CHAPTER 40
Thyroid and Parathyroid Glands

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Demographics

Diseases of the thyroid gland were demonstrated to occur in 3.7% of 4,819 school-aged children at initial examination in the United States; in a followup examination 20 years later, the prevalence had increased to 10.5%.[1] About half of these are diffuse gland hypertrophy or simple goiter. Thyroiditis was the second most common abnormality, followed by thyroid nodules and functional disorders. Malignant neoplasms are exceedingly rare, with only two papillary thyroid carcinomas found in a population of nearly 5,000 children followed up for three years. Data on thyroid diseases in African children are scanty. One series reported four cases of thyroid tumours in children over a ten-year period in Enugu, Nigeria.[2] Three of these were adenomas and the remaining one was a papillary carcinoma. All of the patients were girls younger than 10 years of age. Data from the United States, based on the National Cancer Registry, reported the annual incidence of thyroid tumours as 0.54 per 100,000 individuals.[3]

Evaluation of Thyroid Diseases

Assessment of Thyroid Function

It is often necessary to determine whether a patient has a hyperactive, normal, or hypoactive thyroid function. A detailed history and careful clinical examination will reveal the diagnosis.

Measurement of Thyroid Hormones in the Serum

Thyroid functional status can be established by estimating the serum thyroid hormones and thyroid-stimulating hormone (TSH, or thyrotropin), which are the most important diagnostic tests. Levels of free T_4 and free T_3 in serum provide a better assessment of the thyroid status than total T_4 and T_3. The levels of T_4 and T_3 are decreased in hypothyroidism, and they are increased in hyperthyroidism. Free T_4 and TSH are the most common useful tests in paediatric thyroid disorders, but test results must be interpreted in conjunction with the child's overall clinical condition. T_3 levels usually need to be measured only when a patient is suspected of having hyperthyroidism but has normal T_4 levels, particularly in cases of toxic nodule, multinodular goiter, or recurrent Graves' disease.[4] Graves' disease is discussed later in this chapter.

Thyrotropin is nearly always decreased in the hyperthyroid state and elevated in hypothyroidism and is an extremely sensitive measure of hypothyroid state. The plasma free T_4 level is a measure of biologically active thyroid hormone, unaffected by protein binding. When total plasma T_3 and T_4 are measured, it is necessary to consider the level of unbound biologically active hormone.

Serum Thyroid Antibodies

The autoantibody status is important in determining thyroid autoimmune diseases. Serum thyroid antibodies are frequently elevated in autoimmune thyroid disorders. Approximately 80% of patients with Hashimoto's disease have elevated antimicrosomal autoantibodies,[5] and most patients with Graves' disease have detectable thyroid-stimulating immunoglobulins. The presence of these antibodies is helpful in the diagnosis of autoimmune thyroid disorders.

Test of Hypothalamic Pituitary Axis

The test for thyrotropin-releasing hormones (TRH) is given intravenously. The basal level of serum TSH is raised in a normal individual at 20 minutes and returned to normal in 120 minutes. In hypothyroidism, the already elevated TSH shows a much higher rise, but there is no response in hyperthyroidism. This is known as the TRH stimulation test.

Imaging

Several imaging modalities are available to assist in evaluating the thyroid gland, among them ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and scintigraphy.

Ultrasonography

Ultrasound imaging is very useful in the evaluation of thyroid disease and can determine whether a neck mass actually arises from the thyroid and whether multiple nodules are present. It allows differentiation of solid and cystic lesions. It is useful in detection of thyroid nodules and measurement of their volume. Goiter volume can be assessed precisely with US and is a useful guide in the assessment of goiter shrinkage response under medical treatment. Although this modality can be used in a clinical setting, it may not be appropriate for mass surveys.

Computed tomography and magnetic resonance imaging

A CT scan is useful in the study of the architecture of the thyroid gland and its relation to the surrounding organs. It can be useful in assessing retrosternal extension of the thyroid. Pituitary or hypothalamic tumours can be seen, as can metastatic lesions of thyroid carcinoma, which are usually solitary. MRI provides a good soft tissue resolution and helps in further ascertaining the architecture of the thyroid gland.

Scintigraphy

Scintigraphy tests are based on the avidity or otherwise of the thyroid to absorb or release the isotope of iodine or technetium and the distribution of the isotope within the gland. Isotopic scanning provides information on the size, shape, position, function, and possible nature of thyroid swelling. The uptake by the thyroid of a low dose of either radioiodine ^{123}I or ^{131}I and technetium-99m pertechnetate will demonstrate the distribution of activity in the whole thyroid gland. The test is of value in a toxic patient with a nodule or nodularity of the thyroid. Localisation of overactivity in the gland will differentiate between a toxic nodule with suppression of the remainder of the gland and toxic multinodularity goiter with several areas of increased uptake with important implications for therapy.[6] Scintigraphy may also be useful in detecting ectopic thyroid tissue or metastatic thyroid carcinoma.

