Thyroid disorders in children from birth to adolescence

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Abstract. Thyroid hormones play a crucial role as a regulator of growth, of nervous system myelination, of metabolism, and of organ functions. Disorders affecting the thyroid gland represent the most common endocrinopathies in childhood. The etiology and clinical presentation of thyroid disorders in children and adolescents substantially differ from that in adults. Thus, pediatric medical care requires an appreciation of distict characteristics of thyroid function and dysfunction in childhood and adolescence. Early diagnosis and treatment are essential to prevent irreversible and permanent nervous system damage and developmental delay, especially in infants as they are extremely vulnerable to thyroid dysfunction. Therefore, as well as reviewing distinct features of disorders with hypothyroidism, hyperthyroidism and normal thyroid function in childhood and adolescence, this article will also focus on important aspects of pre- and postnatal thyroid development and physiology.

Keywords: Hypothyroidism – Hyperthyroidism – Thyroid cancer – Goitre – Childhood

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Introduction

Thyroid hormones influence almost all aspects of normal child development and thus play a crucial role as a regulator of nervous system myelination, of growth and of puberty, of dental and skeletal development, of metabolism and of organ functions [1]. Disorders affecting thyroid function may cause irreversible and permanent nervous system damage and developmental delay, especially in early infancy, when the thyroid system is immature and the individual organism is extremely vulnerable to thyroid dysfunction. Appropriate medical care of children with thyroid disorders requires refined knowledge of the ontogeny of the thyroid system and an appreciation of distinct characteristics of thyroid function in childhood. Therefore, as well as reviewing thyroid disorders with hypothyroidism, with hyperthyroidism or with normal thyroid function in childhood and adolescence, with an emphasis on new and important findings, this article will also focus on important aspects of pre- and postnatal thyroid development and physiology.

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Ontogeny and physiology

The thyroid gland evolves in the human embryo from two embryological structures, the thyroid diverticulum and the ultimobranchial bodies [2]. The thyroid anlage arises in the pharyngeal floor and becomes visible as a midline endodermal thickening at embryonic day 20, in close vicinity to the endothelium of the developing heart. Thereafter, the gland reaches its final pretracheal location by caudal migration, and parafollicular or C cells and thyroid follicular cells differentiate further, this being marked by the expression of genes involved in thyroid hormone synthesis, such as the thyrotropin (TSH) receptor, the sodium-iodide symporter (NIS), the thyroperoxidase (TPO), and thyroglobulin (TG) genes. Normal morphogenesis and migration of the embryonic thyroid are independent of TSH because the capacity of the pituitary to synthesize and secrete TSH is not apparent until the 10th to 12th weeks of gestation. Several transcription factors have been identified that govern thyroid ontogeny, are sequentially expressed and regulate thyroid-specific genes during development: thyroid transcription factor 1 (TTF1) [3], TTF2 [4], PAX8 [5] and HOX3 [6]. Accumulation of iodine and synthesis of thyroxine by the fetal thyroid gland commence at gestational week 11. By approximately week 20, the TSH concentration rises in the fetal circulation, indicating the

maturation of the hypothalamic-pituitary axis. This is followed by an increase in thyroxine (T_4). Fetal TSH and T_4 concentrations exceed those observed in preterm neonates of corresponding age. Due to the inner-ring deiodination of iodothyronines in the placenta and fetal liver, plasma concentrations of triiodothyronine (T_3) remain low throughout pregnancy whereas reverse T_3 (rT_3) concentrations are high. Maternal thyroid hormones are significantly transferred to the fetus across the placenta and via the amniotic fluid [7]. Normal fetal development and subsequent neuropsychological development after birth, especially in fetal hypothyroidism, depend on maternal iodothyronines and may even be compromised by maternal hypothyroidism [8, 9]. After birth, a surge in pituitary TSH secretion is followed by an increase in circulating T_3 and T_4 concentrations, reaching hyperthyroid levels when compared with those later in childhood and adolescence. Subsequently, TSH decreases during the first week after birth due to feedback inhibition by the elevated serum T_4 at both the hypothalamic and the pituitary level [10]. These perinatal changes in thyroid hormone secretion have to be considered when thyroid function tests are performed in preterm and full-term neonates. Specific reference values for iodothyronines have been established which take into account the significant effects of age and sex and which provide an essential clinical tool for assessing thyroid function accurately in children and adolescents [11, 12].

