

Diagnosis and Management of Thyroid Disease and the Critically Ill Patient

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ABSTRACT

Objective: To review current concepts in the diagnosis and management of thyroid disease in the critically ill patient.

Data sources: A review of articles reported on thyroid disease and the acutely ill patient.

Summary of review: Normal thyroid function depends on an integrated response between the pituitary and thyroid gland to provide an appropriate circulating T_4 level which is converted to T_3 by peripheral tissues. Thyroid hormone increases oxygen consumption and regulates lipid and carbohydrate metabolism and normal growth and maturation of tissues.

In patients with a severe non-thyroidal illness, the thyroid stimulating hormone (TSH), free thyroxine (FT_4) and free 3,5,3-triiodo-L-thyronine (FT_3) levels decrease. Dopamine, dobutamine or corticosteroid therapy may also reduce TSH levels. The TSH and T_4 levels often return to low normal levels, although with continued severe illness they may remain low. The clinically euthyroid state is maintained in the presence of a reduction in FT_3 levels partly due to an increase in synthesis of tissues T_3 receptors. During the recovery phase of the illness, there is often a transient elevation in the TSH level until the FT_4 and FT_3 levels are returned to normal. There are no clinical data that have shown a consistent reduction in mortality with thyroid hormone treatment in the critically ill patient. In general, in the absence of clinical signs of thyroid disease, abnormal thyroid function tests should not be treated in the critically ill patient and thyroid function studies should be repeated after the acute illness has resolved.

Hypothyroid and hyperthyroid states may present with acute cardiorespiratory failure. Treatment that includes cardiorespiratory resuscitation and thyroid hormone replacement in hypothyroid states and beta adrenergic blockers in hyperthyroid states will often allow correction of the underlying disorder to be achieved successfully.

Conclusions: Abnormal thyroid function tests are commonly found in the critically ill patient and do not require treatment. However, hypothyroid and hyperthyroid states may present with acute cardiorespiratory failure and require careful and specific management strategies to resolve the thyroid disorder (**Critical Care and Resuscitation 2004; 6: 295-305**)

Key words: Myxoedema coma, thyroid crisis, non-thyroidal illness, euthyroid sick syndrome, amiodarone

NORMAL THYROID FUNCTION

There are two thyroid hormones, 3,5,3-triiodo-L-thyronine (T_3) and L-thyroxine (T_4). T_3 is the active hormone whereas T_4 functions as a circulating thyroid

hormone store. T_3 binds to nuclear receptors to increase oxygen consumption (by stimulating Na^+K^+ -ATPase and activating mitochondrial metabolic pathways) and regulates lipid and carbohydrate metabolism and normal

growth and maturation of tissues.¹⁻³ Thyroid function is controlled by thyroid-stimulating hormone, which in turn is controlled by thyrotropin releasing hormone.

Thyrotropin releasing hormone (TRH). The major function of TRH is to release TSH from the adenohypophysis. However, TRH is also found in the neurohypophysis, brain, brainstem, medulla, spinal cord, pancreas, gastrointestinal tract, adrenal and placenta, and can act as a partial opioid antagonist and inhibit pancreatic secretion. It has been used to improve motor function in spinocerebellar degeneration and motor neurone disease, and to reduce mortality in experimental shock and limit the neurological deficit in spinal trauma.^{4,5}

Thyroid stimulating hormone (TSH). TSH is released from the adenohypophysis in response to TRH and the negative feedback effects of T₃ and T₄. By binding to specific thyroid follicular cell surface receptors and activating adenylate cyclase, TSH stimulates synthesis and release of T₃ and T₄.

Thyroid hormones. T₃ and T₄ are synthesised in the colloid of the thyroid gland and bound to thyroglobulin until they are excreted into the circulation as free T₃ (FT₃) and free T₄ (FT₄). The normal daily thyroid secretion consists of approximately 100 nmol (78 µg) of T₄ [35 nmol (27 µg) is converted to T₃ and 45 nmol (35 µg) is converted to rT₃], 5 nmol (4 µg) of T₃ and 2.5 nmol (2 µg) of rT₃. Reverse T₃ (rT₃) has little, if any, metabolic potency. The biological half-lives of T₄ and T₃ are 7 days and 24 hours, respectively.

Thyroid hormones circulate either free (i.e. the active form) or bound to thyroxine-binding globulin (TBG), thyroxine binding prealbumin and albumin. Approximately 99.98% of the circulating T₄ is bound (70% to TBG, 20% to thyroxine binding prealbumin and 10% to albumin) and 99.8% of the circulating T₃ is bound (50% to TBG, 50% to albumin and minimal amounts to thyroxine-binding prealbumin). Measurement of total T₄ or T₃ may be altered due to alteration of the amount of bound thyroid hormone without altering the FT₃ or FT₄ levels.