Fine Needle Aspiration Biopsy and Cytology

Thyroid tissue is obtained percutaneously with a 22–25-gauge needle attached to a 20-ml syringe fixed in a syringe holder. Fine needle aspiration (FNA) is useful in diagnosing papillary, medullary, and anaplastic carcinomas. There is small risk of false negative results. It is difficult to differentiate between simple and malignant follicular tumours by FNA cytology.

Nonneoplastic Diseases of the Thyroid Gland

Congenital Anomalies

Lingual thyroid

Lingual thyroid occurs when the thyroid gland fails to descend to its normal cervical location. Approximately 1 in 600,000 live births present in childhood or adolescence with lingual thyroid.[7] In cases of undescended thyroid, 90% were found within the tongue and 10% in the anterior neck above the hyoid bone.[8] The posterior part of the tongue around the foramen caecum is the most common site of lingual thyroid. It is most common in females. Symptoms usually consist of dysphagia and dyspnea. Diagnosis is confirmed by radioactive iodine scintigraphy. Of patients with lingual thyroids, 75% have no functional thyroid tissue.[9] Therefore, testing for location of thyroid tissue in addition to gland function is necessary.

Treatment consists of complete excision of the lingual thyroid followed by lifelong thyroid hormone therapy. Autotransplantation of the excised lingual gland or pedicle transfer—retaining a vascular pedicle and moving part of the thyroid into the neck—has been successful in several cases.[8,10]

Goiters

An enlarged thyroid gland due to any cause is called a goiter. Goiters are classified as diffusely enlarged or nodular and either toxic or euthyroid. A diffuse thyroid enlargement is the most common form of goiter in small children. Physiologically, diffuse thyroid enlargement may be related to autoimmune diseases, or can be an inflammatory or compensatory response. In a study of 152 school children with goiters, most patients (83%) had adolescent colloid goiter.[11] Goiters may be endemic or sporadic.

Endemic goiters

Endemic goiters exist when more than 10% of any community has goiters,[12] usually in high rocky mountain regions of the world. Endemic goiter has been described in nearly all African countries. Endemic goiter is mainly caused by insufficient iodine intake in the diet. The iodine content of the water supply and the soil in granite mountain regions are very low. Other causes of endemic goiter are goitrogens in food and excessive calcium salts in the water supply. Cassava, which is a common foodstuff in most African communities, contains cyanogenic glycosides, which yields thiocyanate as a metabolic by-product. Thiocyanate inhibits iodine uptake by the thyroid.[12]

The physiologic changes to iodine deficiency are usually accompanied by an increase in the size of the thyroid gland. Generalised epithelial hyperplasia occurs, with cellular hypertrophy and reduction in follicular spaces. In chronic iodine deficiency, the follicles become inactive and distended with colloid accumulation. These changes persist into adulthood, and focal nodular hyperplasia may develop, leading to nodular formation. Some of these nodules retain the ability to secrete thyroxin and form functioning thyroid nodules. Others do not retain this ability, become inactive and form cold nodules. Necrosis and scarring result in fibrous setae, which contribute to the formation of multinodular goiters (Figure 40.1). Some multinodular goiters eventually become toxic. One study reports an increasing risk of toxicity developing in nodular goiters in children and adults in Africa, and 10.7% of adult nodular goiters may develop infective thyroiditis (thyroid abscess), although whether this infective complication occurs in children is not clear.[13,14]

Sporadic goiters

Sporadic goiters occur in areas where goiters are not endemic. Sporadic goiters affect relatively few people and are usually pathological. The persistence of goiters in some areas with adequate iodine prophylaxis and the unequal geographic distribution of goiters in iodine-deficient areas suggest the existence of other goitrogenic factors. Cyanoglucosides are naturally occurring goitrogens found in several staple foods in the tropics, namely, cassava, maize, bamboo shoots, and sweet potatoes. The brassica family of vegetables is a well-known example producing thioglycosides. Flavonoides from millet, a staple food in Sudan, are also known to have antithyroid activity.

Figure 40.1: A ten-year-old boy with endemic multinodular goiter.

Congenital goiter

The majority of neonatal goiters result from maternal ingestion of goitrogens. In the newborn infant, the most commonly implicated drugs are iodides and thiourea derivatives used for treatment of maternal thyrotoxicosis. Congenital goiter has also been described in a newborn with Prader-Willi syndrome.[15] Most goiters in the newborn are of the hyperplastic type and disappear a few weeks after birth.[16]

Ultrasonography provides a useful noninvasive investigation in assessing the size of the goiter as well as the response to therapy. Rarely, goiters may be large enough to produce severe respiratory distress by tracheal compression. These patients may require division of the isthmus or subtotal thyroidectomy to relieve tracheal compression.