Hypothyroidism

Hypothyroidism in children can be classified as primary or secondary (central), and can be either congenital or acquired, transient or permanent. The incidence of congenital hypothyroidism varies with the geographic area. It ranges from as high as 1:3,300 neonates in Europe to as low as 1:5,700 neonates in Japan, but averages 1:4500 neonates in most other areas [13]. The prevalence rates in the neonatal period for the various thyroid disorders that can lead to neonatal hypothyroidism have been reported as being 1:4,000 for thyroid dysgenesis, 1:30,000 for thyroid dyshormonogenesis, 1:40,000 for transient hypothyroidism and 1:100,000 for central hypothyroidism (hypothalamic-pituitary disorders) [10].

Primary hypothyroidism is characterized by thyroid hormone production in the thyroid gland that is inadequate to meet the needs of the organism. A heterogeneous group of developmental abnormalities accounts for 80%–90% of all cases of congenital hypothyroidism due to thyroid dysgenesis; this group includes agenesis (40%), hypogenesis (25%) and ectopia (35%). Defects in one of the steps of thyroid hormone synthesis, referred to as dyshormonogenesis, are found in 10%–20% of the patients with congenital hypothyroidism (TSH unresponsiveness, and NIS, TPO, TG or deiodinase deficiency). Insufficient secretion and action of hypothalamic thyrotropin releasing hormone (TRH) and of pituitary TSH causes secondary or central hypothyroidism (hypothalamic-pituitary anomalies, multiple pituitary hormone deficiencies, isolated TSH deficiency). Patients with thyroid hormone resistance due to a defective nuclear thyroid hormone receptor present with elevated circulating levels of T_4 and T_3 with normal or increased serum TSH concentration. Transient hypothyroidism occurs in 5%–10% of infants with congenital hypothyroidism. The most common causes are maternal TSH receptor blocking auto-antibodies, endemic iodine deficiency, iodine contamination and antithyroid drug or goitrogen ingestion [10].

The majority of cases of congenital hypothyroidism appear to be sporadic, the exceptions being inborn errors of thyroid hormone synthesis or dyshormonogenesis which are autosomal recessive in inheritance [14]. The prevalence of congenital hypothyroidism seems to be higher in girls than in boys. It is more common in Hispanics than in whites, and is thought to be less common in blacks. New data from population-based studies on families of children with congenital hypothyroidism due to thyroid dysgenesis showed a familial clustering of thyroid developmental abnormalities, which indicates that genetic factors could be involved in the aetiology of congenital hypothyroidism. An autosomal dominant mode of inheritance with relatively low penetrance was suggested [15, 16]. In addition a significantly higher frequency of extrathyroidal congenital malformations as compared to the general population, e.g. affecting the heart, the nervous system and the eyes, was reported in infants with congenital hypothyroidism [17, 18]. Recently, several cases of thyroid dysgenesis have been shown to be associated with mutations in genes of transcription factors (TTF1, TTF2, PAX8 and TSH receptor) which are involved in the development of thyroid follicular cells [2]. The affected human neonates present with aplasia or hypoplasia (TSH receptor, PAX8) of the thyroid [19, 20], and with impaired lung maturation and choreoathetosis (TTF1) [21, 22], cleft palate, choanal atresia, bifid epiglottis and spiky hair (TTF2) [23]. The mode of inheritance may be autosomal dominant, autosomal recessive or haploinsufficiency. Disorders with thyroid dyshormonogenesis are frequently found to be associated with goitre formation. Such inherited defects in thyroid hormone synthesis include Pendred's syndrome (congenital deafness and impaired iodine organification due to mutations in the pendrin gene coding for an anion transporter) [24], defects in iodide transport (NIS) [25], defects in the synthesis and processing of TG and general resistance to thyroid hormones. Secondary hypothyroidism has been described in individuals carrying mutations of the TRH receptor and the TSHß subunit, and in patients with deficiencies of the transcription factors PIT1 and PROP1, which are involved in the organogenesis of the pituitary. In the latter, TSH deficiency is combined with other pituitary hormone deficiencies (prolactin,