THYROID FUNCTION TESTS

Serum TSH. Using two specific monoclonal anti-

bodies, the ultrasensitive TSH assay (with a detection limit < 0.1mU/L) has improved the sensitivity of the TSH assay to the extent that both hypo and hyperthyroid states may be discriminated from the euthyroid state using this measurement.^{6,7} However, while a low TSH concentration is compatible with, it is not diagnostic of, hyperthyroidism, because it may occur in hypopituitarism, euthyroid patients in the first trimester of pregnancy, early phase of treatment of hyperthyroidism (the TSH may remain suppressed for up to 6 months despite low circulating thyroxine levels) and in patients treated with dopamine, dobutamine or corticosteroids.^{7,8} In secondary (i.e. pituitary) hypothyroidism, the circulating TSH levels may be within the normal range,⁹ although they are always low relative to the circulating FT₄ levels. The TSH levels are suppressed by adequate T₄ replacement in patients with primary hypothyroidism, but 8 weeks should be allowed after changing the dosage of T₄ to allow adequate equilibration of thyroxine with tissues before measuring TSH levels.

Free thyroxine. The FT₄ assay is a radioimmunoassay that uses a T₄ tracer to measure the non-protein bound T₄. The free hormone concentrations correlate well with the metabolic state and should always be used to assess thyroid status. It is often performed as a second-line test to investigate an abnormal TSH level. In early primary hypothyroidism, the TSH is a more sensitive test than the FT₄, which may be within the normal range.

Free triiodothyronine. The FT₃ assay is a radioimmunoassay that uses a T₃ analogue tracer to measure the non-protein bound T₃ fraction. While elevated levels confirm thyrotoxicosis, the FT₃ estimation is not a useful test to detect hypothyroidism because low levels only occur late in the disease.

The normal, upper borderline, lower borderline and TSH, FT₄ and FT₃ levels diagnostic of primary thyrotoxicosis and hypothyroidism, are listed in Table 1.

Total T₄. The total T₄ measurement includes the protein bound as well as the FT₄ fraction, and is subject to false interpretation of the thyroid status when there are abnormalities of thyroid binding proteins. For example, an increase in TBG occurs during pregnancy, oral contraceptive treatment, hepatitis and biliary cirrho-

Table 1 Free thyroid hormone levels in health and in thyroid disease

	<i>Primary hypothyroid</i>	<i>Lower borderline</i>	<i>Normal</i>	<i>Upper borderline</i>	<i>Primary hyperthyroid</i>
TSH (mU/L)	> 4.5	0.2 - 0.4	0.5 - 3.5	3.6 - 4.5	< 0.2
Free T ₄ (pmol/L)	< 8	8 - 12	13 - 23	24 - 26	> 26
Free T ₃ (pmol/L)			4 - 8	8.1 - 10	> 10

sis, and a decrease in TBG occurs with androgen treatment, corticosteroid treatment, chronic liver disease and severe systemic illness, all of which may alter the total T_4 levels in the absence of thyroid disease. This test is now used rarely.

TRH stimulation test. Following the intravenous infusion of TRH, the serum TSH level increases and reaches a peak within 20 - 45 minutes and then rapidly declines. In hyperthyroidism or secondary hypothyroidism, the response is blunted. While the response may be augmented in patients with primary hypothyroidism, the response is inconsistent.¹⁰

Other tests. Ultrasonography is usually performed first to assess thyroid masses, to detect whether the enlargement is cystic, solid, or multinodular. If it is solid, a radionuclide scan is performed. If a solitary 'cold' lesion is found, the mass is biopsied. The radionuclide scan will also detect 'hot' nodules and metastatic deposits. If the lesion is multinodular, serum autoantibodies (e.g. thyroid peroxidase antibody, antithyroglobulin, antithyroid microsomal antibodies and thyroid-stimulating antibodies) may be measured. A chest CT is performed if a thoracic inlet syndrome due to thoracic extension of the thyroid is suspected.¹⁰

THYROID FUNCTION IN NON-THYROIDAL ILLNESS

Syndrome of non-thyroidal illness or euthyroid sick syndrome

In patients who have a severe non-thyroidal illness, the TSH level may decrease (the degree of which is related to the severity of the illness¹¹) and usually returns to normal or low normal within 24 - 48 hr (although may remain low with absent nocturnal TSH surges¹² with prolonged and severe illness). There is a rapid decrease in FT_3 (maximal by 4 days and proportional to severity of illness) and increase in rT_3 (maximal at 12 hours and unrelated to severity of illness often returning to normal within 2 weeks) which is caused by an inhibition of peripheral 5-monodeiodination (due to an increased inhibition by circulating cytokines,¹³ increased cortisol level¹⁴ and starvation¹⁵) which reduces the peripheral conversion of T_4 to T_3 and decreases the clearance of rT_3 . The total T_4 levels are normal or low in very sick patients and the plasma half-life of T_4 is reduced from 7 days to 1 - 5 days.¹⁵ The absence of a TSH elevation in the presence of a low T_3 is caused by an alteration in set-point at the hypothalamic-pituitary level,¹⁶ as the serum TSH response to TRH is normal.¹²

