Goiter

ASSESSMENT OF THYROID SIZE AND FUNCTION

The thyroid can best be palpated whilst standing behind the sitting patient or with the patient lying with the head falling backwards slightly over the edge of the couch. For accurate documentation of size, one practical method is to draw a line on the skin around the contours of the thyroid gland and to copy this on to a sheet of thin plastic. This plastic can be stored in the case records so that the size can be assessed longitudinally.

Thyromegaly (**Fig. 9.1**) can occur as a result of stimulation, infiltration or inflammation, and may be diffuse or nodular (localized) (**Table 9.1**).

ETIOLOGY

- **Endemic iodine deficiency** – the main cause of goiter, either euthyroid or with hypothyroidism, in areas of the world with poor natural sources of iodine and in the absence of an iodized salt supplementation program.
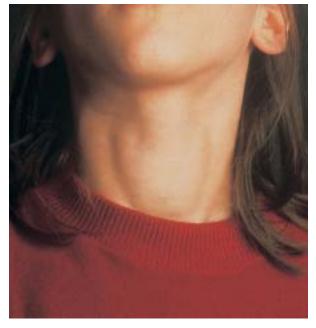

Fig. 9.1 Goiter.

Diffuse thyromegaly
Autoimmune thyroiditis (Hashimoto disease)
Thyrotoxicosis (Graves disease)
Toxic thyroiditis (Hashitoxicosis)
Idiopathic (simple) thyromegaly

Iodine deficiency in endemic areas
Goitrogen ingestion
Antithyroid drugs
Familial dyshormonogenesis
Acute and subacute thyroiditis

TSH-secreting pituitary adenoma (very rare)
Pituitary resistance to thyroid hormone (PRTH) (very rare)

Nodular thyromegaly
Autoimmune thyroiditis
Simple thyroid cyst
Thyroid tumors
    Adenoma — hyperfunctioning (hot)
or non-functioning (cold)
    Carcinoma (medullary thyroid carcinoma or papillary)
    Other tumor
Non-thyroidal masses
Lymphadenopathy
Branchial cleft cyst
Thyroglossal duct cyst

Table 9.1 Causes of thyromegaly

- **Autoimmune thyroiditis (Hashimoto disease)** – the commonest cause of goiter in areas that are not iodine deficient. The pathogenesis of this disorder is uncertain, but a deficiency in antigen-specific suppressor T lymphocytes may be present. Antithyroid antibodies are usually present in high titers. It may be associated with other autoimmune disorders (**Figs 9.2 & 9.3**) and antibodies against adrenal cortex, parathyroid, gastric parietal cells, etc. (polyglandular syndrome type II or III; **Table 9.2**). Patients with euthyroid

Fig. 9.2 Systemic lupus erythematosus (SLE) coexisting with Hashimoto thyroiditis.

Fig. 9.3 Lichen sclerosus of tongue coexisting with Hashimoto thyroiditis.

Hashimoto disease should be followed for a few years to see whether they develop hypothyroidism or hyperthyroidism (see below).

■ **Idiopathic simple goiter or adolescent goiter (Fig. 9.4)** – enlargement of the gland at the time of puberty to form a visible goiter is not uncommon in euthyroid individuals, often with a positive family history of goiter. Regression is usual but nodular changes may occur three or four decades later.

■ **Acute bacterial thyroiditis** – with fever and tenderness.

■ **Subacute thyroiditis** – with lymphocytic infiltration, tenderness and often evidence of intercurrent upper respiratory tract infection.

■ **Ingestion of goitrogens** – either as antithyroid drugs or as naturally occurring compounds in the diet, such as large amounts of soya and cabbage, or unidentified agents in specific geographic areas.

■ **Dyshormonogenesis** – usually presents as goitrous neonatal hypothyroidism (see Ch. 11) but may occasionally present with goiter in later life.

Hypothyroidism and hyperthyroidism will now be discussed as the most important clinical causes of goiter; congenital hypothyroidism with or without goiter is discussed in Chapter 11.