growth hormone and gonadotropins) [14]. Overt hypothyroidism may also develop later in infancy and childhood in patients with iodine deficiency, with thyroid autoimmune disease, with late-onset thyroid dysgenesis or dyshormonogenesis, with cranial neoplasias, with chromosomal anomalies (Ullrich-Turner syndrome, Klinefelter syndrome, Down syndrome), with metabolic disease (diabetes mellitus, cystinosis, thalassaemia), after drug ingestion (iodine, amiodarone, glucocorticoids, dopamine), and after therapeutic or accidental irradiation [10, 13, 14]. The non-thyroidal illness syndrome denotes transient thyroid dysfunction in critical illness or after surgery which biochemically resembles secondary hypothyroidism and which may contribute to the morbidity of critical illness [26, 27].

Clinical manifestations of hypothyroidism depend on the time of onset of thyroid dysfunction. They may be rather unspecific and subtle in early infancy, and may not appear until 2 months of age. Today affected newborns are diagnosed biochemically through screening programmes for congenital hypothyroidism before the onset of any symptoms [28, 29]. During early infancy, signs of hypothyroidism in untreated patients may be prolonged jaundice, lethargy, constipation, feeding problems, umbilical hernia, macroglossia, large fontanelles and hypotonia, whereas later in life delay in developmental milestones, deceleration of linear growth, delayed skeletal and dental maturation, myopathy and weakness, fatigue and delayed puberty may be the predominant symptoms. Other signs of transient thyroid dysfunction may comprise low cardiac output, left ventricular dysfunction, increased vascular resistance and impaired ventilatory drives, which are sequelae of the postoperative intensive care course in children with congenital cardiac malformations recovering from cardiac surgery [26, 27, 30]. The clinical impact of the hypothyroxinaemia with normal TSH concentrations which is frequently observed in preterm infants has been investigated intensively, but no conclusive evidence has been provided that morbidity of preterm infants can be attributed to thyroid dysfunction [31]. This hypothyroxinaemia usually resolves within the first 2 months of life.

Diagnostic measures of hypothyroidism are low plasma concentrations of T_4, free thyroxine (fT_4) and T3 with high TSH in primary hypothyroidism and low or normal TSH in secondary hypothyroidism, whereas in thyroid hormone resistance iodothyronine levels may be normal or even high. Concentrations of plasma TG, the TSH-dependent matrix protein of thyroid hormone synthesis, reflect the extent of intrathyroidal hormone synthesis and may be a useful tool in checking compliance in thyroxine-treated patients [32]. The introduction of neonatal screening for congenital hypothyroidism has greatly improved the overall prognosis of affected children [28, 29]. TSH or T_4 concentrations are measured in capillary blood samples at the end of the first week after birth, before the appearance of any symptoms. When high TSH levels or low T_4 levels are detected, plasma concentrations of TSH, T_4, fT_4, T_3 and TG are measured in order to confirm congenital hypothyroidism. Screening results have to be interpreted with care when specimens are collected during the first 2 days of life, in preterm infants born before gestational week 32, in critically ill neonates, in patients receiving blood transfusions, in neonates exposed during the perinatal phase to iodine-containing topical anti-infective agents or drugs, and in neonates treated in intensive care with drugs which are known to impair thyroid function (e.g. dopamine, glucocorticoids).

Treatment of affected patients with L-thyroxine (10–15 µg/kg body weight, corresponding to 50 µg in full-term neonates) is initiated before day 14 after birth [33]. Plasma TSH should then decline to the normal range during the first month of life, and T_4, fT_4, and T_3 plasma concentrations should be maintained in the upper normal range for age. Thyroxine tablets should be administered before feeding, separately from other medications such as iron, and on the day of a control evaluation after drawing the blood sample. A radioactive iodine uptake scan may be useful to distinguish agenesis, hypogenesis and ectopia of the thyroid gland in cases with thyroid dysgenesis, but routine performance of a scan in neonates with congenital hypothyroidism is no longer recommended. Ultrasonography represents a sensitive diagnostic tool to examine and locate the thyroid gland even in infancy. The follow-up of patients should include hearing tests and neuropsychological examinations. With age, the absolute L-thyroxine dose increases and is adjusted according to the plasma iodothyronine concentrations; however, the dose decreases when it is calculated per kg body weight (2–15 µg/kg body weight, corresponding to 100 µg/m^2). When the diagnosis cannot be confirmed without doubt in the neonatal period and therapy is initiated, L-thyroxine treatment is continued until 2 years of age (after the critical phase of brain development) and then discontinued at least for 4 weeks in order to revaluate the thyroid function. The long-term prognosis has improved substantially since screening was introduced. Normal psychomotor development, longitudinal growth and sexual maturation can be achieved in infants with congenital hypothyroidism after early initiation of treatment (= day 14) and with an appropriate L-thyroxine dose (>10 µg/kg body weight) [34, 35, 36].