The clinically euthyroid state is maintained in the presence of a reduction in FT_3 levels partly due to an increase in synthesis of tissues T_3 receptors.¹⁷ During the recovery phase of the illness, there is often a transient

elevation in the TSH level until the FT_4 and FT_3 levels return to normal.^{14,16,18}

Generally, abnormal thyroid function tests in an acutely ill patient (or during starvation) without clinical signs of thyroid disease should not be treated,¹⁹ as there are no studies that have shown a reduction in mortality with thyroid hormone treatment.²⁰ The thyroid function studies should be repeated after the acute illness has resolved.¹⁵ While the rT_3 is usually elevated in non-thyroidal illness and unmeasurable in hypothyroid patients who are sick, the rT_3 level has not been found to differentiate reliably between the two disorders.²¹ Nevertheless, in the absence of dopamine, dobutamine or corticosteroid therapy (which reduce TSH levels) the TSH level often gives a reasonable reflection of the thyroid function status even in patients with acute illness.

Amiodarone effects on thyroid function

The metabolism of amiodarone yields 3 mg (24 μ mol) of free iodine per 100 mg²² (i.e. a maintenance dose of 200 - 400 mg/24 hr produces 6 - 12 mg or 48 - 96 μ mol of free iodine/24 hr, which is approximately 50-100 times the normal iodine intake). Amiodarone inhibits peripheral conversion of T_4 to T_3 , by inhibiting iodothyronine 5-deiodase, and in the majority of patients it elevates T_4 levels (by about 40% above pretreatment levels), reduces T_3 levels (by about 25% below pretreatment levels), and increases reverse triiodothyronine (rT_3) levels. These effects become evident 1 week after beginning treatment and plateau after 3 months. The TSH level often becomes elevated within a few days of starting treatment, although it usually returns to within the normal range (or even slightly below normal range) after three months.²³ However, the TSH response to TRH is variable (i.e. normal, augmented or absent). The rT_3 level has been used to monitor the drug effect (e.g. rT_3 levels that are greater than 5 times baseline values are thought to be associated with a greater chance of toxicity).²⁴ Amiodarone also has a chemical structure similar to triiodothyronine and may induce the formation of antithyroid antibodies in up to 50% of patients after 30 days.²⁵

Amiodarone may induce hyperthyroidism in 1% - 3% of patients, described as either type 1 (in patients with goitre who live in areas of low iodine intake, i.e. a Jod-Basedow effect), or type 2 (due to a direct toxic effect of the drug on the thyroid follicular epithelial cells causing an inflammatory condition, i.e. an amiodarone-induced thyroiditis²⁶), or hypothyroidism in 1% to 5% of patients (usually in areas with high iodine intake).²⁷ Baseline thyroid function tests should be performed before therapy and again three months after therapy. Normal thyroid function is reflected by high normal

TSH levels, elevated T_4 levels, reduced T_3 levels and elevated rT_3 levels.

Hyperthyroidism is rare after the first 18 months of treatment and may present with worsening of the underlying cardiac disorder (i.e. angina or tachyarrhythmia). It is diagnosed by the presence of an increased T_3 , increased T_4 (greater than 40% above baseline levels) and a decrease in TSH. Treatment of type 2 hyperthyroidism may require glucocorticoids (e.g. prednisolone 30 - 40 mg daily) and β -blockers, as cessation of amiodarone may take 8 months for its effects to subside. Antithyroid drugs or radioactive iodine are of benefit only in patients with type 1 hyperthyroidism.²⁶ In severe cases, or if amiodarone is still needed, thyroidectomy may be required.²⁷

Hypothyroidism usually presents with typical clinical features (e.g. constipation, somnolence, etc) and is diagnosed by the presence of an elevated TSH and reduced T_4 levels.^{27,28} Treatment of hypothyroidism usually only requires a small doses of thyroxine (e.g. 25 -100 $\mu\text{g}/\text{day}$) to achieve normal TSH levels and normal clinical status.²⁷ Amiodarone may be continued in such cases.

THYROID DISEASES

Simple (nontoxic) goitre

This is any enlargement of the thyroid gland, due to hypertrophy and hyperplasia, which is not the result of a neoplastic or inflammatory process and is not initially associated with myxoedema or thyrotoxicosis. The thyroid hypertrophy may be caused by excessive thyroid stimulation due iodine deficiency, ingestion of a goitrogen or a defect in the hormone biosynthetic pathway, although often the cause is unknown.

Clinical features. The thyroid hormone profile is usually normal and the clinical manifestations, commonly due to the mechanical effects of the enlarged gland, include compression and displacement of the trachea or oesophagus, superior mediastinal obstruction, superior vena cava syndrome (may be associated with a positive Pemberton's sign, i.e. raising hands above the head causing facial suffusion, giddiness and syncope).²⁹ Hoarseness due to recurrent laryngeal nerve damage is rare and suggests carcinoma.