JUVENILE HYPOTHYROIDISM

Juvenile hypothyroidism most commonly occurs in patients with Hashimoto disease. It is also strongly

Type	Features
1	Two or more of candidiasis, hypoparathyroidism, Addisonism
2	Addisonism plus type 1 diabetes mellitus and/or thyroid antibodies
3	a) Thyroid antibodies plus type 1 diabetes mellitus b) Thyroid antibodies plus pernicious anemia c) Thyroid antibodies plus vitiligo and alopecia plus other autoimmune disease
	Vitiligo may be a component of any of the syndromes

Table 9.2 The polyglandular syndromes

Fig. 9.4 Simple pubertal goiter.

associated with several syndromes with abnormal karyotype, such as Ullrich–Turner, Klinefelter and Down syndromes, in which there is also an increased incidence of thyroid dysgenesis (see Ch. 11), with non-chromosomal disorders, for instance the Noonan syndrome, and also metabolic disorders such as cystinosis.

HISTORY AND EXAMINATION

The exploration of the presenting history of suspected hypothyroidism should include:

- Family history of overactive or underactive thyroid glands; any other familial autoimmune disease.
- A history of recent growth failure and any tendency to weight gain.
- Any tiredness or weakness.
- Any change in activity levels, school performance or mental state.
- Constipation.
- Any hair loss or changes in the skin.
- Heat preference and intolerance of cold.
- Deepening of the voice.
- In females post-menarche, any menstrual irregularity or long, heavy periods.

On examination search for:

- Height reduced in relation to weight centile (**Fig. 9.5**).
- Back relatively longer than the legs.
- If old records exist, low height velocity.
- Goiter (not always present if thyroid has involuted).
- Delayed or arrested puberty *or* advanced sexual maturation – in boys manifested by enlarging testicles and penis with little hair growth, and in females by sexual precocity and cystic ovarian changes.
- Myxedema – rare in childhood.
- Dry skin, cutis marmorata (**Fig. 9.6**), vitiligo (**Fig. 9.7**).
- Pale skin – noted most on hands in contrast to yellow knuckles (see **Fig. 1.45**).
- Deep voice.
- Hair loss (often in the temporal area) (**Fig. 9.8**).
- Proximal weakness and delayed relaxation of the tendon reflexes (**Fig. 9.9**).
- Rarely the pituitary may enlarge because of hypertrophy of the thyrotropin-producing cells, and produce visual field loss from optic chiasm compression (**Fig. 9.10**).

DIAGNOSTIC WORK-UP

For the detection of hypothyroidism, serum free thyroxine (FT_4) and thyroid-stimulating hormone (TSH) measurements are most valuable. (If no FT_4 assay is available, total T_4 can be used, but it should be borne in mind that the total T_4 level is determined largely by the thyroxine binding globulin (TBG) concentration. The TBG level can be assayed and is low in congenital deficiency without any clinical consequences. Thus, a low total T_4 concentration does not necessarily indicate
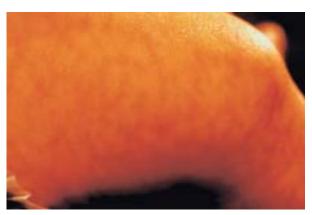

Fig. 9.5 Gross obesity in hypothyroidism. There was a weight loss of 15 kg in the first 2 months of therapy.

Fig. 9.6 Cutis marmorata in hypothyroidism.

Fig. 9.7 Severe vitiligo.

Fig. 9.9 Simple method of demonstrating delayed relaxation of tendon reflexes.
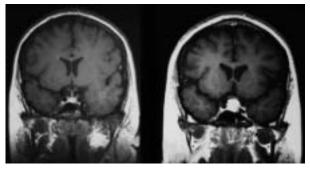

Fig. 9.10 Pituitary enlargement producing compression of the optic chiasm in prolonged hypothyroidism, before and after thyroxine therapy.
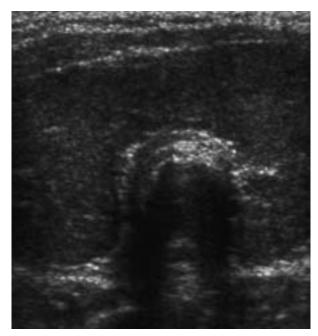

Fig. 9.8 Temporal hair loss in hypothyroidism.

hypothyroidism; see Ch. 11.) The combination of a low $(F)T_4$ with an increased TSH concentration is proof of primary hypothyroidism. Antithyroid antibodies indicate an autoimmune process in the thyroid and are usually present in Hashimoto thyroiditis, as may be antibodies to other glands in the polyendocrinopathy syndromes.