Physiologic goiter

In physiological states such as puberty, menstruation, and pregnancy or lactation, the body's requirement for thyroid hormones is increased due to the increased metabolic activity. If this requirement is not met, TSH secretion is increased to stimulate the thyroid. The thyroid gland undergoes physiological hyperplasia and may therefore enlarge. The thyroid gland is enlarged evenly, and feels comparatively soft. This occurs at puberty and is almost exclusively confined to females. Involution takes place when the hormones are increased in a sufficient amount or the need for an increased amount is over, usually by the twenty-first year.[6,12]

Colloid goiter

Colloid goiter is diffuse hyperplasia of the thyroid gland due to iodine deficiency. It is commonly seen in endemic areas but may also occur sporadically. In endemic areas, children may be affected, but girls from puberty to 20 years of age are most commonly involved.[12] The gland is enlarged, smooth-surfaced, may be firm in areas and soft in others, and has some degree of elasticity. All goiters of puberty that do not subside completely must be considered colloid goiters. The gland may occasionally be big enough to cause tracheal compression. The degree of lateral lobe enlargement determines the extent of displacement or narrowing of the trachea. Spontaneous regression is common, although, on occasion, minimal amounts of thyroxine preparation may be necessary.

Classification of goiter in general is according to the size of the thyroid gland on physical examination and the grading system recommended by the World Health Organization (WHO) in 1960 and modified in 1994:[17]

- Grade 0: No palpable or visible goiter
- Grade 1: Mass consistent with enlarged thyroid that is palpable but not visible when the neck is in the neutral position; it also moves upwards in the neck as the subject swallows.
- Grade 2: Swelling visible in a neutral position of the neck and consistent with an enlarged thyroid when the neck is palpated.

Prevention

The supply of adequate iodine in the diet and the elimination of goitrogens are the means used to prevent endemic goiter. Global iodisation of salt has been successfully introduced with remarkable results worldwide.

Thyroiditis

Hashimoto's disease

Hashimoto's disease (chronic lymphocytic thyroiditis) is an uncommon entity in young patients. This is a common cause of diffuse enlargement of the thyroid gland, occurring frequently in female adolescents. This condition is part of the spectrum of autoimmune thyroid disorders. It is thought that CD_4 T cells are activated against thyroid antigens and recruit cytotoxic CD_8 T cells, which kill thyroid cells, to cause hypothyroidism. In this autoimmune self-destructive state of lymphadenoid goiter, the gland is firm and uniformly enlarged, usually pebbly and granular in nature. Children are initially euthyroid and slowly progress to become hypothyroid. About 10% of children are hyperthyroid (hashitoxicosis).[18] Ninety-five percent of patients with chronic lymphocytic thyroiditis have elevated antithyroid microsomal antibodies or antithyroid peroxidase antibodies. The plasma level of thyroid hormones is normal or low, and TSH levels are elevated in 70% of patients.[18] This condition may also be associated with Down syndrome, Turner syndrome, Noonan syndrome, juvenile diabetes, treated Hodgkin's disease, and phenytoin therapy.[19]

Thyroid imaging may not be necessary if clinical and laboratory findings are strongly suggestive of the diagnosis.

An ultrasound finding is not specific, showing diffuse thyroid hypoechogenicity.

A radionuclide scan usually shows patchy uptake of the tracer and may mimic the findings in Graves' disease or multinodular goiter.

Fine needle aspiration may be needed to confirm the diagnosis.[18] Histology usually reveals the characteristic Askanazy cells.[2]

Treatment

Thyroiditis resolves spontaneously in about one-third of adolescent patients, with the gland becoming normal and the antibodies disappearing. Exogenous thyroid hormone should be given in the hypothyroid patient, but it is not effective in reducing the size of the gland in euthyroid children.[18]

Subacute Thyroiditis

Subacute (de Quervain's) thyroiditis is a viral inflammation of the thyroid gland. It is unusual in children. The thyroid is swollen, painful, and tender. Mild thyroitoxicosis results from injury to the thyroid follicles, with release of thyroid hormone into circulation. Serum T_3 and T_4 levels are elevated and TSH is decreased. Findings of reduced radioactive iodine uptake due to thyroid follicle dysfunction differentiate it from Graves' disease. Histologically, granulomas and epitheliod cells may be seen.[18]

The treatment of subacute thyroiditis is symptomatic, consisting of nonsteroidal anti-inflammatory agents or steroids. The condition typically lasts 2 to 9 months, and complete recovery is expected.

Acute Suppurative Thyroiditis

Acute suppurative thyroiditis is a bacterial infection of the thyroid glands. The gland is acutely inflamed, and the patient is septic. Patients are usually euthyroid. The patient may have a preexisting multinodular goiter.[14] Staphylococci or mixed aerobic and anerobic flora are common causative agents, and a pharyngeal sinus tract may predispose the patient to infection.

Management consists of intravenous antibiotics. Drainage of the abscess may be needed. The thyroid gland may recover completely.