Investigations. These include:

Thyroid function studies. These are performed to identify patients who may have toxic multinodular goitre.

CT scan. This is performed to identify the extent of thyroid enlargement (and whether there is intrathoracic extension or tracheal compression).

Fine needle aspiration. If a solitary nodule exists, fine needle aspiration is the test of choice.³⁰

Treatment. Thyroid hyperplasia is treated by reducing thyroid stimulation (i.e. reducing TSH secretion). If iodine deficiency or a specific goitrogen can be identified these abnormalities are corrected. Often no cause can be found and L-thyroxine 100 μg daily is administered, with the dose increasing over 4 - 8 weeks to a maximum of 150 - 200 $\mu\text{g}/\text{day}$. The gland should regress within 3 - 6 months of complete suppression of TSH (i.e. TSH level < 0.1 mU/L by an ultrasensitive assay). However, before thyroxine is administered, an ultrasensitive TSH level should be performed. If the TSH is less than 0.1 mU/L and a TRH stimulation test indicates functional autonomy of the thyroid gland, thyroxine administration will be of no benefit and the disorder is likely to be a toxic multinodular goitre. Treatment for the latter requires avoidance of iodine and either surgery (e.g. subtotal or total thyroidectomy) or radioiodine therapy.

Hypothyroidism

Myxoedema is a term applied to chronic hypothyroidism associated with a thickening of skin about the eyes, dorsum of hands and supraclavicular fossae. It is caused by an increased amount of hydrophilic polysaccharides, hyaluronic acid and chondroitin sulphate in the ground substance of the dermis. Approximately 95% of hypothyroid patients have a primary hypothyroid disorder, the remaining 5% are secondary to pituitary or hypothalamic hypofunction.

Primary hypothyroidism may be caused by an autoimmune thyroiditis (Hashimoto's disease), post-ablative defect (e.g. surgical removal, radioiodine ablation, radiotherapy to neck), congenital abnormality or goitrous defect (e.g. hereditary, iodine deficiency, lithium, amiodarone).³¹

Clinical features. The clinical features include bradycardia, atrial fibrillation, hypotension, (cardiogenic shock responsive to triiodothyronine has even been reported³²), hypothermia (sometimes missed unless 'low reading' thermometer used), intolerance to cold, erythema ab igne (i.e. reticulate hyperpigmentation, dusky erythema, epidermal atrophy and telangiectasia usually of legs due to repeated exposure to heat), fatigue, lethargy, constipation, stiffness and cramping of muscles, rhinorrhoea, deafness, slowing of motor activity, increase in weight, carpal tunnel syndrome, menorrhagia, dry and icteric skin (due to hypercarotinaemia as the sclera are not icteric), thickening about the eyes and dorsum of the hands (i.e. myxoedema), hyperkeratosis over elbows and knees, and hair which is dry and brittle.

In the elderly, the features may be incorrectly attributed to depression or Alzheimer's disease. The facial features become thickened, the expression is dull and lifeless, the lateral third of the eyebrows may be absent, there may be thinning of the scalp hair (also thinning of the axillary and pubic hair), periorbital puffiness, a large tongue, pale cool skin, and the voice becomes deep and hoarse. Cerebellar ataxia, obstructive sleep apnoea and hypoventilation may also occur. The heart may be enlarged due to both dilation and pericardial effusion, diastolic heart failure may occur, the abdomen may protrude due to an adynamic ileus, and rarely psychiatric symptoms (e.g. myxoedema madness) develops. The relaxation phase of deep tendon reflexes are characteristically prolonged (i.e. 'hung up') although this may also occur with hypothermia and myotonia.

Investigations. These include:

Thyroid function tests. The serum TSH level is characteristically elevated (unless pituitary hypothyroidism exists) to levels above 20 mU/L, and the FT₄ and FT₃ levels are low. Elevation of the TSH to levels of 5 - 10 mU/L with normal circulating levels of FT₄ may represent a diminished thyroid reserve or 'subclinical hypothyroidism'.³³ These patients are often followed up with 6 - 12-monthly thyroid function tests with commencement of T₄ replacement therapy if the TSH doubles from its previous level.³³

Autoantibodies. In primary hypothyroidism, a raised level of antithyroid peroxidase antibodies is indicative of autoimmune chronic lymphocytic thyroiditis.³⁴ Antithyroid thyroid peroxidase antibodies are present in 95% of affected individuals whereas antithyroglobulin antibodies are present in only 60%.³¹ Other autoimmune disorders that are associated with autoimmune chronic lymphocytic thyroiditis include: hypoparathyroidism, adrenal insufficiency, type 1 diabetes mellitus, primary ovarian failure, vitiligo, pernicious anaemia, Sjögrens syndrome and systemic scleriosis.³¹

Plasma biochemistry. Hypercholesterolaemia, hyponatraemia, hypermagnesaemia, hypoglycaemia and increased serum creatine phosphokinase, may be found. Plasma levels of prolactin and homocysteine are also elevated.