Ultrasonography will help to distinguish smooth from nodular goiter and allow serial measurement of volume (**Fig. 9.11**).

Fig. 9.11 Smooth goiter demonstrated by ultrasonography.

The bone age is often markedly delayed and the epiphyses are wider than normal, dysgenetic or eroded. In the presence of early sexual maturation the luteinizing hormone (LH) : follicle stimulating hormone (FSH) ratio may be less than 1, which is abnormal (see Ch. 6).

Although with modern TSH assays this is rarely required, a thyrotropin releasing hormone (TRH) test can sometimes be helpful (see Appendix). If compensated hypothyroidism is suspected with euthyroidism at the expense of mildly raised TSH levels, there will be an exuberant rise of TSH. The test can also be used to differentiate the non-goitrous or artefactual causes of hypothyroidism. An extremely low TSH level during the whole test indicates a pituitary (secondary) deficiency. A pattern in which TSH continues to rise after 20 minutes is indicative for a hypothalamic (tertiary) defect. A normal TRH test result is seen in TBG deficiency. It should be noted that patients with secondary or tertiary hypothyroidism may show few symptoms or signs and that serum $(F)T_4$ is usually not far below the normal range. Urinary iodine excretion can be measured to document iodine deficiency.

THERAPY

Treatment consists of L-thyroxine in sufficient dosage, to normalize serum TSH levels (which will keep the serum $(F)T_4$ in the upper normal range, or even somewhat higher). The child is checked initially at frequent intervals (1–3 months) and then yearly, when a correct dose is determined. The dosage should be individually titrated but is usually in the order of 2–3 μg/kg daily depending on age (or around 100 μg/m²). After the onset of therapy weight often reduces markedly (**Figs 9.12 & 9.13**). Catch-up growth in height is usually seen, but final height is often not as tall as may be expected from the very delayed bone age.
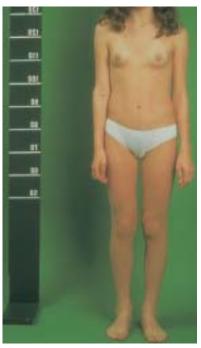
THYROTOXICOSIS

This condition is almost always caused by Graves disease and the presence of thyroid-stimulating antibodies. There is a strong association with infiltration of the orbit by mucopolysaccharide material, which produces the characteristic eye signs. Eye disease is usually less pronounced in children than in adults, and the infiltrative dermopathy seen in adults is very rare indeed in children. Thyrotoxicosis is much more common in females and is strongly familial.

'Hot' secreting adenomas may occur, and in the rare syndrome of pituitary resistance to thyroid hormones (PRTH) there is hyperthyroidism because

Fig. 9.12 Hypothyroidism before therapy.

Fig. 9.13 Same patient as in Fig. 9.12, 6 months after starting treatment. There has been weight loss, progression of puberty and improvement of the lank, greasy hair.

of a lack of feedback inhibition of the pituitary. TSH-secreting pituitary adenomas have been described but are exceedingly rare in childhood.

HISTORY AND EXAMINATION

The exploration of the presenting history of suspected hyperthyroidism should include:

- Family history of overactive or underactive thyroid glands; any other familial autoimmune disease (**Fig. 9.14**).
- A history of recent growth acceleration and any tendency to lose weight, *often in the presence of increased appetite* (**Fig. 9.15**).
- Any tiredness or weakness.
- Any increase in activity levels or change in mental state (decreased ability to concentrate on mental tasks).
- Anxiety (and sometimes frank psychosis).
- Poor school performance.
- Fidgety foot and hand movements, generally increased activity.
- Frequent stools.
- Palpitations.
- Any diplopia, eye pain or redness.
- Cold preference and intolerance of heat.
- In females post-menarche, any menstrual Irregularity, scanty periods or amenorrhea.
- Any thinning of the hair.

On examination search for:

- Weight reduced in relation to height centile.
- If old records exist, increased height velocity (see **Fig. 3.32**).
- Goiter (**Fig. 9.16**).
- Chemosis, exophthalmos, lid lag, ophthalmoplegia, especially in inability to converge the eyes (**Figs 9.17 & 9.18**).
- Tachycardia.
- Increased systolic and decreased diastolic blood pressure, leading to a wide pulse pressure.
- Sweatiness.
- Anxiety or abnormal behavior.
- Tremor – this is best appreciated as a buzz transmitted from the outstretched, spread fingers of the patient to the palm of the examiner's hand, it is of high frequency and may not be visible to the eye.
- Proximal weakness and brisk tendon reflexes.
- Thinning of the hair.