Hyperthyroidism: Graves' Disease

Primary hyperthyroidism (thyrotoxicosis) is a disease associated with an elevation in the circulating long-acting thyroid stimulating (LATS) hormones. Graves' disease, or diffuse toxic goiter, is the most common cause of hyperthyroidism in childhood. The condition is an autoimmune disease caused by the presence of immunoglobulin (Igs) of the IgG class directed against components of the thyroid plasma membrane, possibly including the TSH receptor. These autoantibodies stimulate the thyroid follicles to increase iodide uptake and cyclic adenosine monophosphate production, leading to thyroid growth and inducing the production and secretion of increased thyroid hormones.

TSH receptor antibodies are present in more than 95% of patients with active Graves' disease. The inciting event eliciting the antibody response against TSH is unknown. Reports have suggested the possibility of bacterial infection eliciting antibodies that react with the TSH receptor.[20]

Graves' disease is seen in girls more than boys, with a ratio of 5:1. The incidence steadily increases throughout childhood, peaking in the adolescent years.[18] Thyrotoxicosis is uncommon in African children; a relative incidence of a case or two per year is recorded.[2] A study in conjunction with the British Paediatric Surveillance Unit (BPSU) that analysed data collected between September 2004 and September 2005 from the UK and Ireland reported 110 cases of acquired congenital childhood thyrotoxicosis. This incidence (0.9 cases per 100,000 individuals younger than 15 years of age) is lower than has previously been reported in European studies. Data from Hong Kong report an even higher incidence of thyrotoxicosis: 6.5 cases per 100,000 per year between 1994 and 1998. Ninety-six percent of the cases were due to autoimmune thyrotoxicosis, and the incidence increased with age for both males and females. The incidence in females was significantly higher than in males in the 10–14 year age group.[21]

Congenital Graves' disease, resulting from transplacental passage of maternal antibodies, occurs in about 1% of babies born to women with active Graves' disease. The onset may be delayed until 2 to 3 weeks after birth.[18] In most children, the onset of Graves' disease develops over several months. The clinical manifestations of Graves' disease include goiter (virtually 100%), thyrotoxicosis, and exophthalmus (Figure 40.2). The systemic manifestations of thyrotoxicosis can be classified as initial and later presentations:

- *Early:* Nervousness, emotional lability, decline in school performance.
- *Late:* Weight loss, sweating, palpitations, heat intolerance, staring gaze, increase in appetite, diarrhoea, and general malaise.

Amenorrhea and a swelling above the ankles called pretibial myxoedema may sometimes be present. Above all, thyrotoxicosis must

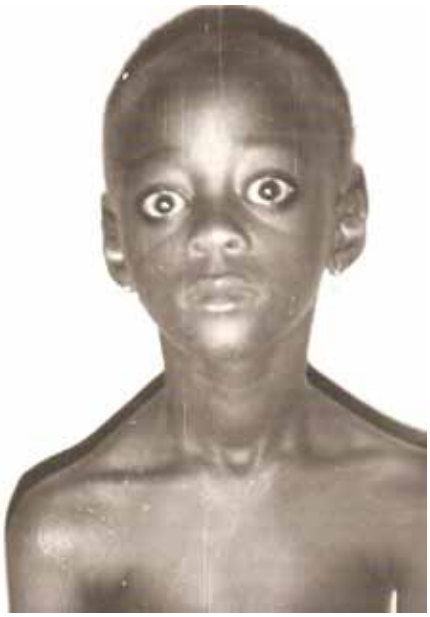

Figure 40.2: Thyrotoxicosis in an 8-year-old girl.

be considered in any child with an unexplained growth spurt, sympathy (e.g., muscle weakness, paraesthesia) or behavioural problems. The gland is uniformly enlarged, smooth, firm, and nontender. It may be so vascular that a bruit is audible over it.

Laboratory evaluation generally reveals elevated free T_4 and decreased TSH levels. In 10–20% of patients, only the T_3 level is elevated, a condition referred to as T_3 toxicosis. The diagnosis of Graves' disease is established by the presence of TSH-receptor antibodies.

Management

The treatment of Graves' disease is palliative, with the goal to allow natural resolution of the underlying autoimmune process. The natural course of untreated Graves' disease is unpredictable.[18] The treatment is designed to reduce the production and secretion of the thyroid hormone. This could be specific or nonspecific. Specific measures include the use of antithyroid drugs (carbimazole, neomercazole, potassium perchlorate). Nonspecific measures include rest and sedation.

Initial therapy is with methimazole or propylthiouracil, which reduces thyroid hormone production by inhibiting follicle cell organification of iodide and the coupling of iodotyrosines. Propylthiouracil also inhibits peripheral conversion of T_4 to T_3, and may be the drug of choice if rapid alleviation of thyrotoxicosis is desired. Both agents may possess some immunosuppressive activity. Methimazole is preferred in most cases due to its increased potency, longer half-life, and associated improved compliance. The initial dose in adolescents is 30 mg once daily, adjusted for younger patients. The dosage is reduced to 10 mg when the patient becomes euthyroid with normal T_3 and T_4.

The thyroid gland decreases in size in about half of the patients. Thyroid enlargement with therapy signals either an intensification of the disease or hypothyroidism with overtreatment.[18]

In general, the disease remission rate is approximately 25% after 2 years of treatment, with a further 25% remission every 2 years.[22] The resolution rate is decreased if TSH-receptor antibodies persist during and after treatment.