Complete blood picture. A normocytic anaemia may occur. Approximately 12% of patients have pernicious anaemia.

Arterial blood gases. Hypercapnia and hypoxia may be found in patients who have alveolar hypoventilation.

ECG. Bradycardia, atrial fibrillation, low voltage QRS complexes, prolonged QT_c, with generalised flattening or inversion of T waves, may be found. In the event of severe hypothermia, J waves may also be present.

Treatment. Management of the hypothyroid patient depends upon whether the patient has non life-threatening hypothyroidism, hypothyroidism with angina or myxoedema coma.

Non life-threatening hypothyroidism

Oral thyroxine is usually started at 125 µg daily in a 70 kg adult and, depending on TSH levels, is increased or decreased by 25 µg increments at 4 - 6 week intervals. In most patients who are otherwise healthy the slow titration of a dose upward from a low 25 - 50 µg/day is unnecessary and only prolongs recovery without benefit.

The daily dose is administered as a single dose and is usually increased until the symptoms resolve, the TSH and FT₃ return to normal limits and the FT₄ is at the upper limit of normal. This usually occurs at a daily dose of 1.8 µg/kg of thyroxine (i.e. 100 - 200 µg/day),^{35,36} although patients with mild hypothyroidism who have some residual thyroid function may require only 0.5µg/day.³⁷ Normalisation of the TSH level is the best marker of adequate therapy with an ideal mean TSH value of 1 mU/L.³⁸

In patients with secondary hypothyroidism, the FT₄ should be monitored and is usually maintained in the upper half of the normal range.³¹ Low levels of TSH should be avoided because of potential adverse effects on morbidity (bone density, atrial fibrillation, dementia) and mortality.³³ Indications for dose reduction include new atrial fibrillation, accelerated loss of bone density, amenorrhoea, tiredness, diarrhoea, palpitations or borderline high T₃ concentrations.³⁹

If the patient is unable to take oral thyroxine, then intravenous T₃ is administered as a loading dose of 10 µg followed by an infusion of 20 µg/day. The total daily dose of T₃ ranges from 30 - 50 µg/day. The patient's thyroid status is assessed by measuring the TSH and FT₃.

Hypothyroidism with angina

Hypothyroid patients who have angina should be treated with thyroxine as angina improves in the majority of patients rather than worsens.^{40,41} However, one should begin with a lower dose (e.g. 25µg daily increasing by 12.5 - 25 µg increments every 4 weeks). In the event of worsening angina during treatment, heparin should be administered and coronary artery angiography and angioplasty or coronary artery bypass

surgery may be required before the hypothyroid state can be corrected.⁴² Management of hyperlipidaemia should also be undertaken.

Myxoedema coma

If myxoedema is poorly controlled or remains undiagnosed, the patient may progress to become somnolent or unconscious, particularly during the winter months, or if hypnotics or opioids are administered, or in the event of trauma, cerebral vascular accident, surgical operation, hypothermia, pulmonary or urinary tract infections or severe hyponatraemia.²⁹

Treatment requires:

Resuscitation. If the patient is hypotensive, intravenous therapy and inotropic agents may be required, monitored with right heart and arterial pressure measurements. Infection requires appropriate antibiotics, and aspiration or respiratory failure may require endotracheal intubation and careful mechanical ventilation as excessive ventilation will produce severe alkalosis as well as exacerbating hypotension. Hypoglycaemia is treated with intravenous dextrose (50 mL of 50% dextrose) and monitored with 1 to 2-hourly blood glucose measurements. Hypothermia is managed by passive warming techniques. If the core temperature is less than 30°C active warming may be undertaken until the core temperature is 33 - 35°C.

Thyroid hormone replacement. Because thyroxine has a long biological half-life (i.e. 7 days c.f. 24 hr for T₃), requires peripheral conversion to T₃ (which is inhibited by systemic illness) and excessive dosages may precipitate myocardial ischaemia or infarction,^{43,44} even in the presence of normal coronary arteries,⁴⁵ T₃ is used for urgent thyroid hormone replacement. Experimentally, T₃ has been shown to reduce post-ischaemic dysfunction,⁴⁶ and while high doses of T₃ (e.g. 0.8 µg/kg i.v.) used in the postoperative cardiothoracic bypass patient have not improved survival, it does not increase the risk of ischaemic myocardial damage.^{47,48}

Urgent thyroid hormone replacement is achieved by administering 10 µg of T₃ as a bolus, (which has an onset time of 0.5 - 3 hr) followed by an infusion of 20 µg/day and increasing to 30 µg/day (using a 5% albumin as the T₃ carrier) and monitoring FT₃, TSH levels, ECG and haemodynamic measurements. The additional administration of 100 µg - 300 µg of T₄ orally or intravenously is also recommended

by some to saturate the large number of unsaturated binding sites.⁴⁹ The 50 µg daily maintenance of T₄ should also be given and adjusted on the basis of clinical and laboratory results.