Recently the acute beneficial effects of T_3 supplementation on myocardial function and on overall recovery could be demonstrated in children with congenital heart defects after cardiopulmonary bypass operations [37].

Hyperthyroidism

Autoimmune hyperthyroidism, referred to as Graves' disease in the English-speaking world and as von Basedow's disease on the continent of Europe, is the most

common of the thyroid diseases in areas of iodine abundance and accounts for at least 95% of cases of hyperthyroidism in children [1]. In comparison to adulthood, hyperthyroidism is rare in childhood and adolescence. Only 1%–5% of thyroid disease with hyperthyroidism begins before the age of 16 years. Recent studies investigating autoimmune hyperthyroidism in children have reported an incidence of 1:10,000,000 [13, 38]. The incidence increases during childhood and peaks during adolescence. It occurs more frequently in females than in males, in a ratio of 3:1 to 5:1.

Hyperthyroidism is defined as excess synthesis and secretion of thyroid hormones by the thyroid gland, i.e. exceeding the need of the organism. Autoimmune hyperthyroidism may occur in neonates of mothers with Graves' disease, as Graves' disease of childhood and in the early phase of autoimmune thyroiditis (Hashitoxicosis). Persisting congenital hyperthyroidism and familial hyperthyroidism of non-autoimmune origin due to gain-of-function mutations in the TSH receptor gene have been identified [39, 40]. The mode of inheritance is autosomal dominant. The onset of hyperthyroidism in these familial cases occurs at various times from infancy to adulthood, but neonatal hyperthyroidism has not been described. In contrast, severe non-familial congenital hyperthyroidism due to gain-of-function mutations has been described in neonates. These mutations are different from those identified in the familial cases and are identical to those found in thyroid adenomas [40]. Other rare causes of hyperthyroidism in childhood are TSH-producing pituitary adenomas, pituitary resistance to thyroid hormones and ingestion of exogenous thyroid hormone or iodine. The plasma concentrations of total thyroxine are increased in familial elevation of the thyroxine binding protein (TBG), but fT_4 concentrations are normal, as is thyroid function. Oestrogens may also increase TBG concentrations.

Graves' disease is characterized clinically by thyromegaly, hyperthyroidism and infiltrative ophthalmopathy. However, severe ophthalmopathy is rare in childhood and occurs in less than 50% of children with Graves' disease. A family history of autoimmune thyroid disease is present in up to 60% of patients. Genetic studies have shown it to be a polygenetic disorder, and most of the genes that have been implicated appear to be involved in immunoregulation. Patients with Graves' disease have an increased incidence of HLA haplotypes A1, B8 and DR3 [41, 42]. Autoantibodies of the immunoglobulin G1 class bind to the extracellular domain of the TSH receptor (TSI) and stimulate follicular cell function and growth. In addition, other autoantibodies to the TSH receptor (TBII) are present that block thyroid cell function. Antibodies to the thyroperoxidase (TPO) and cytotoxic antibodies can also be detected in Graves' disease. Transplacental passage of TSI from mothers with Graves' disease causes neonatal autoimmune-mediated hyperthyroidism in their offspring, but as few as 1% of neonates are affected. Autoantibodies may persist in the maternal circulation for a long time after thyroidectomy or radiation therapy and may still cause hyperthyroidism in the neonate. The presence of a combination of TSH receptor stimulating and blocking antibodies may lead to the development of late-onset neonatal Graves' disease presenting later than 9 days post partum. Neonatal Graves' disease resolves within 3–12 weeks, since maternal TSH receptor stimulating antibodies (of the IgG class) are degraded with a half-life of approximately 12 days [38]. Antithyroid drugs such as carbimazole or methimazole also cross the placenta and temporarily mask the stimulating effects of TSI in the neonate.