Surgery

Surgery is usually contraindicated in children due to the high postoperative incidence of hypothyroidism (35%), recurrence, tetany (17%), and of permanent hypoparathyroidism (10%).[12]

Indications for surgery in children with Grave's disease include:

- idiosyncratic reaction to antithyroid drugs;
- progressive enlargement of the gland, even in a euthyroid state;
- contraindication to radioactive iodine;
- recurrent hyperthyroidism;
- patients who refuse radioiodine;
- failed medical therapy; and
- large thyroid gland compressing the airway.

Surgery in the form of either subtotal thyroidectomy or total thyroidectomy in the suitably prepared patient may be performed. Preoperative antithyroid medication should be administered to decrease T_3 and T_4 levels to the normal range. Beta-blocking agents such as propranolol may be used to ameliorate the adrenergic symptoms of hyperthyroidism.

In addition, Lugol's iodine solution, 5 to 10 drops per day, should be administered for 4 to 7 days before thyroidectomy to reduce the vascularity of the gland.

The incidence of hypothyroidism after subtotal thyroidectomy is 12–54%, and the hypothyroidism may be subclinical in up to 45% of children.[23] The rate of recurrent hyperthyroidism is approximately 13%. The relapse rate may increase with time after surgery. Near total thyroidectomy is advocated by some authors.[2]

Hypothyroidism

Hypothyroidism is a clinical state in which there is reduced thyroid hormonal activity. This is rarely due to thyroid hypofunction secondary to reduced TSH stimulation resulting from hypopituitarism. Hypothyroidism may result from a defect anywhere in the hypothalamic-pituitary-thyroid axis (Table 40.1).

Table 40.1: Causes of hypothyroidism.

Type of hypothyroidism	Cause
Iatrogenic	Following subtotal thyroidectomy
	Hypophysectomy
	Radio-iodine treatment for thyroitoxicosis
	Excessive ingestion of para-aminosalicylic (PAS) acids, phenylbutazone, or antithyroid drugs
Iodine deficiency	Area of endemic goiters
Autoimmune thyroiditis	Secondary to thyroid antibodies
Dyshormonogenesis	Deficiency or absence of enzymes needed for thyroid hormone synthesis
Congenital	Absence of thyroid gland (very rare) or ectopic thyroid gland
	Antenatal goitrogens
	Pituitary-hypothalamic disease

Congenital hypothyroidism

Ninety percent of paediatric hypothyroidism is congenital, detected by neonatal screening programmes, and results from dysgenesis of the thyroid gland**.** Screening programmes have dramatically altered detection and management of congenital hypothyroidism. In the United Kingdom, all newborns are screened for congenital hypothyroidism as part of a national screening programme, which also includes tests to exclude phenylketonuria and cystic fibrosis. The worldwide incidence of congenital hypothyroidism is reported as 1 in 4,000 infants. However, the true incidence is lower in African Americans and higher in Hispanic and Native American populations.[19] Two-thirds of these babies have a rudimentary gland, and complete absence of thyroid tissue is noted in the rest of the patients. The rudimentary gland may be ectopic.[18]

The severe form of hypothyroidism in children is cretinism, which is also congenital, and the child may be born with or without a goiter. The child is usually underdeveloped both physically and mentally. There may be associated deafness, mutism, and neuromotor disorders (e.g., spastic paraplegia, dysarthria).[12]

Evaluation

Infants with congenital hypothyroidism are often normal size at birth, which is a reflection of the fact that thyroid hormones do not appear to be necessary for foetal growth. Physical features are not apparent in the first week of life. Prolonged neonatal jaundice is usually the first symptom, followed by feeding problems, lethargy, constipation, and poor tone. Examination often reveals coarse facies; a large protruding tongue; large open fontanelles; a hoarse cry; coarse, dry, and mottled skin; umbilical hernia; and delayed growth. In severe cases, these features appear within 4 to 8 weeks of birth.[24]

Serum T_4, T_3, and resin uptake are decreased, whereas TSH is elevated. Assessment of skeletal age (by x-ray of the knee) may show bone maturation of less than 36 weeks gestation, suggesting intrauterine hypothyroidism.

Treatment

Treatment is by lifetime thyroid hormone replacement. Synthetic (laevo-) thyroxin is used at a dosage of 10 mg/kg per day, starting with 25 mg per day and increasing to 100 mg per day.

