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A guide to thyroid dysfunction

Thyroid dysfunction is common but can present both diagnostic and management challenges. This article will present a practical approach to patients with hyperthyroidism and hypothyroidism.

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Thyroid dysfunction is common in the community – the prevalence of hyperthyroidism is approximately 1 to 2%[1] and hypothyroidism 5 to 10%.[2] Thyroid dysfunction has a female to male predominance (5:1), and the incidence increases with age. A family history of thyroid disorder is common in affected patients.

Thyroid hormone regulates cellular metabolism, facilitates development of the central nervous system, and is important for normal growth, puberty and protein synthesis. This variety of roles accounts for the constellation of symptoms and signs encountered in patients with thyroid dysfunction. Thyroid storm is a life threatening form of hyperthyroidism, whereas myxoedematous coma refers to severe hypothyroidism. Thyroid dysfunction is commonly primary (arising from the thyroid) but rarely it is secondary (central, arising from the pituitary or hypothalamus). Furthermore, primary thyroid dysfunction can be overt or subclinical, the latter term being applied to individuals with an abnormal thyroid stimulating hormone (TSH) level but normal free thyroxine (T4) level. The interpretation of thyroid function tests is summarised in Table 1.

Hyperthyroidism

Clinical features

Important symptoms and signs of hyperthyroidism are listed in Table 2. A diffuse goitre with a bruit is commonly found in Graves' disease (Figure 1); a nodular goitre may suggest either a toxic multinodular goitre or toxic adenoma (although Graves'

IN SUMMARY

- **Thyroid dysfunction is common in the community. The prevalence of hyperthyroidism is approximately 1 to 2% and hypothyroidism 5 to 10%, with a strong female predominance.**
- **Graves' disease is the most common cause of hyperthyroidism. Other causes include a toxic multinodular goitre, toxic adenoma and thyroiditis.**
- **A technetium-99m nuclear thyroid uptake scan and measurement of thyroid receptor antibodies are the most useful initial investigations for determining the cause of hyperthyroidism, if it is not clinically apparent.**
- **Treatment of hyperthyroidism usually involves antithyroid drugs (carbimazole or propylthiouracil), radioactive iodine or total thyroidectomy.**
- **The presence of autoimmune thyroid disease (Hashimoto's thyroiditis), which is the most common cause of hypothyroidism, is confirmed by the presence of antithyroglobulin and/or antimicrosomal (antithyroid peroxidase) antibodies.**
- **Careful up-titration of thyroxine dose is usually required in treatment of hypothyroidism.**
- **Thyroid dysfunction in pregnancy is an important clinical scenario and requires specialist involvement.**
- **Treatment of subclinical thyroid dysfunction is controversial.**

Table 1. Thyroid function tests: a guide to interpretation of usual findings

	TSH	Free T4	Free T3	Antithyroid antibodies	Thyroid receptor antibodies
Primary hyperthyroidism	Decreased	Increased	Increased or normal	Increased or normal	Increased or normal
T3-toxicosis	Decreased	Normal	Increased	Increased or normal	Increased or normal
Subclinical hyperthyroidism	Decreased	Normal or high-normal	Normal	Increased or normal	Increased or normal
Central hyperthyroidism	Increased or high-normal	Increased or high-normal	Increased or high-normal	Normal	Normal
First trimester pregnancy	Decreased	Normal	Normal	Normal	Normal
Sick euthyroid state	Decreased or low-normal	Decreased or low-normal	Decreased or low-normal	Normal	Normal
Primary hypothyroidism	Increased	Decreased	Decreased or normal	Increased or normal	Normal
Subclinical hypothyroidism	Increased	Normal	Normal	Increased or normal	Normal
Central hypothyroidism	Decreased or low-normal	Decreased or low-normal	Decreased or low-normal	Normal	Normal

Abbreviations: TSH = thyroid stimulating hormone, T4 = thyroxine, T3 = tri-iodothyronine.

disease can also occur within a pre-existing nodular gland). Subacute thyroiditis is associated with a tender, asymmetrically enlarged thyroid, and patients are typically systemically unwell with fever, malaise and anterior neck pain. Eye lid lag and lid retraction can occur in any thyrotoxic state, but proptosis (or exophthalmos) and the very rare 'pretibial myxoedema' are specific for Graves' disease (Figure 2).