Clinical manifestations may be rather unspecific and minimal in the initial phase of Graves' disease because the disease usually develops over several months. Changes in behaviour and school performance, insomnia, restlessness and irritability, and nocturia are common. Classic symptoms and signs include goitre, tachycardia, nervousness, tremor, increased pulse pressure, increased appetite, weight loss and diarrhoea [43]. Ophthalmic features comprise mild eyeball protrusion, lid lag or lid retractions and, less commonly, marked chemosis, pain and double vision. The thyroid gland is usually symmetrically enlarged, smooth, soft and nontender, and slides with swallowing; thyroid bruit can be auscultated. Specific features of congenital hyperthyroidism include severe prenatal dystrophy and premature birth, and in the postnatal period restlessness, irritability, failure to thrive and tachycardia. When the diagnosis is delayed, premature craniosynostosis may evolve.

Plasma levels of T_3 are often more elevated than those of T_4, and TSH concentrations are suppressed, except in the presence of pituitary TSH-secreting adenomas and pituitary resistance to thyroid hormones. Measurements of iodothyronines and antibodies in neonates with congenital hyperthyroidism should be performed at birth in cord blood, after a week, when the effects of maternal antithyroid drugs have disappeared, and after 6–8 weeks of life, when the titres of TBII have decreased and those of TSI persist in the circulation [44]. Free iodothyronines are normal in the circulation of patients with familial elevation of TBG and increased binding capacity, while total iodothyronines are elevated. Antibodies (TSI, TBII, TPO) are detectable in up to 80% of affected patients but do not represent a follow-up parameter for remission or relapse of the disease [45]. Ultrasonography reveals the enlargement of the thyroid gland, with reduced, largely non-homogeneous echogenicity and increased perfusion. Thyroid scintigraphy is performed only in patients with nodules detected by ultrasonography in order to rule out autonomous functioning nodules.

Therapeutic management options for Graves' disease in childhood include antithyroid drug therapy, surgery and radioiodine treatment, all of which are associated with potential complications [46]. Antithyroid drug therapy with thioamides (carbimazole or methimazole and

propylthiouracil) is associated with side-effects such as rash, granulocytopenia, arthritis and hepatitis, and a disappointing long-term remission rate as low as 30%–40% even after prolonged therapy [43, 47, 48]. The equivalent dosages for methimazole and carbimazole (0.5–1 mg/kg body weight; may be given in one dose) are one-tenth of the propylthiouracil dosage (5–10 mg/kg in three divided doses). After achievement of euthyroidism, maintenance therapy may proceed either by reducing the dosage by one-third to one-half to maintain plasma iodothyronine levels in the normal range, or by continuing the initial therapeutic dosage to induce hypothyroidism and initiating L-thyroxine therapy. The latter method is preferred by many paediatricians because it reduces the need for frequent monitoring of thyroid function for the development of hypothyroidism [42]. Simultaneous treatment of patients with antithyroidals and L-thyroxine failed to improve the rates of remission [49]. The treatment is discontinued after 24 months in order to assess whether the disease has remitted. Longer treatment periods may be required in order to improve the efficacy of drug therapy [50]. Propranolol (1 mg/kg body weight) or dexamethasone may be helpful in relieving symptoms from autonomic dysfunction and blocking the conversion of T_4 to the biologically more active T_3 [51, 52]. Thyroid hormone synthesis may be acutely blocked by iodide (Lugol's solution). In contrast to drug therapy, surgery has favourable cure rates (90%) and reverses the hyperthyroid state rapidly, but entails a complex surgical procedure that can result in permanent hypothyroidism, hypoparathyroidism or dysphonia due to damage of the recurrent laryngeal nerves [53]. Thyroidectomy may be useful for the patient who develops drug-related complications or does not achieve lasting remission, and for neonates with severe non-familial congenital hyperthyroidism due to gain-of-function mutations. Radioiodine therapy, which is more frequently used in the United States than in Europe, is associated with cure rates as high as 90% and represents the least expensive treatment option for Graves' disease [13, 46]. However, the long-term safety of iodine-131 in children and adolescents has not been evaluated extensively. The oncogenic potential of radioiodine and the potential risks of genetic damage to any offspring after ^{131}I treatment has raised concern. Radioiodine therapy should be avoided in children less than 5 years of age because the risk of thyroid cancer after external radiation is highest in children less than 5 years of age and progressively declines with advancing age [54, 55]. In older children and adolescents, radioiodine treatment may be considered as an alternative treatment option for Graves' disease, e.g. in patients with large goitres [56].