The aim of treatment is to maintain the serum T_4 level in the high to normal range (10–14 μg/dl). Treatment is monitored with the reversal of clinical signs, linear growth, and TSH levels.[24]

The prognosis is good for linear growth and skeletal maturity. Intellectual progress depends on the age at which treatment is started, and usually poor after 3 months of age.[24]

Acquired hypothyroidism

Acquired, or juvenile, hypothyroidism is commonly caused by autoimmune destruction of the thyroid gland secondary to chronic lymphocytic thyroiditis (Hashimoto's disease). Other rarer causes are goitrogens (e.g., iodide cough syrups, antithyroid drugs), ectopic thyroid dysgenesis, infiltration of the thyroid gland in storage disorders, and secondary involvement from pituitary disorders with TSH deficiency or hypothalamic lesions and TRH deficiency. Onset is usually insidious. There is slowing of linear growth; there may be changes in personality, cold intolerance, diminished appetite, lethargy, and constipation. Girls may have breast development, hypertrophy of labia minora, galactorrhae, and cystic ovarian enlargement; boys may have testicular enlargement without a corresponding development of pubic hair.

Evaluation

Low serum T_4, decreased T_3 resin uptake, and elevated TSH are diagnostic. Skeletal maturation is markedly delayed. There is occasional association with a slipped femoral epiphysis. Assays of circulating thyroid antibodies imply an autoimmune basis for the disease. Low or normal TSH may suggest hypopituitary or a hypothalamic lesion. A TRH stimulation test may be useful in this situation.

Treatment

Thyroid hormone replacement with L thyroxin, 3-5 μg/kg as a single daily oral dose, is given for life. Adequacy of treatment is monitored with measurement of serum T_4, reversal of clinical symptoms, and increased linear growth.

Prognosis is good for catch-up growth and skeletal maturation. Catch-up is not expected if hypothyroidism develops around the time of puberty, when skeletal maturation is nearly complete. Intellect is usually not impaired.[24]

Hypothyroidism is rarely treated surgically.

Neoplastic Diseases of the Thyroid Gland

Thyroid Nodules

A solitary nodule of the thyroid is an uncommon lesion in children.[2,18] This lower incidence may be because fewer children have been exposed to irradiation. It may represent an area of functional hyperplasia (adenoma), which can be associated with secondary hyperthyroidism. Other possible causes of thyroid nodules include:

- adenoma;
- thyroglossal duct remnant;
- cystic hygroma;
- germ cell tumour; and
- infected thyroid cyst.

Thyroid nodules are twice as common in girls than in boys. Most patients present with an asymptomatic anterior neck mass. A thyroid nodule may be a slowly growing, potentially curable, papillary carcinoma.[2] This is frequently clinically indistinguishable from benign lesions, although the former demonstrates a reduced uptake of iodine ^{131}I.

Thyroid imaging studies are unreliable in distinguishing benign from malignant nodules, but ultrasound may reveal multiple nodules. One report has documented an 18% malignant rate by FNA of thyroid nodules in children.[25]

Surgical resection of a thyroid nodule should be performed if it is malignant, of indeterminate cytology, is a benign nodule that is increasing in size, or is an aspirated thyroid cyst that recurred.[18] Thyroid nodules in prepubertal children have a higher risk of malignancy. The natural history of benign lesions in younger children is unknown, and the safety of nonoperative treatment has not been documented. In children younger than 13 years of age, it is currently recommended that all thyroid nodules be removed.[18]

Thyroid Carcinoma

Thyroid carcinoma represents about 3% of all paediatric malignancy in United States.[18] The peak incidence is between the ages of 10 and 18 years, with a female preponderance of 2:1. Thyroid carcinoma is the second most common cancer in females aged 15–19 years in the United States.[19] The incidence of childhood thyroid malignancy was reported to be decreasing in most parts of the world due to the reduced use of radiation to treat benign diseases. Individuals who have been exposed to radiotherapy to the neck have a significantly increased chance of development of thyroid dysfunction. The incidence has been reported as being up to 64%, increasing with time of irradiation, radiation dose, and age at time of irradiation.[19]

The incidence of thyroid carcinoma in children is low in the African community,[2] with four cases over 10 years reported in Enugu, Nigeria. Three were adenoma, and the remaining one was papillary carcinoma. All the patients were girls younger than 10 years of age.[2] In one report, there was only one case of follicular carcinoma, in a 10-year-old girl seen over a 10-year period in Ilorin.[26]

In Nigeria, about 90% of thyroid carcinomas in children are of the well-differentiated type: 70% papillary and 20% follicular. The undifferentiated type, such as medullary carcinoma, is rare.[2] Data from the United States, collected retrospectively for the period from 1973 to 2004, reported 1,753 cases of thyroid carcinoma occurring under the age of 20 years. The condition was more common in females than males, and mean survival was 30.5 years. Sixty percent of the tumours were papillary, 23% were the follicular variant of papillary, 10% were follicular, and 5% were medullary. Tumours of the medullary subtype are often associated with the familial syndrome of multiple endocrine neoplasia type 2 (MEN2). Worse predictors of outcome were male sex, nonpapillary tumour subtypes, the presence of distant metastases, and nonsurgical treatment.[3]

Follicular carcinoma has been described in a neonatal dyshormogenetic hyperplastic goiter. Total thyroidectomy is necessary in this instance.