DIAGNOSTIC WORK-UP

Thyroid stimulating immunoglobulins (TSIs), also called thyrotropin receptor antibodies (TRabs), are almost always present, but require specialized laboratories for their measurement. In clinical practice these assays are rarely necessary as the signs and symptoms are so typical. The diagnosis is confirmed by high $(F)T_4$ levels in the presence of suppressed TSH levels. New, ultra-sensitive TSH assays can distinguish a low TSH level from one in the normal range.

Fig. 9.14 Three generations of patients with autoimmune thyroid disease. Mother and daughter hypothyroid, grandmother thyrotoxic.

Fig. 9.15 Thyrotoxicosis before and after presentation.

Fig. 9.16 Goiter in Graves disease.

Fig. 9.17 Exophthalmos in a patient with Graves disease.

Fig. 9.18
Chemosis in the same patient as in Fig. 9.17.

If used, total T_4 levels may again cause confusion in rare congenital situations of TBG excess, or more commonly secondary to pregnancy or various drug therapies such as the contraceptive pill, where T_4 levels will appear high whilst FT_4 levels will be normal (see Ch. 11).

In rare cases of doubt, a TRH test can be done, which will show a suppressed TSH response in the earliest stages of the disease (see Appendix).

Serum total or free triiodothyronine (FT_3) levels may occasionally be valuable in the rare diagnosis of 'T_3 toxicosis' in which FT_3 levels are raised inappropriately for the levels of FT_4 detected on standard assays.

THERAPY

There are four forms of therapy. All have their advantages and disadvantages, and require the supervision of an experienced endocrinologist, especially in the early stages of treatment.

Symptomatic relief

In addition to therapies directed against the thyroid itself, it may be necessary in the early stages of treatment, before lowered FT_4 levels are achieved, to administer a beta-blocker – usually propranolol in a daily dosage of 1–2 mg/kg three times daily – to alleviate the symptoms of hyperthyroidism. This strategy cannot be used in the presence of a history of asthma.

Antithyroid drugs

Propylthiouracil (PTU), methimazole and carbimazole may be used. PTU may have the theoretic advantage of blocking peripheral $T_4 \rightarrow T_3$ conversion and may reduce the titers of thyrotropin receptor antibodies. It is also less likely to exacerbate hair loss if this is a presenting feature of the condition.

PTU is given in a daily dosage of 5–10 mg/kg in three divided doses. The equivalent dosages for methimazole and carbimazole are approximately one-tenth of the PTU dosage, but have the advantage that they can be administered once daily.

There is some evidence that the chances of later relapse are reduced if the antithyroid drugs are given in a dosage sufficient to suppress FT_4 and in combination with L-thyroxine at a replacement dose. This 'blocking' regimen also has the advantage that it is not necessary constantly to increase and decrease drug dosage to try to titrate antithyroid therapy to maintain euthyroid FT_4 levels.

Therapy is usually continued for 2–3 years, after which remission is achieved in about 50% of cases. The dosage can then be slowly tapered. If relapse occurs, antithyroid therapy may be resumed or the patient may be offered the choice of surgical or radio-iodine therapy (see below). The major disadvantages of drug therapy are its long duration, compliance and the risk of toxic side effects (**Table 9.3**); these require the estimation of full blood count in the first 4 weeks of therapy when myelotoxicity is most likely to occur. If any serious side effects are suspected, therapy must be stopped immediately.

Subtotal thyroidectomy

This can occasionally be a first-line therapy, but is more commonly used in cases of relapse after initial drug treatment. The surgeon must have experience of this procedure in children. Permanent hypoparathyroidism and damage to the recurrent laryngeal nerve are possible hazards of surgical intervention.