Hydrocortisone. This is administered as an intravenous infusion (e.g. 200 µg/day), because an acute adrenal crisis may be precipitated by thyroxine treatment in hypothyroid patients.⁵⁰

Thyroxin therapy in non-thyroid illness

Triiodothyronine administration immediately following coronary artery bypass surgery (while it increases cardiac output within hours after surgery) does not alter mortality or morbidity.⁵¹⁻⁵⁴ In a study of burns patients, triiodothyronine therapy did not alter the rate of recovery or mortality.⁵⁵

THYROTOXICOSIS

Hyperthyroidism may be caused by Grave's disease, toxic multinodular goitre, toxic uninodular goitre (i.e. adenoma), thyroiditis, excess thyroxine administration (i.e. factitious thyrotoxicosis), drug induced (e.g. amiodarone, iodine, radiocontrast agents, lithium), pituitary TSH adenoma, ectopic TSH production (e.g. choriocarcinoma, testicular carcinoma) or thyroid carcinoma.⁵⁶

Graves' disease. This has three major manifestations: hyperthyroidism with diffuse goitre, dermopathy and ophthalmopathy. Any one of these may appear separately. It is caused by excess thyroid stimulation due to a circulating IgG immunoglobulin that attaches to the TSH receptor on the thyroid cell membrane. The disease is associated with other autoimmune diseases (e.g. pernicious anaemia, insulin-dependent diabetes, Addison's disease and myasthenia). The hyperthyroidism of Graves' disease is characterised by phases of exacerbation and remission, with the disease often leading to progressive thyroid failure and hypothyroidism.⁵⁷

Toxic multinodular goitre. This is often seen in the elderly patient who has a long history of goitre and is the result of an autonomous thyroid nodule.

Clinical features. There are many clinical features of hyperthyroidism although the onset of thyrotoxicosis is often subtle with some patients having no symptoms.⁵⁸

The characteristic symptoms include agitation, emotional lability, insomnia, increased appetite, weight loss, loose stools, vomiting, excessive sweating, heat intolerance, hairloss, pruritus, undue fatigue, proximal myopathy (e.g. difficulty in rising from a chair, climbing stairs or keeping a leg extended), dyspnoea, palpitations, gynaecomastia (which may be painful in men⁵⁹) and

amenorrhoea.

The signs include palmar erythema, warm moist skin, soft finger pulps (acropachy) clubbing, onycholysis (separation of the nail from its bed, particularly the distal portion of the ring finger), pretibial myxoedema in patients with Graves' disease (i.e. raised violaceous induration of skin overlying the pretibial area and dorsum of feet. It may rarely appear on the dorsum of hands and face as *peau d'orange*), tachycardia, atrial fibrillation, wide pulse pressure, high output cardiac failure, fine tremor, hyperreflexia, proximal myopathy (with a 'duck waddle' walk), hypokalemic periodic paralysis (particularly in Asian men⁶⁰), myasthenia, diffuse goitre, and thyroid bruit.

In Graves' disease there are also characteristic ocular signs of: sympathetic overstimulation (e.g. widened palpebral fissure, stare, lid lag, failure to wrinkle brow with upward gaze, tremor of lightly closed lids), ophthalmoplegia (e.g. inability to gaze upward and outward, failure to converge, proptosis), congestive oculopathy (e.g. chemosis, conjunctivitis, periorbital swelling, corneal ulceration) and other manifestations (e.g. optic neuritis, optic atrophy, enlarged lacrimal glands).

Apathetic thyrotoxicosis is a rare clinical presentation of thyrotoxicosis; it usually occurs in an elderly patient with resistant atrial fibrillation, fatigue and myopathy (or even absence of clinical symptoms) dominating the clinical picture.

Subclinical hyperthyroidism (e.g. normal thyroid hormone levels and low thyrotropin levels) is associated with an increased incidence of atrial fibrillation⁶¹ and increased all cause mortality.⁶²

Investigations. These include:

Thyroid function studies. The TSH is unrecordable and unresponsive to TRH stimulation, and the FT₃ and FT₄ levels are elevated. Rarely, the FT₃ is elevated in isolation in patients who have a T₃ thyrotoxicosis variant. Subclinical hyperthyroidism has been defined as a thyrotropin concentration less than 0.1 mU/L (as measured by second generation or third generation TSH assays) with thyroid hormone levels within the normal range in the absence of pituitary-hypothalamic dysfunction, an acute non-thyroidal illness or treatment with dopamine, dobutamine or corticosteroids.³⁸

Radionuclide scanning. A radionuclide scan is usually not necessary to diagnose Graves' disease or toxic multinodular goitre, but is usually performed when the cause of hyperthyroidism is not clear (e.g. subacute thyroiditis, 'hot' nodules and metastatic deposits).