Lateral aberrant thyroid tissues, previously thought to be ectopic thyroid glands, are now known to represent thyroid carcinoma secondary to the cervical lymph nodes.[2]

Thyroid carcinoma is usually first seen clinically as a thyroid mass, sometimes with an enlarged cervical lymph node. The most common presentation in childhood is indolent, palpable lymph glands in the lateral side of the neck. Solitary or multiple nodules in the thyroid glands are usually secondary. The cancer is usually more advanced at presentation in children when compared to adults, and regional lymph node metastases are present in 75% of children when the disease is first detected.[27]

Evaluation

Pathologic diagnosis can be made by either FNA or frozen-section biopsy at operation. Most surgeons, however, recommend surgical resection of all thyroid lesions due to concern over false negative interpretation of FNA.[18]

The functional status of the mass is determined by preoperative scintiscan. A preoperative chest radiograph is necessary because of the high incidence of pulmonary metastases in children.

Burkitt lymphoma of the thyroid gland has also been reported in the tropics.[2]

Treatment

Surgical excision is the treatment of choice with or without lymph node dissection.

Lobectomy with isthmus resection may be sufficient for tumours clearly isolated to one lobe. Because thyroid cancer has been documented to be bilateral in as many as 66% of cases, with about 80% of these exhibiting multifocality, most paediatric surgeons recommend either a total or near total thyroidectomy for a differentiated thyroid cancer.

Lymph node dissection is recommended if regional nodes are suggestive of metastasis.

The parathyroid gland can be preserved by identifying and autotransplanting one or two of the glands into the sternocleidomastoid muscle or into the nondominant forearm. The recurrent laryngeal nerve should also be identified and protected.

It is generally recommended that exogenous thyroid hormones be used to treat all endocrine thyroid cancer, to suppress TSH-mediated stimulation of the gland.

Radioiodine ablative therapy is successful in eradicating residual tumours. It is more effective, however, after removal of the entire gland because less functioning endocrine tissue takes up the radionuclide.

Overall survival rate in nonmedulary thyroid carcinoma is 98%.[28] A higher recurrence rate is seen in children who did not receive postoperative radio iodine ^{131}I.

Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) accounts for approximately 5% of thyroid neoplasms in children. It arises from the parafollicular C cells. MTC may occur sporadically or in association with multiple endocrine neoplasia IIA or IIB or the familial MTC syndrome. The neoplasm is particularly virulent in patients with MEN IIB, and may occur in infancy.

The clinical diagnosis of MTC is usually made only after metastatic spread to the adjacent cervical lymph node or to distant sites.

It is recommended that early detection of MTC with RET (REarranged during Transfection) proto-oncogen mutation may improve survival.

Total thyroidectomy is the recommended surgical management of MTC in children. Lymph nodes in the central compartment of the neck, medial to the carotid sheaths and between the hyoid bone and the sternum, should be removed. Surgery is recommended at approximately 5 years of age, especially in children with MEN IIA, before the cancer spreads beyond the thyroid gland.[29] Due to the high virulence of MTC in children with MEN IIB, prophylactic thyroidectomy is recommended at approximately 1 year of age.

Parathyroid Glands: Hyperparathyroidism

Hyperparathyroidism is associated with an increased secretion of parathormone (PTH). This can be primary, secondary, or tertiary.

Primary Hyperparathyroidism

Primary hyperparathyroidism is an unstimulated and inappropriately high parathormone secretion.[6] In childhood, it usually results from a solitary hyperfunctioning adenoma in about 70–90% of patients,[12] and more rarely (10–20%) diffuse hyperplasia of all the four glands.[12] The hyperparathyroidism resulting from hyperfunctioning of all four glands is a feature of MEN-I. Primary hyperparathyroidism of infancy is a rare, often fatal, condition that usually develops within the first 3 months of life. Signs include hypotonicity, respiratory distress, failure to thrive, lethargy, and polyuria. The serum PTH is elevated. There is usually diffuse parathyroid gland hyperplasia. A familial component of the disease is found in about half of the patients. Early recognition and treatment are essential to allow normal growth and development of the baby.[18]

The management of primary hyperparathyroidism in children is surgical. All four parathyroid glands should be identified and biopsies performed. An enlarged and adenomatous gland should be removed. If the other glands are normal, they should be marked with nonabsorbable sutures and left in place.

Secondary Hyperparathyroidism

Increased PTH is secondary or compensatory to conditions that cause low plasma calcium level. Secondary hyperparathyroidism occurs in children with renal insufficiency, malabsorption, or Ricketts. Affected patients typically respond to medical treatment designed to decrease intestinal phosphorus absorption, but, in rare cases, severe renal osteodystrophy develops, manifested by skeletal fracture and metastatic calcifications. Very severe cases can be candidates for total parathyroidectomy with autotransplantation.