Side effects of antithyroid drugs (PTU and carbimazole/methimazole)

Rashes: *common* — exchange drugs or, if no substitution possible, treat with antihistamines and continue therapy

Nausea

Headache

Pruritus

Arthralgia

Alopecia (less with PTU)

Jaundice

Lupus (with PTU)

Agranulocytosis: *Patient told to report ANY symptoms of infection, especially sore throat, as soon as they occur. White cell count should be checked immediately and therapy discontinued if there is any clinical or laboratory evidence suggestive of neutropenia*

Table 9.3 Side effects of antithyroid drugs (PTU and carbimazole/methimazole)

Iodine-131 treatment

This has the advantage that it is effective in around 85% of patients and, once administered, requires merely surveillance for the development of later hypothyroidism (20% within 1 year increasing to around 60% after a decade). There are few short-term risks, and 40 years of experience in some centers indicates that there is little risk of later malignant change. It should, however, be considered only in experienced centers.

Treatment of the eye disease is rarely required in childhood. Occasionally intraocular steroid injections or surgical decompression may be necessary to preserve vision.

In some cases of Graves disease there are detectable levels of antithyroid antibodies of the same kind as found in Hashimoto thyroiditis. In these cases spontaneous hypothyroidism may ensue after initial toxicosis, so-called 'Hashitoxicosis'.

NEONATAL THYROTOXICOSIS

If mothers with Graves disease become pregnant, the circulating thyrotropin receptor antibodies can cross the placenta in the last trimester and cause fetal thyrotoxicosis. This is *not* dependent on the current thyroid status of the mother (the antibodies persist after spontaneous or therapeutically induced hypothyroidism)

Fig. 9.19 Neonatal goiter secondary to maternal PTU treatment for thyrotoxicosis. The goiter has compressed the trachea, requiring endotracheal intubation to maintain the airway.

and so obstetric staff should be alert to the possibility in any mother with a past history suggestive of thyrotoxicosis.

The incidence is approximately 1 in 25 000 pregnancies. During pregnancy, fetal size and heart rate have to be monitored closely. In case of fetal tachycardia, low-dose PTU (25–50 mg) may be given to the mother to treat the fetus *in utero*. If the mother is being treated with antithyroid drugs, these can also cross the placenta and cause fetal hypothyroidism and goiter (**Fig. 9.19**).

Whether or not fetal thyrotoxicosis has been detected and treated *in utero*, after birth the infant may develop the symptoms of thyrotoxicosis with tachycardia, hyperkinesis, restlessness, diarrhea, poor weight gain, premature craniostenosis and advanced bone age (**Fig. 9.20**). The diagnosis is confirmed by high $(F)T_4$ and suppressed TSH levels. As the maternally administered antithyroid drugs will be metabolized by the fifth day, but the TSIs will persist for 3–5 months, the neonate requires frequent reassessment in the first 10 days of life.

Therapy is with PTU 5–10 mg/kg and propranolol 2 mg/kg to achieve symptomatic control, or alternatively saturated potassium iodide (Lugol's solution), one drop every 8 h.

THYROGLOSSAL CYST

These cysts form in remnants of the embryonic thyroglossal duct and are rarely associated with thyroid disease. They lie in, or just to one side of, the midline and may transilluminate brightly (see **Fig. 1.86**). They move upwards on protruding the tongue. They are separate from underlying thyroid tissue on

Fig. 9.20
Neonatal
thyrotoxicosis.
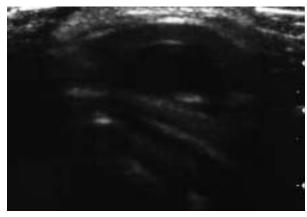

Fig. 9.22 Cold thyroid nodule.

Fig. 9.21 Thyroglossal cyst, separate from underlying thyroid tissue.

Fig. 9.23 Non-secreting thyroid adenoma on ultrasonography.

ultrasonography (**Fig. 9.21**). They require surgical excision to prevent infection.

AUTONOMOUS THYROID NODULE

Thyroid nodules in childhood are rare (**Figs 9.22 & 9.23**). They are often not associated with hormone excess but may occasionally produce thyrotoxicosis and require surgical removal. It is wise to consider ultrasonography and Doppler studies (**Fig. 9.24**) in all cases as well as a needle biopsy to exclude carcinoma of the thyroid.

Multiple nodules are extremely uncommon and may arise from chronically TSH-stimulated goitrous tissue in areas of iodine deficiency or untreated hypothyroidism,

and in the McCune–Albright syndrome. Ultrasonography and needle biopsy are advisable (**Fig. 9.25**).

