leads an individual to ingest thyroxine for the purpose of weight loss. The person usually has some connection with the field of medicine and as a result has no difficulty in procuring thyroxine. The features of thyrotoxicosis occur without goitre or eye signs. The radioactive iodine uptake or technetium scan is negligible and formal psychotherapy may be indicated.

Struma ovarii

A struma ovarii is a form of ectopic source of thyroid hormone arising from a teratoma of an ovary. Thyrotoxicosis occurs in the absence of a goitre. There is absence of uptake in the neck on thyroid scan, but the body scan reveals uptake in the pelvis.

Follicular carcinoma

Follicular carcinoma rarely may secrete active thyroid hormone. There are only a few case reports of patients presenting with hyperthyroidism as a consequence of metastatic carcinoma. In some instances the metastatic deposits may concentrate radioactive iodine. This ability has given rise to the treatment of a follicular thyroid carcinoma with high doses of radioactive iodine.

Trophoblastic disease

Hydatidiform moles and choriocarcinomas produce chorionic gonadotropin which has intrinsic TSH-like activity. This results in suppressed TSH levels and occasionally overt thyrotoxicosis accompanied by elevated T_4 and possibly T_3 concentrations. The thyrotoxicosis is ameliorated by removal of the mole or treatment of the choriocarcinoma.

'Hamburger thyrotoxicosis'

'Hamburger thyrotoxicosis' resulted from the practice of using neck muscles containing beef thyroid tissue to make hamburgers. Currently this practice is illegal.

The syndrome of inappropriate TSH

The inappropriate TSH syndrome (high TSH, high T₄, high T₃) may give rise to thyrotoxicosis by way of the rare entity of a TSH-secreting tumour. This is usually a macroadenoma of the pituitary. The inappropriate TSH syndrome may also be the result of thyroid hormone resistance.

CONCLUSION

Thyrotoxicosis is a frequently encountered clinical condition and its presentation may differ depending on the age of the patient. Thyrotoxicosis is most effectively managed by determining the underlying cause, followed by instituting the most appropriate mode of therapy. Graves' disease is the most common form of thyrotoxicosis. It is recognised by one of the following clinical features, namely ophthalmopathy, a bruit over the thyroid gland or pretibial myxoedema. Antithyroid therapy should be initiated by the primary care physi-

cian, except where the diagnosis is doubtful and the presentation is atypical or complicated.

FURTHER READING

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SINGLE SUTURE**Rich and dark**

There is potentially good news for lovers of plain chocolate. Consumption of plain, dark chocolate resulted in an increase in both the total antioxidant capacity of plasma and the plasma content of the dietary flavonoid epicatechin (which is thought to promote cardiovascular health). Both effects were greatly reduced when the chocolate was consumed with milk, or milk was incorporated as milk chocolate.

(Serafini M, *et al.* *Nature* 2003; **424**: 1013.)

SINGLE SUTURE**Out of Attica**

In Greece, the Attica study found that a high proportion of the population is unaware of having high blood pressure, and blood pressure isn't checked regularly in Greece. Prevalence of hypertension in men was 38% and 24% in women. However, there is a general belief that the so-called Mediterranean diet is helping to prevent hypertension among those predisposed to the condition. But, these results may suggest another reason for the apparently low rate of cardiovascular disease among Mediterranean people — they are simply not being diagnosed.

(Panagiotakos DB, *et al.* *J Hypertens* 2003; **21**: 1483-1489.)