Elderly patients often present with fewer or atypical symptoms and signs, such as atrial fibrillation, congestive cardiac failure or confusion. Some patients are completely asymptomatic with florid biochemical thyrotoxicosis, yet others have many symptoms with only mild biochemical abnormality.

Aetiology

Graves' disease, an autoimmune disorder characterised by stimulatory antibodies against the TSH receptor in the thyroid, is the most common cause of hyperthyroidism. A multinodular goitre with one or more autonomously functioning nodules (toxic multinodular goitre) or a gland with a single autonomous nodule (toxic adenoma) are also common causes.

Various forms of thyroiditis, in which there is inflammation and destruction of thyroid follicles with release of preformed thyroid hormone, can cause thyrotoxicosis. Subacute thyroiditis usually follows a viral infection, whereas postpartum thyroiditis often occurs in the context of underlying autoimmune thyroid disease. Typically, thyroiditis passes from a hyperthyroid to a hypothyroid phase, and occasionally the hypothyroidism can be permanent.

Amiodarone-induced hyperthyroidism is common, occurring in roughly 3% of patients administered this medication. Hyperthyroidism can be due to other drugs, including lithium and interferon, but thyroxine over-replacement is a more common cause. Transient gestational thyrotoxicosis can occur in the first trimester of pregnancy, often in the context of hyperemesis gravidarum, because high levels of β-hCG stimulate the TSH receptor.

Rarer causes of hyperthyroidism include TSH-secreting pituitary tumours, struma ovarii (ovarian

continued

Table 2. Important features of hyperthyroidism

Symptoms

Weight loss
Fatigue
Anxiety
Heat intolerance
Palpitations
Insomnia
Dyspnoea
Diarrhoea or increased bowel frequency
Irregular menses
Muscle weakness
Neck mass or tenderness
Eye soreness

Physical signs

Warm moist skin
Tremor
Tachycardia
Wide pulse pressure
Hyperreflexia
Proximal muscle weakness
Goitre
Rash
Eye signs – lid lag, lid retraction and sometimes proptosis and ophthalmoplegia

teratoma with thyroid tissue) and surreptitious ingestion of thyroid hormone.

Investigations

Primary hyperthyroidism is confirmed by a low (usually suppressed) TSH and elevated free T4, and usually elevated free tri-iodothyronine (T3). Some patients will have an elevated free T3 but not free T4 (T3-toxicosis) with a low TSH. Measurement of thyroid receptor antibodies (human thyrotrophin receptor antibodies and thyroid stimulating immunoglobulins) is useful if Graves' disease is suspected. Antithyroglobulin and antimicrosomal (antithyroid peroxidase) antibodies are less useful, being nonspecific markers of autoimmune thyroid disease (present in

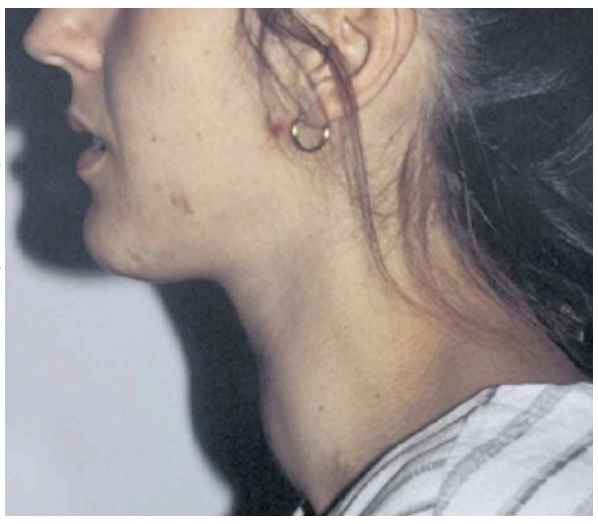

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Figure 1. Diffuse goitre in a woman with Graves' disease.

both Hashimoto's and Graves' diseases and occasionally in subacute thyroiditis), and changing titre over time is not meaningful. The C-reactive protein level or erythrocyte sedimentation rate is typically elevated in subacute thyroiditis.