Disorders with thyroid enlargement and largely normal thyroid function

Thyromegaly, referred to as goitre, is defined as enlargement of the thyroid gland to above the normal volume for the age in question, irrespective of the aetiology and the thyroid function. Patients with endemic goitre are clinically and biochemically euthyroid, but goitre may also be associated with thyroid dysfunction and thyroiditis. Deficiency of iodine, intrathyroidal growth factors such as IGF-I and EGF, and environmental factors which interact with iodine trapping (NIS) and organification (TPO) contribute to thyromegaly [1, 57]. Common goitrogens include the antithyroid drugs (propylthiouracil, methimazole, carbimazole) and foods such as cassava, cabbage, cauliflower and soy. The thyroid volume of children and adolescents correlates with dietary iodine intake and decreases with increased nutritional intake of iodine [58, 59]. Endemic goitre is mostly characterized by diffuse thyroid enlargement and its incidence in childhood can be greatly reduced by the use of iodized salt and by adding iodine to infant formulas. The goitre remains asymptomatic and mainly disfiguring unless adjacent structures, such as the trachea and the oesophagus are compressed. Ultrasonography of the thyroid gland shows the increased thyroid gland volume with an inhomogeneous medium-level echogenicity. Patients with endemic goitre in areas of environmental iodine deficiency are supplemented with iodine after autoimmune thyroiditis has been ruled out as the underlying cause, thus TPO and TG antibodies should be undetectable in their plasma. Thyroid volume can be reduced by appropriate iodine therapy (infants: 100 µg/day; children: 200 µg/day; adolescents 200–300 µg/day) for 6–12 months. When iodine supplementation fails to reduce thyroid volume, L-thyroxine treatment is initiated.

Chronic lymphocytic thyroiditis of childhood and adolescence represents an autoimmune disease which is frequently associated with goitre (Hashimoto's thyroiditis). Cytotoxic mechanisms in this autoimmune thyroiditis cause a chronic inflammatory reaction and result in the characteristic histological abnormalities of lymphocytic infiltration, fibrosis and lymphoid follicles. Thyroid cell damage is mediated either by thyroid antibody-dependent cell-mediated cytotoxicity or by direct cytotoxicity from sensitized effector T lymphocytes, or by both mechanisms in association with production of destructive cytokines [60]. An increased incidence of HLA haplotypes DR3, DR4 and DR5 indicates a genetic background of autoimmune thyroiditis [61]. The disease occurs with a female to male ratio of 3:1. Most children and adolescents with Hashimoto's thyroiditis present with asymptomatic enlargement of the thyroid gland. Less often the disease becomes manifest after the onset of hypothyroidism (atrophic thyroiditis); rarely it presents initially with symptoms and signs of thyrotoxicosis which result from the release of excessive amounts