THYROID CARCINOMA

Thyroid carcinoma usually presents as an asymmetric thyroid mass in teenage life. Females are three times more likely than males to be affected. These tumors are seen after thyroid irradiation (i.e. in Eastern Europe after the Chernobyl disaster) and occasionally
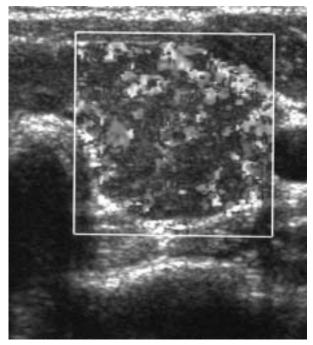
Fig. 9.24 Doppler ultrasonography of goiter showing diffuse vascularity and no regional flow, which may indicate a neoplastic lesion.

Fig. 9.26 Papillary carcinoma of the thyroid on ultrasonography.

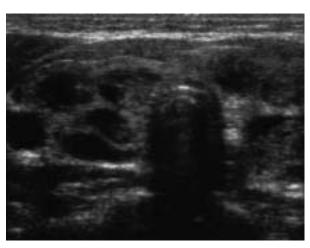**Fig. 9.27** Follicular carcinoma of the thyroid on ultrasonography.

Fig. 9.25 Multinodular goiter on ultrasonography.

in thyroid hormone dyshormonogenesis (see Ch. 11).

Ultrasonography, Doppler studies (which show increased flow around the edge of malignant nodules in comparison to benign adenomas), followed by needle aspiration are mandatory (**Figs 9.26–9.28**). Antithyroid antibodies may be present.

The carcinoma arises from the follicular epithelium and at histologic examination may show papillary (commonest in children) or follicular changes, or a

mixture of the two. Anaplastic cancers are extremely unusual in children. They are often micrometastatic at presentation, but the prognosis is excellent in childhood as they are extremely slow-growing. Treatment involves thyroidectomy followed by iodine-131 treatment and then complete suppression of TSH levels by L-thyroxine. The cells are well differentiated and produce thyroglobulin, which can be used as a marker of the disease process. The outlook with adequate treatment and monitoring is excellent.

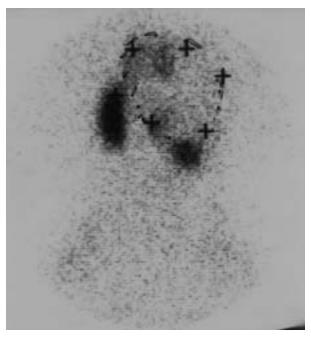Medullary cell carcinoma arising from the calcitonin-producing parafollicular C cells is almost

Fig. 9.28 Follicular carcinoma of the thyroid shown on technetium scan.

always a component of multiple endocrine adenomatosis (MEA) II or IIb (see **Figs 1.72, 1.73 & 3.33**). Diagnosis of this condition on clinical presentation of other components of the syndrome (**Table 9.4**) should prompt immediate removal of the thyroid gland because the risk of malignant change is so great and treatment of distant disease is currently ineffective. Octreotide scanning may help locate malignant metastases. It is now possible to screen relatives of affected individuals by DNA analysis for abnormalities of the *ret* oncogene on chromosome 10q, in informative families, to allow presymptomatic thyroid resection.

Syndrome	Description
MEA-I	Parathyroid (97%), pituitary (30% — prolactin, non-functioning, growth hormone, adrenocorticotropic hormone), pancreatic adenomas (50% — gastrin, insulin, glucagon), carcinoid and lipomata. There is a degree of familial uniformity
MEA-IIa (i)	Medullary cell carcinoma of the thyroid, pheochromocytoma, parathyroid adenomas
MEA-IIa (ii)	Medullary cell carcinoma of the thyroid and pheochromocytoma
MEA-IIa (iii)	Medullary cell carcinoma of the thyroid and parathyroid adenomas
Familial isolated medullary cell carcinoma of the thyroid	
MEA-IIb (III)	Medullary cell carcinoma of the thyroid, pheochromocytoma, mucosal neuromas, intestinal neuronal dysplasia, marfanoid habitus

Table 9.4 Multiple endocrine adenomatosis (MEA) (or multiple endocrine neoplasia; MEN) syndromes