The next most appropriate investigation in a patient with primary hyperthyroidism is a nuclear medicine technetium-99m thyroid uptake scan (rather than a thyroid ultrasound), which will clarify the cause of the thyrotoxicosis (Figures 3a to c). An approach to interpretation is outlined in the flowchart on page 32. Diffuse uptake of isotope is seen in Graves' disease. Focal isotope uptake is seen in a toxic ('hot') nodule, with suppression of uptake in the remaining thyroid. Patchy uptake may be seen in a toxic multinodular goitre, often with one or more hot or 'warm' nodules. Graves' disease occurring in an existing multinodular gland will also give a patchy appearance; the nodules are usually cold with diffuse uptake in between. Due to thyroid gland destruction, minimal or no uptake is seen in thyroiditis. Amiodarone-induced hyperthyroidism or exogenous thyroxine administration will also show absence of isotope uptake. Technetium scans are not performed during pregnancy and usually not while a patient is breastfeeding. Such scans may be omitted if the diagnosis of Graves' disease is obvious (for example, when there is proptosis with a diffuse goitre).

Subclinical hyperthyroidism is characterised by a low TSH and a normal (usually high-normal) free T4. A technetium thyroid uptake scan may be useful in this setting, although there is controversy about whether to treat this abnormality, particularly if TSH is more than 0.1 mIU/L (see below). A low or low-normal TSH may also be found in the 'sick euthyroid' state or in central (pituitary or hypothalamic) hypothyroidism, but in these situations the free T4 and free T3 are usually low or low-normal as well. A low TSH and normal free T4 is a common finding in healthy women at the end of the first trimester of pregnancy. An elevated TSH or high-normal TSH in the presence of high free T4 or T3 levels may suggest the rarer diagnoses of a TSH-secreting pituitary tumour or thyroid hormone resistance, but may also be a method-dependent artefact.

Although discussion of thyroid nodules is beyond the scope of this article, patients presenting with one or more thyroid nodules should have thyroid function tests performed and, if a low TSH level is detected, a technetium scan. Ordinarily, nodules greater than 1 cm in diameter are subjected to fine needle aspiration biopsy; however, if a 'hot' nodule is demonstrated on technetium scan, the chance of malignancy is slim and biopsy is generally not performed.

Treatment

Treatment for hyperthyroidism depends on the underlying cause. Specialist advice is generally recommended.

Graves' disease

Medical therapy with antithyroid drugs, carbimazole (Neo-Mercazole) or propylthiouracil (Propylthiouracil), is generally first line treatment for a first episode of Graves' disease. Carbimazole is sometimes preferred over propylthiouracil because it has a longer half-life and can be given once or twice daily. The starting dose depends on the degree of hyperthyroidism: initial doses range from 10 to 30 mg per day for carbimazole and from 100 to 400 mg per

day for propylthiouracil. Patients should be warned about common adverse effects such as rashes and gastrointestinal upset (a change to the alternative agent can be made in this situation) as well as the more serious adverse effects such as agranulocytosis, liver dysfunction and vasculitis (subsequent definitive therapy is usually then advised). Monitoring of white blood cells is performed urgently if a patient develops a fever or sore throat. A beta blocker, most often propranolol (Deralin, Inderal), 20 to 120 mg/day, is used if a patient has a disabling tachycardia, anxiety or tremor, provided that there is no history of asthma.

Thyroid function should be assessed every four to six weeks during the first six months, keeping in mind that the free T4 level will normalise earlier than the TSH level. Doses of antithyroid drugs are adjusted downwards as thyroid function improves, and therapy should be continued for at least 12 months to minimise the risk of relapse (around 50%). Patients with positive thyroid receptor antibodies at the time of treatment withdrawal are at higher risk of relapse. Occasionally a 'block and replace' regimen using a combination of thyroxine and an antithyroid drug is required to maintain stable thyroid function. Definitive therapies with radioactive iodine and surgery are usually reserved for relapses, but may be used during a first episode that is difficult to control medically or when troublesome side effects to antithyroid drugs develop.