Plasma biochemistry. Hypokalaemia, hypercalcaemia, hypomagnesaemia, increased alkaline phosphatase, hyperglycaemia, renal tubular acidosis (type I) and hyperbilirubinaemia often occur.^{63,64}

Complete blood picture. A mild leucocytosis may be present.

Autoantibodies. In Graves' disease, a raised level of TSH receptor antibodies is often found and may be useful to differentiate Graves' disease from other forms of thyrotoxicosis.

Treatment. The three main treatments consist of antithyroid drugs, surgery and radioiodine with the selection of treatment often depending on clinician preference, cost and availability of radioisotopes and skilled surgeons.⁵⁸ Management also varies depending on whether the thyrotoxicosis is non life-threatening or life threatening (e.g. thyrotoxic crisis).⁶⁵

Therapy consists fundamentally of measures to reduce T₃ and T₄ synthesis and release, reduce peripheral conversion of T₄ to T₃ and inhibit the peripheral effects of T₃ and T₄.

Treatment of non life-threatening thyrotoxicosis

Antithyroid drugs. The antithyroid drugs of carbimazole, methimazole and propylthiouracil are commonly used. Carbimazole is metabolised to methimazole and so these two agents are considered to be interchangeable (methimazole dose is approximately 2/3 that of carbimazole). The antithyroid drugs are ineffective against thyrotoxicosis associated with thyroiditis or toxic adenoma and should not be used in these disorders.⁶³ As propylthiouracil also blocks peripheral conversion of T₄ to T₃ and is highly protein bound, it is often preferred to carbimazole in thyrotoxic crisis or during pregnancy or lactation.⁶⁶

Carbimazole. Carbimazole has a half-life of 6 - 8 hr (i.e. can be given as a single daily dose), is 10 times as potent and is probably less toxic than propylthiouracil, although it has no effect on the peripheral conversion of T₄ to T₃.⁶⁶ The standard dose is 10 - 40 mg daily, or 40 - 60 mg daily with T₄ supplementation.

Propylthiouracil. Propylthiouracil may be used in partially suppressing doses of 300 - 600 mg a day (100 - 200 mg 8-hourly, as the half-life is 6 hr), reducing by half after 2 - 6 weeks and keeping the FT₄ at mid-normal levels and the TSH levels suppressed. Another regimen uses propylthiouracil at 200 - 300 mg 4 to 6-hourly to completely suppress the thyroid gland, which requires additional T₄ replacement therapy (e.g. 100 µg/day) as well. As the latter regimen

completely suppresses TSH, it will also reduce the size of a goitre.

Thyroid function should be assessed every 4 - 6 weekly for the first 6 months. In approximately 5% of patients who are treated with antithyroid drugs, side-effects occur and usually within the first 2 months of treatment. Leukopenia occurs in 0.5% of patients and is the most serious side effect and almost always develops within 90 days of the start of treatment. It occurs suddenly, and thus routine monitoring of the neutrophil count is of little help. A neutrophil count is performed before therapy and the patient is asked to stop therapy and to report if a fever, mouth ulcers, pharyngitis or stomatitis occur. If the neutrophil count decreases to $1.5 \times 10^9/L$, or less, the drug should be discontinued. The agranulocytosis is self limiting and usually lasts 5 - 15 days only, which may resolve more rapidly with glucocorticoid treatment⁶⁷ or granulocyte-colony stimulating factor therapy.⁶⁸

Other side-effects include aplastic anaemia, thrombocytopenia, hepatitis, cholestatic jaundice, nausea, vomiting, headache, skin rashes, urticaria, vasculitis, pruritus, arthralgia, myalgia and fever.

Treatment is continued for 12 - 24 months, thereafter reducing the dose and reviewing the patient for biochemical and clinical signs of any return of thyrotoxicosis.

Beta adrenergic blockers. The adrenergic-excess like features (probably caused by an increase in tissue adrenergic receptor density as circulating catecholamine levels are usually low⁶⁹) of tachycardia, fever, tremor and agitation often respond rapidly to β -blockers. However, they do not return the oxygen consumption or negative nitrogen balance to normal. Beta-blockers should not be used in the presence of cardiac failure.⁷⁰ Propranolol reduces the peripheral effects of thyroid hormones as well as reducing the peripheral conversion of T_4 to T_3 .