of preformed thyroid hormones due to inflammatory destruction of thyroid follicular cells. The associations of autoimmune thyroiditis with multiple autoimmune endocrinopathies have been classified into the autoimmune polyglandular syndromes: type 1: hypoparathyroidism, Addison's disease, mucocutaneous candidiasis; type 2: Addison's disease, insulin-dependent diabetes; type 3: insulin-dependent diabetes, pernicious anaemia [1]. Autoimmune thyroiditis frequently occurs in patients with Ullrich-Turner syndrome and trisomy 21. The diagnosis of Hashimoto's thyroiditis is established by the detection of TPO and TG autoantibodies in the circulation and by the ultrasonographic appearance of the thyroid gland as an enlarged gland with reduced echogenicity [58]. Treatment of Hashimoto's thyroiditis depends on thyroid function. When overt hypothyroidism with elevated plasma TSH and decreased plasma T_3 and T_4 concentrations is present, the child is treated with L-thyroxine. However, the effects of thyroxine on the course of Hashimoto's thyroiditis in patients with elevated plasma levels of TSH but normal T_3 and T_4 concentrations have yet to be confirmed in controlled studies [62]. Patients with hyperthyroid thyroiditis may gradually return to a euthyroid state within 1–2 months and require no specific treatment. Propranolol can relieve severe symptoms from autonomic dysfunction in the hyperthyroid phase of the disease. The treatment with L-thyroxine should be discontinued in adolescents after puberty for re-evaluation of thyroid function since remission of Hashimoto's thyroiditis may occur in a significant number of patients [63].

Isolated thyroid nodules are uncommon in childhood and adolescence and should be further examined in order to distinguish the cyst from a benign or malignant tumour. Patients with a history of previous exposure to ionizing radiation in the head and neck or high-dose total body irradiation and with a positive family history for thyroid cancer are especially at risk of developing thyroid malignancies [64, 65, 66, 67]. Ultrasonography is more sensitive than physical examination in detecting thyroid nodules but neither is specific in differentiating benign and malignant nodules [68]. In contrast, fine-needle aspiration (FNA) exhibits a diagnostic accuracy of about 90% and the diagnosis of thyroid cancer in children and adolescence is established by either an FNA biopsy or an open, excisional biopsy of a thyroid nodule and/or cervical lymph node. About 75% of thyroid nodules explored by FNA are benign [69]. In areas of iodine deficiency most thyroid nodules seem to be benign and are characterized by normal or increased echogenicity on sonographic examination. Hyperfunctioning solitary adenomas (hot nodules) are diagnosed by ^{123}I scan. Thyroid carcinomas in childhood are rare and account for 1.5% of all tumours before the age of 15 years and 7% of the tumours of the head and neck during childhood. More than 60% of these malignancies occur in girls [13]. During childhood, papillary carcinomas (85%–90%) predominate over the other thyroid malignancies such as medullary carcinoma (5%) and follicular and anaplastic thyroid cancers (which rarely occur in children). Papillary and follicular carcinomas are well differentiated and capable of secreting TG into the circulation; TG can be measured in plasma and represents a diagnostic and follow-up parameter. Exposure to ionizing radiation (especially in children <5 years of age), iodine deficiency, prolonged elevation of plasma TSH, and autoimmune thyroiditis (Graves' and Hashimoto's diseases) are considered risk factors for the development of thyroid cancer in childhood and adolescence. Autosomal dominant inheritance has been demonstrated in medullary carcinomas [66].

Total thyroidectomy represents the initial treatment of choice for children and adolescents with thyroid cancer, which facilitates subsequent ^{131}I ablation of the potential thyroid remnant [70]. Survival rates of more than 90% at 20 years have been reported in children and adolescents with differentiated thyroid carcinoma. Unlike in adults, the presence of distant metastases does not predict a poor prognosis in children [71].

Recent guidelines for the diagnosis and therapy of multiple endocrine neoplasia (MEN) type 2 ascertain that the main morbidity from MEN2 is medullary thyroid carcinoma (MTC) and that its variants differ in aggressiveness, in decreasing order as follows: MEN2B >MEN2A >familial MTC [66]. All variants of MEN2 are caused by germline mutations in the RET proto-oncogene. It is recommended that MEN2 carrier detection by RET mutation testing should be the basis for recommending thyroidectomy to prevent or cure MTC. This carrier testing is mandatory in all children at 50% risk. Compared with RET mutation testing, which reveals a RET mutation in more than 95% of MEN2 index cases, immunoassay of basal or stimulated calcitonin results in more frequent false-positive diagnosis and delays the true-positive diagnosis of the MEN2 carrier state. However, measurements of calcitonin should still be performed to monitor the tumour status of MTC and can be the first index of persistent or recurrent disease. Prophylactic thyroidectomy should be performed before the age of 6 months, and perhaps much earlier, in MEN2B, and before the age of 5 years in MEN2A [66].

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