Graves' disease complicating pregnancy – or any cause of hyperthyroidism occurring in pregnancy – requires early specialist referral because untreated hyperthyroidism is associated with miscarriage and other pregnancy complications; furthermore, over-treatment is associated with neonatal hypothyroidism. Propylthiouracil is the preferred drug in pregnancy because it is less likely to cross the placenta and carbimazole has been associated with a rare scalp abnormality in the baby called aplasia cutis; however, the literature supports the use of either drug in pregnancy.[1] Radioactive iodine is contraindicated and surgery is a last resort. The lowest propylthiouracil dose to maintain normal free T4 levels is used, although the TSH level may remain suppressed. Often it is possible to stop propylthiouracil treatment during the later stages of pregnancy, but relapses are common in the postpartum period. Antithyroid drugs are safe in modest doses for breastfeeding mothers, but thyroid function should be monitored in neonates if maternal doses higher than 20 mg of carbimazole or 200 mg of propylthiouracil daily are used.

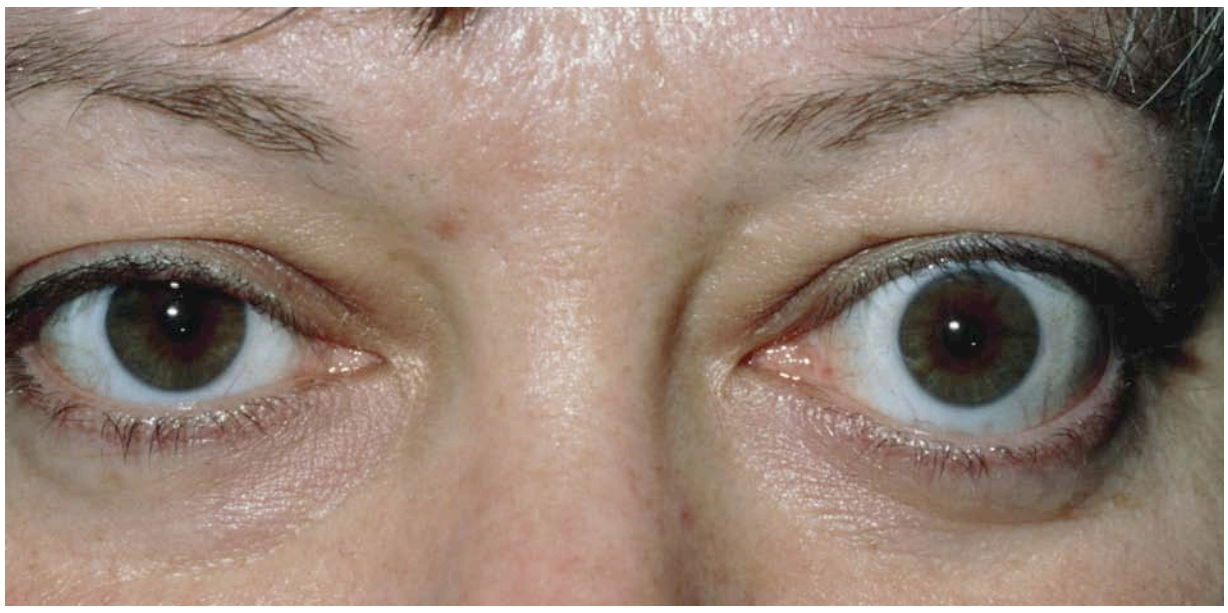

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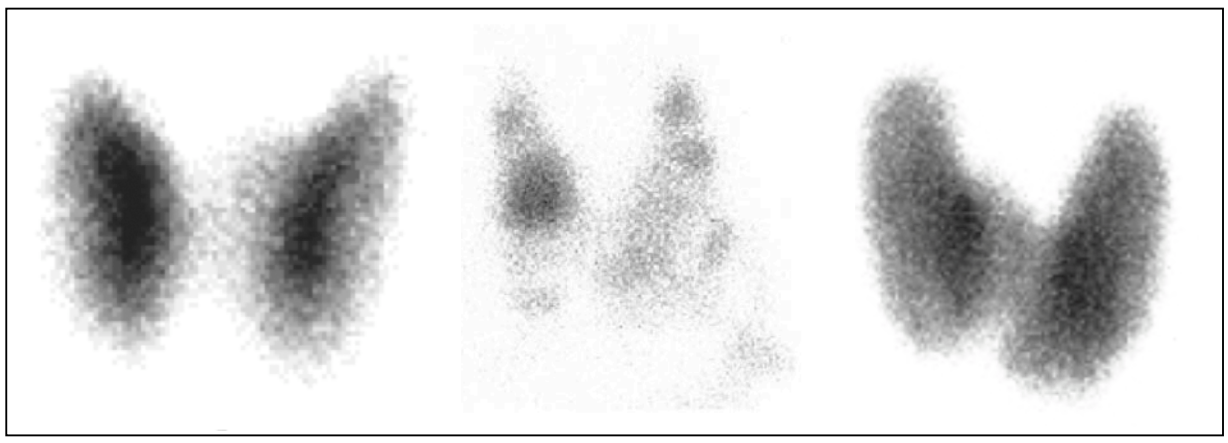
Figure 2. Exophthalmos due to Graves' disease.