Tertiary Hyperparathyroidism

Tertiary hyperparathyroidism occurs when persistent hyperfunction of the parathyroid glands occurs, even after the inciting stimulus has been removed. This is often seen in patients with chronic renal failure and secondary hyperparathyroidism who undergo renal transplantation. It is commonly due to hyperplasia of all four glands, and children with this condition are candidates for total parathyroidectomy with autotransplantation.[18]

Evidence-Based Research

Table 40.2 presents a study that compares the female-to-male prevalence of thyroid disease. Table 40.3 presents a study to evaluate the effect of clinical and treatment factors on thyroid carcinoma control, complications, and recurrence.

Table 40.2: Evidence-based research.

Title	Thyroid diseases in a school population with thyromegaly
Authors	Jaksic J, Dumic M, Filipovic B, Ille J, Cvijetic M, Gjuric G
Institution	Department of Pediatrics, University School of Medicine, Zagreb, Croatia; Department of Pediatrics, Medical Centre, Sibenik, Croatia
Reference	Arch Dis Childhood 1994; 70:103–106
Problem	Goiter is common in childhood and adolescence despite the widespread practice of iodising table salt, which has eliminated the dietary lack of iodine, This study concerns the prevalence and nature of diffuse and nodular goiters found during a survey of 5,462 schoolchildren in Sibenik, Croatia, a seaside region where iodised (0-01% potassium iodide) table salt is regularly available.
Comparison/ control (quality of evidence)	The study compared the prevalence of thyroid disease in boys and girls.
Outcome/ effect	Thyroid enlargement was found in 152 children (2.8%). The most common disorder was simple goiter, which was established in 126 (2.3%) of these—12 (0.45%) boys and 114 (4.07%) girls. Juvenile autoimmune thyroiditis was found in 19 of the children (prevalence, 0.35%), with a female-to-male sex ratio of 8:1.
Historical significance/ comments	This survey of large series of children shows that it is necessary to conduct a thorough examination of the thyroid, even in apparently healthy children in regions where regular iodine intake is established.

Table 40.3: Evidence-based research.

Title	Childhood and adolescent thyroid carcinoma
Authors	Grigsby PW, Gal-or A, Michalski JM, Doherty GM
Institution	Department of Radiation Oncology, Washington University Medical Center, St. Louis, Missouri, USA; Department of Surgery, Washington University Medical Center, St. Louis, Missouri, USA
Reference	Cancer 2002; 95:724–729
Problem	Reports on the specific factors that predict the risk of developing recurrent disease in children are scanty. This study was performed to evaluate the influence of clinical and treatment factors on local tumour control, control of distant metastasis survival, and complications in children and adolescents with thyroid carcinoma.
Outcome/ effect	The study involved 56 children, ages 4–20 years; there were 43 females and 13 males. The overall survival rate was 98% with a follow-up of 0.6–30.7 years (median follow-up, 11.0 years). The 10-year progression-free survival rate was 61%. Nineteen patients (34%) experienced a recurrence of their thyroid carcinoma. The time to first recurrence of disease ranged from 8 months to 14.8 years (mean, 5.3 years). None of those with disease confined to the thyroid developed recurrent disease. The recurrence rate was 50% (17 of 34) in patients with lymph node metastasis and 29% (2 of 7) in patients with lung metastasis ($P = 0.02$).Thyroid capsule invasion ($P = 0.02$), soft tissue invasion ($P = 0.03$), positive margins ($P = 0.006$), and tumour location at diagnosis (thyroid only versus thyroid and lymph nodes versus thyroid, lymph nodes, and lung metastasis, $P = 0.02$) were significant for developing recurrent disease. Patients younger than 15 years of age at diagnosis were more likely to have more extensive tumours at diagnosis than patients who were 15 years of age and older (thyroid only versus thyroid and lymph nodes versus thyroid, lymph nodes, and lung metastasis, $P = 0.02$).
Historical significance/ comments	Carcinoma of the thyroid in children and adolescents has little risk of mortality but a high risk of recurrence. Younger patients present with a more advanced stage of disease and are more likely to have disease recurrence. Total thyroidectomy and lymph node dissection, followed by postoperative ^{131}I therapy, thyroid hormone replacement (suppressive) administration, and diligent surveillance are warranted

Key Summary Points

1. Simple goiter occurs with a wide range of prevalence (1–6%) in different populations of children and adolescents.
2. A diffuse thyroid enlargement is the most common form of goiter in small children.
3. Graves' disease is relatively uncommon in children.
4. Thorough examination of the thyroid, even in apparently healthy children in regions of regular iodine intake, is necessary to detect thyroid disorder.
5. Although thyroid nodules are unusual in childhood and adolescence, they demand careful consideration because of the likelihood that they may represent malignancy.
6. Juvenile autoimmune thyroiditis is one of the most frequent thyroid diseases in childhood.
7. Thyroid hormone treatment is used in established cases of goiter before cystic degeneration sets in to decrease the size of the goiter or arrest its further growth.
8. Endemic goiter can be reversed with iodide and/or thyroxin in the early stages. Response is generally poor or negligible after the formation of nodules and onset of cystic degeneration.
9. Carcinoma of the thyroid in children and adolescents has little risk of mortality but a high risk of recurrence.

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