Ablative therapy. Partial thyroidectomy or radioactive iodine may be used if the disease recurs following drug therapy, if drug toxicity has occurred or a large goitre, toxic multinodular goitre or adenoma exist.⁶⁷ Preoperative preparation for partial thyroidectomy is usually undertaken with propranolol (e.g. 40 - 200 mg orally for 1 - 2 weeks, which is continued for 2 - 8 weeks postoperatively) which allows surgery to be performed safely in patients who have moderate hyperthyroidism.⁷¹

Treatment of life-threatening thyrotoxicosis (i.e. thyrotoxic crisis or thyroid storm)

Thyrotoxic crisis is often precipitated in a poorly controlled or previously undiagnosed thyrotoxic patient,

by infection, trauma, surgery, labour or pre-eclampsia. The cause of the rapid decompensation is unknown but may be partly due to a sudden inhibition in plasma protein thyroid hormone binding causing a sudden rise in an already elevated free thyroid hormone pool.⁷²

Thyrotoxic crisis may also be caused by a massive overdose of thyroxine. Overdoses of up to 10 mg of thyroxine are usually well tolerated.^{73,74} However, with massive overdoses (e.g., 70 - 1200 mg over 2 - 12 days), signs of thyrotoxicosis develop within 3 days and thyrotoxic crisis and coma usually develop after 7 - 10 days.⁷⁵

Clinical features. Thyrotoxic crisis is characterised by hyperpyrexia, irritability, delirium, coma, muscle weakness, rhabdomyolysis, sinus tachycardia, atrial or ventricular tachyarrhythmias, hypotension, vomiting, abdominal pain and diarrhoea. Rarely (particularly in elderly patients) it may present as an apathetic crisis with severe myopathy, tachycardia, hypotension and coma. The differential diagnoses are delirium tremens, opiate withdrawal, phaeochromocytoma, malignant hyperthermia, panic attack, mania and amphetamine overdose.

Treatment. This includes:

Resuscitation. Supportive care with fluids, dextrose and B group vitamins. Ideally oxygen consumption studies and close haemodynamic monitoring should be performed. Digoxin, beta-blockers, verapamil, and amiodarone (which also inhibits peripheral conversion of T_4 to T_3 ;⁷⁶ its metabolism also yields 3 mg (24 μ mol) of free iodine per 100 mg⁷⁷) have all been used to control atrial arrhythmias.

Antithyroid drugs. Propylthiouracil 1000 mg orally (or via the nasogastric tube) as a loading dose followed by 100 mg 2-hourly, is the treatment of choice as it also inhibits peripheral conversion of T_4 to T_3 .⁶⁶ Carbimazole 60 - 100 mg as a loading dose, followed by 100 - 120 mg/day may be administered if propylthiouracil is contraindicated.

Iodine. Large doses of iodine immediately inhibit the uptake of iodine and release of thyroid hormone from a hyperfunctioning gland (Wolff-Chaikoff effect). However the effect is transient (i.e. lasts 1 - 4 weeks), and iodine should be administered at least 1 hr after antithyroid drugs have been given.

The radiocontrast agent, sodium ipodate (1 g/day orally), also inhibits peripheral conversion of T_4 to T_3 , and is often used; otherwise 500 - 1000 mg of sodium iodide is infused intravenously every 8 h. Lithium (500 -

1000 mg) has been used as an alternative to iodine in patients sensitive to iodine, however a steady state is achieved only after 5 - 6 days and it only mildly inhibits thyroid hormone release and synthesis.⁷⁸ Frequent lithium levels are required to ensure nontoxic levels (i.e. < 1.5 mmol/L).

β-adrenergic receptor blockers. Propranolol 40 - 200 mg orally usually alleviates the adrenergic-excess like effects. For rapid effect, 1 - 2 mg of propranolol may be administered intravenously over 1 - 3 minutes up to a total of 20 mg, or until the desired effect is achieved. The fever, tachycardia, diaphoresis, agitation, tremor and myopathic features usually respond rapidly.⁷⁹ While selective β_1 -blockers do not inhibit peripheral conversion of T_4 to T_3 as effectively as propranolol, these agents may be used in patients with reactive airways (e.g. asthma, COPD).⁸⁰ If heart failure exists β -blockers may cause a marked deterioration in cardiac function leading to severe cardiac failure or cardiogenic shock.⁸¹ Cardiac failure and atrial fibrillation in these circumstances should be treated with digoxin⁷⁰ (which may require a higher than usual dose⁸²).

Dexamethasone. Intravenous dexamethasone 4 mg 6-hourly, is administered to severely thyrotoxic patients to reduce the peripheral conversion of T_4 to T_3 .

Other therapy. Oral activated charcoal has been used in patients with severe thyroxine overdosage to increase the gastrointestinal clearance. Plasmapheresis has also been used in thyrotoxic crises,^{83,84} and has been reported to increase T_4 clearance in severe thyroxine overdosage (i.e 70 - 1200 mg over 2 - 12 days).⁷⁵ However, in a patient who ingested 6 mg of thyroxine, plasmapheresis was of no significant clinical or pharmacokinetic benefit.⁸⁵ Dantrolene has also been used successfully in a patient in whom the thyrotoxic crisis mimicked malignant hyperpyrexia.⁸⁶

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