Radioactive iodine (Sodium Iodide ^{131}I) is widely used to treat Graves' disease in the USA, but less so in Australia. It is quite safe in the long term but causes permanent hypothyroidism in most patients. Patients must be monitored long term for hypothyroidism, which may occur many years later. Before receiving radioactive iodine women should be tested to exclude pregnancy, and following therapy they should avoid becoming pregnant for three to six months. They should have normal thyroid function prior to conception. Radioactive iodine has been associated with a deterioration in thyroid eye disease and is generally not used in patients with moderate or severe eye disease.

To avoid recurrent hyperthyroidism, the surgical approach of total thyroidectomy is now preferred over bilateral subtotal thyroidectomy. However, all patients undergoing thyroidectomy will require lifelong thyroxine replacement. Surgery is performed when the patient is euthyroid



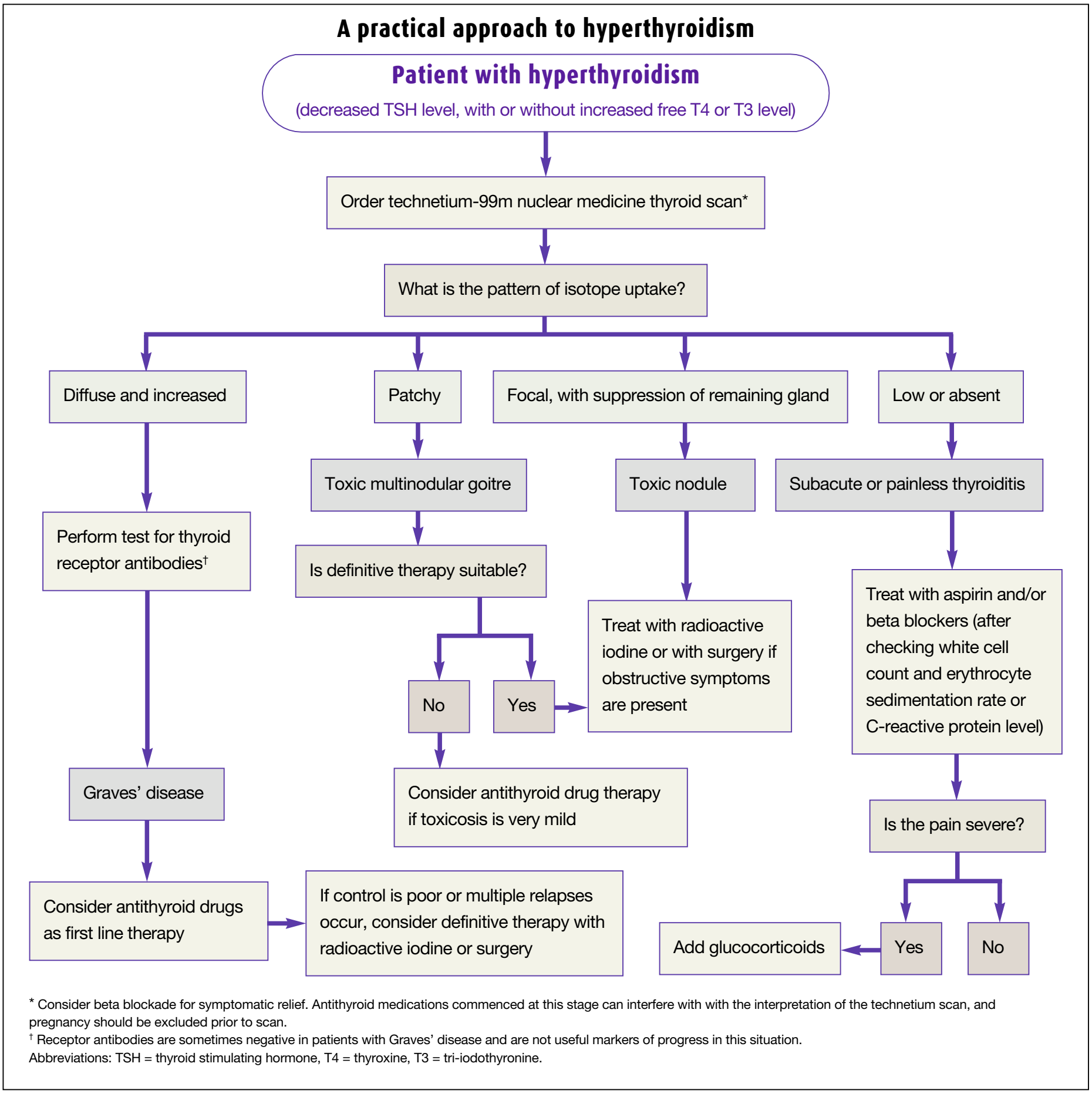
Figures 3a to c. Technetium-99m nuclear thyroid uptake scans. a (left). Normal thyroid with normal percentage isotope uptake. b (centre). A multinodular goitre with dominant functioning adenoma. c (right). A diffuse toxic goitre in Graves' disease with increased percentage isotope uptake.

and is generally preferred for patients who have thyroid eye disease or have large or nodular goitres.

Toxic multinodular goitre or toxic adenoma

Radioactive iodine is the preferred therapy in patients with one or more toxic nodules. Pretreatment with antithyroid drugs is not necessary unless the patient is very toxic at diagnosis, or elderly and at risk of cardiac complications. Patients given radioactive iodine when the TSH level is low avoid isotope uptake into normal surrounding thyroid tissue, and thus permanent hypothyroidism is less common in this situation than after radioactive iodine treatment for Graves' disease.

Surgery is another treatment option, particularly for patients with large compressive goitres. Antithyroid drugs are often used in elderly patients who have mild hyperthyroidism and other comorbidities, but therapy is likely to be needed long term.



* Consider beta blockade for symptomatic relief. Antithyroid medications commenced at this stage can interfere with with the interpretation of the technetium scan, and pregnancy should be excluded prior to scan.
† Receptor antibodies are sometimes negative in patients with Graves' disease and are not useful markers of progress in this situation.
Abbreviations: TSH = thyroid stimulating hormone, T4 = thyroxine, T3 = tri-iodothyronine.

Thyroiditis

Antithyroid drugs are not useful in treating patients with thyroiditis. Subacute thyroiditis can be painful and high dose aspirin or other NSAIDs are effective, with glucocorticoids being reserved for more severe cases. Beta blockers are used to treat thyrotoxic symptoms. Thyroxine treatment might be needed during the hypothyroid phase if there are significant symptoms.

Amiodarone-induced hyperthyroidism

Early specialist referral is advised if amiodarone-induced hyperthyroidism is suspected, as it often occurs in older patients with underlying cardiac disease in whom rapid development of cardiac failure and death can occur. Amiodarone should be ceased and treatment with antithyroid drugs and glucocorticoids given, but drug therapy is frequently ineffective. Recovery may take many months while the amiodarone (which has an extremely long half- life) is cleared from the body. Hospital admission may be required, and semi-urgent total thyroidectomy may be necessary at a time when the patient is thyrotoxic.

Subclinical hyperthyroidism

It is generally accepted that patients receiving thyroxine therapy who have a low TSH should have their dose reduced – except in patients with thyroid cancer where TSH is deliberately suppressed to reduce the risk of relapse. Treatment of endogenous subclinical hyperthyroidism is more controversial and requires specialist input. Large, mostly epidemiological studies have shown an increased risk of atrial fibrillation and lower bone mineral density in patients with subclinical hyperthyroidism, particularly if the TSH is very low.[1,3-4] Generally, older patients who are at risk of atrial fibrillation or osteoporosis (particularly those with nodular goitres and complete TSH suppression) are treated with antithyroid drugs or radioactive iodine. Younger patients with no comorbidities or those with only partial TSH suppression (0.1 to 0.4 mIU/L) may be monitored with regular thyroid function tests but no therapy.[4] A treatment decision is based on the individual case scenario.

Hypothyroidism

Clinical features

Common symptoms of hypothyroidism include weight gain, fatigue, cold intolerance, depression, constipation, dry skin, muscle and joint aches, menorrhagia and slowed mental processing. Physical signs may be few and may include cool and dry skin, bradycardia, 'hung up' reflexes, periorbital oedema, thinning of the outer third of the eyebrows, hoarse voice or goitre. Hypothyroidism is suggested if several of these features occur in combination or with recent onset. Elderly patients may present atypically, with congestive cardiac failure or hypothermia.

Some specialist groups advocate routine screening of thyroid function, particularly in older women, although currently there is insufficient evidence to support population based screening. However, it is generally agreed that patients deemed to be at higher risk of developing hypothyroidism have thyroid function tests at regular intervals (see below).

Aetiology

The causes of hypothyroidism include:

- autoimmune thyroid disease (Hashimoto's thyroiditis), which is the most common cause of primary hypothyroidism
- congenital hypothyroidism (for which newborn TSH screening is performed), see Figure 4
- thyroid or head and neck surgery
- previous neck irradiation
- previous radioactive iodine treatment for thyrotoxicosis
- thyroiditis
- drug treatments (e.g. amiodarone, lithium, interferon)
- pituitary or hypothalamic disease causing secondary (central) hypothyroidism.

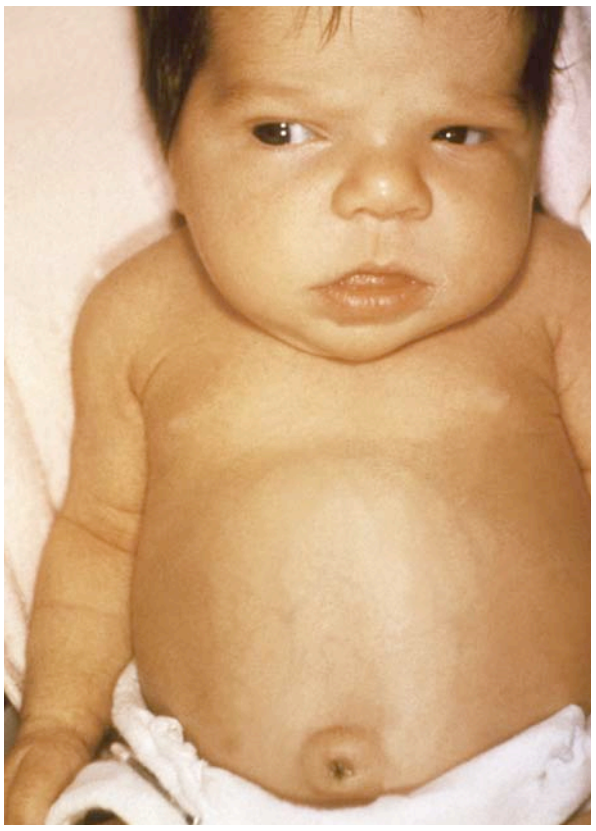


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Figure 4. A 6-week-old baby with jaundice, proven to have hypothyroidism.

Patients with the conditions listed above and patients with other autoimmune disorders, such as type 1 diabetes or a family history of autoimmune thyroid disease, should be screened regularly with thyroid function tests. The presence of hyperlipidaemia, hyponatraemia, hyperprolactinaemia or an elevated creatinine kinase level warrant screening with TSH measurement.

Investigations

Primary hypothyroidism is confirmed by an elevated TSH and decreased free T4 level. Elevated titres of antithyroglobulin and/or antimicrosomal (antithyroid peroxidase) antibodies confirm autoimmune thyroid disease. Patients with autoimmune thyroid disease should have their vitamin B_{12} levels measured. Screening for less common autoimmune conditions is probably not warranted. Central hypothyroidism is suggested by the presence of a low free T4, and usually low or low-normal TSH. Tthe measurement of an elevated TSH in combination with a normal free T4 level is consistent with subclinical hypothyroidism.

Thyroid imaging is not required for patients with hypothyroidism unless there is a clinical suggestion of nodularity that needs to be clarified with ultrasound.

Treatment

Treatment of hypothyroidism with thyroxine therapy (Eutroxsig, Oroxine) is relatively straightforward. Most patients require maintenance doses of 100 to 150 μg daily. A lower initial dose is generally recommended (usually 50 μg daily) because patients with longstanding severe hypothyroidism can experience unpleasant symptoms (e.g. palpitations) if thyroxine is introduced too quickly, but occasionally an initial dose of 100 μg may be used if the TSH level is very high and the patient is young and fit. In the elderly and patients with cardiac disease, a lower starting dose of 25 μg daily is more appropriate.

Thyroid function tests should be performed six weeks after introducing thyroxine and after any dose adjustment (but not within five weeks of the change), with test results guiding gradual dose increases. In patients with cardiac disease, increases should be made very gradually in increments of 25 μg. The aim is to restore euthyroidism, but occasionally patients require TSH levels to be at the lower end of the normal range before they feel completely well. Once euthyroidism is achieved, thyroid function tests should be repeated yearly, unless a dose adjustment is made.

Generally, specialist referral is not required for patients with primary hypothyroidism. In central hypothyroidism, TSH levels are unreliable and free T4 levels are monitored in order to achieve levels in the upper half of the normal range. Specialist involvement is advisable in this situation.

Women who are taking thyroxine and planning pregnancy should be advised that often a dose increment of 30% may be needed during pregnancy and that thyroid function should be checked when pregnancy is confirmed and subsequently every six to eight weeks. The fetal thyroid does not develop until about week 11, so the fetus initially relies on transplacental transfer of thyroxine from the mother, which is important for brain development.

Subclinical hypothyroidism

Patients with subclinical hypothyroidism who are already taking thyroxine and have an elevated TSH but normal free T4 should have their daily dose increased gradually until euthyroidism is reached. Increments of 25 μg are usually used.

Treatment of endogenous subclinical hypothyroidism is controversial. Most clinicians would accept thyroxine treat-

ment in a patient with a high TSH level (>10 mIU/L) – particularly when the free T4 is in the low-normal range and tests for antithyroglobulin and antimicrosomal (antithyroid peroxidase) antibodies are positive – because these patients have a higher risk of progression to overt hypothyroidism (approximately 4% per year). The presence of symptoms is an additional reason for considering thyroxine treatment. There are epidemiological data suggesting an increased future risk of cardiovascular disease and evidence of higher cholesterol levels in patients with subclinical hypothyroidism.[2,4-5] However, there are no randomised trials demonstrating reduction in cardiovascular risk with thyroxine treatment in these patients.

Conclusion

Thyroid dysfunction is common in the general community. Although population screening is not routinely advocated at present, thyroid function tests should be considered in any patient with symptoms or signs suggestive of thyroid disease and in any patient at risk of developing thyroid dysfunction.

The cause of primary hyperthyroidism may be apparent from the history and physical findings; if not, a technetium thyroid uptake scan is more useful than an ultrasound. Management of hyperthyroidism depends on the underlying cause but usually involves antithyroid drug therapy, radioactive iodine or surgery. Primary hypothyroidism is most often due to autoimmune thyroid disease and initiation of thyroxine is often all that is required. The treatment of subclinical thyroid dysfunction is controversial and requires an individualised approach, based on the patient's history and examination findings, with specialist input in some cases. MT

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